S($ 10/97)

UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Docket No: **D-3111**

Total Pages in this Submission

22713 U.S. PTO 082704

19587 U.S. PTO 10/927857 082704

TO THE U.S. PATENT AND TRADEMARK OFFICE
PO BOX 1450
ALEXANDRIA, VA 22313-1450

Transmitted herewith for filing under 35 U.S.C. 111(a) and 37 CFR 1.53(b) is a new utility patent application for an invention entitled:

METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS

and invented by:

ACHEAMPONG ET AL

If a CONTINUATION APPLICATION, *check appropriate box an supply the requisite information:*
[ ]**Continuation** [ ]**Divisional** [ ]**Continuation-in-part (CIP)** of prior application No.:

Enclosed are **Application Elements**:

[X] Filing Fee

[X] Specification having **34** page(s) and including the following:

- [X] Title of the Invention
- [X] Cross References to Related Applications *(if applicable)*
- [X] Background of the Invention
- [X] Brief Summary of the Invention
- [ ] Description of the Drawings
- [X] Detailed Description
- [X] Claim(s) as Classified Below
- [X] Abstract of the Disclosure

[ ] __ Sheets of Drawings(s) (37 CFR 113) [ ] Formal [ ] Informal

[X] Oath or Declaration [X] Executed [ ] Unexecuted
[ ] Copy from prior application (37 CFR 1.63(d)) *(for continuation/divisional application only)*

[X] Power of Attorney [X] Executed [ ] Unexecuted
[ ] Copy from prior application (37 CFR 1.63(d)) *(for continuation/divisional application only)*

[X] Incorporation By Reference -- The entire disclosure of the prior application from which a copy of the oath or declaration is supplied under the above entry, is considered as being part of the disclosure of the accompanying application and is hereby incorporated by reference therein.

[ ] Computer Program in Microfiche *(Appendix)*

Accompanying Application Parts

[X] Assignment Papers (cover sheets & documents(s))
[ ] The prior application is assigned of record to
[ ] Copy from prior application (37 CFR 1.63(d)) *(for continuation/divisional application only)*

[ ] 37 CFR 3.73(B) Statement *(when there is an assignee)*

[ ] English Translation Document *(if applicable)*

[ ] Information Disclosure Statement/PTO-1449 [ ] Copies of _ IDS Cited Reference(s)
[ ] Preliminary Amendment
[X] Acknowledgment postcard
[X] Certificate of Mailing by Express Mail
[X] APPLICATION DATA SHEET
[ ] REQUEST FOR NON-PUBLICATION

Fee Calculation and Transmittal

** The filing fee is calculated on the basis of the claims existing in the prior application as amended by the accompanying preliminary amendment noted above.*

CLAIMS AS FILED					
For	**#Filed**	**#Allowed**	**#Extra**	**Rate**	**Fee**
Total Claims	36	- 20 =	16	X $18.00	$288.00
Independent Claims	2	- 3 =		X $86.00	$ 0.00
Multiple Dependent Claims *(check if applicable)* [ ]					$ 0.00
				BASIC FEE	$ 770.00
OTHER FEE *(specify purpose)*				**ASSIGNMENT**	$ 40.00
(Applicant has small entity status under 37 CFR 1.9 and 1.27)				**SMALL ENTITY STATUS**	--
				TOTAL FILING FEE	$1,098.00

[ ] A check in the amount of $ __ to cover the filing fee and the assignment fee is enclosed.
[X] The Commissioner is hereby authorized to charge and/or credit Deposit Account Number **01-0885** as described below.
[X] Charge the amount of $1,098.00 as filing fee.
[X] Credit any overpayment.
[X] Charge any additional filing fees required under 37 CFR 1.16 and 1.17.

Respectfully Submitted,

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D-3111

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
PATENT

In re application of: ACHEAMPONG ET AL.	)	Group Art Unit: N/A
Serial No. N/A	)	Examiner: N/A
Dated: Submitted herewith	)	
Title: METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS	)	

Express Mail Mailing Label No. EV 464416262 US

Date of Deposit: AUGUST 27, 2004

I hereby certify that the following documents as identified below are being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and are addressed to the Commissioner for Patents, PO Box 1450, Alexandria, VA 22313-1450.

1. Application Transmittal
2. Application Data Sheet;
3. Application;
4. Declaration;
5. Assignment and Recordation Sheet; and
6. Return receipt postcard.

The 6 above-identified documents are enclosed herewith.

Respectfully submitted,

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DOCKET NO.: D-3111

THE ENCLOSED PATENT APPLICATION OF ACHEAMPONG ET AL. IS BEING FILED IN ACCORDANCE WITH SECTION 37 CFR 1.10 BY EXPRESS MAIL AND SHOULD BE ACCORDED A FILING DATE

AUGUST 27, 2004

SEE THE EXPRESS MAIL CERTIFICATE ATTACHED TO THE APPLICATION.

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METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS

Related Application

This application claims the benefit of U.S. Provisional Application No. 60/503,137 filed September 15, 2003, which is incorporated in its entirety herein by reference.

Background of the Invention

The present invention relates to methods of providing desired therapeutic effects to humans or animals using compositions including cyclosporin components. More particularly, the invention relates to methods including administering to an eye of a human or animal a therapeutically effective amount of a cyclosporin component to provide a desired therapeutic effect, preferably a desired ophthalmic or ocular therapeutic effect.

The use of cyclosporin-A and cyclosporin A derivatives to treat ophthalmic conditions has been the subject of various patents, for example Ding et al U.S. Patent 5,474,979; Garst U.S. Patent 6,254,860; and Garst U.S. 6,350,442, this disclosure of each of which is incorporated in its entirely herein by reference. In addition, cyclosporin A compositions used in treating ophthalmic conditions is the subject of a number of publications. Such publications include, for example, "Blood concentrations of cyclosporin a during long-term treatment with cyclosporin a ophthalmic emulsions in patients with moderate to severe dry eye disease," Small et al, *J Ocul Pharmacol Ther, 2002 Oct, 18(5):411-8*; "Distribution of cyclosporin A in ocular tissues after topical

administration to albino rabbits and beagle dogs," Acheampong et al, *Curr Eye Res, 1999 Feb, 18(2):91-103b*; "Cyclosporine distribution into the conjunctiva, cornea, lacrimal gland, and systemic blood following topical dosing of cyclosporine to rabbit, dog, and human eyes," Acheampong et al, *Adv Exp Med Biol, 1998, 438:1001-4*; "Preclinical safety studies of cyclosporine ophthalmic emulsion," Angelov et al, *Adv Exp Med Biol, 1998, 438:991-5*; "Cyclosporin & Emulsion & Eye," Stevenson et al, *Ophthalmology, 2000 May, 107(5):967-74*; and "Two multicenter, randomized studies of the efficacy and safety of cyclosporine ophthalmic emulsion in moderate to severe dry eye disease. CsA Phase 3 Study Group," Sall et al, *Ophthalmology, 2000 Apr, 107(4):631-9*. Each of these publications is incorporated in its entirety herein by reference. In addition, cyclosporin A-containing oil-in-water emulsions have been clinically tested, under conditions of confidentiality, since the mid 1990's in order to obtain U.S. Food and Drug Administration (FDA) regulatory approval.

Examples of useful cyclosporin A-containing emulsions are set out in Ding et al U.S. Patent 5,474,979. Example 1 of this patent shows a series of emulsions in which the ratio of cyclosporin A to castor oil in each of these compositions was 0.08 or greater, except for Composition B, which included 0.2% by weight cyclosporin A and 5% by weight castor oil. The Ding et al patent placed no significance in Composition B relative to Compositions A, C and D of Example 1.

Over time, it has become apparent that cyclosporin A emulsions for ophthalmic use preferably have less than 0.2% by weight of cyclosporin A. With cyclosporin A

concentrations less than 0.2%, the amount of castor oil employed has been reduced since one of the functions of the castor oil is to solubilize the cyclosporin A. Thus, if reduced amounts of cyclosporin are employed, reduced amounts of castor oil are needed to provide effective solubilization of cyclosporin A.

There continues to be a need for providing enhanced methods of treating ophthalmic or ocular conditions with cyclosporin-containing emulsions.

Summary of the Invention

New methods of treating a human or animal using cyclosporin component-containing emulsions have been discovered. Such methods provide substantial overall efficacy in providing desired therapeutic effects. In addition, other important benefits are obtained employing the present methods. For example, patient safety is enhanced. In particular, the present methods provide for reduced risks of side effects and/or drug interactions. Prescribing physicians advantageously have increased flexibility in prescribing such methods and the compositions useful in such methods, for example, because of the reduced risks of harmful side effects and/or drug interactions. The present methods can be easily practiced. In short, the present methods provide substantial and acceptable overall efficacy, together with other advantages, such as increased safety and/or flexibility.

In one aspect of the present invention, the present methods comprise administering to an eye of a human or animal a composition in the form of an emulsion comprising water, a hydrophobic component and a cyclosporin component in a therapeutically effective amount of less than 0.1% by

weight of the composition. The weight ratio of the cyclosporin component to the hydrophobic component is less than 0.08.

It has been found that the relatively increased amounts of hydrophobic component together with relatively reduced, yet therapeutically effective, amounts of cyclosporin component provide substantial and advantageous benefits. For example, the overall efficacy of the present compositions, for example in treating dry eye disease, is substantially equal to an identical composition in which the cyclosporin component is present in an amount of 0.1% by weight. Further, a relatively high concentration of hydrophobic component is believed to provide for a more quick or rapid breaking down or resolving of the emulsion in the eye, which reduces vision distortion which may be caused by the presence of the emulsion in the eye and/or facilitates the therapeutic effectiveness of the composition. Additionally, and importantly, using reduced amounts of the active cyclosporin component mitigates against undesirable side effects and/or potential drug interactions.

In short, the present invention provides at least one advantageous benefit, and preferably a plurality of advantageous benefits.

The present methods are useful in treating any suitable condition which is therapeutically sensitive to or treatable with cyclosporin components. Such conditions preferably are ophthalmic or ocular conditions, that is relating to or having to do with one or more parts of an eye of a human or animal. Included among such conditions are, without limitation, dry eye syndrome, phacoanaphylactic endophthalmitis, uveitis, vernal

conjunctivitis, atopic kerapoconjunctivitis, corneal graft rejection and the like conditions. The present invention is particularly effective in treating dry eye syndrome.

Employing reduced concentrations of cyclosporin component, as in the present invention, is advantageously effective to provide the blood of the human or animal under treatment with reduced concentrations of cyclosporin component, preferably with substantially no detectable concentration of the cyclosporin component. The cyclosporin component concentration of blood can be advantageously measured using a validated liquid chromatography/mass spectrometry-mass spectrometry (VLC/MS-MS) analytical method, such as described elsewhere herein.

In one embodiment, in the present methods the blood of the human or animal has concentrations of clyclosporin component of 0.1 ng/ml or less.

Any suitable cyclosporin component effective in the present methods may be used.

Cyclosporins are a group of nonpolar cyclic oligopeptides with known immunosuppressant activity. Cyclosporin A, along with several other minor metabolites, cyclosporin B through I, have been identified. In addition, a number of synthetic analogs have been prepared.

In general, commercially available cyclosporins may contain a mixture of several individual cyclosporins which all share a cyclic peptide structure consisting of eleven amino acid residues with a total molecular weight of about 1,200, but with different substituents or configurations of some of the amino acids.

The term "cyclosporin component" as used herein is intended to include any individual member of the cyclosporin group and derivatives thereof, as well as

mixtures of two or more individual cyclosporins and derivatives thereof.

Particularly preferred cyclosporin components include, without limitation, cyclosporin A, derivatives of cyclosporin A and the like and mixtures thereof. Cyclosporin A is an especially useful cyclosporin component.

Any suitable hydrophobic component may be employed in the present invention. Advantageously, the cyclosporin component is solubilized in the hydrophobic component. The hydrophobic component may be considered as comprising a discontinuous phase in the presently useful cyclosporin component-containing emulsions.

The hydrophobic component preferably is present in the emulsion compositions in an amount greater than about 0.625% by weight. For example, the hydrophobic component may be present in an amount of up to about 1.0% by weight or about 1.5% by weight or more of the composition.

Preferably, the hydrophobic component comprises one or more oily materials. Examples of useful oil materials include, without limitation, vegetable oils, animal oils, mineral oils, synthetic oils and the like and mixtures thereof. In a very useful embodiment, the hydrophobic component comprises one or more higher fatty acid glycerides. Excellent results are obtained when the hydrophobic component comprises castor oil.

The presently useful compositions may include one or more other components in amounts effective to facilitate the usefulness and effectiveness of the compositions. Examples of such other components include, without limitation, emulsifier components, tonicity components, polyelectrolyte components, surfactant components,

viscosity inducing components, acids and/or bases to adjust the pH of the composition, buffer components, preservative components and the like. Components may be employed which are effective to perform two or more functions in the presently useful compositions. For example, components which are effective as both emulsifiers and surfactants may be employed, and/or components which are effective as both polyelectrolyte components and viscosity inducing components may be employed. The specific composition chosen for use in the present invention advantageously is selected taking into account various factors present in the specific application at hand, for example, the desired therapeutic effect to be achieved, the desired properties of the compositions to be employed, the sensitivities of the human or animal to whom the composition is to be administered, and the like factors.

The presently useful compositions advantageously are ophthalmically acceptable. A composition, component or material is ophthalmically acceptable when it is compatible with ocular tissue, that is, it does not cause significant or undue detrimental effects when brought into contact with ocular tissues.

Such compositions have pH's within the physiological range of about 6 to about 10, preferably in a range of about 7.0 to about 8.0 and more preferably in a range of about 7.2 to about 7.6.

The present methods preferably provide for an administering step comprising topically administering the presently useful compositions to the eye or eyes of a human or animal.

Each and every feature described herein, and each and every combination of two or more of such features, is

included within the scope of the present invention provided that the features included in such a combination are not mutually inconsistent.

These and other aspects and advantages of the present invention are apparent in the following detailed description, example and claims.

Detailed Description

The present methods are effective for treating an eye of a human or animal. Such methods, in general, comprise administering, preferably topically administering, to an eye of a human or animal a cyclosporin component-containing emulsion. The emulsion contains water, for example U.S. pure water, a hydrophobic component and a cyclosporin component in a therapeutically effective amount of less than 0.1% by weight of the emulsion. In addition, beneficial results have been found when the weight ratio of the cyclosporin component to the hydrophobic component is less than 0.08.

As noted above, the present administering step preferably includes topically administering the emulsion to the eye of a patient of a human or animal. Such administering may involve a single use of the presently useful compositions, or repeated or periodic use of such compositions, for example, as required or desired to achieve the therapeutic effect to be obtained. The topical administration of the presently useful composition may involve providing the composition in the form of eye drops or similar form or other form so as to facilitate such topical administration.

The present methods have been found to be very effective in providing the desired therapeutic effect or

effects while, at the same time, substantially reducing, or even substantially eliminating, side effects which may result from the presence of the cyclosporin component in the blood of the human or animal being treated, and eye irritation which, in the past, has been caused by the presence of certain components in prior art cyclosporin-containing emulsions. Also, the use of the present compositions which include reduced amounts of the cyclosporin components allow for more frequent administration of the present compositions to achieve the desired therapeutic effect or effects without substantially increasing the risk of side effects and/or eye irritation.

The present methods are useful in treating any condition which is therapeutically sensitive to or treatable with cyclosporin components. Such conditions preferably are ophthalmic or ocular conditions, that is relating to or having to do with one or more parts of an eye of a human or animal. Included among such conditions are, without limitation, dry eye syndrome, phacoanaphylactic endophthalmitis, uveitis, vernal conjunctivitis, atopic kerapoconjunctivitis, corneal graft rejection and the like conditions. The present invention is particularly effective in treating dry eye syndrome.

The frequency of administration and the amount of the presently useful composition to use during each administration varies depending upon the therapeutic effect to be obtained, the severity of the condition being treated and the like factors. The presently useful compositions are designed to allow the prescribing physician substantial flexibility in treating various ocular conditions to achieve the desired therapeutic effect or effects with reduced risk of side effects and/or eye irritation. Such

administration may occur on an as needed basis, for example, in treating or managing dry eye syndrome, on a one time basis or on a repeated or periodic basis once, twice, thrice or more times daily depending on the needs of the human or animal being treated and other factors involved in the application at hand.

One of the important advantages of the present invention is the reduced concentration of the cyclosporin component in the blood of the human or animal as a result of administering the present composition as described herein. One very useful embodiment of the present administering step provides no substantial detectable concentration of cyclosporin component in the blood of the human or animal. Cyclosporin component concentration in blood preferably is determined using a liquid chromatography-mass spectroscopy-mass spectroscopy (LC-MS/MS), which test has a cyclosporin component detection limit of 0.1 ng/ml. Cyclosporin component concentrations below or less than 0.1 ng/ml are therefore considered substantially undetectable.

The LC-MS/MS test is advantageously run as follows.

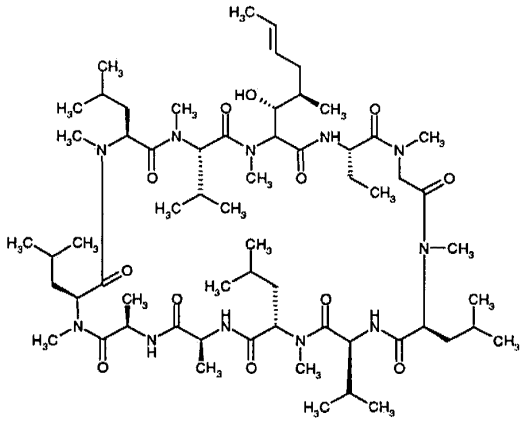
One ml of blood is acidified with 0.2 ml of 0.1 N HCl solution, then extracted with 5 ml of methyl t-butyl ether. After separation from the acidified aqueous layer, the organic phase is neutralized with 2 ml of 0.1 N NaOH, evaporated, reconstituted in a water/acetonitrile-based mobil phase, and injected onto a 2.1 x 50 mm, 3μm pore size C-8 reverse phase high pressure liquid chromatography (HPLC) column (Keystone Scientific, Bellefonte, PA). Compounds are gradient-eluted at 0.2 mL/min and detected using an API III triple quadrupole mass spectrometer with a turbo-ionspray source (PE-Sciex, Concord, Ontario,

Canada). Molecular reaction monitoring enhances the sensitivity and selectivity of this assay. Protonated molecules for the analyte and an internal standard are collisionally dissociated and product ions at m/z 425 are monitored for the analyte and the internal standard. Under these conditions, cyclosporin A and the internal standard cyclosporin G elute with retention times of about 3.8 minutes. The lower limit of quantitation is 0.1 ng/mL, at which concentration the coefficient of variation and deviation from nominal concentration is <15%.

As noted previously, any suitable cyclosporin component effective in the present methods may be employed. Very useful cyclosporin components include, without limitation, cyclosporin A, derivatives of cyclosporin A and the like and mixtures thereof.

The chemical structure for cyclosporin A is represented by Formula 1

Formula I

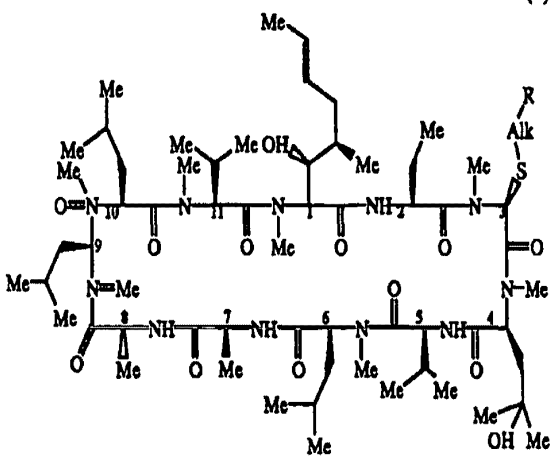


As used herein the term "derivatives" of a cyclosporin refer to compounds having structures sufficiently similar to the cyclosporin so as to function in a manner substantially similar to or substantially identical to the cyclosporin, for example, cyclosporin A, in the present methods. Included, without limitation, within the useful cyclosporin A derivatives are those selected from ((R)-methylthio-Sar)^3-(4'-hydroxy-MeLeu) cyclosporin A, ((R)-(Cyclo)alkylthio-Sar)^3-(4'-hydroxy-MeLeu)^4-cyclosporin A, and ((R)-(Cyclo)alkylthio-Sar)^3-cyclosporin A derivatives described below.

These cyclosporin derivatives are represented by the following general formulas (II), (III), and (IV) respectively:

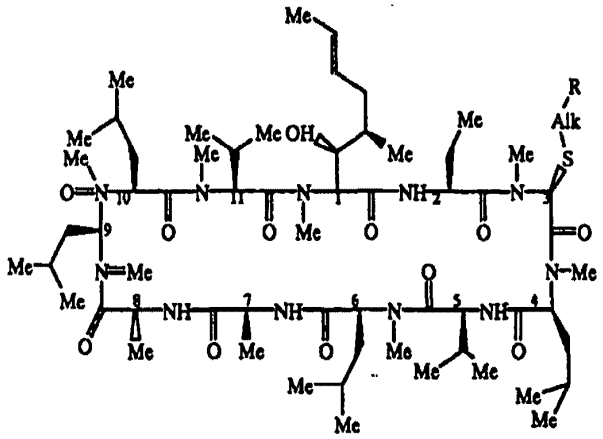
Formula II

(II)



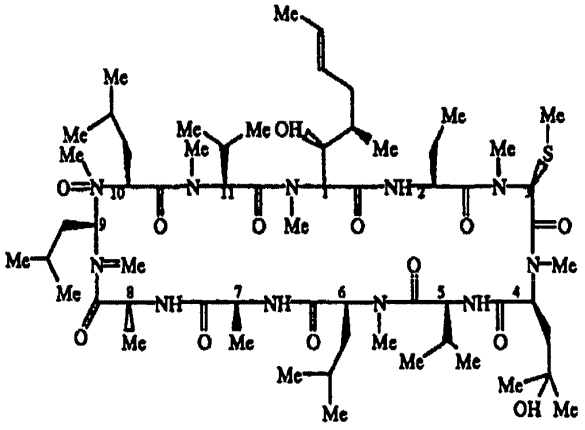
Formula III

(III)



Formula IV

(I)



wherein Me is methyl; Alk is 2-6C alkylene or 3-6C cycloalkylene; R is OH, COOH, alkoxycarbonyl, $-NR_1R_2$ or $N(R_3)-(CH_2)-NR_1R_2$; wherein R_1, R_2 is H, alkyl, 3-6C cycloalkyl, phenyl (optionally substituted by halo, alkoxy, alkoxycarbonyl, amino, alkylamino or dialkylamino), benzyl or saturated or unsaturated heterocyclyl having 5 or 6 members and 1-3 heteroatoms; or NR_1R_2 is a 5 or 6 membered heterocycle which may contain a further N, O or S heteroatom and may be alkylated; R_3 is H or alkyl and n is 2-4; and the alkyl moieties contain 1-4C.

In one embodiment, the cyclosporin component is effective as an immunosuppressant. Without wishing to be limited to any particular theory of operation, it is believed that, in certain embodiments of the present invention, the cyclosporin component acts to enhance or restore lacrimal gland tearing in providing the desired therapeutic effect.

One important feature of the present invention is that the presently useful compositions contain less than 0.1% by

weight of the cyclosporin component. The advantages of such low-concentrations of cyclosporin components have been discussed in some detail elsewhere herein. Low concentrations of cyclosporin component, together with concentrations of the hydrophobic component such that the weight ratio of cyclosporin component to hydrophobic component is greater than 0.08, provides one or more substantial advantages in the present methods.

Any suitable hydrophobic component may be employed in the present invention. Such hydrophobic component may be considered as comprising a discontinuous phase in the presently useful cyclosporin component-containing emulsions, with the water or aqueous phase being considered the continuous phase in such emulsion. The hydrophobic component is preferably selected so as to solubilize the cyclosporin component, which is often substantially insoluble in the aqueous phase. Thus, with a suitable hydrophobic component included in the presently useful emulsions, the cyclosporin component is preferably solubilized in the emulsions.

In one very useful embodiment, the hydrophobic component comprises an oily material, in particular, a material which is substantially not miscible in water. Examples of useful oily materials include, without limitation, vegetable oils, animal oils, mineral oils, synthetic oils, and the like and mixtures thereof. Thus, the present hydrophilic components may comprise naturally occurring oils, including, without limitation refined naturally occurring oils, or naturally occurring oils which have been processed to alter their chemical structures to some extent or oils which are substantially entirely synthetic. One very useful hydrophobic component includes

higher fatty acid glycerides.

Examples of useful hydrophobic components include, without limitation, olive oil, arachis oil, castor oil, mineral oil, silicone fluid and the like and mixtures thereof. Higher fatty acid glycerides such as olive oil, peanut oil, castor oil and the like and mixtures thereof are particularly useful in the present invention. Excellent results are obtained using a hydrophobic component comprising castor oil. Without wishing to limit the invention to any particular theory of operation, it is believed that castor oil includes a relatively high concentration of ricinoleic acid which itself may be useful in benefitting ocular tissue and/or in providing one or more therapeutic effects when administered to an eye.

The hydrophobic component is preferably present in the presently useful cyclosporin component-containing emulsion compositions in an amount greater than about 0.625% by weight. For example, the hydrophobic component may be present in an amount up to about 0.75% by weight or about 1.0% by weight or about 1.5% by weight or more of the presently useful emulsion compositions.

The presently useful compositions may include one or more other components in amounts effective to facilitate the usefulness and effectiveness of the present methods and/or the presently useful compositions. Examples of such other components include, without limitation, emulsifier components, surfactant components, tonicity components, poly electrolyte components, emulsion stability components, viscosity inducing components, demulcent components, acid and/or bases to adjust the pH of the composition, buffer components, preservative components and the like.

In one very useful embodiment, the presently useful

compositions are substantially free of preservatives. Thus, the presently useful compositions may be sterilized and maintained in a sterile condition prior to use, for example, provided in a sealed package or otherwise maintained in a substantially sterile condition.

Any suitable emulsifier component may be employed in the presently useful compositions, provided, that such emulsifier component is effective in forming maintaining the emulsion and/or in the hydrophobic component in emulsion, while having no significant or undue detrimental effect or effects on the compositions during storage or use.

In addition, the presently useful compositions, as well as each of the components of the present compositions in the concentration present in the composition advantageously are ophthalmically acceptable.

Useful emulsifier components may be selected from such component which are conventionally used and well known in the art. Examples of such emulsifier components include, without limitation, surface active components or surfactant components which may be anionic, cationic, nonionic or amphorteric in nature. In general, the emulsifier component includes a hydrophobic constituent and a hydrophilic constituent. Advantageously, the emulsifier component is water soluble in the presently useful compositions. Preferably, the emulsifier component is nonionic. Specific examples of suitable emulsifier components include, without limitation, polysorbate 80, polyoxyalkylene alkylene ethers, polyalkylene oxide ethers of alkyl alcohols, polyalkylene oxide ethers of alkylphenols, other emulsifiers/surfactants, preferably nonionic emulsifiers/surfactants, useful in ophthalmic

compositions, and the like and mixtures thereof.

The emulsifier component is present in an amount effective in forming the present emulsion and/or in maintaining the hydrophobic component in emulsion with the water or aqueous component. In one preferred embodiment, the emulsifier component is present in an amount in a range of about 0.1% to about 5%, more preferably about 0.2% to about 2% and still more preferably about 0.5% to about 1.5% by weight of the presently useful compositions.

Polyelectrolyte or emulsion stabilizing components may be included in the presently useful compositions. Such components are believed to be effective in maintaining the electrolyte balance in the presently useful emulsions, thereby stabilizing the emulsions and preventing the emulsions from breaking down prior to use. In one embodiment, the presently useful compositions include a polyanionic component effective as an emulsion stabilizing component. Examples of suitable polyanionic components useful in the presently useful compositions include, without limitation, anionic cellulose derivatives, anionic acrylic acid-containing polymers, anionic methacrylic acid-containing polymers, anionic amino acid-containing polymers and the like and mixtures thereof.

A particularly useful class of polyanionic components include one or more polymeric materials having multiple anionic charges. Examples include, but are not limited to:

metal carboxy methylcelluloses
metal carboxy methylhydroxyethylcelluloses
metal carboxy methylstarchs
metal carboxy methylhydroxyethylstarchs
hydrolyzed polyacrylamides and polyacrylonitriles

heparin
gucoaminoglycans
hyaluronic acid
chondroitin sulfate
dermatan sulfate
peptides and polypeptides
alginic acid
metal alginates
homopolymers and copolymers of one or more of:
- acrylic and methacrylic acids
- metal acrylates and methacrylates
- vinylsulfonic acid
- metal vinylsulfonate
- amino acids, such as aspartic acid, glutamic acid and the like
- metal salts of amino acids
- p-styrenesulfonic acid
- metal p-styrenesulfonate
- 2-methacryloyloxyethylsulfonic acids
- metal 2-methacryloyloxethylsulfonates
- 3-methacryloyloxy-2-hydroxypropylsulonic acids
- metal 3-methacryloyloxy-2-hydroxypropylsulfonates
- 2-acrylamido-2-methylpropanesulfonic acids
- metal 2-acrylamido-2-methylpropanesulfonates
- allylsulfonic acid
- metal allylsulfonate and the like.

One particularly useful emulsion stabilizing component includes crosslinked polyacrylates, such as carbomers and Pemulen® materials. Pemulen® is a registered trademark of B.F. Goodrich for polymeric emulsifiers and are

commercially available from B.F. Goodrich Company, Specialty Polymers & Chemicals Division, Cleveland, Ohio. Pemulen® materials include acrylate/C10-30 alkyl acrylate cross-polymers, or high molecular weight co-polymers of acrylic acid and a long chain alkyl methacrylate cross-linked with allyl ethers of pentaerythritol.

The presently useful polyanionic components may also be used to provide a suitable viscosity to the presently useful compositions. Thus, the polyanionic components may be useful in stabilizing the presently useful emulsions and in providing a suitable degree of viscosity to the presently useful compositions.

The polyelectrolyte or emulsion stabilizing component advantageously is present in an amount effective to at least assist in stabilizing the cyclosporin component-containing emulsion. For example, the polyelectrolyte/emulsion stabilizing component may be present in an amount in a range of about 0.01% by weight or less to about 1% by weight or more, preferably about 0.02% by weight to about 0.5% by weight, of the composition.

Any suitable tonicity component may be employed in accordance with the present invention. Preferably, such tonicity component is non-ionic, for example, in order to avoid interfering with the other components in the presently useful emulsions and to facilitate maintaining the stability of the emulsion prior to use. Useful tonicity agents include, without limitation, glycerine, mannitol, sorbitol and the like and mixtures thereof. The presently useful emulsions are preferably within the range of plus or minus about 20% or about 10% from being isotonic.

Ophthalmic demulcent components may be included in

effective amounts in the presently useful compositions. For example, ophthalmic demulcent components such as carboxymethylcellulose, other cellulose polymers, dextran 70, gelatin, glycerine, polyethylene glycols (e.g., PEG 300 and PEG 400), polysorbate 80, propylene glycol, polyvinyl alcohol, povidone and the like and mixtures thereof, may be used in the present ophthalmic compositions, for example, compositions useful for treating dry eye.

The demulcent components are preferably present in the compositions, for example, in the form of eye drops, in an amount effective in enhancing the lubricity of the presently useful compositions. The amount of demulcent component in the present compositions may be in a range of at least about 0.01% or about 0.02% to about 0.5% or about 1.0% by weight of the composition.

Many of the presently useful polyelectrolyte/emulsion stabilizing components may also be effective as demulcent components, and vice versa. The emulsifier/surfactant components may also be effective as demulcent components and vice versa.

The pH of the emulsions can be adjusted in a conventional manner using sodium hydroxide and/or hydrochloric acid to a physiological pH level. The pH of the presently useful emulsions preferably is in the range of about 6 to about 10, more preferably about 7.0 to about 8.0 and still more preferably about 7.2 to about 7.6.

Although buffer components are not required in the presently useful compositions, suitable buffer components, for example, and without limitation, phosphates, citrates, acetates, borates and the like and mixtures thereof, may be employed to maintain a suitable pH in the presently useful compositions.

The presently useful compositions may include an effective amount of a preservative component. Any suitable preservative or combination of preservatives may be employed. Examples of suitable preservatives include, without limitation, benzalkonium chloride, methyl and ethyl parabens, hexetidine, phenyl mercuric salts and the like and mixtures thereof. The amounts of preservative components included in the present compositions are such to be effective in preserving the compositions and can vary based on the specific preservative component employed, the specific composition involved, the specific application involved, and the like factors. Preservative concentrations often are in the range of about 0.00001% to about 0.05% or about 0.1% (w/v) of the composition, although other concentrations of certain preservatives may be employed.

Very useful examples of preservative components in the present invention include, but are not limited to, chlorite components. Specific examples of chlorite components useful as preservatives in accordance with the present invention include stabilized chlorine dioxide (SCD), metal chlorites such as alkali metal and alkaline earth metal chlorites, and the like and mixtures thereof. Technical grade (or USP grade) sodium chlorite is a very useful preservative component. The exact chemical composition of many chlorite components, for example, SCD, is not completely understood. The manufacture or production of certain chlorite components is described in McNicholas U.S. Patent 3,278,447, which is incorporated in its entirety by reference herein. Specific examples of useful SCD products include that sold under the trademark Dura Klor by Rio Linda Chemical Company, Inc., and that sold under the

trademark Anthium Dioxide® by International Dioxide, Inc. An especially useful SCD is a product sold under the trademark Bio-Cide® by Bio-Cide International, Inc., as well as a product identified by Allergan, Inc. by the trademark Purite®.

Other useful preservatives include antimicrobial peptides. Among the antimicrobial peptides which may be employed include, without limitation, defensins, peptides related to defensins, cecropins, peptides related to cecropins, magainins and peptides related to magainins and other amino acid polymers with antibacterial, antifungal and/or antiviral activities. Mixtures of antimicrobial peptides or mixtures of antimicrobial peptides with other preservatives are also included within the scope of the present invention.

The compositions of the present invention may include viscosity modifying agents or components, such as cellulose polymers, including hydroxypropyl methyl cellulose (HPMC), hydroxyethyl cellulose (HEC), ethyl hydroxyethyl cellulose, hydroxypropyl cellulose, methyl cellulose and carboxymethyl cellulose; carbomers (e.g. carbopol, and the like); polyvinyl alcohol; polyvinyl pyrrolidone; alginates; carrageenans; and guar, karaya, agarose, locust bean, tragacanth and xanthan gums. Such viscosity modifying components are employed, if at all, in an amount effective to provide a desired viscosity to the present compositions. The concentration of such viscosity modifiers will typically vary between about 0.01 to about 5 % w/v of the total composition, although other concentrations of certain viscosity modifying components may be employed.

The presently useful compositions may be produced using conventional and well known methods useful in

producing ophthalmic products including oil-in-water emulsions.

In one example, the oily phase of the emulsion can be combined with the cyclosporin component to solubilize the cyclosporin component in the oily material phase. The oily phase and the water may be separately heated to an appropriate temperature. This temperature may be the same in both cases, generally a few degrees to about 10°C above the melting temperature of the ingredient(s) having the highest melting point in the case of a solid or semi-solid oily phase for emulsifier components in the oily phase. Where the oily phase is a liquid at room temperature, a suitable temperature for preparation of a composition may be determined by routine experimentation in which the melting point of the ingredients aside from the oily phase is determined. In cases where all components of either the oily phase or the water phase are soluble at room temperature, no heating may be necessary. Non-emulsifying agents which are water soluble are dissolved in the water and oil soluble components including the surfactant components are dissolved in the oily phase.

To create an oil-in-water emulsion, the final oil phase is gently mixed into either an intermediate, preferably de-ionized water, phase or into the final water phase to create a suitable dispersion and the product is allowed to cool with or without stirring. In the case where the final oil phase is first gently mixed into an intermediate water phase, the resulting emulsion concentrate is thereafter mixed in the appropriate ratio with the final aqueous phase. In such cases, the emulsion concentrate and the final aqueous phase may not be at the same temperature or heated above room temperature, as the

emulsion may be already formed at this point.

The oil-in-water emulsions of the present invention can be sterilized after preparation using heat, for example, autoclave steam sterilization or can be sterile filtered using, for example, a 0.22 micron sterile filter. Sterilization employing a sterilization filter can be used when the emulsion droplet (or globule or particle) size and characteristics allows this. The droplet size distribution of the emulsion need not be entirely below the particle size cutoff of the 0.22 micron sterile filtration membrane to be sterile-filtratable. In cases wherein the droplet size distribution of the emulsion is above the particle size cutoff of the 0.22 micron sterile filtration membrane, the emulsion needs to be able to deform or change while passing through the filtration membrane and then reform after passing through. This property is easily determined by routine testing of emulsion droplet size distributions and percent of total oil in the compositions before and after filtration. Alternatively, a loss of a small amount of larger droplet sized material may be acceptable.

The present oil-in-water emulsions preferably are thermodynamicaly stable, much like microemulsions, and yet may not be isotropic transparent compositions as are microemulsions. The emulsions of the present invention advantageously have a shelf life exceeding one year at room temperature.

The following non-limiting examples illustrate certain aspects of the present invention.

EXAMPLE 1

Two compositions are selected for testing. These compositions are produced in accordance with well known techniques and have the following make-ups:

	Composition I	Composition II
	wt%	wt%
Cyclosporin A	0.1	0.05
Castor Oil	1.25	1.25
Polysorbate 80	1.00	1.00
Premulen®	0.05	0.05
Glycerine	2.20	2.20
Sodium hydroxide	qs	qs
Purified Water	qs	qs
pH	7.2-7.6	7.2-7.6
Weight Ratio of Cyclosporin A to Castor Oil	0.08	0.04

These compositions are employed in a Phase 3, double-masked, randomized, parallel group study for the treatment of dry eye disease.

The results of this study indicate that Composition II, in accordance with the present invention, which has a reduced concentration of cyclosporin A and a cyclosporin A to castor oil ratio of less than 0.08, provides overall efficacy in treating dry eye disease substantially equal to that of Composition I. This is surprising for a number of reasons. For example, the reduced concentration of cyclosporin A in Composition II would have been expected to result in reduced overall efficacy in treating dry eye disease. Also, the large amount of castor oil relative to the amount of cyclosporin A in Composition II might have

been expected to cause increased eye irritation relative to Composition I. However, both Composition I and Composition II are found to be substantially non-irritating in use.

Using relatively increased amounts of castor oil, with reduced amounts of cyclosporin component, as in Composition II, is believed to take advantage of the benefits, for example the ocular lubrication benefits, of castor oil, as well as the presence of ricinoleic acid in the castor oil, to at least assist in treating dry eye syndrome in combination with cyclosporin A.

In addition, it is found that the high concentration of castor oil relative to cyclosporin component, as in Composition II, provides the advantage of more quickly or rapidly (for example, relative to a composition which includes only 50% as much castor oil) breaking down or resolving the emulsion in the eye, for example, as measured by split-lamp techniques to monitor the composition in the eye for phase separation. Such rapid break down of the emulsion in the eye reduces vision distortion as the result of the presence of the emulsion in the eye, as well as facilitating the therapeutic effectiveness of the composition in treating dry eye disease.

Using reduced amounts of cyclosporin A, as in Composition II, to achieve therapeutic effectiveness mitigates even further against undesirable side effects and potential drug interactions. Prescribing physicians can provide (prescribe) Composition II to more patients and/or with fewer restrictions and/or with reduced risk of the occurrence of adverse events, e.g., side effects, drug interactions and the like, relative to providing Composition I.

While this invention has been described with respect

to various specific examples and embodiments, it is to be understood that the invention is not limited thereto and that it can be variously practiced within the scope of the following claims.

WHAT IS CLAIMED IS:

1. A method of treating an eye of a human or animal comprising:

administering to an eye of a human or animal a composition in the form of an emulsion comprising water, a hydrophobic component and a cyclosporin component in a therapeutically effective amount of less than 0.1% by weight of the composition, the weight ratio of the cyclosporin component to the hydrophobic component is less than 0.08.

2. The method of claim 1 wherein the administering step is effective in treating a condition selected from the group consisting of dry eye syndrome, phacoanaphylactic endophthalmitis, uveitis, vernal conjunctivitis, atopic keratoconjunctivitis and corneal graft rejection.

3. The method of claim 1 wherein the administering step is effective in treating dry eye syndrome.

4. The method of claim 1 wherein the blood of the human or animal has substantially no detectable concentration of the cyclosporin component.

5. The method of claim 1 wherein the blood of the human or animal has substantially no detectable concentration of the cyclosporin component as measured using a validated liquid chromatography/mass spectrometry-mass spectrometry analytical method.

6. The method of claim 1 wherein the blood of the

human or animal has a concentration of the cyclosporin component of 0.1 ng/ml or less.

7. The method of claim 1 wherein the cyclosporin component comprises a material selected from cyclosporin A, derivatives of cyclosporin A and mixtures thereof.

8. The method of claim 1 wherein the cyclosporin component comprises cyclosporin A.

9. The method of claim 1 wherein the cyclosporin component is solubilized in the hydrophobic component present in the composition.

10. The method of claim 1 wherein the hydrophobic component is present in the composition in an amount greater than 0.625% by weight of the composition.

11. The method of claim 1 wherein the hydrophobic component comprises an oily material.

12. The method of claim 1 wherein the hydrophobic component comprises an ingredient selected from the group consisting of vegetable oils, animal oils, mineral oils, synthetic oils and mixtures thereof.

13. The method of claim 1 wherein the hydrophobic component comprises castor oil.

14. The method of claim 1 wherein the administering step comprises topically administering the composition to the eye of the human.

15. The method of claim 1 wherein the composition comprises an effective amount of an emulsifier component.

16. The method of claim 1 wherein the composition comprises an effective amount of a tonicity component.

17. The method of claim 1 wherein the composition comprises an effective amount of an organic tonicity component.

18. The method of claim 1 wherein the composition comprises a polyelectrolyte component in an amount effective in stabilizing the composition.

19. The method of claim 1 wherein the composition has a pH in the range of about 7.0 to about 8.0.

20. The method of claim 1 wherein the composition has a pH in the range of about 7.2 to about 7.6.

21. A composition for treating an eye of a human or animal comprising an emulsion comprising water, a hydrophobic component, and a cyclosporin component in a therapeutically effective amount of less than 0.1% by weight, the weight ratio of the cyclosporin component to the hydrophobic component being less than 0.08.

22. The composition of claim 21 having a make-up so that when the composition is administered to an eye of a human in an effective amount in treating dry eye syndrome, the blood of the human has substantially no detectable concentration of the cyclosporin component.

23. The composition of claim 21 wherein the cyclosporin component comprises a material selected from cyclosporin A, derivatives of cyclosporin A and mixtures thereof.

24. The composition of claim 21 wherein the cyclosporin component comprises cyclosporin A.

25. The composition of claim 21 in the form of an emulsion.

26. The composition of claim 21 wherein the hydrophobic component is present in an amount greater than 0.625% by weight of the composition.

27. The composition of claim 21 wherein the hydrophobic component is an oily material.

28. The composition of claim 21 wherein the hydrophobic component comprises an ingredient selected from the group consisting of vegetable oils, animal oils, mineral oils, synthetic oils, and mixtures thereof.

29. The composition of claim 21 wherein the hydrophobic component comprises castor oil.

30. The composition of claim 21 wherein the administering step comprises topically administering the composition to the eye of the human.

31. The composition of claim 21 wherein the composition comprises an effective amount of an emulsifier

component.

32. The composition of claim 21 wherein the composition comprises an effective amount of a tonicity component.

33. The composition of claim 21 wherein the composition comprises an effective amount of an organic tonicity component.

34. The composition of claim 21 wherein the composition comprises a polyelectrolytic component in an amount effective in stabilizing the composition.

35. The composition of claim 21 wherein the composition includes water and has a pH in the range of about 7.0 to about 8.0.

36. The composition of claim 21 wherein the composition includes water and has a pH in the range of about 7.2 to about 7.6.

METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS

Abstract of the Disclosure

Methods of treating an eye of a human or animal include administering to an eye of a human or animal a composition in the form of an emulsion including water, a hydrophobic component and a cyclosporin component in a therapeutically effective amount of less than 0.1% by weight of the composition. The weight ratio of the cyclosporin component to the hydrophobic component is less than 0.8.

DECLARATION FOR PATENT APPLICATION

D-3111

As a below named inventor, I hereby declare that:

My residence post office address and citizenship are as stated below next to my name.

I believe I am the original first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled **METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS** the specification of which

(check one) [X] is attached hereto
[ ] was filed on
as US Application Serial Number or PCT International Application Number
and was amended on ___ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the patentability as defined in 37 CFR § 1.56.
I hereby claim foreign priority benefits under 35 U.S.C. §119(a)-(d) or §365(b) of any foreign application(s) for patent or inventor's certificate, or §365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed. **NONE**

I hereby claim the benefit under 35 U.S.C. §119(e) of any United States provisional application(s) listed below.

Serial No. 60/503,137, September 15, 2003

I hereby claim the benefit under 35 U.S.C. §120 of any United States application(s), or §365(c) of any PCT International application designation the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. §112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR §1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application. **NONE**

I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith: Martin A. Voet, Reg. No. 25,208, Robert Baran, Reg. No. 25,806, Carlos A. Fisher, Reg. No. 36,510, Stephen Donovan, Reg. No. 33,433, Brent A. Johnson, Reg. No. 51,851, Dean G. Stathakis, Reg. No. 54,465, Frank J. Uxa, Reg. No. 25,612, Donald E. Stout, Reg. No. 34,493; Robert D. Buyan, Reg. No. 32,460; Kenton R. Mullins, Reg. No. 36,331; Jo Anne M. Ybaben, Reg. No. 42,243, Linda Allyson Fox, Reg. No. 38,883, and Greg S. Hollrigel, Reg. No. 45,374.

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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Continued...

Docket No. D-3111

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Application Information

Title Line One::	METHODS OF PROVIDING THERAPEUTIC
Title Line Two::	EFFECTS USING CYCLOSPORIN COMPONENTS
Total Drawing Sheets::	
Formal Drawings?::	
Application Type::	Utility

Representative Information

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Registration Number Three::	Robert D. Buyan	32,460
Registration Number Four::	Kenton R. Mullins	36,331
Registration Number Five::	Jo Anne M. Ybaben	42,243
Registration Number Six::	Linda Allyson Fox	38,883
Registration Number Seven::	Greg S. Hollrigel, Ph. D	45,374
Registration Number Eight::	Martin A. Voet	25,208
Registration Number Nine::	Robert J. Baran	25,806
Registration Number Ten::	Carlos A. Fisher	36,510
Registration Number Eleven::	Stephen Donovan	33,433
Registration Number Twelve::	Brent A. Johnson	51,851

Registration Number Thirteen::	Dean G. Stathakis.....	54,465

Continuity Information

This application claims the benefit of::	
>Application One::	60/503,137
Filing Date::	September 15, 2003

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PATENT APPLICATION FEE DETERMINATION RECORD
Effective October 1, 2003

Application or Docket Number: 10927857

CLAIMS AS FILED - PART I

	(Column 1)	(Column 2)
TOTAL CLAIMS	36	
FOR	NUMBER FILED	NUMBER EXTRA
TOTAL CHARGEABLE CLAIMS	36 minus 20=	* 16
INDEPENDENT CLAIMS	2 minus 3 =	*
MULTIPLE DEPENDENT CLAIM PRESENT		☐

* If the difference in column 1 is less than zero, enter "0" in column 2

SMALL ENTITY TYPE ☐		OR	OTHER THAN SMALL ENTITY	
RATE	FEE		RATE	FEE
BASIC FEE	385.00	OR	BASIC FEE	770.00
XS 9=		OR	X$18=	288
X43=		OR	X86=	
+145=		OR	+290=	
TOTAL		OR	TOTAL	1058

CLAIMS AS AMENDED - PART II

AMENDMENT A

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X43=		OR	X86=	
+145=		OR	+290=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT B

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X43=		OR	X86=	
+145=		OR	+290=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT C

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X43=		OR	X86=	
+145=		OR	+290=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20."
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The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

PATENT APPLICATION SERIAL NO. _____

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE
FEE RECORD SHEET

08/31/2004 EHAILE1 00000072 010885 10927857

01 FC:1001 770.00 DA
02 FC:1202 288.00 DA

PTO-1556
(5/87)

*U.S. Government Printing Office: 2002 — 489-267/69033

D-3111

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
PATENT

In re application of:
Acheampong et al) Group Art Unit: 1636
)
Serial No. 10/927,857) Examiner: N/A
)
Filed: August 27, 2004)
)

For: METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS

CERTIFICATE OF FACSIMILE TRANSMISSION

I hereby certify that this paper for Application Serial No. 10/927,857 is being facsimile transmitted to the Patent and Trademark Office fax number 703-872-9306 on the date shown below.

Janet McGhee 11/12/04
Signature Date

LETTER

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Submitted herewith is a copy of the Power of Attorney filed in the above-identified application.

Pursuant to 37 CFR 1.32, indicated below is a list of the patent practitioners named in the Power of Attorney to be recognized by the Office as being of record in the application.

Frank J. Uxa,	Reg. No. 25,612
Martin A. Voet,	Reg. No. 25,208
Robert J. Baran,	Reg. No. 25,806
Carlos Fisher,	Reg. No. 36,510
Stephen Donovan,	Reg. No. 33,433
Dean G. Stathakis,	Reg. No. 54,465
Brent A. Johnson,	Reg. No. 51,851
Linda A. Fox,	Reg. No. 38,883
Greg S. Hollrigel,	Reg. No. 45,374

Respectfully submitted,

Frank J. Uxa
Attorney for Applicant
Reg. No. 25,612
4 Venture, Suite 300
Irvine, CA 92618
(949) 450-1750
Facsimile (714) 450-1764

DECLARATION FOR PATENT APPLICATION

D-3111

As a below named inventor, I hereby declare that:

My residence post office address and citizenship are as stated below next to my name.

I believe I am the original first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled **METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS** the specification of which

(check one) [X] is attached hereto
[ ] was filed on
as US Application Serial Number or PCT International Application Number
and was amended on ___ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the patentability as defined in 37 CFR § 1.56.
I hereby claim foreign priority benefits under 35 U.S.C. §119(a)-(d) or §365(b) of any foreign application(s) for patent or inventor's certificate, or §365(a) of any PCT international application which designated at least one country other than the United States, listed below and have also identified below any foreign application for patent or inventor's certificate, or PCT international application having a filing date before that of the application on which priority is claimed. **NONE**

I hereby claim the benefit under 35 U.S.C. §119(e) of any United States provisional application(s) listed below.

Serial No. 60/503,137, September 15, 2003

I hereby claim the benefit under 35 U.S.C. §120 of any United States application(s), or §365(c) of any PCT International application designation the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. §112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR §1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application. **NONE**

I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith: Martin A. Voet, Reg. No. 25,208, Robert Baran, Reg. No. 25,806, Carlos A. Fisher, Reg. No. 38,510, Stephen Donovan, Reg. No. 33,433, Brent A. Johnson, Reg. No. 51,861, Dean G. Stathakis, Reg. No. 54,465, Frank J. Uxa, Reg. No. 25,612, Donald E. Stout, Reg. No. 34,493; Robert D. Buyan, Reg. No. 32,460; Kenton R. Mullins, Reg. No. 36,331; Jo Anne M. Ybaben, Reg. No. 42,243, Linda Allyson Fox, Reg. No. 38,883, and Greg S. Hellriegel, Reg. No. 45,374.

Address all telephone calls to Frank J. Uxa - Telephone: 949-450-1750
Address all correspondence to Frank J. Uxa
4 Venture, Suite 300
Irvine, CA 92618

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of sole or first inventor (given name, family name) **ANDREW ACHEAMPONG**

Inventor's signature _____ Date 8/12/04
Residence Irvine, California Citizenship U.S.A.
Post Office Address 16 Wintergreen
Irvine, CA 92604

Full name of second inventor (given name, family name) **DIANE TANG-LIU**

Inventor's signature _____ Date 8-12-2004
Residence Newport Beach, California Citizenship U.S.A.
Post Office Address 2815 Blackthorn Street
Newport Beach, CA 92660

BEST AVAILABLE COPY

Continued... Docket No. D-3111

Full name of third inventor (given name, family name) JAMES N. CHANG

Inventor's signature _____ Date 8/12/04
Residence Newport Beach, California Citizenship U.S.A.
Post Office Address 36 Cervantes
Newport Beach, CA 92660

Full name of fourth inventor (given name, family name) DAVID F. POWER

Inventor's signature _____ Date 8/12/04
Residence Trabuco Canyon, California Citizenship U.S.A.
Post Office Address 28335 Quiet Hill Lane
Trabuco Canyon, CA 92679-1131

P-3111

IFW

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

PATENT

In re application of:
ACHEAMPONG et al.) Group Art Unit: 1636
)
Serial No. 10/927,857) Examiner: Unknown
)
Filed: August 27, 2004)
)
For: METHODS OF PROVIDING)
THERAPEUTIC EFFECTS USING)
CYCLOSPORIN COMPONENTS)

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, PO Box 1450, Alexandria, VA 22313-1450, on or before

December 22, 2004
Date

Janet McGhee

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

INFORMATION DISCLOSURE STATEMENT

Dear Sir:

Applicant wishes to call to the attention of the Examiner the documents cited on the accompanying Form PTO-1449. No concession is made that these documents are prior art, and applicant expressly reserves the right to antedate the documents as may be appropriate. Applicant requests that each of these documents be made of record in the above-identified application.

Respectfully submitted,

Frank J. Uxa
Attorney for Applicant
Reg. No. 25,612
4 Venture, Suite 300
Irvine, CA 92618
(949) 450-1750
Facsimile (949) 450-1764

FJUxa/ac

Form PTO-1449

INFORMATION DISCLOSURE CITATION IN AN APPLICATION
(Use several sheets if necessary)

DEC 27 2004 PATENT & TRADEMARK OFFICE

Docket No.: D-3111	Application No.: 10/927,857
Applicant: Acheampong et al.	
Filing Date: August 27, 2004	Group Art Unit: 1636

U. S. PATENT DOCUMENTS

EXAMINER INITIAL	DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
	3,278,447	10/1966	McNicholas			
	4,388,307	06/1983	Cavanak			
	4,649,047	03/1987	Kaswan			
	4,814,323	3/1989	Andrieu			
	4,839,342	06/1989	Kaswan			
	4,970,076	11/1990	Horrobin			
	4,990,337	02/1991	Kurihara et al.			
	4,996,193	02/1991	Hewitt et al.			
	5,286,730	02/1994	Caufield et al.			
	5,286,731	02/1994	Caufield et al.			
	5,342,625	08/1994	Hauer et al.			
	5,411,952	05/1995	Kaswan			

FOREIGN PATENT DOCUMENTS

	DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

	AA	Acheampong et al,"Cyclosporine Distribution into the Conjunctiva, Cornea, Lacrimal Gland, and Systemic Blood Following Topical Dosing of Cyclosporine to Rabbit, Dog, and Human Eyes," *Lacrimal Gland, Tear Film, and Dry Eye Syndromes 2 - Basic Science and Clinical Relevance, Plenum Press, New York & London, ©1998, pp. 1001-1004.*
	AB	Acheampong et al, "Distribution of Cyclosporin A in Ocular Tissues After Topical Administration to Albino Rabbits and Beagle Dogs," *Curr Eye Res, Feb 1999, 18(2):91-103b.*
	AC	Angelov et al, "Preclinical Safety Studies of Cyclosporine Ophthalmic Emulsion," *Lacrimal Gland, Tear Film, and Dry Eye Syndromes 2 - Basic Science and Clinical Relevance, Plenum Press, New York & London, ©1998, pp. 991-5.*
	AD	Brewster et al, "Enhanced Delivery of Ganciclovir to the Brain through the Use of Redox Targeting," *Antimicrobial Agents and Chemotherapy, April 1994, 38(4):817-823.*
	AE	Brewster et al, "Intravenous and Oral Pharmacokinetic Evaluation of a 2-Hydroxypropyl-β-cyclodextrin-Based Formulation of Carbamazepine in the Dog: Comparison with Commercially Available Tablets and Suspensions, " *J Pharm Sci, March 1997, 86(3):335-9.*

EXAMINER	DATE CONSIDERED

EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP § 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to the applicant.

Form PTO-1449	Docket No.: D-3111	Application No.: 10/927,857
INFORMATION DISCLOSURE CITATION IN AN APPLICATION (Use several sheets if necessary)	Applicant: Acheampong et al.	
	Filing Date: August 27, 2004	Group Art Unit: 1636

U. S. PATENT DOCUMENTS

EXAMINER INITIAL	DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
	5,474,979	12/1995	Ding et al.			
	5,504,068	04/1996	Komiya et al.			
	5,540,931	07/1996	Hewitt et al.			
	5,719,123	02/1998	Morley et al.			
	5,739,105	04/1998	Kim et al.			
	5,807,820	09/1998	Elias			
	5,843,452	12/1998	Wiedmann et al.			
	5,843,891	12/1998	Sherman			
	5,858,401	01/1999	Bhalani et al.			
	5,866,159	02/1999	Hauer et al.			
	5,891,846	04/1999	Ishida et al.			
	5,916,589	06/1999	Hauer et al.			

FOREIGN PATENT DOCUMENTS

	DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

	AA	Brewster et al, "Preparation, Characterization, and Anesthetic Properties of 2-Hydroxypropyl-β-cyclodextrin Complexes of Pregnanolone and Pregnenolone in Rat and Mouse," *J Pharm Sci, October 1995, 84(10):1154-9.*
	AB	Sall et al, "Two Multicenter, Randomized Studies of the Efficacy and Safety of Cyclosporine Ophthalmic Emulsion in Moderate to Severe Dry Eye Disease. CsA Phase 3 Study Group," *Ophthalmology, April 2000, 107(4):631-9.*
	AC	Small et al,"Blood Concentrations of Cyclosporin A During Long-Term Treatment With Cyclosporin A Ophthalmic Emulsions in Patients With Moderate to Severe Dry Eye Disease," *J Ocul Pharmacol Ther, Oct 2002, 18(5):411-8.*
	AD	Stevenson et al., "Efficacy and Safety of Cyclosporin A Ophthalmic Emulsion in the Treatment of Moderate-to-severe Dry Eye Disease," *Ophthalmology, May 2000, 107(5):967-74.*
	AE	
	AF	

EXAMINER	DATE CONSIDERED

EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP § 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to the applicant.

Form PTO-1449	Docket No.: D-3111	Application No.: 10/927,857
INFORMATION DISCLOSURE CITATION IN AN APPLICATION (Use several sheets if necessary)	Applicant: Acheampong et al.	
	Filing Date: August 27, 2004	Group Art Unit: 1636

U. S. PATENT DOCUMENTS

EXAMINER INITIAL	DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
	5,951,971	09/1999	Kawashima et al.			
	5,962,017	10/1999	Hauer et al.			
	5,981,479	11/1999	Ko et al.			
	5,981,607	11/1999	Ding et al.			
	5,998,365	12/1999	Sherman			
	6,008,191	12/1999	Singh et al.			
	6,008,192	12/1999	Al-Razzak et al.			
	6,022,852	02/2000	Klokkers et al.			
	6,024,978	02/2000	Hauer et al.			
	6,046,163	04/2000	Stuchlik et al.			
	6,159,933	12/2000	Sherman			
	6,254,860	07/2001	Garst			
	6,323,204	11/2001	Burke et al.			

FOREIGN PATENT DOCUMENTS

	DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION	

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

	AA	
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	AE	
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	AH	

EXAMINER	DATE CONSIDERED

EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP § 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to the applicant.

Form PTO-1449

INFORMATION DISCLOSURE CITATION IN AN APPLICATION
(Use several sheets if necessary)

Docket No.: D-3111	Application No.: 10/927,857
Applicant: Acheampong et al.	
Filing Date: August 27, 2004	Group Art Unit: 1636

U. S. PATENT DOCUMENTS

EXAMINER INITIAL	DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
	6,346,511	02/2002	Singh et al.			
	6,350,442	02/2002	Garst			
	6,413,547	07/2002	Bennett et al.			
	6,420,355	07/2002	Richter et al.			
	6,468,968	10/2002	Cavanak et al.			
	6,486,124	11/2002	Olbrich et al.			
	2001/0014665	08/2001	Fisher et al.			
	2003/0021816	01/2003	Kang et al.			
	2003/0044452	03/2003	Ueno			
	2003/0060402	03/2003	Cavanak et al.			
	2003/0087813	05/2003	Or et al			
	2003/0104992	06/2003	Or et al			
	2003/0109425	06/2003	Or et al			
	2003/0109426	06/2003	Or et al.			
	2003/0143250	07/2003	Hauer et al.			

FOREIGN PATENT DOCUMENTS

	DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO

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	AD	
	AE	
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EXAMINER	DATE CONSIDERED

EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP § 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to the applicant.

IFW

D-3111

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

PATENT

In re application of:
ACHEAMPONG et al.) Group Art Unit: 1636
)
Serial No. 10/927,857) Examiner: Unknown
)
Filed: August 27, 2004)
)
For: METHODS OF PROVIDING)
THERAPEUTIC EFFECTS USING)
CYCLOSPORIN COMPONENTS)

I hereby certify that this correspondent is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, PO Box 1450, Alexandria, VA 22313-1450, on or before

March 22, 2005
Date

Alicia Curran

Commissioner for Patents
P.O. Box 1450
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SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

Dear Sir:

Applicant wishes to call to the attention of the Examiner the documents cited on the accompanying Form PTO-1449. No concession is made that these documents are prior art, and applicant expressly reserves the right to antedate the documents as may be appropriate. Applicant requests that each of these documents be made of record in the above-identified application.

This SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT is being filed pursuant to 37 CFR 1.97(c) and is accompanied by a certification as specified in 37 CFR 1.97(e).

CERTIFICATION UNDER 37 CFR 1.97(e)

Each item of information contained in this Supplemental Information Disclosure Statement was cited in a communication

(the International Search Report) from a foreign patent office (The European Patent Office) acting as the International Search Authority in a counterpart foreign (PCT) patent application no more than three months prior to the filing of this Supplemental Information Disclosure Statement (a copy of the International Search Report is enclosed).

Respectfully submitted,

Frank J. Uxa
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Reg. No. 25,612
4 Venture, Suite 300
Irvine, CA 92618
(949) 450-1750
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FJUxa/ac

Form PTO-1449

INFORMATION DISCLOSURE CITATION IN AN APPLICATION

(Use several sheets if necessary)

Docket No.: D-3111	Application No.: 10/927,857
Applicant: Acheampong et al.	
Filing Date: August 27, 2004	Group Art Unit: 1636

U. S. PATENT DOCUMENTS

EXAMINER INITIAL	DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
	2001/0036449 A1	11/2001	Garst			

FOREIGN PATENT DOCUMENTS

	DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO

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EXAMINER	DATE CONSIDERED

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2006 10/03

10/927,857

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FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT
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L31 (        25)SEA FILE=HCAPLUS ABB=ON  PLU=ON  ACHEAMPONG A?/AU
L32 (        71)SEA FILE=HCAPLUS ABB=ON  PLU=ON  TANG LIU D?/AU
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L40 (     23233)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L39
L41 (         1)SEA FILE=HCAPLUS ABB=ON  PLU=ON  ((L31 OR L32 OR L33 OR L34))
              AND L40 AND L36 AND L37 AND L38
L42 (        29)SEA FILE=HCAPLUS ABB=ON  PLU=ON  ((L31 OR L32 OR L33 OR L34))
              AND L40
L43 (         4)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L42 AND ((L36 OR L37 OR L38))

L44           4 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L41 OR L43
```

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=> FILE MEDLINE
FILE 'MEDLINE' ENTERED AT 16:30:01 ON 02 OCT 2006

 FILE LAST UPDATED: 30 Sep 2006 (20060930/UP).  FILE COVERS 1950 TO DATE.

 On December 11, 2005, the 2006 MeSH terms were loaded.

 The MEDLINE reload for 2006 is now (26 Feb.) available.  For details
 on the 2006 reload, enter HELP RLOAD at an arrow prompt (=>).
 See also:

    http://www.nlm.nih.gov/mesh/
    http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html
    http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_med_data_changes.html
    http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_2006_MeSH.html

 OLDMEDLINE is covered back to 1950.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2006 vocabulary.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> D QUE L62
L45 (        24)SEA FILE=MEDLINE ABB=ON  PLU=ON  ACHEAMPONG A?/AU
L46 (        63)SEA FILE=MEDLINE ABB=ON  PLU=ON  TANG LIU D?/AU
L47 (      3663)SEA FILE=MEDLINE ABB=ON  PLU=ON  CHANG J?/AU
L48 (       322)SEA FILE=MEDLINE ABB=ON  PLU=ON  POWER D?/AU
L49 (         1)SEA FILE=REGISTRY ABB=ON  PLU=ON  CYCLOSPORIN A/CN
L50 (      9221)SEA FILE=MEDLINE ABB=ON  PLU=ON  EMULSIONS+NT/CT
L51 (       124)SEA FILE=MEDLINE ABB=ON  PLU=ON  EMULSIFYING AGENTS/CT
L52 (     34652)SEA FILE=MEDLINE ABB=ON  PLU=ON  OILS+NT/CT
L53 (         0)SEA FILE=MEDLINE ABB=ON  PLU=ON  L45 AND L46 AND L47 AND L48
L54             SEL  PLU=ON  L49 1- CHEM :      38 TERMS
L55 (     39885)SEA FILE=MEDLINE ABB=ON  PLU=ON  L54
L56 (    320609)SEA FILE=MEDLINE ABB=ON  PLU=ON  EYE DISEASES+NT/CT
L57 (         0)SEA FILE=MEDLINE ABB=ON  PLU=ON  ((L45 OR L46 OR L47 OR L48))
                  AND L56 AND L55 AND ((L50 OR L51)) AND L52
L58 (         2)SEA FILE=MEDLINE ABB=ON  PLU=ON  ((L45 OR L46 OR L47 OR L48))
                  AND L56 AND L55 AND ((L50 OR L51))
L59 (         0)SEA FILE=MEDLINE ABB=ON  PLU=ON  ((L45 OR L46 OR L47 OR L48))
                  AND L56 AND L55 AND L52
L60 (         5)SEA FILE=MEDLINE ABB=ON  PLU=ON  ((L45 OR L46 OR L47 OR L48))
                  AND L56 AND L55
L61 (         5)SEA FILE=MEDLINE ABB=ON  PLU=ON  (L57 OR L58 OR L59 OR L60)
L62           5 SEA FILE=MEDLINE ABB=ON  PLU=ON  L61 OR L53


=> FILE WPIX
FILE 'WPIX' ENTERED AT 16:30:10 ON 02 OCT 2006
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FILE LAST UPDATED:          2 OCT 2006      <20061002/UP>
MOST RECENT DERWENT UPDATE:     200663        <200663/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

>>> FOR A COPY OF THE DERWENT WORLD PATENTS INDEX STN USER GUIDE,
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http://www.stn-international.de/training_center/patents/stn_guide.pdf <

>>> FOR DETAILS OF THE PATENTS COVERED IN CURRENT UPDATES, SEE
http://scientific.thomson.com/support/patents/coverage/latestupdates/

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http://www.stn-international.de/stndatabases/details/ipc_reform.html and
http://scientific.thomson.com/media/scpdf/ipcrdwpi.pdf <<<

>>> FOR FURTHER DETAILS ON THE FORTHCOMING DERWENT WORLD PATENTS
INDEX ENHANCEMENTS PLEASE VISIT:
http://www.stn-international.de/stndatabases/details/dwpi_r.html <<<
'BI,ABEX' IS DEFAULT SEARCH FIELD FOR 'WPIX' FILE

=> D QUE L71
L63 (1)SEA FILE=REGISTRY ABB=ON PLU=ON CYCLOSPORIN A/CN
L64 (1)SEA FILE=WPIX ABB=ON PLU=ON ACHEAMPONG A?/AU
L65 (7)SEA FILE=WPIX ABB=ON PLU=ON TANG LIU D?/AU
L66 (3666)SEA FILE=WPIX ABB=ON PLU=ON CHANG J?/AU
L67 (57)SEA FILE=WPIX ABB=ON PLU=ON POWER D?/AU
L68 SEL PLU=ON L63 1- CHEM : 38 TERMS
L69 (2231)SEA FILE=WPIX ABB=ON PLU=ON L68
L70 (959)SEA FILE=WPIX ABB=ON PLU=ON RA0135/DCN OR 90981-1-0-0/DCRE
L71 6 SEA FILE=WPIX ABB=ON PLU=ON ((L64 OR L65 OR L66 OR L67)) AND
((L69 OR L70))

=> DUP REM L62 L14 L30 L71 L44
FILE 'MEDLINE' ENTERED AT 16:31:07 ON 02 OCT 2006

FILE 'BIOSIS' ENTERED AT 16:31:07 ON 02 OCT 2006
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FILE 'HCAPLUS' ENTERED AT 16:31:07 ON 02 OCT 2006
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PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2006 AMERICAN CHEMICAL SOCIETY (ACS)
PROCESSING COMPLETED FOR L62
PROCESSING COMPLETED FOR L14
PROCESSING COMPLETED FOR L30
PROCESSING COMPLETED FOR L71
PROCESSING COMPLETED FOR L44
L72 19 DUP REM L62 L14 L30 L71 L44 (10 DUPLICATES REMOVED)
ANSWERS '1-5' FROM FILE MEDLINE
ANSWERS '6-11' FROM FILE BIOSIS
ANSWERS '12-13' FROM FILE EMBASE
ANSWERS '14-19' FROM FILE WPIX

=> D IALL 1-5; D IALL 6-11; D IALL 12-13; D IALL ABEQ TECH 14-19

L72 ANSWER 1 OF 19 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2005132189 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 15762768
TITLE: Ocular pharmacokinetics and safety of **ciclosporin**

, a novel topical treatment for dry eye.
AUTHOR: **Tang-Liu Diane D-S; Acheampong Andrew**
CORPORATE SOURCE: Department of Pharmacokinetics and Drug Metabolism, Allergan Inc., Irvine, California 92612, USA..
tang-liu_diane@allergan.com
SOURCE: Clinical pharmacokinetics, (2005) Vol. 44, No. 3, pp. 247-61. Ref: 87
Journal code: 7606849. ISSN: 0312-5963.
PUB. COUNTRY: New Zealand
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200506
ENTRY DATE: Entered STN: 15 Mar 2005
Last Updated on STN: 28 Jun 2005
Entered Medline: 27 Jun 2005

ABSTRACT:
Ciclosporin is a potent immunomodulator that acts selectively and locally when administered at the ocular surface. 0.05% **ciclosporin** ophthalmic emulsion has recently been approved by the US FDA for treatment of keratoconjunctivitis sicca (KCS) [dry-eye disease]. After topical application, ***ciclosporin*** accumulates at the ocular surface and cornea, achieving concentrations (>/=0.236 microg/g) that are sufficient for immunomodulation. Very little drug penetrates through the ocular surface to intraocular tissues. ***Ciclosporin*** is not metabolised in rabbit or dog eyes and may not be prone to metabolism in human eyes. Cultured human corneal endothelial and stromal cells exposed to **ciclosporin** in vitro exhibited no adverse effects and only minor effects on DNA synthesis. No ocular or systemic toxicity was seen with long-term ocular administration of **ciclosporin** at concentrations up to 0.4%, given as many as six times daily for 6 months in rabbits and 1 year in dogs. Systemic blood **ciclosporin** concentration after ocular administration was extremely low or undetectable in rabbits, dogs and humans, obviating concerns about systemic toxicity. In 12-week and 1-year clinical safety studies in dry-eye patients, the most common adverse event associated with the ophthalmic use of **ciclosporin** emulsion was ocular burning. No serious drug-related adverse events occurred.These data from in vitro, nonclinical and clinical studies indicate effective topical delivery of ***ciclosporin*** to desired target tissues along with a favourable safety profile, making 0.05% **ciclosporin** ophthalmic emulsion a promising treatment for KCS.

CONTROLLED TERM:
Animals
Chemistry, Physical
Cyclosporine: AE, adverse effects
***Cyclosporine: PK, pharmacokinetics**
Cyclosporine: TU, therapeutic use
***Dry Eye Syndromes: DT, drug therapy**
***Dry Eye Syndromes: ME, metabolism**
*Eye: ME, metabolism
Humans
Immunosuppressive Agents: AE, adverse effects
*Immunosuppressive Agents: PK, pharmacokinetics
Immunosuppressive Agents: TU, therapeutic use
CAS REGISTRY NO.: **59865-13-3 (Cyclosporine)**
CHEMICAL NAME: 0 (Immunosuppressive Agents)

L72 ANSWER 2 OF 19 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 2002660073 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 12419092
TITLE: Blood concentrations of **cyclosporin a**

during long-term treatment with **cyclosporin a** ophthalmic emulsions in patients with moderate to severe dry eye disease.

AUTHOR: Small David S; **Acheampong Andrew**; Reis Brenda; Stern Katherine; Stewart William; Berdy Gregg; Epstein Randy; Foerster Robert; Forstot Lance; **Tang-Liu Diane D-S**

CORPORATE SOURCE: Allergan, Inc Irvine, CA 92715, USA.

SOURCE: Journal of ocular pharmacology and therapeutics : the official journal of the Association for Ocular Pharmacology and Therapeutics, (2002 Oct) Vol. 18, No. 5, pp. 411-8. Journal code: 9511091. ISSN: 1080-7683.

PUB. COUNTRY: United States

DOCUMENT TYPE: (CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE III)
Journal; Article; (JOURNAL ARTICLE)
(MULTICENTER STUDY)
(RANDOMIZED CONTROLLED TRIAL)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200212

ENTRY DATE: Entered STN: 7 Nov 2002
Last Updated on STN: 17 Dec 2002
Entered Medline: 9 Dec 2002

ABSTRACT:
To quantify blood **cyclosporin A** (CsA) concentrations during treatment with CsA topical ophthalmic emulsions, blood was collected from 128 patients enrolled in a Phase 3, multicenter, double-masked, randomized, parallel-group study of CsA eyedrops for treatment of moderate to severe dry eye disease. Patients received 0.05% CsA, 0.1% CsA, or vehicle b.i.d. for 6 months; vehicle-treated patients then crossed over to 0.1% CsA b.i.d. for 6 months. CsA concentrations were measured using a validated LC/MS-MS assay (quantitation limit = 0.1 ng/mL). No patient receiving 0.05% CsA had any quantifiable CsA in the blood (n = 96 samples). All but 7 of 128 (5.5%) trough blood samples from the 0.1% CsA group were below the quantitation limit for CsA; none exceeded 0.3 ng/mL. CsA was also below the limit of quantitation in 205 of 208 (98.6%) of serial postdose blood samples collected from 26 patients during 1 dosing interval between months 9 and 12. The highest C(max) measured, 0.105 ng/mL at 3 hours postdose, occurred in a 0.1% CsA-treated patient. These results indicate that long-term use of topical CsA ophthalmic emulsions at doses that are clinically efficacious for treating dry eye will not cause any system-wide effects.

CONTROLLED TERM: Check Tags: Female; Male
Adult
Aged
Aged, 80 and over
Anti-Inflammatory Agents, Non-Steroidal: AD, administration & dosage
*Anti-Inflammatory Agents, Non-Steroidal: BL, blood
Anti-Inflammatory Agents, Non-Steroidal: TU, therapeutic use
Area Under Curve
Chromatography, High Pressure Liquid
Cyclosporine: AD, administration & dosage
***Cyclosporine: BL, blood**
Cyclosporine: TU, therapeutic use
Double-Blind Method
Emulsions
Humans
Instillation, Drug

Keratoconjunctivitis Sicca: BL, blood
***Keratoconjunctivitis Sicca: DT, drug therapy**
Middle Aged
Ophthalmic Solutions
CAS REGISTRY NO.: **59865-13-3 (Cyclosporine)**
CHEMICAL NAME: 0 (Anti-Inflammatory Agents, Non-Steroidal); 0 (Emulsions); 0 (Ophthalmic Solutions)

L72 ANSWER 3 OF 19 MEDLINE on STN DUPLICATE 5
ACCESSION NUMBER: 1998348699 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 9684074
TITLE: Topical **Cyclosporine A** in the management of postkeratoplasty glaucoma and corticosteroid-induced ocular hypertension (CIOH) and the penetration of topical 0.5% **cyclosporine A** into the cornea and anterior chamber.
AUTHOR: Perry H D; Donnenfeld E D; **Acheampong A**; Kanellopoulos A J; Sforza P D; D'Aversa G; Wallerstein A; Stern M
CORPORATE SOURCE: Department of Ophthalmology, North Shore University Hospital, Manhasset, New York 11030, USA.
SOURCE: The CLAO journal : official publication of the Contact Lens Association of Ophthalmologists, Inc, (1998 Jul) Vol. 24, No. 3, pp. 159-65.
Journal code: 8302065. ISSN: 0733-8902.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199810
ENTRY DATE: Entered STN: 29 Oct 1998
Last Updated on STN: 29 Oct 1998
Entered Medline: 19 Oct 1998

ABSTRACT:
PURPOSE: To evaluate the effect on intraocular pressure (IOP) of substituting topical **Cyclosporine A** 0.5% for topical corticosteroids in patients with postkeratoplasty glaucoma and corticosteroid-induced ocular hypertension (CIOH). We also sought to determine the penetration of topical 0.5% **Cyclosporine A** into the cornea and anterior chamber.
METHODS: Topical **Cyclosporine A** 0.5% was prospectively substituted for topical corticosteroids in 47 patients (52 eyes) with postkeratoplasty glaucoma and CIOH in order to eliminate the IOP-elevating effect of topical corticosteroids, while maintaining protection against allograft rejection. Ten patients received 0.5% topical **Cyclosporine** before keratoplasty. Their corneal tissue and aqueous samples were evaluated by high pressure liquid chromatography for **Cyclosporine** levels.
RESULTS: Forty-eight of 52 eyes (92.3%) demonstrated a reduction of IOP at first followup (mean: -7.9 mmHg; range: -19 to +2). Mean followup was 10.3 months, ranging from 1 to 37 months. At last follow-up, mean IOP was -8.2 mm Hg. There were six allograft rejections, five of which were reversed with the reintroduction of topical corticosteroids. Graft clarity was maintained in 46 of 52 eyes (88%). The mean cornea **Cyclosporine** concentration was 3679 ng/gm (range: 1980 to 5520 ng/ gm) and aqueous humor mean concentration was 6.05 ng/mL (range: 0.4 to 15.5 ng/mL). CONCLUSIONS: Topical ***Cyclosporine*** **A** 0.5% may be substituted for topical corticosteroids to aid in the management of postkeratoplasty glaucoma and CIOH. However, the use of **Cyclosporine** in place of corticosteroids may be associated with an increased risk of immune rejections. The corneal penetration of topical **Cyclosporine** is excellent while the penetration into the anterior chamber is poor.

CONTROLLED TERM: Check Tags: Female; Male
Administration, Topical
Adolescent
Adult
Aged
Aged, 80 and over
Anterior Chamber: DE, drug effects
*Anterior Chamber: ME, metabolism
Anterior Chamber: SU, surgery
Chromatography, High Pressure Liquid
Comparative Study
Cornea: DE, drug effects
Cornea: ME, metabolism
Cornea: SU, surgery
***Cyclosporine: AD, administration & dosage**
Cyclosporine: PK, pharmacokinetics
Follow-Up Studies
***Glaucoma: DT, drug therapy**
Glaucoma: ET, etiology
*Glucocorticoids: AE, adverse effects
Humans
*Immunosuppressive Agents: AD, administration & dosage
Immunosuppressive Agents: PK, pharmacokinetics
Intraocular Pressure: DE, drug effects
*Keratoplasty, Penetrating: AE, adverse effects
Middle Aged
***Ocular Hypertension: CI, chemically induced**
Ocular Hypertension: DT, drug therapy
Ophthalmic Solutions
Prospective Studies
CAS REGISTRY NO.: **59865-13-3 (Cyclosporine)**
CHEMICAL NAME: 0 (Glucocorticoids); 0 (Immunosuppressive Agents); 0 (Ophthalmic Solutions)

L72 ANSWER 4 OF 19 MEDLINE on STN
ACCESSION NUMBER: 1998298741 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 9635002
TITLE: **Cyclosporine** distribution into the conjunctiva, cornea, lacrimal gland, and systemic blood following topical dosing of **cyclosporine** to rabbit, dog, and human eyes.
AUTHOR: **Acheampong A**; Shackleton M; Lam S; Rudewicz P; **Tang-Liu D**
CORPORATE SOURCE: Allergan, Irvine, California, USA.
SOURCE: Advances in experimental medicine and biology, (1998) Vol. 438, pp. 1001-4.
Journal code: 0121103. ISSN: 0065-2598.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199809
ENTRY DATE: Entered STN: 25 Sep 1998
Last Updated on STN: 25 Sep 1998
Entered Medline: 15 Sep 1998
CONTROLLED TERM: Administration, Topical
Animals
*Conjunctiva: ME, metabolism
*Cornea: ME, metabolism
Cyclosporine: AD, administration & dosage

Cyclosporine: BL, blood
***Cyclosporine: PK, pharmacokinetics**
Dogs
Dose-Response Relationship, Drug
Humans
Keratoconjunctivitis Sicca: DT, drug therapy
***Keratoconjunctivitis Sicca: ME, metabolism**
*Lacrimal Apparatus: ME, metabolism
Metabolic Clearance Rate
Rabbits
Tissue Distribution
CAS REGISTRY NO.: **59865-13-3 (Cyclosporine)**

L72 ANSWER 5 OF 19 MEDLINE on STN
ACCESSION NUMBER: 1998298739 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 9635000
TITLE: Preclinical safety studies of **cyclosporine** ophthalmic emulsion.
AUTHOR: Angelov O; Wiese A; Yuan Y; Andersen J; **Acheampong A**; Brar B
CORPORATE SOURCE: Allergan, Irvine, California, USA.
SOURCE: Advances in experimental medicine and biology, (1998) Vol. 438, pp. 991-5.
Journal code: 0121103. ISSN: 0065-2598.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199809
ENTRY DATE: Entered STN: 25 Sep 1998
Last Updated on STN: 25 Sep 1998
Entered Medline: 15 Sep 1998
CONTROLLED TERM: Check Tags: Female; Male
Animals
Conjunctivitis: CI, chemically induced
Cyclosporine: AD, administration & dosage
***Cyclosporine: TO, toxicity**
Dogs
Emulsions
Eye: CY, cytology
*Eye: DE, drug effects
Eye: PA, pathology
Rabbits
Time Factors
CAS REGISTRY NO.: **59865-13-3 (Cyclosporine)**
CHEMICAL NAME: 0 (Emulsions)

L72 ANSWER 6 OF 19 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
DUPLICATE 4
ACCESSION NUMBER: 1998:276410 BIOSIS Full-text
DOCUMENT NUMBER: PREV199800276410
TITLE: Effects of synthetic inhibitor of metalloproteinase and **cyclosporin A** on corneal haze after excimer laser photorefractive keratectomy in rabbits.
AUTHOR(S): **Chang, Jin Ho** [Reprint author]; Kook, Myeong Cherl; Lee, Jin Hak; Chung, Hum; Wee, Won Ryang
CORPORATE SOURCE: Dep. Ophthalmol., Seoul City Boramae Hosp., 395

Shindaebang-Dong, Tongjak-Gu, Seoul 1560-012, South Korea
SOURCE: Experimental Eye Research, (April, 1998) Vol. 66, No. 4, pp. 389-396. print.
CODEN: EXERA6. ISSN: 0014-4835.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 24 Jun 1998
Last Updated on STN: 24 Jun 1998
ABSTRACT:To evaluate the effects of synthetic inhibitor of metalloproteinase (SIMP) and **cyclosporin A** (CsA) on corneal haze after excimer laser photorefractive keratectomy (PRK) in rabbits, PRK was performed on 60 rabbits. They were randomized to one of four groups: group A which received topical SIMP, group B which received topical CsA, group C which received both SIMP and CsA, and group D which received vehicles. Another 16 rabbits did not undergo PRK and were randomized to one of four groups: group E which received topical SIMP, group F which received topical CsA, group G which received both SIMP and CsA, and group H which received vehicles. SIMP solution (1 mM) was instilled every two hours and 2% **cyclosporin** was instilled four times a day, this was carried out for as long as 6 weeks after surgery. At one, two, four, and six weeks after surgery, slit lamp examination was performed with haze gradings recorded, and corneal specimens were obtained from groups A, B, C, and D. In groups E-H, all rabbits were killed after six weeks of eyedrops instillation. Light microscopy and immunohistochemistry for collagen types III, IV, and VI were performed on the specimens obtained. Slit lamp examination and light microscopy revealed that SIMP significantly reduced corneal haze after PRK, but CsA did not. Immunohistochemistry revealed that deposition of types III and IV collagen was detected in ablated area in groups A-D, and SIMP reduced the frequency of positive staining for type III collagen. In groups E-F, corneas were normal. These findings suggest that SIMP significantly reduced corneal haze and the synthesis of type III collagen after excimer laser PRK in rabbits.
CONCEPT CODE: Pharmacology - General 22002
Sense organs - General and methods 20001
INDEX TERMS: Major Concepts
Pharmacology; Sense Organs (Sensory Reception)
INDEX TERMS: Parts, Structures, & Systems of Organisms
cornea: sensory system
INDEX TERMS: Diseases
corneal haze: **eye** disease
INDEX TERMS: Chemicals & Biochemicals
collagen: type III, type IV, type VI;
cyclosporin A: topical administration;
synthetic inhibitor of metalloproteinase [SIMP]: topical administration
INDEX TERMS: Methods & Equipment
excimer laser photorefractive keratectomy: surgical method; immunohistochemistry: histochemical method; light microscopy: microscopy method; slit lamp examination: examination method
ORGANISM: Classifier
Leporidae 86040
Super Taxa
Lagomorpha; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
rabbit
Taxa Notes
Animals, Chordates, Lagomorphs, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Vertebrates
REGISTRY NUMBER: **59865-13-3 (cyclosporin A)**
81669-70-7 (METALLOPROTEINASE)

L72 ANSWER 7 OF 19 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2006:105948 BIOSIS Full-text
DOCUMENT NUMBER: PREV200600105839
TITLE: Cytochrome P450 3A expression and activity in the rabbit lacrimal gland: Glucocorticoid modulation and the impact on androgen metabolism.
AUTHOR(S): Attar, Mayssa [Reprint Author]; Ling, Kah-Hiing John; **Tang-Liu, Diane D.-S.**; Neamati, Nouri; Lee, Vincent H. L.
CORPORATE SOURCE: Allergan Pharmaceut Inc, Dept Pharmacokinet and Drug Metab, Irvine, CA 92612 USA
attar_mayssa@allergan.com
SOURCE: IOVS, (DEC 2005) Vol. 46, No. 12, pp. 4697-4706.
CODEN: IOVSDA. ISSN: 0146-0404.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 8 Feb 2006
Last Updated on STN: 8 Feb 2006

ABSTRACT:PURPOSE. Cytochrome P450 3A (CYP3A) is an enzyme of paramount importance to drug metabolism. The expression and activity of CYP3A, an enzyme responsible for active androgen clearance, was investigated in the rabbit lacrimal gland.METHODS. Analysis of CYP3A expression and activity was performed on lacrimal gland tissues obtained from naive untreated and treated New Zealand White rabbits. For 5 days, treated rabbits received daily administration of vehicle or 0.1% or 1.0% dexamethasone, in the lower cul-de-sac of each **eye**. Changes in mRNA expression were monitored by real-time RT-PCR. Protein expression was confirmed by Western blot. Functional activity was measured by monitoring the metabolism of CYP3A probe substrates - namely, 7-benzyloxyquinoline (BQ) and [H-3] testosterone.RESULTS. Cytochrome P450 heme protein was detected at a concentration of 44.6 picomoles/mg protein, along with its redox partner NADPH reductase and specifically CYP3A6 in the naive rabbit lacrimal gland. Genes encoding CYP3A6, in addition to the pregnane-X-receptor (PXR) and P-glycoprotein (P-gp) were expressed in the untreated tissue. BQ dealkylation was measured in the naive rabbit lacrimal gland at a rate of 14 +/- 7 picomoles/mg protein per minute. Changes in CYP3A6, P-gp, and androgen receptor mRNA expression levels were detected after dexamethasone treatment. In addition, dexamethasone treatment resulted in significant increases in BQ dealkylation and CYP3A6-mediated [H-3] testosterone metabolism. Concomitant increases in CYP3A6-mediated hydroxylated testosterone metabolites were observed in the treated rabbits. Furthermore, ketoconazole, all-trans retinoic acid, and **cyclosporine** inhibited CYP3A6 mediated [H-3] testosterone 6 beta hydroxylation in a concentration-dependent manner, with IC50 ranging from 3.73 to 435 mu M.CONCLUSIONS. The results demonstrate, for the first time, the expression and activity of CYP3A6 in the rabbit lacrimal gland. In addition, this pathway was shown to be subject to modulation by a commonly prescribed glucocorticoid and can be inhibited by known CYP3A inhibitors.

CONCEPT CODE: Biochemistry studies - General 10060
Biochemistry studies - Nucleic acids, purines and pyrimidines 10062
Biochemistry studies - Proteins, peptides and amino acids 10064
Biochemistry studies - Lipids 10066
Biochemistry studies - Sterols and steroids 10067
Biochemistry studies - Carbohydrates 10068
Enzymes - General and comparative studies: coenzymes 10802
Pathology - Therapy 12512
Metabolism - General metabolism and metabolic pathways

13002
Endocrine - General 17002
Sense organs - Physiology and biochemistry 20004
Pharmacology - General 22002
Pharmacology - Endocrine system 22016

INDEX TERMS: Major Concepts
Pharmacology; Metabolism; Enzymology (Biochemistry and Molecular Biophysics); Endocrine System (Chemical Coordination and Homeostasis)

INDEX TERMS: Parts, Structures, & Systems of Organisms
eye: sensory system; lacrimal gland: sensory system

INDEX TERMS: Chemicals & Biochemicals
mRNA [messenger RNA]: expression; all-trans retinoic acid; glucocorticoids; androgen receptor; androgens; **cyclosporine**; P-glycoprotein [P-gp] [EC 3.6.3.44]; heme protein; ketoconazole; pregnane-X-receptor; 7-benzyloxyquinoline; cytochrome P450 3A [CYP3A]: expression; tritiated testosterone; NADPH reductase; cytochrome P450 3A6; dexamethasone: glucocorticoid-drug, pharmacokinetics

INDEX TERMS: Methods & Equipment
Western blot: electrophoretic techniques, immunologic techniques, laboratory techniques

ORGANISM: Classifier
Leporidae 86040
Super Taxa
Lagomorpha; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
New Zealand White rabbit (common)
Taxa Notes
Animals, Chordates, Lagomorphs, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Vertebrates

REGISTRY NUMBER: 302-79-4 (all-trans retinoic acid)
63798-73-2 (**cyclosporine**)
65277-42-1 (ketoconazole)
131802-60-3 (7-benzyloxyquinoline)
329322-82-9 (cytochrome P450 3A)
329322-82-9 (CYP3A)
9055-50-9 (NADPH reductase)
359435-35-1 (cytochrome P450 3A6)
50-02-2 (dexamethasone)

L72 ANSWER 8 OF 19 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2000:236076 BIOSIS Full-text
DOCUMENT NUMBER: PREV200000236076
TITLE: Blood concentrations of **cyclosporin A** (CsA) during twice-daily treatment of 0.05% and 0.1% **cyclosporine** ophthalmic emulsions in patients with moderate to severe keratoconjunctivitis sicca.
AUTHOR(S): Small, D. S. [Reprint author]; **Acheampong, A.** [Reprint author]; Reis, B. [Reprint author]; Stewart, W.; Berdy, G.; Epstein, R.; Foerster, R.; Forstot, L.; **Tang-Liu, D.** [Reprint author]
CORPORATE SOURCE: Allergan Inc, Irvine, CA, USA
SOURCE: IOVS, (March 15, 2000) Vol. 41, No. 4, pp. S69. print.
Meeting Info.: Annual Meeting of the Association for Research in Vision and Ophthalmology. Fort Lauderdale, Florida, USA. April 30-May 05, 2000. Association for Research in Vision and Ophthalmology.

DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 7 Jun 2000
Last Updated on STN: 5 Jan 2002
CONCEPT CODE: Biochemistry studies - Proteins, peptides and amino acids 10064
Pathology - Therapy 12512
Sense organs - Pathology 20006
Pharmacology - Immunological processes and allergy 22018
Pharmacology - Clinical pharmacology 22005
General biology - Symposia, transactions and proceedings 00520
INDEX TERMS: Major Concepts
Ophthalmology (Human Medicine, Medical Sciences); Pharmacology
INDEX TERMS: Diseases
keratoconjunctivitis sicca: **eye** disease, treatment
Keratoconjunctivitis Sicca (MeSH)
INDEX TERMS: Chemicals & Biochemicals
cyclosporin A: immunosuppressant-drug, blood concentrations, ophthalmic emulsions, twice-daily treatment
INDEX TERMS: Miscellaneous Descriptors
Meeting Abstract
ORGANISM: Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
human: patient
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates
REGISTRY NUMBER: **59865-13-3** (**cyclosporin A**)

L72 ANSWER 9 OF 19 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 1997:540426 BIOSIS Full-text
DOCUMENT NUMBER: PREV199799839629
TITLE: Preclinical safety of **cyclosporine** ophthalmic emulsion.
AUTHOR(S): Angelov, O.; Wiese, A.; Andersen, J.; Small, D.; **Acheampong, A.**; Yuan, Y.; Brar, B.
CORPORATE SOURCE: Allergan, Irvine, CA, USA
SOURCE: Journal of Rheumatology, (1997) Vol. 24, No. SUPPL. 50, pp. 50.
Meeting Info.: VIth International Symposium on Sjogren's Syndrome. Avon, Connecticut, USA. October 15-18, 1997.
CODEN: JRHUA9. ISSN: 0315-162X.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 12 Dec 1997
Last Updated on STN: 12 Dec 1997
CONCEPT CODE: General biology - Symposia, transactions and proceedings 00520
Biochemistry studies - General 10060
Pathology - Therapy 12512
Sense organs - General and methods 20001

Pharmacology - General 22002
Routes of immunization, infection and therapy 22100

INDEX TERMS: Major Concepts
Biochemistry and Molecular Biophysics; Pharmacology; Sense Organs (Sensory Reception)

INDEX TERMS: Chemicals & Biochemicals
CYCLOSPORINE

INDEX TERMS: Miscellaneous Descriptors
CYCLOSPORINE; DRY **EYES**; OPHTHALMIC EMULSION; OPHTHALMIC-DRUG; PHARMACOKINETICS; PHARMACOLOGY; PRECLINICAL SAFETY; SENSE ORGANS; TOPICAL ADMINISTRATION

ORGANISM: Classifier
Canidae 85765
Super Taxa
Carnivora; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
dog
Taxa Notes
Animals, Carnivores, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Vertebrates

ORGANISM: Classifier
Leporidae 86040
Super Taxa
Lagomorpha; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
rabbit
Taxa Notes
Animals, Chordates, Lagomorphs, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Vertebrates

REGISTRY NUMBER: **59865-13-3Q** (**CYCLOSPORINE**)
63798-73-2Q (**CYCLOSPORINE**)

L72 ANSWER 10 OF 19 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 1997:540385 BIOSIS Full-text
DOCUMENT NUMBER: PREV199799839588
TITLE: A dose-ranging clinical trial to assess the safety and efficacy of **cyclosporine** ophthalmic emulsion for the treatment of the ocular surface disease and inflammation associated with keratoconjunctivitis sicca (KCS).
AUTHOR(S): Donshik, P.; Reis, B. L.; Burk, C. T.; Stern, K. L.; **Acheampong, A.**
CORPORATE SOURCE: Allergan, Irvine, CA, USA
SOURCE: Journal of Rheumatology, (1997) Vol. 24, No. SUPPL. 50, pp. 43.
Meeting Info.: VIth International Symposium on Sjogren's Syndrome. Avon, Connecticut, USA. October 15-18, 1997.
CODEN: JRHUA9. ISSN: 0315-162X.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 12 Dec 1997
Last Updated on STN: 12 Dec 1997
CONCEPT CODE: General biology - Symposia, transactions and proceedings 00520
Biochemistry studies - General 10060
Pathology - Inflammation and inflammatory disease 12508
Pathology - Therapy 12512

Sense organs - General and methods 20001
Pharmacology - General 22002

INDEX TERMS: Major Concepts
Biochemistry and Molecular Biophysics; Pathology; Pharmacology; Sense Organs (Sensory Reception)

INDEX TERMS: Chemicals & Biochemicals
CYCLOSPORINE

INDEX TERMS: Miscellaneous Descriptors
CYCLOSPORINE; EFFICACY; **EYE** DISEASE; KERATOCONJUNCTIVITIS SICCA; OCULAR INFLAMMATION; OCULAR SURFACE DISEASE; OPHTHALMIC EMULSION; OPHTHALMIC-DRUG; OPHTHALMOLOGY; PATIENT; PHARMACOLOGY; SAFETY

ORGANISM: Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
human
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates

REGISTRY NUMBER: **59865-13-3Q** (**CYCLOSPORINE**)
63798-73-2Q (**CYCLOSPORINE**)

L72 ANSWER 11 OF 19 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 1996:206571 BIOSIS Full-text
DOCUMENT NUMBER: PREV199698762700
TITLE: Ocular absorption of **cyclosporine** from an aqueous emulsion: Comparison to other eyedrop formulations.
AUTHOR(S): **Acheampong, A.; Tang-Liu, D.;** Shackleton, M.; Lam, S.; Angelov, O.; Ding, S.
CORPORATE SOURCE: Allergan Inc., Irvine, CA, USA
SOURCE: Investigative Ophthalmology and Visual Science, (1996) Vol. 37, No. 3, pp. S1026.
Meeting Info.: 1996 Annual Meeting of the Association for Research in Vision and Ophthalmology. Fort Lauderdale, Florida, USA. April 21-26, 1996.
CODEN: IOVSDA. ISSN: 0146-0404.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 2 May 1996
Last Updated on STN: 2 May 1996
CONCEPT CODE: General biology - Symposia, transactions and proceedings 00520
Biochemistry studies - General 10060
Pathology - Inflammation and inflammatory disease 12508
Pathology - Therapy 12512
Sense organs - General and methods 20001
Sense organs - Physiology and biochemistry 20004
Pharmacology - Drug metabolism and metabolic stimulators 22003
Pharmacology - Immunological processes and allergy 22018
Pharmacology - Sense organs, associated structures and functions 22031
Routes of immunization, infection and therapy 22100
Immunology - Immunopathology, tissue immunology 34508
INDEX TERMS: Major Concepts

Immune System (Chemical Coordination and Homeostasis); Pathology; Pharmacology; Sense Organs (Sensory Reception)

INDEX TERMS: Chemicals & Biochemicals
CYCLOSPORINE

INDEX TERMS: Miscellaneous Descriptors
CYCLOSPORINE; DRUG DELIVERY SYSTEM; IMMUNOINFLAMMATORY **EYE** DISEASE; IMMUNOSUPPRESSANT-DRUG; MEETING ABSTRACT; MEETING POSTER; OPHTHALMIC-DRUG; PHARMACOKINETICS

ORGANISM: Classifier
Leporidae 86040
Super Taxa
Lagomorpha; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
rabbit
Taxa Notes
Animals, Chordates, Lagomorphs, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Vertebrates

REGISTRY NUMBER: **59865-13-3Q** (**CYCLOSPORINE**)
63798-73-2Q (**CYCLOSPORINE**)

L72 ANSWER 12 OF 19 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2005269839 EMBASE Full-text
TITLE: Acute anterior uveitis and HLA-B27.
AUTHOR: **Chang J.H.**; McCluskey P.J.; Wakefield D.
CORPORATE SOURCE: Dr. D. Wakefield, School of Medical Sciences, University of New South Wales, Sydney, NSW 2052, Australia
SOURCE: Survey of Ophthalmology, (2005) Vol. 50, No. 4, pp. 364-388. .
Refs: 236
ISSN: 0039-6257 CODEN: SUOPAD
PUBLISHER IDENT.: S 0039-6257(05)00041-X
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 012 Ophthalmology
026 Immunology, Serology and Transplantation
036 Health Policy, Economics and Management
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 18 Aug 2005
Last Updated on STN: 18 Aug 2005

ABSTRACT: Acute anterior uveitis is the most common form of uveitis. HLA-B27-associated acute anterior uveitis is a distinct clinical entity that has wide-ranging medical significance due to its ocular, systemic, immunologic, and genetic features. The association between HLA-B27 and the spectrum of HLA-B27-associated inflammatory diseases remains one of the strongest HLA-disease associations known to date. This review examines acute anterior uveitis with particular focus on HLA-B27-associated acute anterior uveitis, including the epidemiology, immunopathology, association with HLA-B27 and its subtypes, clinical features, complications, prognosis, and potential new therapies such as anti-TNFα therapy and oral HLA-B27-peptide tolerance. There have been substantial recent advances in both clinical and basic scientific research in this field, including studies of the various animal

models of acute anterior uveitis and the HLA-B27 transgenic animals, and these are summarized in this review. To the ophthalmologist, HLA-B27-associated acute anterior uveitis is an important clinical entity that is common, afflicts relatively young patients in their most productive years, and is associated with significant ocular morbidity due to its typically recurrent attacks of inflammation and its potentially vision-threatening ocular complications. Furthermore, to the ophthalmologist and the internist, HLA-B27-associated acute anterior uveitis is also of systemic importance due to its significant association with extraocular inflammatory diseases.

CONTROLLED TERM: Medical Descriptors:

***iridocyclitis: CO, complication**
***iridocyclitis: DM, disease management**
***iridocyclitis: DR, drug resistance**
***iridocyclitis: DT, drug therapy**
***iridocyclitis: EP, epidemiology**
***iridocyclitis: ET, etiology**
***iridocyclitis: PC, prevention**
***iridocyclitis: SU, surgery**
disease association
systemic disease: CO, complication
systemic disease: DT, drug therapy
systemic disease: ET, etiology
immunological tolerance
recurrent disease: CO, complication
recurrent disease: DT, drug therapy
recurrent disease: PC, prevention
ankylosing spondylitis: DT, drug therapy
ankylosing spondylitis: ET, etiology
reactive arthritis: ET, etiology
enteritis: DI, diagnosis
enteritis: ET, etiology
psoriatic arthritis: DT, drug therapy
spondyloarthropathy: CO, complication
spondyloarthropathy: ET, etiology
juvenile rheumatoid arthritis: DT, drug therapy
sarcoidosis
Behcet disease: DT, drug therapy
mucocutaneous lymph node syndrome
endophthalmitis
Herpes simplex virus
Varicella zoster virus
Epstein Barr virus
Cytomegalovirus
Human immunodeficiency virus
Human T cell leukemia virus 1
onchocerciasis: ET, etiology
Onchocerca volvulus
DNA polymorphism
autoimmune disease: CO, complication
autoimmune disease: DM, disease management
autoimmune disease: DR, drug resistance
autoimmune disease: DT, drug therapy
autoimmune disease: EP, epidemiology
autoimmune disease: ET, etiology
autoimmune disease: PC, prevention
autoimmune disease: SU, surgery
chorioretinopathy: ET, etiology
Vogt Koyanagi syndrome: ET, etiology

drug cost
side effect: SI, side effect
drug safety
human
nonhuman
clinical trial
review
priority journal

CONTROLLED TERM: Drug Descriptors:
tumor necrosis factor alpha antibody: CT, clinical trial
tumor necrosis factor alpha antibody: DT, drug therapy
tumor necrosis factor alpha antibody: IV, intravenous drug administration
tumor necrosis factor alpha antibody: PD, pharmacology
tumor necrosis factor alpha antibody: SC, subcutaneous drug administration
HLA B27 antigen: CT, clinical trial
HLA B27 antigen: DT, drug therapy
HLA B27 antigen: PO, oral drug administration
HLA antigen class 1: EC, endogenous compound
HLA antigen class 2: EC, endogenous compound
immunosuppressive agent: DT, drug therapy
corticosteroid: DT, drug therapy
corticosteroid: IO, intraocular drug administration
corticosteroid: VI, intravitreal drug administration
corticosteroid: TP, topical drug administration
endotoxin
bacterium lipopolysaccharide
melanin
cyclosporin
myelin basic protein
cytokine: EC, endogenous compound
HLA DR4 antigen: EC, endogenous compound
transporter associated with antigen processing 1: EC, endogenous compound
epitope: EC, endogenous compound
cycloplegic agent: DT, drug therapy
cycloplegic agent: TP, topical drug administration
infliximab: CT, clinical trial
infliximab: DT, drug therapy
infliximab: IV, intravenous drug administration
infliximab: PD, pharmacology
etanercept: CT, clinical trial
etanercept: DT, drug therapy
etanercept: PD, pharmacology
etanercept: SC, subcutaneous drug administration
methotrexate
myelin: CT, clinical trial
myelin: DT, drug therapy
myelin: PO, oral drug administration
collagen: CT, clinical trial
collagen: DT, drug therapy
collagen: PO, oral drug administration
uveitogenic peptide: CT, clinical trial
uveitogenic peptide: DT, drug therapy
uveitogenic peptide: PO, oral drug administration
peptide derivative: CT, clinical trial
peptide derivative: DT, drug therapy
peptide derivative: PO, oral drug administration
antibiotic agent: DT, drug therapy

salazosulfapyridine: DT, drug therapy
ciprofloxacin: AE, adverse drug reaction
ciprofloxacin: CT, clinical trial
ciprofloxacin: DT, drug therapy
ciprofloxacin: PE, pharmacoeconomics
unclassified drug

CAS REGISTRY NO.: (melanin) 8049-97-6; (**cyclosporin**) 79217-60-0; (infliximab) 170277-31-3; (etanercept) 185243-69-0, 200013-86-1; (methotrexate) 15475-56-6, 59-05-2, 7413-34-5; (collagen) 9007-34-5; (salazosulfapyridine) 599-79-1; (ciprofloxacin) 85721-33-1

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ACCESSION NUMBER: 2001289213 EMBASE Full-text
TITLE: Corneal neovascularization.
AUTHOR: **Chang J.-H.**; Gabison E.E.; Kato T.; Azar D.T.
CORPORATE SOURCE: Dr. D.T. Azar, Massachusetts Eye and Ear Infirmary, 243 Charles Street, Boston, MA 02114, United States. dazar@meei.harvard.edu
SOURCE: Current Opinion in Ophthalmology, (2001) Vol. 12, No. 4, pp. 242-249. .
Refs: 102
ISSN: 1040-8738 CODEN: COOTEF
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 012 Ophthalmology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 30 Aug 2001
Last Updated on STN: 30 Aug 2001

ABSTRACT: Corneal neovascularization (NV) is a sight-threatening condition usually associated with inflammatory or infectious disorders of the ocular surface. It has been shown in the field of cancer angiogenesis research that a balance exists between angiogenic factors (such as fibroblast growth factor and vascular endothelial growth factor) and anti-angiogenic molecules (such as angiostatin, endostatin, or pigment epithelium derived factor) in the cornea. Several inflammatory, infectious, degenerative, and traumatic disorders are associated with corneal NV, in which the balance is tilted towards angiogenesis. The pathogenesis of corneal NV may be influenced by matrix metalloproteinases and other proteolytic enzymes. New medical and surgical treatments, including angiostatic steroids, nonsteroidal inflammatory agents, argon laser photocoagulation, and photodynamic therapy have been effective in animal models to inhibit corneal NV and transiently restore corneal "angiogenic privilege." .COPYRGT. 2001 Lippincott Williams & Wilkins, Inc.

CONTROLLED TERM: Medical Descriptors:
***cornea neovascularization: DT, drug therapy**
***cornea neovascularization: ET, etiology**
***cornea neovascularization: SU, surgery**
visual impairment
eye inflammation
eye infection
disease association
eye injury
degeneration
pathogenesis
protein degradation
argon plasma coagulation

photodynamic therapy
transplantation
human
nonhuman
animal experiment
animal model
review
priority journal
Drug Descriptors:
angiogenic factor
fibroblast growth factor
vasculotropin
angiogenesis inhibitor
angiostatin
endostatin
pigment epithelium derived factor
matrix metalloproteinase
proteinase
steroid: DT, drug therapy
nonsteroid antiinflammatory agent: DT, drug therapy
calcitriol: DT, drug therapy
thrombocyte activating factor antagonist: DT, drug therapy
cyclosporin A: DT, drug therapy
tsukubaenolide: DT, drug therapy
thalidomide: DT, drug therapy
prolactin: DT, drug therapy
curcumin: DT, drug therapy
protein farnesyltransferase inhibitor: DT, drug therapy
methotrexate: DT, drug therapy
indometacin: DT, drug therapy
prostaglandin synthase inhibitor: DT, drug therapy

CAS REGISTRY NO.: (fibroblast growth factor) 62031-54-3; (vasculotropin) 127464-60-2; (angiostatin) 172642-30-7, 86090-08-6; (endostatin) 187888-07-9; (pigment epithelium derived factor) 197980-93-1; (proteinase) 9001-92-7; (calcitriol) 32222-06-3, 32511-63-0, 66772-14-3; (**cyclosporin A**) **59865-13-3**, 63798-73-2; (tsukubaenolide) 104987-11-3; (thalidomide) 50-35-1; (prolactin) 12585-34-1, 50647-00-2, 9002-62-4; (curcumin) 458-37-7; (methotrexate) 15475-56-6, 59-05-2, 7413-34-5; (indometacin) 53-86-1, 74252-25-8, 7681-54-1

L72 ANSWER 14 OF 19 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN DUPLICATE 1
ACCESSION NUMBER: 2005-232171 [24] WPIX
DOC. NO. CPI: C2005-073704
TITLE: Use of emulsions containing water, hydrophobic component, and reduced concentration of **cyclosporin** component for treating ophthalmic conditions e.g. dry eye syndrome.
DERWENT CLASS: B03 B04
INVENTOR(S): **ACHEAMPONG, A; CHANG, J N; POWER, D F; TANG-LIU, D**
PATENT ASSIGNEE(S): (ALLR) ALLERGAN INC
COUNTRY COUNT: 108
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC

US 2005059583 A1 20050317 (200524)* 10 A61K038-13
WO 2005032577 A1 20050414 (200526) EN A61K038-13
RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE
LS LU MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE
DK DM DZ EC EE EG 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 MZ NA NI NO NZ
OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG
US UZ VC VN YU ZA ZM ZW

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 2005059583	A1 Provisional	US 2003-503137P	20030915
		US 2004-927857	20040827
WO 2005032577	A1	WO 2004-US29067	20040907

PRIORITY APPLN. INFO: US 2003-503137P 20030915; US 2004-927857 20040827
INT. PATENT CLASSIF.:
MAIN: A61K038-13
SECONDARY: A61K047-44; A61P027-02
BASIC ABSTRACT:

US2005059583 A UPAB: 20050414

NOVELTY - Treatment of ophthalmic conditions involves administration of a composition in the form of an emulsion comprising water, a **cyclosporin** component (less than 0.1 weight%) and a hydrophobic component. A weight ratio of the **cyclosporin** component to the hydrophobic component is less than 0.08.

ACTIVITY - Ophthalmological; Immunosuppressive; Antiinflammatory. Test details are described but no results are given.

MECHANISM OF ACTION - None given.

USE - For treating ophthalmic conditions including dry eye syndrome, phacoanaphylactic endophthalmitis, uveitis, vernal conjunctivitis, atopic keratoconjunctivitis, and corneal graft rejection (claimed).

ADVANTAGE - The method improves therapeutic efficacy of **cyclosporin**; reduces risks of side effects and/or drug interactions by reducing the drug concentration such that the blood of the human or animal has at most 0.1 ng/ml or no detectable concentration of the **cyclosporin** component; enhances patient safety; and provides increased flexibility to physicians for prescribing such an easily administrable composition. The emulsion is thermodynamically stable and exhibits a shelf life of greater than a year at room temperature. The relatively high concentration of hydrophobic component provides for a more rapid breaking down or resolving of the emulsion in the eye, which reduces vision distortion caused by the presence of the emulsion in the eye. Dwg.0/0

FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; DCN
MANUAL CODES: CPI: B02-C; B04-A10; B04-B01C1; B12-M03; B14-G02C; B14-N03
TECH UPTX: 20050414

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Composition: The composition comprises greater than 0.625 wt.% of the hydrophobic component, and additionally an emulsifier component, tonicity (preferably organic tonicity) component, and a polyelectrolyte component for stabilizing the composition. The composition has a pH of 7 - 8 (preferably 7.2 - 7.6).

Preferred Components: The **cyclosporin** component is **cyclosporin** A and/or its derivatives; and is solubilized in the

hydrophobic component. The hydrophobic component is an oily material selected from vegetable oil, animal oil, mineral oil and/or synthetic oil (preferably castor oil).
Preferred Method: The blood of the human or animal has substantially no detectable concentration of the **cyclosporin** component as measured using a validated liquid chromatography/mass spectrometry-mass spectrometry analytical method. The blood of the human or animal has a concentration of the **cyclosporin** component of at most 0.1 ng/ml.

L72 ANSWER 15 OF 19 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2006-253421 [26] WPIX
DOC. NO. CPI: C2006-082531
TITLE: Biodegradable lacrimal canalicular insert for treating ophthalmic conditions e.g. dry eye comprises biodegradable polymer and therapeutic component in member structured to be placed in lacrimal canaliculus.
DERWENT CLASS: A96 B05 B07 D22
INVENTOR(S): CHANG, C; **CHANG**, J; JORDAN, R S; SCHIFFMAN, R
PATENT ASSIGNEE(S): (ALLR) ALLERGAN INC
COUNTRY COUNT: 111
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
WO 2006031658	A2	20060323	(200626)*	EN	27	A61K009-00

RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IS IT KE LS LT LU LV MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KM KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NG NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SM SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2006031658	A2	WO 2005-US32222	20050907

PRIORITY APPLN. INFO: US 2004-608628P 20040910
INT. PATENT CLASSIF.:
MAIN: A61K009-00
BASIC ABSTRACT:
WO2006031658 A UPAB: 20060421
NOVELTY - A biodegradable lacrimal canalicular insert (D1) comprises a biodegradable polymer component (P1) and a therapeutic component (P2) in a member structured to be placed in a lacrimal canaliculus of an individual and to release (P2) to provide a benefit to the individual.
DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for producing (D1) involving: forming at least one (P1) and at least one (P2) into a member structured to be placed in a lacrimal canaliculus of an individual.
ACTIVITY - Ophthalmological; Antiinflammatory; Antidiabetic; Vasotropic; Antitubercular; Tuberculostatic; Vulnerary; Cytostatic; Antibacterial; Osteopathic.
MECHANISM OF ACTION - None given.
USE - As biodegradable lacrimal canalicular insert placed into a lacrimal canaliculus of an individual e.g. human or animal to treat conditions of at least one of eye, a nasolacrimal system, and a nose of the human or animal; in

the treatment of ophthalmic conditions (claimed) such as dry eye and ocular conditions such as anterior segment disease, anterior uveitis, conjunctivitis, glaucoma, keratitis, scleritis, maculopathies, retinal degeneration, age related macular degeneration, diabetic retinopathy, ocular sarcoidosis, Vogt-Koyanagi-Harada syndrome, cystoid macular edema, uveitis, Behcet's disease, infections (Syphilis, Lyme, tuberculosis, and toxoplasmosis), subretinal fibrosis, carotid artery disease (CAD), vascular diseases, exudative diseases, trauma, proliferative diabetic retinopathy, bone marrow transplantation retinopathy, viral retinitis, ocular tuberculosis, retinal tears, intraocular lymphoid tumors, mylasis, genetic disorders such as retinitis pigmentosa, Eales disease, parafoveal telangiectasia, and acute retinal pigment epithelitis.

ADVANTAGE - The inserts effectively provide extended or sustained release of therapeutic agents on or into the eye and/or nasolacrimal system of an individual and provide therapeutic effect to the eye which is effective in stabilizing, enhancing or improving the patient's vision. The inserts are relatively easy to manufacture compared to previously described punctual plugs; address patient compliance concerns of administering therapeutic agents to an eye and provide enhancements in the amount of therapeutic agent that may be provided in the drug delivery systems. The insert effectively resolves compliance issues; is easy to administer to the patient; and easy to manufacture. The polymers are biologically inert and non-allergenic; degrade or erode for extended periods of time thus providing sustained drug release from the insert. The insert provides extended release of the therapeutic agent (preferably for more than 1 month, especially for more than 6 months). Dwg.0/5

FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; DCN
MANUAL CODES: CPI: A09-A07; A12-V02A; B01-B02; B03-A; B04-C01C; B04-C01E; B04-C01H; B04-C03D; B04-H03; B04-N03G; B06-A03; B06-D06; B07-E03; B07-F03; B09-D01; B11-C04A; B12-M12H; B14-A01A; B14-A01B1A; B14-A03C; B14-F02; B14-H01L; B14-N03; B14-N05; B14-N07C; B14-N17B; D09-C01

TECH UPTX: 20060421

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Components: (P2) is a steroidal or non-steroidal antiinflammatory agent, retinoid, prostaglandin, tyrosine kinase inhibitor, adrenoreceptor (ant)agonist, dopaminergic agonist, cholinergic agonist, carbonic anhydrase inhibitor, guanylate cyclase activator, cannabinoid, endothelin, adenosine agonist, anti-angiogenic compound, angiostatic compound, neuroprotectant, analgesic, antipyretic, antihistamine, antibiotic, beta blocker, anti-neoplastic agent, immunosuppressive agent, antiviral agent and/or antioxidant (preferably non-steroidal antiinflammatory agent). (P2) is: a combination of brimonidine or its salts and timolol or its salts; at least one of bimatoprost, latanoprost, travoprost, unoprostone isopropyl or their salts; or at least one of **cyclosporin** and prednisolone acetate, memantine, triamcinolone or their salts (preferably triamcinolone acetate). Preferred Member: The member comprises a head portion structure to be placed in proximity to a punctum, and a body portion structured to be placed in a lacrimal canaliculus. The body portion comprises a distal end and a neck located between the distal end and the head portion, where the distal end has a greater diameter relative to the diameter of the neck. When the member has a peripheral surface, (D1) further comprises a coating located on the peripheral surface except for portions of the peripheral surface, which contact an eye of the individual, where the coating is impermeable to the therapeutic component. The member comprises a distal end structured to be placed in a lacrimal canaliculus, and an aperture in the coating provided at the distal end of the member. Preferred Insert: (D1) In the form of an extrusion-molded member comprises a blend of at least one (P1) and at least one (P2).

TECHNOLOGY FOCUS - POLYMERS - Preferred Components: (P1) Comprises at least one biodegradable copolymer or at least one polymer selected from poly lactic acid, poly glycolic acid and their copolymer and derivatives.

L72 ANSWER 16 OF 19 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2006-612328 [63] WPIX
CROSS REFERENCE: 2006-352698 [36]
DOC. NO. CPI: C2006-189048
TITLE: Use of **cyclosporine** component for the treatment of a human or animal having a condition e.g. systemic lupus erythematosis, rheumatoid arthritis, and multiple sclerosis, maloplakia of the skin.
DERWENT CLASS: B04
INVENTOR(S): **POWER**, D; STERN, M E
PATENT ASSIGNEE(S): (ALLR) ALLERGAN INC
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
US 2006199760	A1	20060907	(200663)*		8	A61K038-12

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 2006199760	A1 Div ex	US 2004-990054	20041115
		US 2006-429050	20060505

PRIORITY APPLN. INFO: US 2004-990054 20041115; US 2006-429050 20060505
INT. PATENT CLASSIF.:
MAIN: A61K038-12; A61K038-13
BASIC ABSTRACT:
US2006199760 A UPAB: 20061002
NOVELTY - Treating a human or animal suffering from systemic lupus erythematosus, rheumatoid arthritis, and multiple sclerosis, comprising topically administering a **cyclosporine** component to the subject, is new.
ACTIVITY - Dermatological; Antiinflammatory; Immunosuppressive; Antirheumatic; Antiarthritic; Neuroprotective; Keratolytic; Antipruritic; Antiulcer; Gastrointestinal-Gen.
A male patient (age 51) suffering from ulcerative colitis was treated with a composition containing **cyclosporin** A (0.3 weight%) in a conventional carrier. The composition, in the form of a rectal suppository, was administered once daily for two weeks. After such administration, the patient reports that at least one symptom e.g. pain, associated with the ulcerative colitis was reduced in severity.
MECHANISM OF ACTION - None given.
USE - The method is used for the treatment of a human or animal having a condition e.g. systemic lupus erythematosus, rheumatoid arthritis, and multiple sclerosis, maloplakia of the skin, oral frictional hyperkeratosis, oral manifestations of autoimmune blistering disease, oral lichen planus, aphthous ulcers, nasal polyps, rhinosporiodosis, sinusitis, iritis, carcinoid lung, laryngitis and atrophic gastritis (all claimed), dry mouth syndrome, verruciform xanthoma, achlorhydria, mucous cysts, oral submucous fibrosis, oral nevi, cancer of the oral mucosa, maloplakia of the genito-urinary tract, vulvovaginitis, helicobacter plylori infection, duodenal ulcers, peptic

ulcers, conditions affecting the uterus and appendicitis, inflammatory bowel disease.

ADVANTAGE - The **cyclosporine** component provide substantial overall efficacy in providing the desired therapeutic effect or effects; can be easily and effectively practiced by the prescribing physician and patient without causing substantial or undue patient stress; ease of practice and reduced patient stress. Dwg.0/0

FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; GI; DCN
MANUAL CODES: CPI: B04-C01C; B04-C01H; B12-M12B; B14-A02B3; B14-C09B; B14-E10B; B14-G02D; B14-H01; B14-N04; B14-N05; B14-N17; B14-S01; B14-S16

TECH UPTX: 20061002

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Components: The **cyclosporine** component is selected from **cyclosporines** and/or **cyclosporine** derivatives, or their salts and mixtures, especially derivatives of **cyclosporin** A, its salt and mixtures.

L72 ANSWER 17 OF 19 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2006-352699 [36] WPIX
DOC. NO. CPI: C2006-115197
TITLE: Use of **cyclosporin** A component to treat mucin deficiency of mucosal tissue (being located in oral cavity) or dysfunctional mucosal tissue of a human or animal.
DERWENT CLASS: B04
INVENTOR(S): **POWER**, D; STERN, M E
PATENT ASSIGNEE(S): (ALLR) ALLERGAN INC
COUNTRY COUNT: 113
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
US 2006105945	A1	20060518	(200636)*		9	A61K038-12
WO 2006055418	A1	20060526	(200636)	EN		A61K038-12

RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IS IT KE LS LT LU LV MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KM KN KP KR KZ LC LK LR LS LT LU LV LY MA MD MG MK MN MW MX MZ NA NG NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SM SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 2006105945	A1	US 2004-990055	20041115
WO 2006055418	A1	WO 2005-US40928	20051111

PRIORITY APPLN. INFO: US 2004-990055 20041115
INT. PATENT CLASSIF.:
MAIN: A61K038-12; A61K038-13
SECONDARY: A61P001-00; A61P001-02; A61P001-04; A61P015-00; A61P015-02; A61P017-00; A61P035-00

BASIC ABSTRACT:
US2006105945 A UPAB: 20060607

NOVELTY - Treating a mucin deficiency of mucosal tissue and dysfunctional mucosal tissue, comprises topically administering a **cyclosporin** A component (I) to mucosal tissue of a human or animal having a mucin deficiency, the mucosal tissue, being located in an oral cavity of the human or animal.

ACTIVITY - Antiulcer; Antiinflammatory; Cytostatic; Gynecological; Uropathic; Gastrointestinal-Gen.; Dermatological; Antimicrobial.

MECHANISM OF ACTION - None given.

USE - (I) is useful to treat: a mucin deficiency, dysfunctional mucosal tissue (results in a condition of oral submucous fibrosis, oral nevi and cancers of the oral mucosa) of mucosal tissue, located in an oral cavity of a human or animal; and a dry mouth syndrome (claimed). (I) is useful to treat: appendicitis, genito-urinary tract and gastrointestinal tract conditions, verruciform xanthoma, achlorhydria, mucous cysts, maloplakia of the genito-urinary tract, helicobacter plylori infection, duodenal ulcers and peptic ulcers of a human or animal.

ADVANTAGE - (I) is effective in the treatment of mucin deficiency, dysfunctional mucosal tissue and dry mouth syndrome (claimed). (I) provides the treatment without causing substantial or undue patient stress.

Dwg.0/0

FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; DCN
MANUAL CODES: CPI: B02-C01; B04-C01H; B12-M12N; B14-A01A; B14-E08; B14-E10; B14-H01K1; B14-N05; B14-N07
TECH UPTX: 20060607

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Components: (I) is **cyclosporin** A, derivatives of **cyclosporin** A and/or their salts. (I) comprises **cyclosporin** A. The oral rinse includes 0.03-15 (preferably 0.1-5) wt.% of (I). The emulsion includes 0.03-15 (preferably 0.1-5) wt.% of (I).

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Method: The human or animal has dry mouth syndrome resulting at least in part from the mucin deficiency and immune inflammation salivary gland secretion variation, the administering is effective in treating the dry mouth syndrome. (I) is administered in an oral rinse or in an emulsion.

L72 ANSWER 18 OF 19 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2006-352698 [36] WPIX
CROSS REFERENCE: 2006-612328 [63]
DOC. NO. CPI: C2006-115196
TITLE: Treating an inflammatory bowel disease comprises topically administering a **cyclosporin** A component (e.g. **cyclosporin** A) in a rectal suppository.
DERWENT CLASS: B04
INVENTOR(S): **POWER**, D; STERN, M E
PATENT ASSIGNEE(S): (ALLR) ALLERGAN INC
COUNTRY COUNT: 113
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
US 2006105944	A1	20060518	(200636)*		8	A61K038-12
WO 2006055417	A2	20060526	(200636)	EN		A61K038-12

RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IS IT KE LS LT LU LV MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KM KN KP KR KZ LC LK LR LS LT LU LV LY MA MD MG MK MN MW MX MZ NA

NG NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SM SY TJ TM TN
TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 2006105944	A1	US 2004-990054	20041115
WO 2006055417	A2	WO 2005-US40926	20051111

PRIORITY APPLN. INFO: US 2004-990054 20041115
INT. PATENT CLASSIF.:
MAIN: A61K038-12; A61K038-13
BASIC ABSTRACT:
US2006105944 A UPAB: 20061002
NOVELTY - Treating an inflammatory bowel disease in a human or animal comprising topically administering a **cyclosporin** A component (I) (**cyclosporin** A and/or its salts) in a rectal suppository to a human or animal, is new.
ACTIVITY - Antiinflammatory; Gastrointestinal-Gen.; Antiulcer; Dermatological; Immunosuppressive; Antiarthritic; Antirheumatic; Neuroprotective; Keratolytic; Antipruritic; Cytostatic.
No biological data is given.
MECHANISM OF ACTION - None given.
USE - (I) is useful for the treatment of an inflammatory bowel disease (ulcerative colitis) (claimed). (I) is useful for the treatment of systemic lupus erythematosis, rheumatoid arthritis, multiple sclerosis, maloplakia of the skin, oral frictional hyperkeratosis, oral manifestations of autoimmune blistering disease, oral lichen planus, aphthous ulcers, nasal polyps, rhinosporiodosis, sinusitis, iritis, carcinoid lung, laryngitis and atrophic gastritis. (I) was tested for its ability to treat systemic lupus erythematosis in a patient. The results showed that (I) reduced the severity of the systemic lupus erythematosis.
ADVANTAGE - The method can be easily and effectively practiced by the prescribing physician and patient without causing substantial or undue patient stress. The method is effective to treat an inflammatory bowel disease.
Dwg.0/0
FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; DCN
MANUAL CODES: CPI: B04-C01B; B04-C01H; B12-M08; B12-M12P; B14-C09B; B14-E08; B14-E10B; B14-E10C1; B14-G02D; B14-H01K3; B14-N04; B14-N05A; B14-N17; B14-S01
TECH UPTX: 20060607
TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Method: The administering step comprises topically administering (I) at or near a tissue area of the human or animal affected by the inflammatory bowel disease (preferably ulcerative colitis). Treating comprises reducing the severity of at least one symptom of the inflammatory bowel disease (preferably ulcerative colitis).

L72 ANSWER 19 OF 19 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2006-054193 [06] WPIX
DOC. NO. CPI: C2006-020316
TITLE: Liquid, useful to treat dry eye disease, comprises a therapeutically effective concentration of a **cyclosporin** and a vitamin E tocopherol polyethylene glycol succinate.
DERWENT CLASS: A96 B05
INVENTOR(S): **CHANG, J N**; GRAHAM, R; TIEN, W L
PATENT ASSIGNEE(S): (ALLR) ALLERGAN INC

COUNTRY COUNT: 111
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
US 2005277584	A1	20051215	(200606)*		5	A61K038-13
WO 2006001963	A1	20060105	(200606)	EN		A61K009-08

RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IS IT KE LS LT LU MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KM KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NG NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SM SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 2005277584	A1	US 2004-865638	20040609
WO 2006001963	A1	WO 2005-US18025	20050519

PRIORITY APPLN. INFO: US 2004-865638 20040609
INT. PATENT CLASSIF.:
MAIN: A61K009-08; A61K038-13
SECONDARY: A61K031-355; A61K047-22; A61P027-04
BASIC ABSTRACT:

US2005277584 A UPAB: 20060124

NOVELTY - Liquid (I) comprises a therapeutically effective concentration of a **cyclosporin** and a vitamin E tocopherol polyethylene glycol succinate (A) (where (I) is in aqueous solution and no hydrophilic organic solvent is present at a mass concentration greater than half of that of the **cyclosporin**).

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for a composition (A1) comprising therapeutically effective concentration of a **cyclosporin** A and (A) (where (A1) is in aqueous liquid solution which is intended for ophthalmic use and no hydrophilic organic solvent is present at a mass concentration greater than or equal to that of **cyclosporin** A).

USE - (I) is useful to treat dry eye disease (claimed). (I) is also useful to treat or prevent other conditions or diseases related to immune response, inflammatory response, parasitic and other infection.

ADVANTAGE - (I) has improved bioavilability. Dwg.0/0

FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; DCN
MANUAL CODES: CPI: A10-E07; A12-V01; B02-C01; B12-M07; B14-A01; B14-A02; B14-B02; B14-C03; B14-G01; B14-N03
TECH UPTX: 20060124

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Components: (I) contains essentially no hydrophilic organic solvent. The vitamin E tocopherol polyethylene glycol succinate is present at a concentration which is at least 8 times that of the **cyclosporin** and the vitamin E tocopherol polyethylene glycol succinate is present at a concentration which is no more than 15 times that of the **cyclosporin**. At least 10 mg of the vitamin E tocopherol polyethylene glycol succinate is present for every mg of the **cyclosporin** present in the solution. The vitamin E tocopherol polyethylene glycol succinate and the **cyclosporin** have a concentration ratio of about 10-1. The vitamin E tocopherol polyethylene glycol succinate is present at a concentration that is no less than 0.5% and the vitamin E tocopherol polyethylene glycol

succinate is present at a concentration that is no greater than 5%. (I) comprises about 0.1% **cyclosporin** A and 1% vitamin E tocopherol polyethylene glycol succinate. (I) comprises **cyclosporin** A which is present at a concentration of at least 0.01% and not greater than 0.2%. (I) is consisting essentially of a therapeutically effective concentration of **cyclosporin** A, an effective amount of a vitamin E tocopherol polyethylene glycol succinate, water and one or more combination of excipients such as buffers, thickening agents, tonicity agents, preservatives or chelating agents. The **cyclosporin** A is present at concentration at or below 1 (preferably less than or equal to 0.15)%. (A1) comprises about 0.05 (preferably 1)% of **cyclosporin** A and vitamin E tocopherol polyethylene glycol succinate.

```
=> => FILE BIOSIS
FILE 'BIOSIS' ENTERED AT 16:36:17 ON 02 OCT 2006
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FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT
FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 27 September 2006 (20060927/ED)


=> D QUE L81
L73 (         1)SEA FILE=REGISTRY ABB=ON  PLU=ON  CYCLOSPORIN A/CN
L74 (    213487)SEA FILE=BIOSIS ABB=ON  PLU=ON  EYE OR  ASTHENOPIA OR CONJUNCTI
                VAL DISEASES OR CORNEAL DISEASES OR EYELID DISEASES OR
                LACRIMAL APPARATUS DISEASES  OR LENS DISEASES OR OCULAR
                HYPERTENSION
L75 (      7948)SEA FILE=BIOSIS ABB=ON  PLU=ON  OCULAR HYPOTENSION  OR OCULAR
                MOTILITY DISORDERS OR OPTIC NERVE DISEASES OR ORBITAL DISEASES
                OR PUPIL DISORDERS  OR REFRACTIVE ERRORS OR RETINAL DISEASES
                OR  SCLERAL DISEASES OR UVEAL DISEASES OR VISION DISORDERS OR
                VITREORETINOPATHY OR VITREOUS DETACHMENT
L76 (    124285)SEA FILE=BIOSIS ABB=ON  PLU=ON  OIL
L77 (     23151)SEA FILE=BIOSIS ABB=ON  PLU=ON  EMULSI?
L78             SEL  PLU=ON  L73 1- CHEM :      38 TERMS
L79 (     46884)SEA FILE=BIOSIS ABB=ON  PLU=ON  L78
L80 (         8)SEA FILE=BIOSIS ABB=ON  PLU=ON  ((L74 OR L75)) AND L76 AND L77
                AND L79
L81           8 SEA FILE=BIOSIS ABB=ON  PLU=ON  L80 NOT PY>2004


=> S L81 NOT L14
L134          8 L81 NOT L14

=> FILE EMBASE
FILE 'EMBASE' ENTERED AT 16:36:48 ON 02 OCT 2006
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 EMBASE has been reloaded. Enter HELP RLOAD for details.

 EMBASE is now updated daily.  SDI frequency remains weekly (default)
 and biweekly.

 This file contains CAS Registry Numbers for easy and accurate
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=> D QUE L94
L82 (         1)SEA FILE=REGISTRY ABB=ON  PLU=ON  CYCLOSPORIN A/CN
L83             SEL  PLU=ON  L82 1- CHEM :      38 TERMS
L84 (     74476)SEA FILE=EMBASE ABB=ON  PLU=ON  L83
L85 (    301867)SEA FILE=EMBASE ABB=ON  PLU=ON  EYE DISEASE+NT/CT
L86 (      5657)SEA FILE=EMBASE ABB=ON  PLU=ON  OIL/CT
L87 (     46238)SEA FILE=EMBASE ABB=ON  PLU=ON  D3.60.650./CT
L88 (    225955)SEA FILE=EMBASE ABB=ON  PLU=ON  L85/MAJ
L89 (        22)SEA FILE=EMBASE ABB=ON  PLU=ON  L88 AND L84 AND ((L86 OR L87))
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L90 (        17)SEA FILE=EMBASE ABB=ON  PLU=ON  L89 NOT PY>2004
L91 (       416)SEA FILE=EMBASE ABB=ON  PLU=ON  L84(L)TP/CT
L92 (        12)SEA FILE=EMBASE ABB=ON  PLU=ON  L91 AND L85 AND ((L86 OR L87))

L93 (         9)SEA FILE=EMBASE ABB=ON  PLU=ON  L92 NOT PY>2004
L94          21 SEA FILE=EMBASE ABB=ON  PLU=ON  L90 OR L93


=> S L94 NOT L30
L135         21 L94 NOT L30

=> FILE HCAPLUS
FILE 'HCAPLUS' ENTERED AT 16:37:21 ON 02 OCT 2006
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FILE COVERS 1907 - 2 Oct 2006  VOL 145 ISS 15
FILE LAST UPDATED: 1 Oct 2006  (20061001/ED)

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'OBI' IS DEFAULT SEARCH FIELD FOR 'HCAPLUS' FILE

=> D QUE L111
L95 (         1)SEA FILE=REGISTRY ABB=ON  PLU=ON  CYCLOSPORIN A/CN
L96 (     36733)SEA FILE=HCAPLUS ABB=ON  PLU=ON  EYE, DISEASE+OLD,NT/CT
L97 (     24550)SEA FILE=HCAPLUS ABB=ON  PLU=ON  EMULSIFYING AGENTS/CT
L98 (    388102)SEA FILE=HCAPLUS ABB=ON  PLU=ON  OILS+OLD,NT/CT
L99             SEL  PLU=ON  L95 1- CHEM :       38 TERMS
L100(     23233)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L99
L101(         2)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L100 AND L96 AND L97 AND L98
L102(         4)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L96 AND L100 AND L97
L103(        17)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L96 AND L100 AND L98
L104(     28869)SEA FILE=HCAPLUS ABB=ON  PLU=ON  EMULSIONS/CT
L105(         1)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L96 AND L100 AND L104 AND L98

L106(         2)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L96 AND L100 AND L104
L107(        20)SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L101 OR L102 OR L103 OR L105
                OR L106)
L108(        19)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L107 AND PATENT/DT
L109(         1)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L107 NOT L108
L110(        19)SEA FILE=HCAPLUS ABB=ON  PLU=ON  ((L108 OR L109)) NOT (PRY>2004
                 OR PR>2004)
L111         18 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L110 NOT LIPOSOMAL COCHLEATE/T
                I
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=> S L111 NOT L44
L136        17 L111 NOT L44

=> FILE MEDLINE
FILE 'MEDLINE' ENTERED AT 16:37:49 ON 02 OCT 2006

 FILE LAST UPDATED: 30 Sep 2006 (20060930/UP).  FILE COVERS 1950 TO DATE.

 On December 11, 2005, the 2006 MeSH terms were loaded.

 The MEDLINE reload for 2006 is now (26 Feb.) available.  For details
 on the 2006 reload, enter HELP RLOAD at an arrow prompt (=>).
 See also:

    http://www.nlm.nih.gov/mesh/
    http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html
    http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_med_data_changes.html
    http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_2006_MeSH.html

 OLDMEDLINE is covered back to 1950.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2006 vocabulary.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> D QUE L122
L112(         1)SEA FILE=REGISTRY ABB=ON  PLU=ON  CYCLOSPORIN A/CN
L113(      9221)SEA FILE=MEDLINE ABB=ON  PLU=ON  EMULSIONS+NT/CT
L114(       124)SEA FILE=MEDLINE ABB=ON  PLU=ON  EMULSIFYING AGENTS/CT
L115(     34652)SEA FILE=MEDLINE ABB=ON  PLU=ON  OILS+NT/CT
L116            SEL  PLU=ON  L112 1- CHEM :      38 TERMS
L117(     39885)SEA FILE=MEDLINE ABB=ON  PLU=ON  L116
L118(    320609)SEA FILE=MEDLINE ABB=ON  PLU=ON  EYE DISEASES+NT/CT
L119(         1)SEA FILE=MEDLINE ABB=ON  PLU=ON  L118 AND L117 AND ((L113 OR
                 L114)) AND L115
L120(        19)SEA FILE=MEDLINE ABB=ON  PLU=ON  L118 AND L117 AND ((L113 OR
                 L114))
L121(         4)SEA FILE=MEDLINE ABB=ON  PLU=ON  L118 AND L117 AND L115
L122         16 SEA FILE=MEDLINE ABB=ON  PLU=ON  ((L119 OR L120 OR L121)) NOT
                 PY>2004


=> S L122 NOT L62
L137        14 L122 NOT L62

=> FILE WPIX
FILE 'WPIX' ENTERED AT 16:38:39 ON 02 OCT 2006
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FILE LAST UPDATED:          2 OCT 2006      <20061002/UP>
MOST RECENT DERWENT UPDATE:     200663        <200663/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

>>> FOR A COPY OF THE DERWENT WORLD PATENTS INDEX STN USER GUIDE,
    PLEASE VISIT:
 http://www.stn-international.de/training_center/patents/stn_guide.pdf <
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>>> FOR DETAILS OF THE PATENTS COVERED IN CURRENT UPDATES, SEE
http://scientific.thomson.com/support/patents/coverage/latestupdates/

>>> PLEASE BE AWARE OF THE NEW IPC REFORM IN 2006, SEE
http://www.stn-international.de/stndatabases/details/ipc_reform.html and
http://scientific.thomson.com/media/scpdf/ipcrdwpi.pdf <<<

>>> FOR FURTHER DETAILS ON THE FORTHCOMING DERWENT WORLD PATENTS
    INDEX ENHANCEMENTS PLEASE VISIT:
http://www.stn-international.de/stndatabases/details/dwpi_r.html <<<
'BI,ABEX' IS DEFAULT SEARCH FIELD FOR 'WPIX' FILE

=> D QUE L133
L123(         1)SEA FILE=REGISTRY ABB=ON  PLU=ON  CYCLOSPORIN A/CN
L124(     73228)SEA FILE=WPIX ABB=ON  PLU=ON  EYE/BI,ABEX OR  ASTHENOPIA/BI,ABE
                X OR CONJUNCTIVAL DISEASES/BI,ABEX OR CORNEAL DISEASES/BI,ABEX
                OR EYELID DISEASES/BI,ABEX OR LACRIMAL APPARATUS DISEASES/BI,AB
                EX  OR LENS DISEASES/BI,ABEX OR OCULAR HYPERTENSION/BI,ABEX
L125(       650)SEA FILE=WPIX ABB=ON  PLU=ON  OCULAR HYPOTENSION/BI,ABEX  OR
                OCULAR MOTILITY DISORDERS/BI,ABEX OR OPTIC NERVE DISEASES/BI,AB
                EX OR ORBITAL DISEASES/BI,ABEX OR PUPIL DISORDERS/BI,ABEX  OR
                REFRACTIVE ERRORS/BI,ABEX OR RETINAL DISEASES/BI,ABEX OR
                SCLERAL DISEASES/BI,ABEX OR UVEAL DISEASES/BI,ABEX OR VISION
                DISORDERS/BI,ABEX OR VITREORETINOPATHY/BI,ABEX OR VITREOUS
                DETACHMENT/BI,ABEX
L126(    444197)SEA FILE=WPIX ABB=ON  PLU=ON  OIL/BI,ABEX
L127(    169370)SEA FILE=WPIX ABB=ON  PLU=ON  EMULSI?/BI,ABEX OR (A10-B03 OR
                B12-M03 OR C12-M03 OR A12-B01A)/MC
L128(       598)SEA FILE=WPIX ABB=ON  PLU=ON  (K04-E01 OR H06-B09 OR G06-F01B)/
                MC
L129            SEL  PLU=ON  L123 1- CHEM :      38 TERMS
L130(      2231)SEA FILE=WPIX ABB=ON  PLU=ON  L129
L131(       959)SEA FILE=WPIX ABB=ON  PLU=ON  RA0135/DCN OR 90981-1-0-0/DCRE
L132(        20)SEA FILE=WPIX ABB=ON  PLU=ON  ((L130 OR L131)) AND ((L124 OR
                L125)) AND L126 AND ((L127 OR L128))
L133         17 SEA FILE=WPIX ABB=ON  PLU=ON  L132 NOT PRY>2004


=> S L133 NOT L71
L138         16 L133 NOT L71

=> DUP REM L137 L134 L135 L138 L136
FILE 'MEDLINE' ENTERED AT 16:39:41 ON 02 OCT 2006

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PROCESSING COMPLETED FOR L137
PROCESSING COMPLETED FOR L134
PROCESSING COMPLETED FOR L135
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PROCESSING COMPLETED FOR L138
PROCESSING COMPLETED FOR L136
L139 73 DUP REM L137 L134 L135 L138 L136 (3 DUPLICATES REMOVED)
ANSWERS '1-14' FROM FILE MEDLINE
ANSWERS '15-21' FROM FILE BIOSIS
ANSWERS '22-41' FROM FILE EMBASE
ANSWERS '42-57' FROM FILE WPIX
ANSWERS '58-73' FROM FILE HCAPLUS

=> D IALL 1-14; D IALL 15-21; D IALL 22-41; D IALL ABEQ TECH 42-57; D IBIB ED ABS 58-73

L139 ANSWER 1 OF 73 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2000269229 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 10811092
TITLE: Efficacy and safety of **cyclosporin A** ophthalmic emulsion in the treatment of moderate-to-severe dry eye disease: a dose-ranging, randomized trial. The **Cyclosporin A** Phase 2 Study Group.
AUTHOR: Stevenson D; Tauber J; Reis B L
CORPORATE SOURCE: Mercy Hospital, New Orleans, Louisiana, USA.
SOURCE: Ophthalmology, (2000 May) Vol. 107, No. 5, pp. 967-74. Journal code: 7802443. ISSN: 0161-6420.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL) Journal; Article; (JOURNAL ARTICLE) (MULTICENTER STUDY) (RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200005
ENTRY DATE: Entered STN: 25 May 2000
Last Updated on STN: 25 May 2000
Entered Medline: 18 May 2000

ABSTRACT:
OBJECTIVE: To investigate the efficacy, safety, formulation tolerability, and optimal dosing of a novel **cyclosporin A** oil-in-water emulsion formulation for the treatment of moderate-to-severe dry eye disease. DESIGN: Randomized, multicenter, double-masked, parallel-group, dose-response controlled trial. PARTICIPANTS: Total enrollment: 162 patients; ***cyclosporin*** **A** groups: 129 patients; vehicle group: 33 patients. INTERVENTION: Patients instilled study medication (***cyclosporin*** **A** ophthalmic emulsion 0.05%, 0.1%, 0.2%, or 0.4%, or vehicle) twice daily into both eyes for 12 weeks, followed by a 4-week posttreatment observation period. MAIN OUTCOME MEASURES: Efficacy: rose bengal staining, superficial punctate keratitis, Schirmer tear test, symptoms of ocular discomfort, and the Ocular Surface Disease Index (OSDI; a measure of symptom frequency and impact on vision-related functioning). Safety: biomicroscopy, **cyclosporin A** blood levels, conjunctival microbiology, intraocular pressure, visual acuity, and monitoring of adverse events. RESULTS: In a subset of 90 patients with moderate-to-severe keratoconjunctivitis sicca, the most significant improvements with ***cyclosporin*** **A** treatment were in rose bengal staining, superficial punctate keratitis, sandy or gritty feeling, dryness, and itching, with improvements persisting into the posttreatment period in some treatment groups. There was also a decrease in OSDI scores, indicating a decrease in the effect of ocular symptoms on patients' daily lives. There was no clear dose-response relationship, but **cyclosporin A** 0.1% produced the most consistent improvement in objective and subjective end points and ***cyclosporin*** **A** 0.05% gave the most consistent improvement in

patient symptoms. The vehicle also performed well, perhaps because of its long residence time on the ocular surface. There were no significant adverse effects, no microbial overgrowth, and no increased risk of ocular infection in any treatment group. The highest **cyclosporin A** blood concentration detected was 0.16 ng/ml. All treatments were well tolerated by patients. CONCLUSIONS: **Cyclosporin A** ophthalmic emulsions, 0.05%, 0.1%, 0.2%, and 0.4%, were safe and well tolerated, significantly improved the ocular signs and symptoms of moderate-to-severe dry eye disease, and decreased the effect of the disease on vision-related functioning. ***Cyclosporin*** **A** 0.05% and 0.1% were deemed the most appropriate formulations for future clinical studies because no additional benefits were observed with the higher concentrations.

CONTROLLED TERM: Check Tags: Female; Male
Adult
Aged
Aged, 80 and over
***Cyclosporine: AD, administration & dosage**
Cyclosporine: AE, adverse effects
Dose-Response Relationship, Drug
Double-Blind Method
***Dry Eye Syndromes: DT, drug therapy**
Dry Eye Syndromes: ME, metabolism
Dry Eye Syndromes: PP, physiopathology
Emulsions
Humans
Intraocular Pressure
Middle Aged
Ophthalmic Solutions: AD, administration & dosage
Ophthalmic Solutions: AE, adverse effects
Research Support, Non-U.S. Gov't
Safety
Tears: SE, secretion
Visual Acuity

CAS REGISTRY NO.: **59865-13-3 (Cyclosporine)**
CHEMICAL NAME: 0 (Emulsions); 0 (Ophthalmic Solutions)

L139 ANSWER 2 OF 73 MEDLINE on STN
ACCESSION NUMBER: 2004493329 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 15461545
TITLE: Topical 0.05% **cyclosporin** in the treatment of dry eye.
AUTHOR: Perry Henry D; Donnenfeld Eric D
CORPORATE SOURCE: North Shore University Hospital, Department of Ophthalmology, Long Island Jewish Medical Centre, Great Neck, New York, USA.. hankcornea@aol.com
SOURCE: Expert opinion on pharmacotherapy, (2004 Oct) Vol. 5, No. 10, pp. 2099-107. Ref: 24
Journal code: 100897346. E-ISSN: 1744-7666.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200506
ENTRY DATE: Entered STN: 6 Oct 2004
Last Updated on STN: 3 Jun 2005
Entered Medline: 2 Jun 2005

ABSTRACT:
Dry eye disease is a common and often underdiagnosed condition that affects > 10% of the adult population, > 65 years of age in the US. This condition has

been classified into two separate, but overlapping, categories--aqueous deficiency and evaporative loss. Diagnosis is confused by the lack of a single diagnostic test. Fluorescein break-up time is one of the best screening tests and is augmented by Lissamine green supravital staining. New concepts of pathogenesis have shown that dry eye disease appears to be caused by inflammation mediated by T-cell lymphocytes. This finding led to the study and FDA-approval of topical 0.05% **cyclosporin A** (***Restasis***) for the treatment of dry eye disease. 0.05% ***Cyclosporin*** **A** offers the first therapeutic treatment for patients with moderate-to-severe dry eye disease due to aqueous deficiency.

CONTROLLED TERM: Administration, Topical
*Anti-Inflammatory Agents, Non-Steroidal: AD, administration & dosage
Clinical Trials, Phase III
***Cyclosporine: AD, administration & dosage**
Dry Eye Syndromes: CL, classification
Dry Eye Syndromes: DI, diagnosis
***Dry Eye Syndromes: DT, drug therapy**
Dry Eye Syndromes: ET, etiology
Dry Eye Syndromes: IM, immunology
Emulsions
Humans
*Immunosuppressive Agents: AD, administration & dosage
Ophthalmic Solutions

CAS REGISTRY NO.: **59865-13-3 (Cyclosporine)**

CHEMICAL NAME: 0 (Anti-Inflammatory Agents, Non-Steroidal); 0 (Emulsions); 0 (Immunosuppressive Agents); 0 (Ophthalmic Solutions)

L139 ANSWER 3 OF 73 MEDLINE on STN

ACCESSION NUMBER: 2003313129 MEDLINE Full-text

DOCUMENT NUMBER: PubMed ID: 12843889

TITLE: [Flow cytometry in impression cytology during keratoconjunctivitis sicca: effects of topical **cyclosporin A** on HLA DR expression].
Cytofluorimetrie sur empreintes conjonctivales au cours de la keratoconjonctivite seche: effets de la ciclosporine topique sur l'expression d'antigene HLA DR.

AUTHOR: Galatoire O; Baudouin C; Pisella P J; Brignole F

CORPORATE SOURCE: Service d'Ophtalmologie 3, Hopital des Quinze-Vingts, 28, rue de Charenton, 75012 Paris.

SOURCE: Journal francais d'ophtalmologie, (2003 Apr) Vol. 26, No. 4, pp. 337-43.
Journal code: 7804128. ISSN: 0181-5512.

PUB. COUNTRY: France

DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(MULTICENTER STUDY)
(RANDOMIZED CONTROLLED TRIAL)

LANGUAGE: French

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200308

ENTRY DATE: Entered STN: 5 Jul 2003
Last Updated on STN: 21 Aug 2003
Entered Medline: 20 Aug 2003

ABSTRACT:
PURPOSE: Immune-based inflammation has been observed as a common mechanism of keratoconjunctivitis sicca (KCS). In KCS-affected eyes, up-regulated expression of HLA DR by conjunctival epithelial cells has been demonstrated in impression cytology (IC) specimens using a technique of flow cytometry. The purpose of this study was to monitor the effects of topical **cyclosporin**

A on the expression of this marker over a 12-month period of treatment. METHODS: Patients with moderate-to-severe KCS included in a large European multicenter clinical trial (**Cyclosporin** Dry Eye Study, Allergan, Irvine, CA) underwent collection of IC specimens at baseline, month 3, month 6, and month 12. They randomly received 0.05% or 0.1% **cyclosporin** ***A*** or vehicle. Patients randomized to receive vehicle received 0.1% ***cyclosporin*** **A** from month 6 onwards. Specimens were processed and analyzed in a masked manner by flow cytometry, using monoclonal antibodies directed to HLA DR. RESULTS: We included 169 patients in this study. HLA DR expression, both in percentage of positive cells and level of expression, was highly significantly reduced after 0.05% and 0.1% **cyclosporin** ***A*** treatment at months 3, 6, and 12 compared with baseline values, whereas vehicle did not induce any change in HLA DR expression over time. The 0.05% and 0.1% **cyclosporin** emulsions were significantly more effective than the vehicle in reducing HLA DR at months 3 and 6 (0.05%) and at month 6 (0.1%). CONCLUSIONS: Topical **cyclosporin A** strikingly reduced HLA DR, whereas the vehicle, used as a control tear substitute, had almost no effect. This study confirms that **cyclosporin** ***A*** may be effective in reducing conjunctival inflammation in moderate-to-severe KCS and is consistent with clinical results in this indication.

CONTROLLED TERM: Check Tags: Female; Male
Administration, Topical
Adolescent
Adult
Aged
Aged, 80 and over
Cyclosporine: AD, administration & dosage
***Cyclosporine: TU, therapeutic use**
Double-Blind Method
Emulsions
English Abstract
*Flow Cytometry
Fluorescent Antibody Technique, Indirect
*HLA-DR Antigens: BI, biosynthesis
HLA-DR Antigens: GE, genetics
Humans
***Keratoconjunctivitis Sicca: DT, drug therapy**
Keratoconjunctivitis Sicca: IM, immunology
Keratoconjunctivitis Sicca: PA, pathology
Middle Aged
Ophthalmic Solutions
Prospective Studies
Sjogren's Syndrome: CO, complications
Sjogren's Syndrome: IM, immunology
Sjogren's Syndrome: PA, pathology
Treatment Outcome
Vehicles

CAS REGISTRY NO.: **59865-13-3 (Cyclosporine)**

CHEMICAL NAME: 0 (Emulsions); 0 (HLA-DR Antigens); 0 (Ophthalmic Solutions); 0 (Vehicles)

L139 ANSWER 4 OF 73 MEDLINE on STN

ACCESSION NUMBER: 2003200578 MEDLINE Full-text

DOCUMENT NUMBER: PubMed ID: 12718570

TITLE: **Cyclosporin** - allergan. **Ciclosporin** - allergan, **cyclosporin** ophthalmic emulsion, **cyclosporine** - Allergan, **Restasis**.

AUTHOR: Anonymous

SOURCE: Drugs in R&D, (2003) Vol. 4, No. 2, pp. 126-7.

Journal code: 100883647. ISSN: 1174-5886.
PUB. COUNTRY: New Zealand
DOCUMENT TYPE: (CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE III)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200311
ENTRY DATE: Entered STN: 1 May 2003
Last Updated on STN: 17 Dec 2003
Entered Medline: 18 Nov 2003
CONTROLLED TERM: ***Cyclosporine: AE, adverse effects**
Drugs, Investigational
Emulsions
***Eye Diseases: DT, drug therapy**
Humans
Immunosuppressive Agents: AE, adverse effects
Ophthalmic Solutions: AE, adverse effects
*Ophthalmic Solutions: TU, therapeutic use
CAS REGISTRY NO.: **59865-13-3 (Cyclosporine)**
CHEMICAL NAME: 0 (Drugs, Investigational); 0 (Emulsions); 0 (Immunosuppressive Agents); 0 (Ophthalmic Solutions)

L139 ANSWER 5 OF 73 MEDLINE on STN
ACCESSION NUMBER: 2004024662 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 14723112
TITLE: Considerations in the pharmacoeconomics of dry eye.
AUTHOR: Hirsch Jan D
CORPORATE SOURCE: Prescription Solution, Cost Mesa, Calif., USA.
SOURCE: Managed care (Langhorne, Pa.), (2003 Dec) Vol. 12, No. 12 Suppl, pp. 33-8.
Journal code: 9303583. ISSN: 1062-3388.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Health
ENTRY MONTH: 200403
ENTRY DATE: Entered STN: 16 Jan 2004
Last Updated on STN: 10 Mar 2004
Entered Medline: 9 Mar 2004

ABSTRACT:
Dry eye disease diminishes the quality of patients' lives and drives utilization of health care resources. Until recently, all treatments for dry eye have been palliative. A new treatment, **cyclosporine A** ophthalmic emulsion, addresses the disease's underlying causes. It warrants pharmacoeconomic analysis to determine its place in managed care.

CONTROLLED TERM: Check Tags: Female; Male
Anti-Inflammatory Agents: EC, economics
Anti-Inflammatory Agents: TU, therapeutic use
Cost of Illness
Cyclosporine: EC, economics
***Cyclosporine: TU, therapeutic use**
***Dry Eye Syndromes: DT, drug therapy**
Dry Eye Syndromes: EC, economics
Dry Eye Syndromes: PP, physiopathology
Economics, Pharmaceutical
Emulsions
Humans
*Managed Care Programs: EC, economics
Middle Aged

Ophthalmic Solutions: EC, economics
Ophthalmic Solutions: TU, therapeutic use
Palliative Care
Quality of Life
Questionnaires
Treatment Outcome

CAS REGISTRY NO.: **59865-13-3 (Cyclosporine)**
CHEMICAL NAME: 0 (Anti-Inflammatory Agents); 0 (Emulsions); 0 (Ophthalmic Solutions)

L139 ANSWER 6 OF 73 MEDLINE on STN
ACCESSION NUMBER: 2000228811 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 10768324
TITLE: Two multicenter, randomized studies of the efficacy and safety of **cyclosporine** ophthalmic emulsion in moderate to severe dry eye disease. CsA Phase 3 Study Group.
AUTHOR: Sall K; Stevenson O D; Mundorf T K; Reis B L
CORPORATE SOURCE: Sall Eye Surgery Center, Bellflower, California, USA.
SOURCE: Ophthalmology, (2000 Apr) Vol. 107, No. 4, pp. 631-9. Journal code: 7802443. ISSN: 0161-6420.
COMMENT: Erratum in: Ophthalmology 2000 Jul;107(7):1220
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(MULTICENTER STUDY)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200004
ENTRY DATE: Entered STN: 27 Apr 2000
Last Updated on STN: 22 Sep 2000
Entered Medline: 18 Apr 2000

ABSTRACT:
OBJECTIVE: To compare the efficacy and safety of **cyclosporin**
A ([CsA] 0.05% and 0.1% ophthalmic emulsions) to vehicle in patients with moderate to severe dry eye disease. DESIGN: Multicenter, randomized, double-masked, parallel-group, 6-month, vehicle-controlled. PARTICIPANTS: A total of 877 patients with defined moderate to severe dry eye disease (292 to 293 in each treatment group). METHODS: Two identical clinical trials; patients were treated twice daily with either CsA, 0.05% or 0.1%, or vehicle. The results of these two trials were combined for analysis. MAIN OUTCOME MEASURES: Efficacy: corneal and interpalpebral dye staining, Schirmer tear test (with and without anesthesia), tear break-up time, Ocular Surface Disease Index (OSDI), facial expression, patient subjective rating scale, symptoms of dry eye, investigator's evaluation of global response to treatment, treatment success, and daily use of artificial tears. Safety: occurrence of adverse events, best-corrected visual acuity, intraocular pressure, biomicroscopy, and blood trough CsA concentrations. RESULTS: Treatment with CsA, 0.05% or 0.1%, gave significantly ($P < or = 0.05$) greater improvements than vehicle in two objective signs of dry eye disease (corneal staining and categorized Schirmer values). CsA 0.05% treatment also gave significantly greater improvements ($P < 0.05$) in three subjective measures of dry eye disease (blurred vision, need for concomitant artificial tears, and the physician's evaluation of global response to treatment). There was no dose-response effect. Both CsA treatments exhibited an excellent safety profile, and there were no significant topical or systemic adverse safety findings. CONCLUSIONS: The novel ophthalmic formulations CsA 0.05% and 0.1% were safe and effective in the treatment of moderate to severe dry eye disease yielding improvements in both objective and subjective measures. Topical CsA represents a new pharmacologically based

treatment for dry eye disease that may provide significant patient benefits.
CONTROLLED TERM: Check Tags: Female; Male
Comparative Study
Cornea: DE, drug effects
Cyclosporine: AD, administration & dosage
Cyclosporine: AE, adverse effects
***Cyclosporine: TU, therapeutic use**
Double-Blind Method
Drug Evaluation
***Dry Eye Syndromes: DT, drug therapy**
Emulsions
Humans
Intraocular Pressure
Middle Aged
Ophthalmic Solutions: AD, administration & dosage
Ophthalmic Solutions: AE, adverse effects
*Ophthalmic Solutions: TU, therapeutic use
Research Support, Non-U.S. Gov't
Safety
Tears: ME, metabolism
Visual Acuity
CAS REGISTRY NO.: **59865-13-3 (Cyclosporine)**
CHEMICAL NAME: 0 (Emulsions); 0 (Ophthalmic Solutions)

L139 ANSWER 7 OF 73 MEDLINE on STN
ACCESSION NUMBER: 2001033774 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 10928765
TITLE: Interleukin-6 levels in the conjunctival epithelium of patients with dry eye disease treated with **cyclosporine** ophthalmic emulsion.
AUTHOR: Turner K; Pflugfelder S C; Ji Z; Feuer W J; Stern M; Reis B L
CORPORATE SOURCE: Bascom Palmer Eye Institute, Department of Ophthalmology, University of Miami School of Medicine, Florida 33136, USA.
SOURCE: Cornea, (2000 Jul) Vol. 19, No. 4, pp. 492-6.
Journal code: 8216186. ISSN: 0277-3740.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(MULTICENTER STUDY)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200011
ENTRY DATE: Entered STN: 22 Mar 2001
Last Updated on STN: 22 Mar 2001
Entered Medline: 30 Nov 2000
ABSTRACT:
PURPOSE: To evaluate interleukin-6 (IL-6) levels in the conjunctival epithelium of patients with moderate to severe dry eye disease before and after treatment with **cyclosporin A** ophthalmic emulsion (CsA) or its vehicle. METHODS: Conjunctival cytology specimens were obtained from a subset of patients enrolled in a 6-month randomized, double-masked clinical trial of the efficacy and safety of topical CsA at baseline and after 3 and 6 months of B.I.D. treatment with 0.05% **cyclosporine** emulsion (n = 13), 0.1% ***cyclosporine*** emulsion (n = 8), or vehicle (n = 10). RNA was extracted and a competitive reverse transcriptase polymerase chain reaction (RT-PCR) was used to evaluate the levels of mRNA encoding the inflammatory cytokine IL-6 and a housekeeping gene, G3PDH. Levels of IL-6 and G3PDH were measured and compared. RESULTS: There was no change from baseline in the level of G3PDH

after 3 or 6 months in any group. IL-6 normalized for G3PDH (IL-6/G3PDH ratio) was not different from baseline at 3 months but showed a significant decrease from baseline in the group treated with 0.05% CsA (p = 0.048) at 6 months. No significant between-group differences were noted and no correlation was observed between the change in IL-6/G3PDH and corneal fluorescein staining. CONCLUSIONS: This preliminary, small-cohort study showed a decrease in IL-6 in the conjunctival epithelium of moderate to severe dry eye patients treated with 0.05% CsA for 6 months. The observed decrease suggests that dry eye disease involves immune-mediated inflammatory processes that may be decreased by treatment with topical ophthalmic **cyclosporine**.

CONTROLLED TERM: Administration, Topical
Biological Markers
Comparative Study
*Conjunctiva: ME, metabolism
Conjunctiva: PA, pathology
***Cyclosporine: TU, therapeutic use**
DNA Primers: CH, chemistry
Double-Blind Method
***Dry Eye Syndromes: DT, drug therapy**
Dry Eye Syndromes: ME, metabolism
Dry Eye Syndromes: PA, pathology
Emulsions
*Epithelium: ME, metabolism
Epithelium: PA, pathology
Glyceraldehyde-3-Phosphate Dehydrogenases: ME, metabolism
Humans
*Immunosuppressive Agents: TU, therapeutic use
Interleukin-6: GE, genetics
*Interleukin-6: ME, metabolism
Prospective Studies
RNA, Messenger: ME, metabolism
Research Support, Non-U.S. Gov't
Reverse Transcriptase Polymerase Chain Reaction

CAS REGISTRY NO.: **59865-13-3 (Cyclosporine)**

CHEMICAL NAME: 0 (Biological Markers); 0 (DNA Primers); 0 (Emulsions); 0 (Immunosuppressive Agents); 0 (Interleukin-6); 0 (RNA, Messenger); EC 1.2.1.- (Glyceraldehyde-3-Phosphate Dehydrogenases)

L139 ANSWER 8 OF 73 MEDLINE on STN

ACCESSION NUMBER: 1999410206 MEDLINE Full-text

DOCUMENT NUMBER: PubMed ID: 10482480

TITLE: **Ciclosporin** microemulsion preconcentrate treatment of patients with Behcet's disease.

AUTHOR: Fujino Y; Joko S; Masuda K; Yagi I; Kogure M; Sakai J; Usui M; Kotake S; Matsuda H; Ikeda E; Mochizuki M; Nakamura S; Ohno S

CORPORATE SOURCE: Department of Ophthalmology, University of Tokyo School of Medicine, Japan.

SOURCE: Japanese journal of ophthalmology, (1999 Jul-Aug) Vol. 43, No. 4, pp. 318-26.
Journal code: 0044652. ISSN: 0021-5155.

PUB. COUNTRY: United States

DOCUMENT TYPE: (CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE III)
(CONTROLLED CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(MULTICENTER STUDY)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199909
ENTRY DATE: Entered STN: 12 Oct 1999
Last Updated on STN: 12 Oct 1999
Entered Medline: 29 Sep 1999

ABSTRACT:
PURPOSE: The new microemulsion preconcentrate (MEPC) formulation of ***ciclosporin*** has been developed to reduce problems in intestinal absorption and to stabilize fluctuations in blood levels. A multicenter, open-label clinical trial of MEPC was conducted to assess its efficacy and safety in Behcet's disease patients with ocular involvement. METHODS: The patient population comprised 17 de novo patients (patients not previously treated with **ciclosporin** in the currently available formulation) and 30 patients whose **ciclosporin** formulation was switched from the conventional formulation to MEPC. The patients were treated with the test formulation for 16 weeks in the former (de novo) group and for 12 weeks in the latter (switched) group. RESULTS: In the de novo group, ocular attacks decreased significantly as compared to the pretreatment incidence in 11 of the 14 patients (78.6%) evaluated after MEPC therapy. Ocular attacks also decreased significantly in the switched group. In the de novo group, visual acuity improved with MEPC therapy in 20 of the 28 eyes (71.4%) examined, and the overall efficacy evaluation was "improved" or "markedly improved" in 13 of the 16 patients evaluated (81.3%). The one case each of onset of neuro-Behcet's disease and intestinal Behcet's disease observed in the de novo group were regarded as adverse reactions. CONCLUSION: It was concluded that ***ciclosporin*** MEPC is useful for controlling the ocular symptoms of Behcet's disease, and that it can be used as effectively and safely as the conventional formulation.

CONTROLLED TERM: Check Tags: Female; Male
Adult
Aged
***Behcet Syndrome: DT, drug therapy**
Behcet Syndrome: ME, metabolism
Biological Availability
Cyclosporine: AE, adverse effects
Cyclosporine: PK, pharmacokinetics
***Cyclosporine: TU, therapeutic use**
Drug Evaluation
Emulsions
Humans
Immunosuppressive Agents: AE, adverse effects
Immunosuppressive Agents: PK, pharmacokinetics
*Immunosuppressive Agents: TU, therapeutic use
Middle Aged
Pharmaceutical Preparations
Safety
Treatment Outcome

CAS REGISTRY NO.: **59865-13-3 (Cyclosporine)**
CHEMICAL NAME: 0 (Emulsions); 0 (Immunosuppressive Agents); 0 (Pharmaceutical Preparations)

L139 ANSWER 9 OF 73 MEDLINE on STN
ACCESSION NUMBER: 1998426790 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 9754182
TITLE: A randomized, placebo-controlled trial of topical **cyclosporin A** in steroid-dependent atopic keratoconjunctivitis.
AUTHOR: Hingorani M; Moodaley L; Calder V L; Buckley R J; Lightman S
CORPORATE SOURCE: Moorfields Eye Hospital, London, United Kingdom.
SOURCE: Ophthalmology, (1998 Sep) Vol. 105, No. 9, pp. 1715-20.

Journal code: 7802443. ISSN: 0161-6420.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199810
ENTRY DATE: Entered STN: 21 Oct 1998
Last Updated on STN: 21 Oct 1998
Entered Medline: 13 Oct 1998

ABSTRACT:
OBJECTIVE: This study aimed to investigate the therapeutic effect of topical ***cyclosporin*** **A** (CsA) 2% in maize oil as a steroid-sparing agent in steroid-dependent atopic keratoconjunctivitis. DESIGN: Prospective, randomized, double-masked, placebo-controlled trial. PARTICIPANTS: Twenty-one patients with steroid-dependent atopic keratoconjunctivitis were studied. INTERVENTION: Patients used either topical CsA or vehicle four times daily for 3 months in addition to their usual therapy, and the clinical response was used to taper or stop topical steroids when possible. MAIN OUTCOME MEASURES: Steroid drop usage per week, ability to cease steroid use, scores for symptoms and clinical signs, drop side effects, and overall subjective rating of trial drop by patients and clinician were measured. RESULTS: **Cyclosporin** ***A*** had a greater steroid-sparing effect than did placebo. Nine of 12 CsA patients ceased steroids compared to 1 of 9 placebo patients ($P = 0.01$), the final steroid use was lower in the CsA group (2.6 +/- 1.4 vs. 27.7 +/- 17.7, $P = 0.005$), and the mean reduction in steroid use was greater for CsA (85.5 +/- 14.7 vs. 13.9 +/- 16.0, $P = 0.005$). Clinical signs and symptom scores were reduced to a greater level for CsA. Serious side effects were lid skin maceration in one patient using CsA and an allergic reaction in one placebo patient. Marked blurring of vision after drop instillation was common in both groups, but intense stinging was more common in CsA patients (9/12 vs. 1/9, $P = 0.01$), limiting frequency of drop use. The clinician rated the trial drops as good or excellent more frequently for CsA (11/12 vs. 0/9, $P < 0.0001$). CONCLUSIONS: Topical CsA is an effective and safe steroid-sparing agent in atopic keratoconjunctivitis and, despite difficulties in patient tolerance, also improves symptoms and signs.

CONTROLLED TERM: Check Tags: Female; Male
Administration, Topical
Adult
***Conjunctivitis, Allergic: DT, drug therapy**
Corn Oil: AD, administration & dosage
***Cyclosporine: AD, administration & dosage**
Cyclosporine: AE, adverse effects
Double-Blind Method
Drug Carriers
*Glucocorticoids: TU, therapeutic use
Humans
*Immunosuppressive Agents: AD, administration & dosage
Immunosuppressive Agents: AE, adverse effects
Ophthalmic Solutions
Prospective Studies
Safety
Treatment Outcome

CAS REGISTRY NO.: **59865-13-3 (Cyclosporine)**; 8001-30-7 (Corn Oil)
CHEMICAL NAME: 0 (Drug Carriers); 0 (Glucocorticoids); 0 (Immunosuppressive Agents); 0 (Ophthalmic Solutions)

L139 ANSWER 10 OF 73 MEDLINE on STN
ACCESSION NUMBER: 1998298735 MEDLINE Full-text

DOCUMENT NUMBER: PubMed ID: 9634996
TITLE: A dose-ranging clinical trial to assess the safety and efficacy of **cyclosporine** ophthalmic emulsion in patients with keratoconjunctivitis sicca. The **Cyclosporine** Study Group.
AUTHOR: Tauber J
SOURCE: Advances in experimental medicine and biology, (1998) Vol. 438, pp. 969-72.
Journal code: 0121103. ISSN: 0065-2598.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(MULTICENTER STUDY)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199809
ENTRY DATE: Entered STN: 25 Sep 1998
Last Updated on STN: 25 Sep 1998
Entered Medline: 15 Sep 1998
CONTROLLED TERM: Administration, Topical
Cyclosporine: AD, administration & dosage
Cyclosporine: BL, blood
***Cyclosporine: TU, therapeutic use**
Dose-Response Relationship, Drug
Double-Blind Method
Emulsions
Humans
***Keratoconjunctivitis Sicca: DT, drug therapy**
CAS REGISTRY NO.: **59865-13-3 (Cyclosporine)**
CHEMICAL NAME: 0 (Emulsions)

L139 ANSWER 11 OF 73 MEDLINE on STN
ACCESSION NUMBER: 1998042343 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 9374930
TITLE: **Neoral**--new **cyclosporin** for old?.
AUTHOR: Somerville M F; Scott D G
CORPORATE SOURCE: Rheumatology Department, Norfolk & Norwich Health Care NHS Trust, Norwich.
SOURCE: British journal of rheumatology, (1997 Oct) Vol. 36, No. 10, pp. 1113-5.
Journal code: 8302415. ISSN: 0263-7103.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199712
ENTRY DATE: Entered STN: 9 Jan 1998
Last Updated on STN: 9 Jan 1998
Entered Medline: 15 Dec 1997

ABSTRACT:
Cyclosporin A is now well established as an effective second-line drug to treat rheumatoid arthritis. In April 1995, the microemulsion-based formulation of **cyclosporin** (**Neoral**) was introduced based on its increased bioavailability at 'no extra cost'. There may have been concerns that with increased bioavailability of **Neoral**, some patients might experience increased toxicity, particularly if transferring from **Sandimmun** to **Neoral** at the same dose. We describe our experience of 51 patients treated with **Neoral**--39 with rheumatoid

arthritis, six with psoriatic arthritis and the remainder with a variety of diseases, including Behcet's, systemic lupus erythematosus and juvenile chronic arthritis. All patients continued their other medication including non-steroidal anti-inflammatory drugs and analgesics. Five continued low dose prednisolone (average 7.5 mg per day) all patients were monitored for safety and efficacy throughout their treatment according to standard protocol. Five patients were enrolled in a study of efficacy and safety where the dose of ***cyclosporin*** was reduced to 2.5 mg/kg/day at the time of conversion, i.e. to **Neoral** 2.5 mg/kg/day; 19 patients were converted dose for dose, **cyclosporin A** dose range 2.5-4 mg/kg/day converted to ***Neoral*** dose range 2.5-4 mg/kg/day and 27 patients started ***Neoral*** de novo. We conclude that **cyclosporin** is a useful disease modifying anti-rheumatic agent, and our experience suggests that the new formulation, **Neoral**, has a similar safety and efficacy profile to the original preparation (**Sandimmun**). **Neoral** was relatively easy to manage and we noted a slight reduction in dose when compared to **Sandimmun**. With dose adjustments over 18 months the mean dose for patients with RA fell from 3.2 to 2.7 mg/kg/day and of the 27 patients starting ***Neoral*** de novo only seven required an increased dose above 2.5 mg/kg/day in order to establish efficacy.

CONTROLLED TERM: Adolescent
Adult
Anti-Inflammatory Agents: TU, therapeutic use
Antirheumatic Agents: AD, administration & dosage
Antirheumatic Agents: PK, pharmacokinetics
*Antirheumatic Agents: TU, therapeutic use
Arthritis, Juvenile Rheumatoid: DT, drug therapy
Arthritis, Psoriatic: DT, drug therapy
Arthritis, Rheumatoid: DT, drug therapy
Behcet Syndrome: DT, drug therapy
Biological Availability
Cyclosporine: AD, administration & dosage
Cyclosporine: PK, pharmacokinetics
***Cyclosporine: TU, therapeutic use**
Dose-Response Relationship, Drug
Drug Therapy: EC, economics
Emulsions
Humans
Lupus Erythematosus, Systemic: DT, drug therapy
Middle Aged
Prednisolone: TU, therapeutic use
Questionnaires
*Rheumatic Diseases: DT, drug therapy
Severity of Illness Index

CAS REGISTRY NO.: 50-24-8 (Prednisolone); **59865-13-3 (Cyclosporine)**

CHEMICAL NAME: 0 (Anti-Inflammatory Agents); 0 (Antirheumatic Agents); 0 (Emulsions)

L139 ANSWER 12 OF 73 MEDLINE on STN

ACCESSION NUMBER: 1998209717 MEDLINE Full-text

DOCUMENT NUMBER: PubMed ID: 9550347

TITLE: Effect of topical **cyclosporin A** on Thygeson's superficial punctate keratitis.

AUTHOR: Del Castillo J M; Del Castillo J B; Garcia-Sanchez J

CORPORATE SOURCE: Instituto de Investigaciones Oftalmologicas Ramon Castroviejo, Madrid, Spain.

SOURCE: Documenta ophthalmologica. Advances in ophthalmology, (1996-1997) Vol. 93, No. 3, pp. 193-8.
Journal code: 0370667. ISSN: 0012-4486.

PUB. COUNTRY: Netherlands

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199806
ENTRY DATE: Entered STN: 25 Jun 1998
Last Updated on STN: 25 Jun 1998
Entered Medline: 16 Jun 1998

ABSTRACT:
Thygeson's superficial punctate keratitis (Thygeson's SPK) is a distinct clinical entity, characterized by round conglomerates of discrete, granular, white-gray, fine intraepithelial dots without conjunctival involvement. The only effective treatment with regard to relieving symptoms and diminishing lesions has been topical corticosteroids, but their prolonged use can be associated with severe side-effects. The purpose of this study is to present the long-term results of the use of 2% topical **cyclosporin A** in olive oil in Thygeson's SPK. Eight patients diagnosed as having Thygeson's SPK were included. All the patients were treated with 2% **cyclosporin** dissolved in olive oil four times a day for three months, and two times a day for one month before withdrawing therapy. The follow-up period ranged from twelve to twenty-five months. The number of corneal lesions varied between 5 and 15 before treatment. After **cyclosporin** treatment, no corneal lesion was observed and the cornea remained clear after the follow-up period. In conclusion, 2% **cyclosporin** in olive oil is a safe alternative to corticosteroids in the treatment of Thygeson's SPK, and resulted in satisfactory control of the condition.

CONTROLLED TERM: Check Tags: Female; Male
Administration, Topical
Adolescent
Adult
*Cornea: DE, drug effects
Cornea: PA, pathology
Cyclosporine: AD, administration & dosage
***Cyclosporine: TU, therapeutic use**
Drug Combinations
Follow-Up Studies
Humans
Immunosuppressive Agents: AD, administration & dosage
*Immunosuppressive Agents: TU, therapeutic use
***Keratitis: DT, drug therapy**
Keratitis: ET, etiology
Keratitis: PA, pathology
Middle Aged
Ophthalmic Solutions
Plant Oils: AD, administration & dosage
***Plant Oils: TU, therapeutic use**
Treatment Outcome

CAS REGISTRY NO.: **59865-13-3 (Cyclosporine)**; 8001-25-0 (olive oil)
CHEMICAL NAME: 0 (Drug Combinations); 0 (Immunosuppressive Agents); 0 (Ophthalmic Solutions); 0 (Plant Oils)

L139 ANSWER 13 OF 73 MEDLINE on STN
ACCESSION NUMBER: 94208262 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 8156785
TITLE: Influence of topically applied **cyclosporine A** in olive oil on corneal epithelium permeability.
AUTHOR: Benitez del Castillo J M; del Aguila C; Duran S; Hernandez J; Garcia Sanchez J
CORPORATE SOURCE: Department of Ophthalmology, Hospital Universitario San Carlos, Universidad Complutense de Madrid, Spain.
SOURCE: Cornea, (1994 Mar) Vol. 13, No. 2, pp. 136-40.

Journal code: 8216186. ISSN: 0277-3740.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199405
ENTRY DATE: Entered STN: 26 May 1994
Last Updated on STN: 6 Feb 1998
Entered Medline: 19 May 1994

ABSTRACT:
The effect that topically administered **cyclosporine A** (CsA) dissolved in olive oil has on corneal epithelial permeability was determined by fluorophotometry. Twenty-six healthy volunteers, who had no ocular or general disease and were not receiving any topical or systemic treatments, were studied. A Fluorotron Master fluorophotometer was used. Measurements were taken before and 45 min after the instillation of 40 microliters of a 2% aqueous solution of sodium fluorescein without preservatives. Basal corneal epithelial permeability, as well as the permeability 24 h after the instillation of 2% CsA-olive oil and of the solvent alone, were calculated. Under sterile conditions, the **Sandimmun** oral solution (Sandoz, Basel, Switzerland) was used to prepare the topical 2% CsA. Immediately after the 2% CsA-olive oil or the solvent alone were instilled, the volunteers complained of itching for approximately 1 h and developed punctate keratopathy, which improved the next day. Epithelial permeability 24 h after instillation of 2% CsA-olive oil increased 7.03 times ($p < 0.001$), and that of the solvent alone increased 6.68 times ($p < 0.001$). No differences in corneal permeability were found between CsA-olive oil and the vehicle ($p = 0.651$). We concluded that the olive oil used to dissolve CsA is responsible for the increased corneal epithelial permeability.

CONTROLLED TERM: Check Tags: Female; Male
Administration, Topical
Adult
Cell Membrane Permeability: DE, drug effects
*Cornea: ME, metabolism
Corneal Diseases: CI, chemically induced
Cyclosporine: AE, adverse effects
***Cyclosporine: PD, pharmacology**
Emulsions
Fluorescein
Fluoresceins: PK, pharmacokinetics
Fluorophotometry
Humans
Ophthalmic Solutions
Plant Oils
Pruritus: CI, chemically induced

CAS REGISTRY NO.: 2321-07-5 (Fluorescein); **59865-13-3 (Cyclosporine)** ; 8001-25-0 (olive oil)

CHEMICAL NAME: 0 (Emulsions); 0 (Fluoresceins); 0 (Ophthalmic Solutions); 0 (Plant Oils)

L139 ANSWER 14 OF 73 MEDLINE on STN
ACCESSION NUMBER: 89334669 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 2757551
TITLE: Spontaneous canine keratoconjunctivitis sicca. A useful model for human keratoconjunctivitis sicca: treatment with **cyclosporine** eye drops.
AUTHOR: Kaswan R L; Salisbury M A; Ward D A
CORPORATE SOURCE: Department of Small Animal Medicine, College of Veterinary Medicine, University of Georgia, Athens 30602.
SOURCE: Archives of ophthalmology, (1989 Aug) Vol. 107, No. 8, pp.

1210-6.
Journal code: 7706534. ISSN: 0003-9950.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 198909
ENTRY DATE: Entered STN: 9 Mar 1990
Last Updated on STN: 9 Mar 1990
Entered Medline: 1 Sep 1989

ABSTRACT:
Thirty-six sequential cases of canine keratoconjunctivitis sicca (KCS) were treated with ophthalmic **cyclosporine**. The effects of topical ***cyclosporine*** were twofold: (1) **cyclosporine** increased tear production by 5 mm/min or greater in all cases of spontaneous KCS having an initial Schirmer's Tear Test value greater than 2 mm/min and in 59% of eyes with an initial Schirmer's Tear Test value of 0 to 2 mm/min, and (2) ***cyclosporine*** caused marked regression of chronic corneal neovascularization and granulation even in eyes in which lacrimation failed to improve. Additional benefits of topical **cyclosporine** were reduced mucopurulent conjunctivitis, rapid healing of nonhealing corneal ulcers, and reduced dependence on frequent topical treatments of KCS. Twelve normal beagles treated with topical **cyclosporine** also had a reversible increase in lacrimation compared with baseline or placebo control-treated dogs.

CONTROLLED TERM: Check Tags: Female; Male
Animals
Cornea: PA, pathology
Cyclosporins: AD, administration & dosage
***Cyclosporins: TU, therapeutic use**
Disease Models, Animal
*Dog Diseases: DT, drug therapy
Dog Diseases: PA, pathology
Dogs
Double-Blind Method
***Keratoconjunctivitis: VE, veterinary**
Keratoconjunctivitis Sicca: DT, drug therapy
Keratoconjunctivitis Sicca: PA, pathology
***Keratoconjunctivitis Sicca: VE, veterinary**
Ophthalmic Solutions
Plant Oils
Tears: DE, drug effects
Tears: SE, secretion
Vehicles
CAS REGISTRY NO.: 8001-25-0 (olive oil)
CHEMICAL NAME: 0 (**Cyclosporins**); 0 (Ophthalmic Solutions); 0 (Plant Oils); 0 (Vehicles)

L139 ANSWER 15 OF 73 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN DUPLICATE 3
ACCESSION NUMBER: 1990:113390 BIOSIS Full-text
DOCUMENT NUMBER: PREV199089062881; BA89:62881
TITLE: THE EFFECT ON THE CORNEA OF VARIOUS VEHICLES FOR **CYCLOSPORIN EYE** DROPS.
AUTHOR(S): ALBA R M JR [Reprint author]; KANAI A; TAKANO T; KOBAYASHI C; NAKAJIMA A; KURIHARA K; FUKAMI M
CORPORATE SOURCE: DEP OPHTHALMOL, JUNTENDO UNIV SCH MED, 3-1-3 HONGO, BUNKYO-KU, TOKYO 113, JAPAN

SOURCE: Folia Ophthalmologica Japonica, (1989) Vol. 40, No. 5, pp. 902-908.
CODEN: NGKYA3. ISSN: 0015-5667.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 21 Feb 1990
Last Updated on STN: 22 Feb 1990

ABSTRACT:We tested several solvents, possible vehicles for **Cyclosporin**, (CYA) as to which had the least corneal toxicity. They were: peanut ***oil*** , palm **oil**, polyoxyethylene castor **oil**, medium chain-length triglyceride **emulsion** (MCT) and alpha cyclo-dextrin (α-CD). The concentration of CYA in each vehicle was: 1% in peanut ***oil*** , palm **oil** and MCT; 0.1% in polyoxyethylene castor ***oil*** and 0.08% in α-CD. The drugs and normal saline, which served as control, were instilled to rat corneas at frequencies of 10 + (every 30 min.) and 5+. Light microscopy revealed that in the MCT, α-CD and peanut **oil** groups, corneal thickness approximated that in the controls. In the next phase, done on rabbit corneas, we instilled MCT (with and without CYA), α-CD and peanut **oil** 10+ (every 30 min.). Normal saline was applied to the control **eye**. The Draize test, ultrasonic pachymetry, light and electron microscopic examination indicated that, compared to the other vehicles, α-CD exhibited significant corneal toxicity was evidenced by edema, diminution of microvilli on the epithelium and epithelial craters. Radioimmunoassay of CYA levels in the cornea and aq. humor indicated that α-CD afforded the greatest CYA penetration of the cornea. We then tested 4 different concentrations of α-CD to determine the least toxic concentration. The concentrations were: 80, 40, 20 and 10 mg/ml. of α-CD combined with 0.75, 0.25, 0.09 and 0.03 mg./ml. of CYA. They were applied to rabbit corneas 4+ (every 2 hrs.) Histological and RIA studies indicate that 40.0 mg/ml α-CD with 0.25 mg./ml. CYA is an acceptable concentration.

CONCEPT CODE: Microscopy - Histology and histochemistry 01056
Cytology - Human 02508
Radiation biology - Radiation and isotope techniques 06504
Biochemistry studies - General 10060
Biochemistry studies - Proteins, peptides and amino acids 10064
Biochemistry studies - Lipids 10066
Anatomy and Histology - Microscopic and ultramicroscopic anatomy 11108
Pathology - Therapy 12512
Sense organs - General and methods 20001
Sense organs - Pathology 20006
Pharmacology - Immunological processes and allergy 22018
Pharmacology - Sense organs, associated structures and functions 22031
Routes of immunization, infection and therapy 22100
Immunology - General and methods 34502
Immunology - Immunopathology, tissue immunology 34508

INDEX TERMS: Major Concepts
Immune System (Chemical Coordination and Homeostasis); Morphology; Pharmacology; Sense Organs (Sensory Reception)

INDEX TERMS: Miscellaneous Descriptors
RABBIT IMMUNOSUPPRESSANT-DRUG PEANUT **OIL** PALM **OIL** ALPHA CYCLODEXTRIN MEDIUM CHAIN-LENGTH TRIGLYCERIDE **EMULSION** ULTRASONIC PACHYMETRY

DRAIZE TEST LIGHT MICROSCOPY ELECTRON MICROSCOPY
RADIOIMMUNOASSAY

ORGANISM: Classifier
Leporidae 86040
Super Taxa
Lagomorpha; Mammalia; Vertebrata; Chordata; Animalia
Taxa Notes
Animals, Chordates, Lagomorphs, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Vertebrates

REGISTRY NUMBER: **59865-13-3Q (CYCLOSPORIN)**
79217-60-0Q (**CYCLOSPORIN**)
10016-20-3 (ALPHA-CYCLODEXTRIN)

L139 ANSWER 16 OF 73 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 2004:38676 BIOSIS Full-text
DOCUMENT NUMBER: PREV200400039347
TITLE: Method and composition for dry **eye** treatment.
AUTHOR(S): Benita, Simon [Inventor, Reprint Author]; Lambert, Gregory [Inventor]
CORPORATE SOURCE: Mevaseret Zion, Israel
ASSIGNEE: Yissum Research Development, Jerusalem, Israel; Company of the Hebrew University of Jerusalem Novagali S.A.S., Evry, France
PATENT INFORMATION: US 6656460 20031202
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (Dec 2 2003) Vol. 1277, No. 1. http://www.uspto.gov/web/menu/patdata.html. e-file. ISSN: 0098-1133 (ISSN print).
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 7 Jan 2004
Last Updated on STN: 7 Jan 2004

ABSTRACT:A method and composition for treating a dry **eye** condition by topically applying to the **eye** surfaces an **emulsion** forming a tear film that acts to lubricate the **eye** and to inhibit evaporation therefrom. The **emulsion** is constituted by water in which is dispersed a mixture that includes a phospholipid, a non-polar **oil**, a non-toxic **emulsifying** agent and a polar lipid that imparts a net positive charge to the film that is distributed throughout the film, causing the film to be electrostatically attracted to the anionic surface of the ***eye*** whereby the film adheres thereto and cannot be washed away. Includable in the mixture is a non-soluble therapeutic agent, such as ***cyclosporin*** which is effective against an **eye** disease and is delivered to the **eye** by the film.

NAT. PATENT. CLASSIF.:424780400
CONCEPT CODE: Pathology - Therapy 12512
Sense organs - Pathology 20006
Pharmacology - General 22002
Pharmacology - Sense organs, associated structures and functions 22031
INDEX TERMS: Major Concepts
Methods and Techniques; Pharmacology
INDEX TERMS: Diseases
dry **eye**: **eye** disease, drug therapy
Dry **Eye** Syndromes (MeSH)
INDEX TERMS: Chemicals & Biochemicals
dry **eye** treatment composition: ophthalmic-drug
INDEX TERMS: Methods & Equipment
dry **eye** treatment method: clinical techniques,

US005474979A

United States Patent [19]

Ding et al.

[11] Patent Number: 5,474,979

[45] Date of Patent: Dec. 12, 1995

[54] **NONIRRITATING EMULSIONS FOR SENSITIVE TISSUE**

[75] Inventors: **Shulin Ding**; **Walter L. Tien**, both of Irvine; **Orest Olejnik**, Trabuco Canyon, all of Calif.

[73] Assignee: **Allergan, Inc.**, Irvine, Calif.

[21] Appl. No.: **243,279**

[22] Filed: **May 17, 1994**

[51] **Int. Cl.**[6] **A61K 38/13**; A61K 47/34

[52] **U.S. Cl.** **514/11**; 514/785; 514/786; 514/912; 514/941; 514/943; 514/975

[58] **Field of Search** 530/317, 321; 514/9, 11, 785, 786, 912, 913, 914, 915, 941, 943, 975, 178, 179, 180, 181, 420, 784; A61K 9/107, 47/14

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,347,238	8/1982	Hollingsbee	514/179
4,839,342	6/1989	Kaswan	514/11
4,990,337	2/1991	Kurihara et al.	424/427
4,996,193	2/1991	Hewitt et al.	514/11
5,051,402	9/1991	Kurihara et al.	514/11
5,364,632	11/1994	Benita et al.	514/943

Primary Examiner—Jeffrey E. Russel
Attorney, Agent, or Firm—Walter A. Hackler

[57] **ABSTRACT**

A pharmaceutical composition is disclosed in the form of a nonirritating emulsion which includes at least one cyclosporin in admixture with a higher fatty acid glyceride and polysorbate 80. More particularly, the cyclosporin may be cyclosporin A and the higher fatty acid glyceride may be castor oil. Composition has been found to be of a high comfort level and low irritation potential suitable for delivery of medications to sensitive areas such as ocular tissues. In addition, the composition has stability for up to nine months without crystallization of cyclosporin.

8 Claims, No Drawings

NONIRRITATING EMULSIONS FOR SENSITIVE TISSUE

The present invention generally relates to novel pharmaceutical compositions incorporating chemicals which are poorly soluble in water and is more particularly related to a novel ophthalmic emulsion including cyclosporin in admixture with castor oil and polysorbate 80 with high comfort level and low irritation potential.

Cyclosporins are a group of nonpolar cyclic oligopeptides with known immunosuppressant activity. In addition, as set forth in U.S. Pat. No. 4,839,342, cyclosporin (sometimes referred to in the literature as "cyclosporine") has been found as effective in treating immune medicated keratoconjunctivitis sicca (KCS or dry eye disease) in a patient suffering therefrom.

As hereinabove noted, cyclosporin comprises a group of cyclic oligopeptides and the major component thereof is cyclosporin A ($C_{62}H_{111}N_{11}O_{12}$) which has been identified along with several other minor metabolites, cyclosporin B through I. In addition, a number of synthetic analogs have been prepared.

In general, commercially available cyclosporins may contain a mixture of several individual cyclosporins which all share a cyclic peptide structure consisting of eleven amino acid residues with a total molecular weight of about 1,200, but with different substituents or configurations of some of the amino acids.

It should be appreciated that reference to the term "cyclosporin" or "cyclosporins" is used throughout the present specification in order to designate the cyclosporin component in the composition of the present invention.

However, this specific reference is intended to include any individual member of the cyclosporin group as well as admixtures of two or more individual cyclosporins, whether natural or synthetic.

The activity of cyclosporins, as hereinabove noted, is as an immunosuppressant and in the enhancement or restoring of lacrimal gland tearing.

Unfortunately, the solubility of cyclosporin in water is extremely low and as elaborated in U.S. Pat. No. 5,051,402, it has been considered not merely difficult but practically impossible to prepare a pharmaceutical composition containing cyclosporin dissolved in an aqueous medium.

As reported, the solubility of cyclosporin in water is between about 20 μg/ml to 30 μg/ml for cyclosporin A. Hence, heretofore prepared formulations incorporating cyclosporin have been prepared as oily solutions containing ethanol. However, these preparations limit the bioavailability to oral preparations and this is believed to be due to the separation of cyclosporin as a solid immediately after it comes into contact with water, such as in the mouth or eye of a patient.

In the case of injectable preparations of cyclosporin, they first must be diluted with physiological saline before intravenous administration but this is likely to result in the precipitation of cyclosporin and therefore may be considered undesirable for intravenous administration.

Surface active agents such as polyoxyethylated castor oil have been utilized as solubilizers to inject preparations in order to prevent cyclosporin from separating. However, this also may give rise to safety problems (see U.S. Pat. No. 5,051,402).

The practical usefulness of cyclosporin would be greatly enhanced if administration thereof could be effective; for example, cyclosporin's effectiveness in the treatment of ocular symptoms of Behcet's Syndrome. However, if it is

administered orally for the treatment of these symptoms, the accompanying side effects due to systemic circulation may cause adverse reactions such as hypertrichosis or renal dysfunction.

On the other hand, if oily preparations containing cyclosporin are applied directly to the eyes, irritation or a clouding of visual field may result: This plus the difficulty in formulating cyclosporin limits its use in formulations that would be useful during keratoplasty as well in the treatment of herpetic keratitis and spring catarrh.

Heretofore, as for example in U.S. Pat. No. 5,051,402, attempts have been made to dissolve sufficient cyclosporin in an aqueous solvent system so as to reach an effective concentration for treatment. Importantly, this solvent system does not contain any surface active agent such as polyoxyethylated castor oil.

Conceptually, the purpose of dissolving the cyclosporin in an aqueous solvent system is to enable contact with body fluids which would merely constitute dilution of the aqueous solvent system which hopefully would eliminate the immediate precipitation of cyclosporin when contacted with the water content of the body fluids.

For direct use in the eye, cyclosporin has been formulated with a number of pharmaceutically acceptable excipients, for example, animal oil, vegetable oil, an appropriate organic or aqueous solvent, an artificial tear solution, a natural or synthetic polymer or an appropriate membrane.

Specific examples of these pharmaceutically acceptable excipients, which may be used solely or in combination, are olive oil, arachis oil, castor oil, mineral oil, petroleum jelly, dimethyl sulfoxide, chremophor, liposomes, or liposome-like products or a silicone fluid, among others.

In summary, a great deal of effort has been expended in order to prepare a pharmaceutical composition containing cyclosporin dissolved in an aqueous medium or cyclosporin prepared as an oily solution. However, successful formulations have yet to be accomplished as evidenced by the lack of commercial products.

As hereinabove noted, it has been reported that cyclosporin has demonstrated some solubility in oily preparations containing higher fatty acid glycerides such as olive oil, peanut oil, and/or castor oil. These formulations frequently produce an unpleasant sensation when applied to the eye because of stimulation or the viscousness which is characteristic of these oils.

Another drawback of these formulations is that they contain a high concentration of oils, and oils exacerbate the symptoms of certain ocular surface diseases such as dry eyes, indicated by cyclosporin. Therefore, these oily formulations may not be clinically acceptable. Additionally, these formulations often suffer from physical instability due to cyclosporin's propensity to undergo conformational change and crystallize out. The crystallization problem has been noticed in formulations containing corn oil or medium chain triglycerides. Lastly, these formulations often have a low thermodynamic activity (degree of saturation) of cyclosporin which leads to a poorer drug bioavailability.

It may be possible to minimize the problems related to unpleasant sensation and syndrome exacerbation by reducing the oil content and dispersing the oil phase in water into an emulsion. However, it is not an easy task to formulate an ophthalmic emulsion because one indispensable class of ingredients in an emulsion system is emulsifiers, and the majority of emulsifiers is highly irritating to the eyes.

The present invention is directed to an emulsion system which utilizes higher fatty acid glycerides but in combination with polysorbate 80 which results in an emulsion with

a high comfort level and low irritation potential suitable for delivery of medications to sensitive areas such as ocular tissues.

SUMMARY OF THE INVENTION

In accordance with the present invention, a nonirritating pharmaceutical composition with high comfort level and low irritation potential suitable for delivery to sensitive areas such as ocular tissues comprises cyclosporin in admixture with an emulsifying amount of a higher fatty acid glycerol and polysorbate 80. More particularly, the composition may comprise cyclosporin A and the higher fatty acid glyceride may comprise castor oil.

Preferably, the weight ratio of the castor oil to the polysorbate 80 is between about 0.3 to about 30 and a weight ratio of the cyclosporin to castor oil is below 0.16. More preferably, the weight ratio of castor oil to polysorbate 80 is between 0.5 and 12.5, and the weight ratio of cyclosporin to castor oil is between 0.12 and 0.02.

When cyclosporin is dissolved in the oil phase in accordance with the present invention, the emulsion is found to be physically stable upon long term storage. No crystallization of cyclosporin was noticed after nine months at room temperature. Moreover, the cyclosporin emulsion is formulated in such a way that the drug has reasonably high thermodynamic activity, yet without the crystallization problem.

DETAILED DESCRIPTION

As hereinabove noted, cyclosporin is available as a mixture in which the principal ingredient is cyclosporin A with significant, but smaller, quantities of other cyclosporins such as cyclosporin B through I. However, as also hereinabove noted, the present invention may be applied to either a pure cyclosporin or to a mixture of individual cyclosporins.

The discovery on which the present invention is founded relates to a combination of a higher fatty acid glyceride and an emulsifier and dispersing agent, polysorbate 80. The selection of these components could not have been anticipated on the basis of conventional thinking.

For example, although it is well-known that cyclosporin may be used in combination with castor oil, this combination is irritating to sensitive tissues such as the eye. Thus, conventional teaching in the art is away from a formulation which utilizes a higher fatty acid glyceride, such as castor oil, and cyclosporin.

Stated another way, there is no way of deducing that the use of an emulsifier and dispersing agent such as polysorbate 80 will reduce the irritation potential of an emulsion utilizing castor oil. There are no examples of polysorbate in combination with castor oil which, when admixed to cyclosporin, produces an emulsion with a high comfort level and low irritation potential suitable for the delivery of medication to sensitive areas such as ocular tissues.

The present invention achieves a stable solution state of cyclosporin. This stable solution state is another important performance characteristic differentiating the present invention from the conventional oil systems. Cyclosporin is notorious for its tendency to precipitate out in conventional oil systems in which it is fully dissolved initially.

In accordance with the present invention, the emulsions can be further stabilized using a polyelectrolyte, or polyelectrolytes if more than one, from the family of cross-linked polyacrylates, such as carbomers and Pemulen®.

Pemulen® is a registered trademark of B. F. Goodrich for polymeric emulsifiers and commercially available from B. F. Goodrich Company, Specialty Polymers & Chemicals Division, Cleveland, Ohio. Pemulens are Acrylates/C10-30 Alkyl Acrylate Cross-Polymers. They are high molecular weight co-polymers of acrylic acid and a long chain alkyl methacrylate cross-linked with allyl ethers of pentaerythritol. They contain not less than 52.0 percent and not more than 62.0 percent of carboxylic acid groups. The viscosity of a neutralized 1.0 percent aqueous dispersion is between 9,500 and 26,500 centipoises.

In addition, the tonicity of the emulsions can be further adjusted using glycerine, mannitol, or sorbitol if desired. The pH of the emulsions can be adjusted in a conventional manner using sodium hydroxide to a near physiological pH level and while buffering agents are not required, suitable buffers may include phosphates, citrates, acetates and borates.

While the preferable medications in accordance with the present invention include cyclosporin, other chemicals which are poorly soluble in water such as indomethacin and steroids such as androgens, prednisolone, prednisolone acetate, fluorometholone, and dexamethasones, may be emulsified with castor oil and polysorbate 80 resulting in a composition with similar low irritation potential.

The invention is further illustrated by the following examples with all parts and percentages expressed by weight. The cyclosporin used in the examples was supplied by Sandoz.

Example 1

	A	B	C	D	E
Cyclosporin A	0.40%	0.20%	0.20%	0.10%	0.05%
Castor oil	5.00%	5.00%	2.50%	1.25%	0.625%
Polysorbate 80	1.00%	1.00%	1.00%	1.00%	1.00%
Pemulen ®	0.05%	0.05%	0.05%	0.05%	0.05%
Glycerine	2.20%	2.20%	2.20%	2.20%	2.20%
NaOH	qs	qs	qs	qs	qs
Purified water	qs	qs	qs	qs	qs
pH	7.2–7.6	7.2–7.6	7.2–7.6	7.2–7.6	7.2–7.6

Example 2

	A	B	C	D
Castor oil	5.00%	2.50%	1.25%	0.625%
Polysorbate 80	1.00%	1.00%	1.00%	1.00%
Pemulen ®	0.05%	0.05%	0.05%	0.05%
Glycerine	2.20%	2.20%	2.20%	2.20%
NaOH	qs	qs	qs	qs
Purified water	qs	qs	qs	qs
pH	7.2–7.6	7.2–7.6	7.2–7.6	7.2–7.6

Example 3

	A
Castor oil	2.50%
Polysorbate 80	0.75%
Carbomer 1382	0.05%
Glycerine	2.20%
NaOH	qs
Purified water	qs
pH	7.2–7.6

Example 4

	A
Castor oil	5.00%

0.05 / 1.25

-continued

Polysorbate 80	0.75%
Carbomer 981	0.05%
Glycerin	2.20%
NaOH	qs
Purified water	qs
pH	7.2–7.6

The formulations set forth in Examples 1–4 were made for treatment of keratoconjunctivitis sicca (dry eye) syndrome with Examples 2, 3 and 4 without the active ingredient cyclosporin utilized to determine the toxicity of the emulsified components.

The formulations in Examples 1–4 were applied to rabbit eyes eight times a day for seven days and were found to cause only slight to mild discomfort and slight hyperemia in the rabbit eyes. Slit lamp examination revealed no changes in the surface tissue. In addition, the cyclosporin containing castor oil emulsion, as hereinabove set forth in Examples 1A–1D, was also tested for ocular bioavailability in rabbits; and the therapeutic level of cyclosporin was found in the tissues of interest after dosage. This substantiates that cyclosporin in an ophthalmic delivery system is useful for treating dry eye as set forth in U.S. Pat. No. 4,839,342.

In addition, no difference in toxicity was found between formulations with cyclosporin (Examples 1A–1D) and formulations without cyclosporin (Examples 2–4).

The formulations set forth in Examples 1–4 were found to be physically stable upon long term storage. With regard to formulations 1A–1D, no crystallization of cyclosporin was noticed after nine months at room temperature.

Further, other higher fatty acid glycerides such as olive oil, peanut oil and the like may also be utilized with the polysorbate 80 with similar results regarding biotoxicity.

Although there has been hereinabove described a particular pharmaceutical composition in the form of a nonirritating emulsion for the purpose of illustrating the manner in which the invention may be used to advantage, it should be appreciated that the invention is not limited thereto. Accordingly, any and all modifications, variations, or equivalent arrangements, which may occur to those skilled in the art, should be considered to be within the scope of the present invention as defined in the appended claims.

What is claimed is:

1. A pharmaceutical composition comprising a nonirritating emulsion of at least one cyclosporin in admixture with a higher fatty acid glyceride, polysorbate 80 and an emulsion stabilizing amount of Pemulen in water suitable for topical application to ocular tissue.

2. The pharmaceutical composition according to claim 1 wherein the cyclosporin comprises cyclosporin A.

3. The pharmaceutical composition according to claim 2 wherein the weight ratio of the higher fatty acid glyceride to the polysorbate 80 is between about 0.3 and about 30.

4. The pharmaceutical composition according to claim 3 wherein the higher fatty acid glyceride comprises castor oil and the weight ratio of cyclosporin to castor oil is below about 0.16.

5. The composition according to claim 1 wherein the higher fatty acid glyceride and polysorbate 80 are present in amounts sufficient to prevent crystallization of cyclosporin for a period of up to about nine months.

6. A pharmaceutical emulsion comprising of cyclosporin A, castor oil, Pemulen, glycerine, polysorbate 80 water in amounts sufficient to prevent crystallization of cyclosporin A for a period of up to about nine months, said pharmaceutical emulsion being suitable for topical application to ocular tissue.

7. The pharmaceutical emulsion according to claim 6 wherein the cyclosporin A is present in an amount of between about 0.05 to and about 0.40%, by weight, the castor oil is present in an amount of between about 0.625%, by weight, and about 5.0%, by weight, the polysorbate 80 is present in an amount of about 1.0%, by weight, the Pemulen is present in an amount of about 0.05%, by weight, and the glycerine is present in an amount of about 2.2%, by weight.

8. A pharmaceutical emulsion consisting of between about 0.05% and about 0.40%, by weight, cyclosporin A, between about 0.625% and about 5.0%, by weight, castor oil, about 1.0%, by weight, polysorbate 80, about 0.05%, by weight, Pemulen and about 2.2%, by weight, glycerine in water with a pH of between about 7.2 and 7.6 suitable for topical application to ocular tissue.

* * * * *

0.05 cycl.
1.25 % cast oil

WHAT IS CLAIMED IS:

1. A method of treating an eye of a human or animal comprising:

administering to an eye of a human or animal a composition in the form of an emulsion comprising water, a hydrophobic component and a cyclosporin component in a therapeutically effective amount of less than 0.1% by weight of the composition, the weight ratio of the cyclosporin component to the hydrophobic component is less than 0.08.

2. The method of claim 1 wherein the administering step is effective in treating a condition selected from the group consisting of dry eye syndrome, phacoanaphylactic endophthalmitis, uveitis, vernal conjunctivitis, atopic keratoconjunctivitis and corneal graft rejection.

3. The method of claim 1 wherein the administering step is effective in treating dry eye syndrome.

4. The method of claim 1 wherein the blood of the human or animal has substantially no detectable concentration of the cyclosporin component.

5. The method of claim 1 wherein the blood of the human or animal has substantially no detectable concentration of the cyclosporin component as measured using a validated liquid chromatography/mass spectrometry-mass spectrometry analytical method.

6. The method of claim 1 wherein the blood of the

human or animal has a concentration of the cyclosporin component of 0.1 ng/ml or less.

7. The method of claim 1 wherein the cyclosporin component comprises a material selected from cyclosporin A, derivatives of cyclosporin A and mixtures thereof.

8. The method of claim 1 wherein the cyclosporin component comprises cyclosporin A.

9. The method of claim 1 wherein the cyclosporin component is solubilized in the hydrophobic component present in the composition.

10. The method of claim 1 wherein the hydrophobic component is present in the composition in an amount greater than 0.625% by weight of the composition.

11. The method of claim 1 wherein the hydrophobic component comprises an oily material.

12. The method of claim 1 wherein the hydrophobic component comprises an ingredient selected from the group consisting of vegetable oils, animal oils, mineral oils, synthetic oils and mixtures thereof.

13. The method of claim 1 wherein the hydrophobic component comprises castor oil.

14. The method of claim 1 wherein the administering step comprises topically administering the composition to the eye of the human.

15. The method of claim 1 wherein the composition comprises an effective amount of an emulsifier component.

16. The method of claim 1 wherein the composition comprises an effective amount of a tonicity component.

17. The method of claim 1 wherein the composition comprises an effective amount of an organic tonicity component.

18. The method of claim 1 wherein the composition comprises a polyelectrolyte component in an amount effective in stabilizing the composition.

19. The method of claim 1 wherein the composition has a pH in the range of about 7.0 to about 8.0.

20. The method of claim 1 wherein the composition has a pH in the range of about 7.2 to about 7.6.

21. A composition for treating an eye of a human or animal comprising an emulsion comprising water, a hydrophobic component, and a cyclosporin component in a therapeutically effective amount of less than 0.1% by weight, the weight ratio of the cyclosporin component to the hydrophobic component being less than 0.08.

22. The composition of claim 21 having a make-up so that when the composition is administered to an eye of a human in an effective amount in treating dry eye syndrome, the blood of the human has substantially no detectable concentration of the cyclosporin component.

23. The composition of claim 21 wherein the cyclosporin component comprises a material selected from cyclosporin A, derivatives of cyclosporin A and mixtures thereof.

24. The composition of claim 21 wherein the cyclosporin component comprises cyclosporin A.

25. The composition of claim 21 in the form of an emulsion.

26. The composition of claim 21 wherein the hydrophobic component is present in an amount greater than 0.625% by weight of the composition.

27. The composition of claim 21 wherein the hydrophobic component is an oily material.

28. The composition of claim 21 wherein the hydrophobic component comprises an ingredient selected from the group consisting of vegetable oils, animal oils, mineral oils, synthetic oils, and mixtures thereof.

29. The composition of claim 21 wherein the hydrophobic component comprises castor oil.

30. The composition of claim 21 wherein the administering step comprises topically administering the composition to the eye of the human.

31. The composition of claim 21 wherein the composition comprises an effective amount of an emulsifier

component.

32. The composition of claim 21 wherein the composition comprises an effective amount of a tonicity component.

33. The composition of claim 21 wherein the composition comprises an effective amount of an organic tonicity component.

34. The composition of claim 21 wherein the composition comprises a polyelectrolytic component in an amount effective in stabilizing the composition.

35. The composition of claim 21 wherein the composition includes water and has a pH in the range of about 7.0 to about 8.0.

36. The composition of claim 21 wherein the composition includes water and has a pH in the range of about 7.2 to about 7.6.

therapeutic and prophylactic techniques

L139 ANSWER 17 OF 73 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2004:98054 BIOSIS Full-text
DOCUMENT NUMBER: PREV200400099351
TITLE: **Cyclosporine A** delivery to the **eye**: A pharmaceutical challenge.
AUTHOR(S): Lallemand, F.; Felt-Baeyens, O.; Besseghir, K.; Behar-Cohen, F.; Gurny, R. [Reprint Author]
CORPORATE SOURCE: School of Pharmacy, University of Geneva, 30, quai E. Ansermet, CH-1211, Geneva, 4, Switzerland robert.gurny@pharm.unige.ch
SOURCE: European Journal of Pharmaceutics and Biopharmaceutics, (November 2003) Vol. 56, No. 3, pp. 307-318. print. ISSN: 0939-6411 (ISSN print).
DOCUMENT TYPE: Article
General Review; (Literature Review)
LANGUAGE: English
ENTRY DATE: Entered STN: 18 Feb 2004
Last Updated on STN: 18 Feb 2004
ABSTRACT:Systemic administration of **cyclosporine A** (CsA) is commonly used in the treatment of local ophthalmic conditions involving cytokines, such as coreal graft rejection, autoimmune uveitis and dry ***eye*** syndrome. Local administration is expected to avoid the various side effects associated with systemic delivery. However, the currently available systems using **oils** to deliver CsA topically are poorly tolerated and provide a low bioavailability. These difficulties may be overcome through formulations aimed at improving CsA water solubility (e.g. cyclodextrins), or those designed to facilitate tissue drug penetration using penetration enhancers. The use of colloidal carriers (micelles, ***emulsions*** , liposomes and nanoparticles) as well as the approach using hydrosoluble prodrugs of CsA have shown promising results. Solid devices such as shields and particles of collagen have been investigated to enhance retention time on the **eye** surface. Some of these topical formulations have shown efficacy in the treatment of extraocular diseases but were inefficient at reaching intraocular targets. Microspheres, implants and liposomes have been developed to be directly administered subconjunctivally or intravitreally in order to enhance CsA concentration in the vitreous. Although progress has been made, there is still room for improvement in CsA ocular application, as none of these formulations is ideal.
CONCEPT CODE: Biochemistry studies - Proteins, peptides and amino acids 10064
Pathology - Therapy 12512
Sense organs - Physiology and biochemistry 20004
Pharmacology - General 22002
Pharmacology - Immunological processes and allergy 22018
INDEX TERMS: Major Concepts
Pharmacology; Sense Organs (Sensory Reception)
INDEX TERMS: Parts, Structures, & Systems of Organisms
eye: sensory system; vitreous: sensory system
INDEX TERMS: Chemicals & Biochemicals
cyclosporine A: immunologic-drug, immunosuppressant-drug, ocular delivery, systemic administration, topical administration, water solubility
INDEX TERMS: Methods & Equipment
emulsions: drug delivery device; implants: drug delivery device; liposomes: drug delivery device; micelles: drug delivery device; microspheres: drug delivery device; nanoparticles: drug delivery device

ORGANISM: Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
rat (common): animal model
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates
REGISTRY NUMBER: **59865-13-3 (cyclosporine A)**

L139 ANSWER 18 OF 73 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2002:182305 BIOSIS Full-text
DOCUMENT NUMBER: PREV200200182305
TITLE: **Cyclosporine A** formulation affects its ocular distribution in rabbits.
AUTHOR(S): Kuwano, Mitsuaki [Reprint author]; Ibuki, Hajime; Morikawa, Nobuo; Ota, Atsutoshi; Kawashima, Yoichi
CORPORATE SOURCE: Ophthalmic Research Division, Santen Pharmaceutical Co., LTD., Ikoma-shi, Nara, 630-0101, Japan
kuwanom@santen.co.jp
SOURCE: Pharmaceutical Research (New York), (January, 2002) Vol. 19, No. 1, pp. 108-111. print.
CODEN: PHREEB. ISSN: 0724-8741.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 6 Mar 2002
Last Updated on STN: 6 Mar 2002
CONCEPT CODE: Sense organs - Physiology and biochemistry 20004
Pathology - Therapy 12512
Pharmacology - General 22002
Pharmacology - Drug metabolism and metabolic stimulators 22003
Pharmacology - Immunological processes and allergy 22018
Pharmacology - Sense organs, associated structures and functions 22031
INDEX TERMS: Major Concepts
Pharmacology; Sense Organs (Sensory Reception)
INDEX TERMS: Parts, Structures, & Systems of Organisms
eye: sensory system
INDEX TERMS: Chemicals & Biochemicals
HCO-60-**cyclosporine A**: immunologic-drug, immunosuppressant-drug, ophthalmic-drug; MYS-40-**cyclosporine A**: immunologic-drug, immunosuppressant-drug, ophthalmic-drug; Tween 80-**cyclosporine A**: immunologic-drug, immunosuppressant-drug, ophthalmic-drug; nonionic surfactants; **oil-cyclosporine A**: immunologic-drug, immunosuppressant-drug, ophthalmic-drug; **oil** /water **emulsion-cyclosporine A**: immunologic-drug, immunosuppressant-drug, ophthalmic-drug
INDEX TERMS: Methods & Equipment
high performance liquid chromatography: liquid chromatography, measurement method; topical application: drug administration method
INDEX TERMS: Miscellaneous Descriptors
ocular distribution; pharmacokinetics

ORGANISM: Classifier
Leporidae 86040
Super Taxa
Lagomorpha; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
rabbit: animal model, breed-Japanese white
Taxa Notes
Animals, Chordates, Lagomorphs, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Vertebrates

L139 ANSWER 19 OF 73 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 1998:104244 BIOSIS Full-text
DOCUMENT NUMBER: PREV199800104244
TITLE: **Cyclosporine** ophthalmic O/W **emulsion**: Formulation and **emulsion** characterization.
AUTHOR(S): Ding, Shulin; Olejnik, Orest
CORPORATE SOURCE: Pharmaceutical Sci., Research and Development, Allergan Inc., Irvine, CA 92612, USA
SOURCE: Pharmaceutical Research (New York), (Nov., 1997) Vol. 14, No. 11 SUPPL., pp. S41. print.
Meeting Info.: Annual Meeting of the American Association of Pharmaceutical Scientists. Boston, Massachusetts, USA. November 2-6, 1997. American Association of Pharmaceutical Scientists.
CODEN: PHREEB. ISSN: 0724-8741.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 3 Mar 1998
Last Updated on STN: 3 Mar 1998
CONCEPT CODE: Pharmacology - General 22002
Biochemistry studies - General 10060
Sense organs - General and methods 20001
Routes of immunization, infection and therapy 22100
General biology - Symposia, transactions and proceedings 00520
INDEX TERMS: Major Concepts
Pharmacology
INDEX TERMS: Chemicals & Biochemicals
cyclosporine: ophthalmic-drug, **eye** drop, formulation, ophthalmic **oil**-in-water **emulsion**, topical use
INDEX TERMS: Miscellaneous Descriptors
Meeting Abstract; Meeting Poster
ORGANISM: Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
human
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates
REGISTRY NUMBER: **59865-13-3Q** (**cyclosporine**)
63798-73-2Q (**cyclosporine**)

L139 ANSWER 20 OF 73 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 1997:77192 BIOSIS Full-text
DOCUMENT NUMBER: PREV199799383895
TITLE: Tissue concentration of nanoencapsulated radio-labelled **cyclosporin** following peroral delivery in mice or ophthalmic application in rabbits.
AUTHOR(S): Bonduelle, Sylvie; Carrier, Michel; Pimienta, Clara; Benoit, Jean-Pierre; Lenaerts, Vincent [Reprint author]
CORPORATE SOURCE: Lab. Inc., 140 rue Blainville Est., Sainte-Therese, Quebec J7E 1M5, Canada
SOURCE: European Journal of Pharmaceutics and Biopharmaceutics, (1996) Vol. 42, No. 6, pp. 313-319.
ISSN: 0939-6411.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 26 Feb 1997
Last Updated on STN: 26 Feb 1997

ABSTRACT:Cold and tritiated **cyclosporin A** was entrapped into polyisohexylcyanoacrylate nanocapsules dispersed in an aqueous vehicle. This preparation was then instilled in the **eyes** of rabbits. After several time intervals post-dose, the animals were sacrificed and their ***eyes*** dissected. Radioactivity was determined in the different tissues. Concentrations superior to the therapeutic level were noted for over 48 h in the cornea, and 24 h in the posterior and anterior sclera. In the retina with choroid and in the anterior uvea, concentrations peaked at 1 and 6 h post-dose respectively. A secondary increase of the tissue concentration was then observed from 12 h post-dose on, with levels above the therapeutic threshold being observed at 24 h post-dose. The formulation was well tolerated, no clinical sign of irritation was noted. Thus nanocapsules may be an interesting alternative to the olive **oil** solution or ointments tested so far for the delivery of **cyclosporin A** to the **eye**. In addition to being safely applied locally, they maintain therapeutic levels in several tissues for longer time periods than the solution in olive **oil** and allow therapeutic concentrations to be reached in the anterior uvea and retina with choroid, which has not been observed with the olive **oil** solution. The same type of formulation was administered perorally to fasted mice and compared to a commercial **emulsion** and a control ***emulsion*** (same preparation as nanocapsules without polymeric wall). As compared to the **emulsions**, nanoencapsulated **cyclosporin** had an increased bioavailability (blood AUC = 20500 mu-g h ml-1 for nanocapsules vs. 1650 and 1300 mu-g h ml-1 for the **emulsions**), a slower clearance from the blood and a reduced uptake by organs rich in reticuloendothelial cells (liver AUC = 22% of blood AUC for nanocapsules vs. 189% and 311% for the ***emulsions***). Concentration in the kidneys was lower with nanocapsules (kidneys AUC 9% of blood AUC for nanocapsules vs. 34% and 92% for the ***emulsions***), indicating that nanocapsules, in addition to allowing an increased bioavailability, also bear some promise at reducing the nephrotoxic adverse reactions of **cyclosporin A**.

CONCEPT CODE: Pharmacology - Drug metabolism and metabolic stimulators 22003
Pharmacology - Immunological processes and allergy 22018
Pharmacology - Sense organs, associated structures and functions 22031
Routes of immunization, infection and therapy 22100
INDEX TERMS: Major Concepts
Pharmacology
INDEX TERMS: Chemicals & Biochemicals
CYCLOSPORIN
INDEX TERMS: Miscellaneous Descriptors
BIOAVAILABILITY; IMMUNOSUPPRESSANT-DRUG; NANOENCAPSULATED RADIOLABELLED **CYCLOSPORIN**;

NEW ZEALAND WHITE RABBIT; NMRI MOUSE; OPHTHALMIC APPLICATION; OPHTHALMIC-DRUG; PERORAL DELIVERY; PHARMACOKINETICS; PHARMACOLOGY; TISSUE CONCENTRATION

ORGANISM: Classifier
Leporidae 86040
Super Taxa
Lagomorpha; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
Leporidae
Taxa Notes
Animals, Chordates, Lagomorphs, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Vertebrates

ORGANISM: Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
Muridae
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates

REGISTRY NUMBER: **59865-13-3Q** (**CYCLOSPORIN**)
79217-60-0Q (**CYCLOSPORIN**)

L139 ANSWER 21 OF 73 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 1997:161965 BIOSIS Full-text
DOCUMENT NUMBER: PREV199799461168
TITLE: Tissue concentration of nanoencapsulated radio-labelled **cyclosporin** following peroral delivery in mice or ophthalmic application in rabbits.
AUTHOR(S): Bonduelle, Sylvie; Carrier, Michel; Pimienta, Clara; Benoit, Jean-Pierre; Lenaerts, Vincent [Reprint author]
CORPORATE SOURCE: Labopharm Inc., 140 rue Blainville Est, Sainte-Therese, PQ J7E 1M5, Canada
SOURCE: European Journal of Pharmaceutics and Biopharmaceutics, (1996) Vol. 42, No. 5, pp. 313-319.
ISSN: 0939-6411.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 15 Apr 1997
Last Updated on STN: 15 Apr 1997

ABSTRACT:Cold and tritiated **cyclosporin A** was entrapped into polyisohexylcyanoacrylate nanocapsules dispersed in an aqueous vehicle. This preparation was then instilled in the **eyes** of rabbits. After several time intervals post-dose, the animals were sacrificed and their ***eyes*** dissected. Radioactivity was determined in the different tissues. Concentrations superior to the therapeutic level were noted for over 48 h in the cornea, and 24 h in the posterior and anterior sclera. In the retina with choroid and in the anterior uvea, concentrations peaked at 1 and 6 h post-dose respectively. A secondary increase of the tissue concentration was then observed from 12 h post-dose on, with levels above the therapeutic threshold being observed at 24 h post-dose. The formulation was well tolerated, no clinical sign of irritation was noted. Thus nanocapsules may be an interesting alternative to the olive **oil** solution or ointments tested so far for the delivery of **cyclosporin A** to the **eye**. In addition to being safely applied locally, they maintain therapeutic levels in several tissues for longer time periods than the solution in olive **oil** and allow therapeutic concentrations to be reached in the anterior uvea and retina with choroid, which has not been observed with the olive **oil**

solution. The same type of formulation was administered perorally to fasted mice and compared to a commercial **emulsion** and a control ***emulsion*** (same preparation as nanocapsules without polymeric wall). As compared to the **emulsions**, nanoencapsulated **cyclosporin** had an increased bioavailability (blood AUC = 20500 mu-g h ml-1 for nanocapsules vs. 1650 and 1300 mu-g h ml-1 for the **emulsions**), a slower clearance from the blood and a reduced uptake by organs rich in reticuloendothelial cells (liver AUC = 22% of blood AUC for nanocapsules vs. 189% and 311% for the ***emulsions***). Concentration in the kidneys was lower with nanocapsules (kidneys AUC = 9% of blood AUC for nanocapsules vs. 34% and 92% for the ***emulsions***), indicating that nanocapsules, in addition to allowing an increased bioavailability, also bear some promise at reducing the nephrotoxic adverse reactions of **cyclosporin A**.

CONCEPT CODE: Pharmacology - Drug metabolism and metabolic stimulators 22003
Pharmacology - Immunological processes and allergy 22018
Pharmacology - Sense organs, associated structures and functions 22031
Routes of immunization, infection and therapy 22100

INDEX TERMS: Major Concepts
Pharmacology

INDEX TERMS: Chemicals & Biochemicals
CYCLOSPORIN

INDEX TERMS: Miscellaneous Descriptors
BIOAVAILABILITY; IMMUNOSUPPRESSANT-DRUG; NANOENCAPSULATED RADIOLABELLED **CYCLOSPORIN**; OPHTHALMIC APPLICATION; OPHTHALMIC-DRUG; PERORAL DELIVERY; PHARMACEUTICAL FORMULATION; PHARMACOKINETICS; PHARMACOLOGY; TISSUE CONCENTRATION

ORGANISM: Classifier
Leporidae 86040
Super Taxa
Lagomorpha; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
rabbit
Taxa Notes
Animals, Chordates, Lagomorphs, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Vertebrates

ORGANISM: Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
mouse
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates

REGISTRY NUMBER: **59865-13-3Q** (**CYCLOSPORIN**)
79217-60-0Q (**CYCLOSPORIN**)

L139 ANSWER 22 OF 73 EMBASE

ACCESSION NUMBER: 2004467671 EMBASE Full-text
TITLE: The economic burden of dry eye: A conceptual framework and preliminary assessment.
AUTHOR: Reddy P.; Grad O.; Rajagopalan K.
CORPORATE SOURCE: P. Reddy, Abt Associates Inc., 55 Wheeler Street,

Cambridge, MA 02138, United States.
prabashni_reddy@abtassoc.com
SOURCE: Cornea, (2004) Vol. 23, No. 8, pp. 751-761. .
Refs: 84
ISSN: 0277-3740 CODEN: CORNDB.
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 012 Ophthalmology
036 Health Policy, Economics and Management
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 19 Nov 2004
Last Updated on STN: 19 Nov 2004
ABSTRACT: Purpose: To develop a conceptual framework for analyzing the economic burden of dry eye and a preliminary assessment of key factors that contribute to that burden. Methods: The MEDLINE database was searched from 1966 to May 2003 combining the term "dry eye" with various economic terms. In addition, individual interviews with a panel of clinicians were conducted to provide additional insight on resource use. Results: Direct resource utilization among dry eye sufferers includes healthcare professional visits, nonpharmacological therapies, pharmacological treatments, and surgical procedures, with the latter 2 categories being the major cost drivers. Complementary and alternative medicine (CAM) therapies are a newly recognized component of the dry eye economic burden. There is wide variation in patterns of diagnosis and treatment, but current therapies are not universally effective. Given the prevalence of the condition, indirect costs may be large. Utilization of pharmacological therapies, especially those other than tear replacements, the extent of CAM use, cost of complications of surgical procedures, and indirect costs are unknown. The natural history and probability that patients will transition between therapies, based on underlying disease severity, need to be elucidated. Conclusions: Dry eye is a prevalent condition with the potential for a high economic burden; additional studies are needed to further characterize the economic impact.

CONTROLLED TERM: Medical Descriptors:
***dry eye: DI, diagnosis**
***dry eye: DM, disease management**
***dry eye: DT, drug therapy**
***dry eye: ET, etiology**
***dry eye: SI, side effect**
***dry eye: SU, surgery**
***dry eye: TH, therapy**
*economic aspect
disease severity
resource management
health care personnel
economic evaluation
health care cost
clinical feature
practice guideline
treatment indication
cataract: SI, side effect
glaucoma: SI, side effect
superinfection: SI, side effect
drug indication
alternative medicine
acupuncture
diet supplementation

blepharitis: DT, drug therapy
eye surgery
cost benefit analysis
drug cost
medical fee
keratomileusis
human
article
priority journal
Drug Descriptors:
amiodarone: AE, adverse drug reaction
antidepressant agent: AE, adverse drug reaction
neuroleptic agent: AE, adverse drug reaction
isotretinoin: AE, adverse drug reaction
interferon: AE, adverse drug reaction
artificial tear
corticosteroid: AE, adverse drug reaction
corticosteroid: DT, drug therapy
corticosteroid: PE, pharmacoeconomics
corticosteroid: TP, topical drug administration
cyclosporin: DT, drug therapy
cyclosporin: PE, pharmacoeconomics
cyclosporin: TP, topical drug administration
linseed oil: DT, drug therapy
linseed oil: PE, pharmacoeconomics
fish oil: DT, drug therapy
fish oil: PE, pharmacoeconomics
antibiotic agent: DT, drug therapy
antibiotic agent: PE, pharmacoeconomics
antibiotic agent: PO, oral drug administration
antibiotic agent: TP, topical drug administration
pilocarpine: DT, drug therapy
pilocarpine: PO, oral drug administration
cevimeline: DT, drug therapy
nonsteroid antiinflammatory agent: DT, drug therapy
nonsteroid antiinflammatory agent: PE, pharmacoeconomics
tsukubaenolide: DT, drug therapy
eledoisin: PD, pharmacology
purinergic receptor stimulating agent: PD, pharmacology
n,n dimethylphenethylamine
androgen
estrogen
retinol
botulinum toxin
antioxidant: PO, oral drug administration
zidovudine
calcium
antivirus agent
antihistaminic agent: DT, drug therapy
antihistaminic agent: PE, pharmacoeconomics
unclassified drug

CAS REGISTRY NO.: (amiodarone) 1951-25-3, 19774-82-4, 62067-87-2; (isotretinoin) 4759-48-2; (**cyclosporin**) 79217-60-0; (linseed oil) 8001-26-1; (fish oil) 8016-13-5; (pilocarpine) 148-72-1, 54-71-7, 92-13-7; (cevimeline) 107220-27-9, 107220-28-0, 107233-08-9, 153504-70-2; (tsukubaenolide) 104987-11-3; (eledoisin) 69-25-0; (retinol) 68-26-8, 82445-97-4; (zidovudine) 30516-87-1; (calcium) 7440-70-2

CHEMICAL NAME: Af 2975

L139 ANSWER 23 OF 73 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2004180365 EMBASE Full-text
TITLE: Lacrimostimulants and lacrimomimetics.
AUTHOR: Grahn B.H.; Storey E.S.
CORPORATE SOURCE: B.H. Grahn, Dept. of Small Animal Clinical Sci., Western College of Veterinary Med., University of Saskatchewan, 52 Campus Drive, Saskatoon, Sask. S7N 5B4, Canada. bruce.grahn@usask.ca
SOURCE: Veterinary Clinics of North America - Small Animal Practice, (2004) Vol. 34, No. 3, pp. 739-753. .
Refs: 64
ISSN: 0195-5616 CODEN: VCNAA6
PUBLISHER IDENT.: S 0195-5616(03)00187-6
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
012 Ophthalmology
030 Pharmacology
037 Drug Literature Index
052 Toxicology
LANGUAGE: English
ENTRY DATE: Entered STN: 13 May 2004
Last Updated on STN: 13 May 2004
CONTROLLED TERM: Medical Descriptors:
*tear film
***lacrimal gland disease: DT, drug therapy**
***lacrimal gland disease: ET, etiology**
clinical feature
diagnostic procedure
treatment outcome
lacrimal gland
goblet cell
nictitating membrane
meibomian gland
ophthalmology
veterinary medicine
drug tissue level
drug blood level
drug structure
lacrimation
dry eye: DT, drug therapy
nonhuman
review
CONTROLLED TERM: Drug Descriptors:
*immunomodulating agent: AN, drug analysis
*immunomodulating agent: CM, drug comparison
*immunomodulating agent: CR, drug concentration
*immunomodulating agent: DT, drug therapy
*immunomodulating agent: TO, drug toxicity
*immunomodulating agent: PD, pharmacology
*immunomodulating agent: TP, topical drug administration
*cholinergic receptor stimulating agent: CB, drug combination
*cholinergic receptor stimulating agent: DT, drug therapy
*cholinergic receptor stimulating agent: TO, drug toxicity
*cholinergic receptor stimulating agent: PD, pharmacology
*cholinergic receptor stimulating agent: PO, oral drug administration

*cholinergic receptor stimulating agent: TP, topical drug administration
*electrolyte: DT, drug therapy
*electrolyte: PD, pharmacology
cyclosporin: AN, drug analysis
cyclosporin: CM, drug comparison
cyclosporin: CR, drug concentration
cyclosporin: DT, drug therapy
cyclosporin: TO, drug toxicity
cyclosporin: PD, pharmacology
cyclosporin: TP, topical drug administration
tsukubaenolide: AN, drug analysis
tsukubaenolide: CM, drug comparison
tsukubaenolide: DT, drug therapy
tsukubaenolide: TO, drug toxicity
tsukubaenolide: PD, pharmacology
tsukubaenolide: TP, topical drug administration
rapamycin: CM, drug comparison
rapamycin: DT, drug therapy
rapamycin: PD, pharmacology
rapamycin: TP, topical drug administration
pilocarpine: CB, drug combination
pilocarpine: DT, drug therapy
pilocarpine: TO, drug toxicity
pilocarpine: PD, pharmacology
pilocarpine: PO, oral drug administration
pilocarpine: TP, topical drug administration
calcineurin inhibitor: AN, drug analysis
calcineurin inhibitor: CM, drug comparison
calcineurin inhibitor: DT, drug therapy
calcineurin inhibitor: TO, drug toxicity
calcineurin inhibitor: PD, pharmacology
calcineurin inhibitor: TP, topical drug administration
nonsteroid antiinflammatory agent: CB, drug combination
nonsteroid antiinflammatory agent: DT, drug therapy
anesthetic agent: CB, drug combination
anesthetic agent: DT, drug therapy
polyvinyl alcohol: CB, drug combination
polyvinyl alcohol: DT, drug therapy
carboxymethylcellulose: DT, drug therapy
hydroxypropylmethylcellulose: CB, drug combination
hydroxypropylmethylcellulose: DT, drug therapy
hydroxymethylcellulose: DT, drug therapy
methylcellulose: DT, drug therapy
polymer: CB, drug combination
polymer: DT, drug therapy
dextran 70: CB, drug combination
dextran 70: DT, drug therapy
povidone: CB, drug combination
povidone: DT, drug therapy
dextran: CB, drug combination
dextran: DT, drug therapy
glycerol: CB, drug combination
glycerol: DT, drug therapy
polycarbophil: CB, drug combination
polycarbophil: DT, drug therapy
macrogol: CB, drug combination
macrogol: DT, drug therapy
petroleum: CB, drug combination
petroleum: DT, drug therapy

mineral oil: CB, drug combination
mineral oil: DT, drug therapy
lanolin: CB, drug combination
lanolin: DT, drug therapy
hyaluronic acid derivative: DT, drug therapy
benzalkonium chloride
thiomersal
chlorbutol
unindexed drug
akwa tears
liquifilm forte
liquifilm tears
dry eyes
hypotears
hypotears pf
ocutears
ocutears pf
tearfair solution
theratears
celluvisc lubricant
refresh tears
lacri lubricant
refresh plus
isopto alkaline
comfort tears
murocell
genteal lubricating eye drops
tearisol
teargard
lubrifair
naphazoline
tears renewed
adsorbotear
bio tears
tear naturale ii
tear naturale
free tears plus
lubri tears
moisture drops
aquasite
lubrifair solution
murine eye lubricant
natures tears
duratears naturale
lacrilube
lacrilube np
lacrilube sop
refresh pm
duolobe
lipotears
ocutube
petroleum ointment
hyashield
hyashield nite
dry eye therapy
eye lube a

CAS REGISTRY NO.: (**cyclosporin**) 79217-60-0; (tsukubaenolide) 104987-11-3; (rapamycin) 53123-88-9; (pilocarpine) 148-72-1, 54-71-7, 92-13-7; (polyvinyl alcohol) 37380-95-3, 9002-89-5; (carboxymethylcellulose) 8050-38-2, 9000-11-7,

9004-32-4, 9050-04-8; (hydroxypropylmethylcellulose) 9004-65-3; (hydroxymethylcellulose) 37353-59-6; (methylcellulose) 79484-92-7, 9004-67-5; (povidone) 9003-39-8; (dextran) 87915-38-6, 9014-78-2; (glycerol) 56-81-5; (polycarbophil) 9003-97-8; (macrogol) 25322-68-3; (petroleum) 8002-05-9; (lanolin) 70321-63-0, 8006-54-0, 8020-84-6, 8031-44-5, 8038-28-6; (benzalkonium chloride) 66331-30-4, 78244-97-0, 81181-32-0; (thiomersal) 54-64-8; (chlorbutol) 57-15-8; (naphazoline) 5144-52-5, 550-99-2, 835-31-4

CHEMICAL NAME: (1) Akwa tears; (2) Liquifilm forte; (3) Liquifilm tears; (4) Dry eyes; (5) Hypotears; (6) Hypotears pf; (7) Ocutears; (8) Ocutears pf; (9) Tearfair solution; (10) Theratears; (11) Celluvisc lubricant; (12) Refresh tears; (13) Lacri lubricant; (14) Refresh plus; (15) Cellufresh; (16) Isopto alkaline; (17) Isopto tears; (18) Comfort tears; (19) Murocell; (20) Genteal lubricating eye drops; (21) Tearisol; (22) Teargard; (23) Lubrifair; (24) Clear eyes; (25) Tears renewed; (26) Adsorbotear; (27) Bio tears; (28) Tear naturale ii; (29) Tear naturale; (30) Free tears plus; (31) Lubri tears; (32) Moisture drops; (33) Aquasite; (34) Hypotears; (35) Hypotears pf; (36) Lubrifair solution; (37) Murine eye lubricant; (38) Natures tears; (39) Duratears naturale; (40) Lacrilube; (41) Lacrilube np; (42) Lacrilube sop; (43) Refresh pm; (44) Duolobe; (45) Lipotears; (46) Ocutube; (47) Petroleum ointment; (48) Hyashield; (49) Hyashield nite; (50) Dry eye therapy; (51) Eye lube a; Fk 506

COMPANY NAME: (10) Advanced Vision Research; (18) Barnes Hind; (22) Med tec; (25) Akorn; (33) Ciba Vision; (35) Iolab; (37) Ross; (38) Rugby; (39) Alcon; (43) Allergan; (45) Coopervision; (46) Ocumed; (47) Pharmafair; (49) I-Med; (50) Bausch and Lomb; (51) Optoptics

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ACCESSION NUMBER: 2004505791 EMBASE Full-text

TITLE: Immunomodulatory therapy in ophthalmology - Is there a place for topical application?.

AUTHOR: Bertelmann E.; Pleyer U.

CORPORATE SOURCE: E. Bertelmann, Augenklinik Charite, Universitatsmedizin Berlin, Campus Virchow Klinikum, Augustenburger Platz 1, DE-13353 Berlin, Germany. eckart.bertelmann@charite.de

SOURCE: Ophthalmologica, (2004) Vol. 218, No. 6, pp. 359-367. .
Refs: 71
ISSN: 0030-3755 CODEN: OPHTAD

COUNTRY: Switzerland

DOCUMENT TYPE: Journal; General Review

FILE SEGMENT: 012 Ophthalmology
026 Immunology, Serology and Transplantation
037 Drug Literature Index
038 Adverse Reactions Titles
039 Pharmacy

LANGUAGE: English

SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 9 Dec 2004
Last Updated on STN: 9 Dec 2004

ABSTRACT: Topical corticosteroids, although effective in the treatment of ocular immune-mediated diseases, are well known for their ocular side-effects. Not surprisingly, a variety of alternative immunomodulatory agents have been

tested for topical use including cyclosporin A (CsA), mycophenolate mofetil (MMF), tacrolimus (FK506), rapamycin (sirolimus) and leflunomide. Local application bears the possibility to avoid the severe side-effects of systemic therapy. The effect of topical therapy is naturally restricted to local immune response mechanisms, such as antigen presentation by Langerhans and dendritic cells. Moreover, many immunomodulatory agents (e.g. CsA) are lipophilic and thus have low water solubility and penetrate insufficiently intraocularly, often being stored in the lipophilic corneal epithelial barrier. Therefore, the therapeutical success is limited for intra-ocular immune-mediated diseases like anterior uveitis. However, a multitude of strategies have been introduced to circumvent these problems including complexing substances such as cyclodextrins (CDs) and liposomes. In the prevention and treatment of transplant rejection after keratoplasty, many attempts to introduce topical immunomodulatory therapy have failed; on the other hand, further therapeutic options not primarily expected are being evaluated today such as treatment of severe keratoconjunctivitis sicca. In our own studies, we investigated the pharmacokinetics of topical treatment with different agents including MMF and evaluated the efficacy of topical treatment in animal models for uveitis and keratoplasty. Taken together, topical immunomodulatory therapy will not replace systemic therapy but further treatment options can be expected.

CONTROLLED TERM: Medical Descriptors:
*immunomodulation
drug mechanism
drug activity
drug synthesis
drug formulation
drug bioavailability
acquired immune deficiency syndrome: DT, drug therapy
cornea disease: DT, drug therapy
cornea disease: PC, prevention
dry eye: DT, drug therapy
eye disease: DT, drug therapy
nephrotoxicity: SI, side effect
graft rejection: CO, complication
graft rejection: DT, drug therapy
graft rejection: PC, prevention
penetrating keratoplasty
immunopathology: DT, drug therapy
treatment outcome
side effect: SI, side effect
topical treatment
immune response
antigen presentation
Langerhans cell
dendritic cell
lipophilicity
drug solubility
drug penetration
iridocyclitis: DT, drug therapy
treatment failure
disease severity
keratoconjunctivitis sicca: DT, drug therapy
drug tissue level
aqueous solution
gel
rheumatoid arthritis: DT, drug therapy
virus infection: DT, drug therapy
herpes simplex keratitis: DT, drug therapy

atopy: DT, drug therapy
vernal conjunctivitis: DT, drug therapy
cornea ulcer: DT, drug therapy
Sjoegren syndrome: DT, drug therapy
graft versus host reaction: CO, complication
graft versus host reaction: DT, drug therapy
graft versus host reaction: PC, prevention
postoperative complication: CO, complication
postoperative complication: DT, drug therapy
human
nonhuman
clinical trial
review

CONTROLLED TERM: Drug Descriptors:
*immunomodulating agent: AE, adverse drug reaction
*immunomodulating agent: AD, drug administration
*immunomodulating agent: AN, drug analysis
*immunomodulating agent: CB, drug combination
*immunomodulating agent: CM, drug comparison
*immunomodulating agent: CR, drug concentration
*immunomodulating agent: DO, drug dose
*immunomodulating agent: DT, drug therapy
*immunomodulating agent: IP, intraperitoneal drug administration
*immunomodulating agent: PO, oral drug administration
*immunomodulating agent: PA, parenteral drug administration
*immunomodulating agent: PR, pharmaceutics
*immunomodulating agent: PK, pharmacokinetics
*immunomodulating agent: PD, pharmacology
*immunomodulating agent: TP, topical drug administration
*cyclosporin A: AN, drug analysis
*cyclosporin A: CB, drug combination
*cyclosporin A: CM, drug comparison
*cyclosporin A: CR, drug concentration
*cyclosporin A: DO, drug dose
*cyclosporin A: DT, drug therapy
*cyclosporin A: PR, pharmaceutics
*cyclosporin A: PK, pharmacokinetics
*cyclosporin A: PD, pharmacology
***cyclosporin A: TP, topical drug administration**
*mycophenolic acid 2 morpholinoethyl ester: CT, clinical trial
*mycophenolic acid 2 morpholinoethyl ester: CB, drug combination
*mycophenolic acid 2 morpholinoethyl ester: CM, drug comparison
*mycophenolic acid 2 morpholinoethyl ester: CR, drug concentration
*mycophenolic acid 2 morpholinoethyl ester: DT, drug therapy
*mycophenolic acid 2 morpholinoethyl ester: PR, pharmaceutics
*mycophenolic acid 2 morpholinoethyl ester: PK, pharmacokinetics
*mycophenolic acid 2 morpholinoethyl ester: PD, pharmacology
*tsukubaenolide: AE, adverse drug reaction
*tsukubaenolide: CM, drug comparison
*tsukubaenolide: DT, drug therapy
*tsukubaenolide: PR, pharmaceutics

*tsukubaenolide: PD, pharmacology
*tsukubaenolide: TP, topical drug administration
*rapamycin: AE, adverse drug reaction
*rapamycin: AN, drug analysis
*rapamycin: CM, drug comparison
*rapamycin: IP, intraperitoneal drug administration
*rapamycin: PA, parenteral drug administration
*rapamycin: PD, pharmacology
prednisolone acetate: PD, pharmacology
macrolide: AN, drug analysis
macrolide: CB, drug combination
macrolide: CM, drug comparison
macrolide: CR, drug concentration
macrolide: DO, drug dose
macrolide: DT, drug therapy
macrolide: PR, pharmaceutics
macrolide: PK, pharmacokinetics
macrolide: PD, pharmacology
macrolide: TP, topical drug administration
amphotericin B: PR, pharmaceutics
chloramphenicol: PR, pharmaceutics
carbonate dehydratase inhibitor: PR, pharmaceutics
nonsteroid antiinflammatory agent: PR, pharmaceutics
diclofenac: PR, pharmaceutics
thalidomide: PR, pharmaceutics
liposome: PR, pharmaceutics
everolimus: PO, oral drug administration
everolimus: PD, pharmacology
steroid: CB, drug combination
steroid: CM, drug comparison
azathioprine: CB, drug combination
azathioprine: CM, drug comparison
corticosteroid: AE, adverse drug reaction
corticosteroid: DT, drug therapy
corticosteroid: TP, topical drug administration
cyclodextrin: PR, pharmaceutics
oligosaccharide: PR, pharmaceutics
eye drops: PR, pharmaceutics
eye drops: TP, topical drug administration
eye ointment: PR, pharmaceutics
eye ointment: TP, topical drug administration
chitosan: PR, pharmaceutics
chitosan: TP, topical drug administration
water oil cream: PR, pharmaceutics
water oil cream: TP, topical drug administration

CAS REGISTRY NO.: (cyclosporin A) 59865-13-3, 63798-73-2; (mycophenolic acid 2 morpholinoethyl ester) 116680-01-4, 128794-94-5; (tsukubaenolide) 104987-11-3; (rapamycin) 53123-88-9; (prednisolone acetate) 52-21-1, 52628-64-5; (amphotericin B) 1397-89-3, 30652-87-0; (chloramphenicol) 134-90-7, 2787-09-9, 56-75-7; (diclofenac) 15307-79-6, 15307-86-5; (thalidomide) 50-35-1; (everolimus) 159351-69-6; (azathioprine) 446-86-6; (cyclodextrin) 12619-70-4; (chitosan) 9012-76-4

CHEMICAL NAME: Fk 506

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ACCESSION NUMBER: 2004199621 EMBASE Full-text

TITLE: Vernal keratoconjunctivitis.

AUTHOR: Bonini S.; Coassin M.; Aronni S.; Lambiase A.
CORPORATE SOURCE: S. Bonini, Interdisciplinary Ctr. Biomed. Res., Laboratory of Ophthalmology, University of Rome, Via Emilio Longoni 83, 00155 Rome, Italy. sbonini@mclink.it
SOURCE: Eye, (2004) Vol. 18, No. 4, pp. 345-351. .
Refs: 69
ISSN: 0950-222X CODEN: EYEEEC
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
012 Ophthalmology
026 Immunology, Serology and Transplantation
037 Drug Literature Index
038 Adverse Reactions Titles
039 Pharmacy
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20 May 2004
Last Updated on STN: 20 May 2004
ABSTRACT: Vernal keratoconjunctivitis (VKC) is an allergic eye disease that especially affects young boys. The most common symptoms are itching, photophobia, burning, and tearing. The most common signs are giant papillae, superficial keratitis, and conjunctival hyperaemia. Patients with VKC frequently have a family or medical history of atopic diseases, such as asthma, rhinitis, and eczema. However, VKC is not associated with a positive skin test or RAST in 42-47% of patients, confirming that it is not solely an IgE-mediated disease. On the basis of challenge studies as well as immunohistochemical and mediator studies, a Th2-driven mechanism with the involvement of mast cells, eosinophils, and lymphocytes has been suggested. Th2 lymphocytes are responsible for both hyperproduction of IgE (interleukin 4, IL-4) and for differentiation and activation of mast cells (IL-3) and eosinophils (IL-5). Other studies have demonstrated the involvement of neural factors such as substance P and NGF in the pathogenesis of VKC, and the overexpression of oestrogen and progesterone receptors in the conjunctiva of VKC patients has introduced the possible involvement of sex hormones. Thus, the pathogenesis of VKC is probably multifactorial, with the interaction of the immune, nervous, and endocrine systems. The clinical management of VKC requires a swift diagnosis, correct therapy, and evaluation of the prognosis. The diagnosis is generally based on the signs and symptoms of the disease, but in difficult cases can be aided by conjunctival scraping, demonstrating the presence of infiltrating eosinophils. Therapeutic options are many, in most cases topical, and should be chosen on the basis of the severity of the disease. The most effective drugs, steroids, should however be carefully administered, and only for brief periods, to avoid secondary development of glaucoma. A 2% solution of **cyclosporine** in olive oil or in castor oil should be considered as an alternative. The long-term prognosis of patients is generally good; however 6% of patients develop corneal damage, cataract, or glaucoma.

CONTROLLED TERM: Medical Descriptors:
***vernal conjunctivitis: DI, diagnosis**
***vernal conjunctivitis: DT, drug therapy**
***vernal conjunctivitis: ET, etiology**
allergic disease: DI, diagnosis
allergic disease: DT, drug therapy
allergic disease: ET, etiology
symptomatology
pruritus
photophobia
burning sensation

lacrimation
  keratitis
  conjunctival hyperemia
family history
anamnesis
disease association
skin test
immunopathogenesis
immunohistochemistry
Th2 cell
mast cell
eosinophil
lymphocyte activation
immunoglobulin production
cell differentiation
gene overexpression
diagnostic value
prognosis
cell infiltration
treatment planning
disease severity
  glaucoma: SI, side effect
drug efficacy
drug formulation
  cornea injury: CO, complication
  cataract: CO, complication
outcomes research
human
review
Drug Descriptors:
immunoglobulin E: EC, endogenous compound
interleukin 4: EC, endogenous compound
interleukin 3: EC, endogenous compound
interleukin 5: EC, endogenous compound
substance P: EC, endogenous compound
nerve growth factor: EC, endogenous compound
estrogen receptor: EC, endogenous compound
progesterone receptor: EC, endogenous compound
sex hormone: EC, endogenous compound
steroid: AE, adverse drug reaction
steroid: DT, drug therapy
steroid: PD, pharmacology
steroid: TP, topical drug administration
  cyclosporin A: CB, drug combination
  cyclosporin A: DT, drug therapy
  cyclosporin A: PR, pharmaceutics
  olive oil: CB, drug combination
  olive oil: DT, drug therapy
  olive oil: PR, pharmaceutics
castor oil: CB, drug combination
castor oil: DT, drug therapy
castor oil: PR, pharmaceutics
cromoglycate disodium: DT, drug therapy
cromoglycate disodium: PD, pharmacology
cromoglycate disodium: TP, topical drug administration
lodoxamide trometamol: DT, drug therapy
lodoxamide trometamol: PD, pharmacology
lodoxamide trometamol: TP, topical drug administration
nedocromil sodium: DT, drug therapy
nedocromil sodium: PD, pharmacology

nedocromil sodium: TP, topical drug administration
spaglumic acid: DT, drug therapy
spaglumic acid: PD, pharmacology
spaglumic acid: TP, topical drug administration
antiallergic agent: DT, drug therapy
antiallergic agent: PD, pharmacology
antiallergic agent: TP, topical drug administration
antihistaminic agent: CM, drug comparison
antihistaminic agent: DT, drug therapy
antihistaminic agent: PD, pharmacology
antihistaminic agent: PO, oral drug administration
antihistaminic agent: TP, topical drug administration
nonsteroid antiinflammatory agent: DT, drug therapy
nonsteroid antiinflammatory agent: PD, pharmacology
nonsteroid antiinflammatory agent: TP, topical drug administration
acetylsalicylic acid: CM, drug comparison
acetylsalicylic acid: DT, drug therapy
acetylsalicylic acid: PD, pharmacology
montelukast: CM, drug comparison
montelukast: DT, drug therapy
montelukast: PD, pharmacology
montelukast: PO, oral drug administration
unclassified drug

CAS REGISTRY NO.: (immunoglobulin E) 37341-29-0; (substance P) 33507-63-0; (nerve growth factor) 9061-61-4; (**cyclosporin A**) **59865-13-3**, 63798-73-2; (olive oil) 8001-25-0; (castor oil) 8001-79-4; (cromoglycate disodium) 15826-37-6, 16110-51-3, 93356-79-7, 93356-84-4; (lodoxamide trometamol) 63610-09-3; (nedocromil sodium) 69049-74-7; (acetylsalicylic acid) 493-53-8, 50-78-2, 53663-74-4, 53664-49-6, 63781-77-1; (montelukast) 151767-02-1, 158966-92-8

CHEMICAL NAME: Aspirin

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ACCESSION NUMBER: 2004309369 EMBASE Full-text

TITLE: Sjogren's syndrome.

AUTHOR: Venables P.J.W.

CORPORATE SOURCE: Dr. P.J.W. Venables, Kennedy Inst. of Rheumatology Div., Imperial College School of Medicine, Dept. of Viral Immunorheumatology, 1 Aspenlea Road, London W6 8LH, United Kingdom. p.venables@imperial.ac.uk

SOURCE: Best Practice and Research in Clinical Rheumatology, (2004) Vol. 18, No. 3, pp. 313-329. .
Refs: 48
ISSN: 1521-6942 CODEN: BPRCC7

PUBLISHER IDENT.: S 1521-6942(04)00036-1

COUNTRY: United Kingdom

DOCUMENT TYPE: Journal; General Review

FILE SEGMENT: 005 General Pathology and Pathological Anatomy
030 Pharmacology
031 Arthritis and Rheumatism
037 Drug Literature Index
038 Adverse Reactions Titles

LANGUAGE: English

SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 5 Aug 2004
Last Updated on STN: 5 Aug 2004

ABSTRACT: Sjogren's syndrome is an autoimmune disease characterized by inflammation of the exocrine glands, leading to impaired function. Here, I review the relatively short history of the syndrome and explain why it is frequently underdiagnosed, undertreated and under-researched. Attempts to provide classification criteria have culminated in the revised American-European Consensus Criteria, which provide a sound basis for both clinical management and research. The recognition that Sjogren's syndrome is a disease of considerable morbidity has led to a more aggressive approach to therapy ranging from topical therapies to systemic treatment with secretagogues such as pilocarpine and cemiveline, and immunomodulatory drugs such as hydroxychloroquine and interferon-alpha. The central role of the glandular epithelial cell is identified as the key to understanding the pathogenesis of the disease. Hypofunction rather than destruction of these cells is now regarded as the main mechanism of secretory failure in Sjogren's syndrome.

CONTROLLED TERM: Medical Descriptors:
***Sjoegren syndrome: DI, diagnosis**
***Sjoegren syndrome: DT, drug therapy**
***Sjoegren syndrome: ET, etiology**
autoimmune disease: DI, diagnosis
autoimmune disease: DT, drug therapy
autoimmune disease: ET, etiology
exocrine gland
inflammation
diagnostic error
medical research
disease classification
consensus development
morbidity
epithelium cell
exocrine cell
cell function
pathogenesis
cell destruction
dry eye: CO, complication
dry eye: DT, drug therapy
flushing
skin manifestation: SI, side effect
sweat gland disease: SI, side effect
diarrhea: SI, side effect
urinary frequency
micturition disorder: SI, side effect
headache: SI, side effect
abdominal pain: SI, side effect
nausea: SI, side effect
drug selectivity
human
clinical trial
review
priority journal
Drug Descriptors:
pilocarpine: AE, adverse drug reaction
pilocarpine: DT, drug therapy
pilocarpine: TP, topical drug administration
cevimeline: AE, adverse drug reaction
cevimeline: CT, clinical trial
cevimeline: DT, drug therapy
cevimeline: PD, pharmacology
cevimeline: TP, topical drug administration

immunomodulating agent: DT, drug therapy
hydroxychloroquine sulfate: DT, drug therapy
alpha interferon: DT, drug therapy
steroid: CT, clinical trial
steroid: DT, drug therapy
cyclophosphamide: DT, drug therapy
tears naturale: DT, drug therapy
tears naturale: TP, topical drug administration
polyvinyl alcohol: DT, drug therapy
polyvinyl alcohol: TP, topical drug administration
hydroxypropylmethylcellulose: DT, drug therapy
hydroxypropylmethylcellulose: TP, topical drug administration
carbomer: DT, drug therapy
carbomer: TP, topical drug administration
paraffin: DT, drug therapy
paraffin: TP, topical drug administration
acetylcysteine: DT, drug therapy
acetylcysteine: TP, topical drug administration
methotrexate: CT, clinical trial
methotrexate: DT, drug therapy
cyclosporin: CT, clinical trial
cyclosporin: DT, drug therapy
azathioprine: CT, clinical trial
azathioprine: DT, drug therapy
cytotoxic agent: DT, drug therapy
infliximab: DT, drug therapy
B lymphocyte antibody: DT, drug therapy
rituximab: DT, drug therapy
liquifilm
viscotears
geltears
lacri lube
lubri tears
ilube
glandosane
luborant
saliva substitute
oralbalance
bioxtra

CAS REGISTRY NO.: (pilocarpine) 148-72-1, 54-71-7, 92-13-7; (cevimeline) 107220-27-9, 107220-28-0, 107233-08-9, 153504-70-2; (hydroxychloroquine sulfate) 747-36-4; (cyclophosphamide) 50-18-0; (polyvinyl alcohol) 37380-95-3, 9002-89-5; (hydroxypropylmethylcellulose) 9004-65-3; (carbomer) 9007-20-9, 9062-04-8; (acetylcysteine) 616-91-1; (methotrexate) 15475-56-6, 59-05-2, 7413-34-5; (**cyclosporin**) 79217-60-0; (azathioprine) 446-86-6; (infliximab) 170277-31-3; (rituximab) 174722-31-7; (lacri lube) 78200-24-5

CHEMICAL NAME: Salagen; Bioxtra; Oralbalance; Saliva orthana; Luborant; Glandosane; Ilube; Lubri tears; Lacri lube; Geltears; Viscotears; Liquifilm; Sno tears; Tears naturale

L139 ANSWER 27 OF 73 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2004377151 EMBASE Full-text

TITLE: [Biological availability of ophthalmic preparations 2. Ophthalmic therapeutic systems].
BIOLOGICKA DOSTUPNOST OCNICH LEKU 2. OCNI TERAPEUTICKE

SYSTEMY.

AUTHOR: Masteikova R.; Chalupova Z.; Savickas A.
CORPORATE SOURCE: R. Masteikova, Palackeho 1/3, 612 42 Brno, Czech Republic. masteikovar@vfu.cz

SOURCE: Ceska a Slovenska Farmacie, (2004) Vol. 53, No. 5, pp. 211-218. .
Refs: 122
ISSN: 1210-7816 CODEN: CSLFEK
COUNTRY: Czech Republic
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 004 Microbiology
012 Ophthalmology
037 Drug Literature Index
039 Pharmacy
LANGUAGE: Czech
SUMMARY LANGUAGE: English; Czech
ENTRY DATE: Entered STN: 24 Sep 2004
Last Updated on STN: 24 Sep 2004

ABSTRACT: Ophthalmic therapeutic systems, which rank among the drugs of the second and third generation, make possible prolonged and controlled drug release, or the introduction of the drug direct into the site of action (a specific eye tissue) with minimal distribution into the adjacent tissues. The group mainly consists of solid ophthalmic preparations, in a lesser extent there are systems developed from hydrogels, colloidal carriers, etc. The present review lists both insoluble ophthalmic therapeutic systems and those soluble in water (degradable, erodible). Insoluble systems include membrane-controlled ophthalmic therapeutic systems (e.g. Ocusert®), therapeutic eye lenses, eye implants, and other insoluble preparations. In the group of soluble preparations, topical inserts and systems are described, which are introduced into eye tissues as implants or injections.

CONTROLLED TERM: Medical Descriptors:
***eye disease: DT, drug therapy**
*drug implant
*eye implant
*eye insert
*therapeutic eye lens
*ophthalmic therapeutic system
*soluble ocular drug insert
acquired immune deficiency syndrome
cytomegalovirus infection: CO, complication
cytomegalovirus infection: DT, drug therapy
retinitis: CO, complication
retinitis: DT, drug therapy
bioavailability
solubility
drug release
controlled drug release
drug delivery system
hydrogel
colloid
human
review
Drug Descriptors:
*pilocarpine: PR, pharmaceutics
*agents acting on the eye: DT, drug therapy
*agents acting on the eye: PR, pharmaceutics
*agents acting on the eye: TP, topical drug administration
antivirus agent: DT, drug therapy
antivirus agent: PR, pharmaceutics

ganciclovir: DT, drug therapy
ganciclovir: PR, pharmaceutics
corticosteroid: DT, drug therapy
corticosteroid: PR, pharmaceutics
fluocinolone: DT, drug therapy
fluocinolone: PR, pharmaceutics
triamcinolone: DT, drug therapy
triamcinolone: PR, pharmaceutics
cyclosporin: DT, drug therapy
cyclosporin: PR, pharmaceutics
amphotericin B: DT, drug therapy
amphotericin B: PR, pharmaceutics
antibiotic agent: DT, drug therapy
antibiotic agent: PR, pharmaceutics
ciprofloxacin: DT, drug therapy
ciprofloxacin: PR, pharmaceutics
fluorouracil: DT, drug therapy
fluorouracil: PR, pharmaceutics
polymer
macrogol
polymacon
povidone
polyacrylic acid
collagen
hyaluronic acid
xanthan
fibrin
methylcellulose
hydroxypropylmethylcellulose
hydroxypropylcellulose
ethyl cellulose
chitosan
polyvinyl acetate
eudragit
eudragit rs
unindexed drug

CAS REGISTRY NO.: (pilocarpine) 148-72-1, 54-71-7, 92-13-7; (ganciclovir) 82410-32-0; (fluocinolone) 807-38-5; (triamcinolone) 124-94-7; (**cyclosporin**) 79217-60-0; (amphotericin B) 1397-89-3, 30652-87-0; (ciprofloxacin) 85721-33-1; (fluorouracil) 51-21-8; (macrogol) 25322-68-3; (polymacon) 25053-81-0, 25249-16-5, 98932-78-6; (povidone) 9003-39-8; (polyacrylic acid) 74350-43-9, 87003-46-1, 9003-01-4, 9003-04-7; (collagen) 9007-34-5; (hyaluronic acid) 31799-91-4, 9004-61-9, 9067-32-7; (xanthan) 11138-66-2; (fibrin) 9001-31-4; (methylcellulose) 79484-92-7, 9004-67-5; (hydroxypropylmethylcellulose) 9004-65-3; (hydroxypropylcellulose) 9004-64-2; (ethyl cellulose) 9004-57-3; (chitosan) 9012-76-4; (polyvinyl acetate) 9003-20-7; (eudragit) 24938-16-7, 51822-44-7, 9065-11-6; (eudragit rs) 33434-24-1

CHEMICAL NAME: (1) Ocusert; (2) Vitrasert; (3) Lacrisert

NAME OF PRODUCT: (1) Oculex Drug Delivery System; ProShield; New Ophthalmic Delivery System; Bio-Cor; Bioadhesive Ophthalmic Drug Insert; MediLens; Soluble Ocular Drug Insert

COMPANY NAME: (1) Alza; (2) Chiron; (3) Merck Sharp and Dohme

COMPANY NAME: (1) Oculex

L139 ANSWER 28 OF 73 EMBASE

ACCESSION NUMBER: 2004167588 EMBASE Full-text
TITLE: Nanomedicines for overcoming biological barriers.
AUTHOR: Alonso M.J.
CORPORATE SOURCE: M.J. Alonso, Dept. Pharm. Pharmaceutical Technol., School of Pharmacy, Univ. Santiago de Compostela, Santiago de Compostela 15782, Spain. ffmjalon@usc.es
SOURCE: Biomedicine and Pharmacotherapy, (2004) Vol. 58, No. 3, pp. 168-172. .
Refs: 26
ISSN: 0753-3322 CODEN: BIPHEX
PUBLISHER IDENT.: S 0753-3322(04)00013-7
COUNTRY: France
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 026 Immunology, Serology and Transplantation
030 Pharmacology
037 Drug Literature Index
039 Pharmacy
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 29 Apr 2004
Last Updated on STN: 29 Apr 2004

ABSTRACT: Drug delivery is an interdisciplinary area of research that aims at making the administration of complex new drugs feasible, as well as adding critical value to the drugs that are currently in the market. At present, one of the most attractive areas of research in drug delivery is the design of nanomedicines consisting of nanosystems that are able to deliver drugs to the right place, at appropriate times. The goal of the present article is to review the advances we have made in the development and characterization of nanosystems intended to be used as drug carriers for mucosal administration. These nanocarriers are able to protect the associated drug against degradation and facilitate its transport across critical and specific barriers. Some of them, are further able to release the associated drug to the target tissue in a controlled manner. These nanocarriers have been made of safe materials, including synthetic biodegradable polymers, lipids and polysaccharides. A number of nanotechnologies have been developed that enable the association of a variety of drugs to these nanocarriers, ranging from classical small drug to large DNA fragments. The in vitro cell culture studies and the in vivo experiments have evidenced the potential of these nanocarriers for overcoming important mucosal barriers, such as the intestinal, nasal and ocular barriers. Hopefully, this will soon represent a strategy for making cheaper and faster, more efficacious medicines. .COPYRGT. 2004 Published by Elsevier SAS.

CONTROLLED TERM: Medical Descriptors:
*nanotechnology
drug delivery system
drug degradation
drug transport
biodegradability
in vitro study
cell culture
nanoparticle
drug absorption
humoral immunity
mucosal immunity
cornea injury
drug penetration
nonhuman
review
priority journal
Drug Descriptors:

*drug carrier: AD, drug administration
*drug carrier: NA, intranasal drug administration
*drug carrier: PO, oral drug administration
*drug carrier: PR, pharmaceutics
*drug carrier: TP, topical drug administration
polymer: PO, oral drug administration
polymer: PR, pharmaceutics
lipid: NA, intranasal drug administration
lipid: PO, oral drug administration
lipid: PR, pharmaceutics
polysaccharide: PR, pharmaceutics
DNA fragment: PR, pharmaceutics
chitosan: NA, intranasal drug administration
chitosan: PO, oral drug administration
chitosan: PR, pharmaceutics
chitosan: TP, topical drug administration
macrogol: NA, intranasal drug administration
macrogol: PO, oral drug administration
macrogol: PR, pharmaceutics
oil: NA, intranasal drug administration
oil: PO, oral drug administration
oil: PR, pharmaceutics
polyester: NA, intranasal drug administration
polyester: PO, oral drug administration
polyester: PR, pharmaceutics
polyester: TP, topical drug administration
polystyrene: PR, pharmaceutics
insulin: NA, intranasal drug administration
insulin: PO, oral drug administration
insulin: PR, pharmaceutics
insulin: PK, pharmacokinetics
poly(cyanoacrylate): TO, drug toxicity
poly(cyanoacrylate): PO, oral drug administration
poly(cyanoacrylate): PR, pharmaceutics
poly(cyanoacrylate): TP, topical drug administration
nanocapsule: PO, oral drug administration
nanocapsule: PR, pharmaceutics
copolymer: PO, oral drug administration
copolymer: PR, pharmaceutics
DNA vaccine: NA, intranasal drug administration
DNA vaccine: PR, pharmaceutics
tetanus toxin: NA, intranasal drug administration
tetanus toxin: PR, pharmaceutics
tetanus toxin: PD, pharmacology
indometacin: PR, pharmaceutics
indometacin: PK, pharmacokinetics
indometacin: TP, topical drug administration
cyclosporin A: IO, intraocular drug administration
cyclosporin A: PR, pharmaceutics
cyclosporin A: PK, pharmacokinetics
cyclosporin A: TP, topical drug administration
unclassified drug

CAS REGISTRY NO.: (lipid) 66455-18-3; (chitosan) 9012-76-4; (macrogol) 25322-68-3; (polystyrene) 9003-53-6; (insulin) 9004-10-8; (indometacin) 53-86-1, 74252-25-8, 7681-54-1; (cyclosporin A) 59865-13-3, 63798-73-2

L139 ANSWER 29 OF 73 EMBASE

ACCESSION NUMBER: 2004194261 EMBASE Full-text

TITLE: Evaluation and Treatment of Dry Eye in Laser Vision Correction.

AUTHOR: Pascucci S.E.
CORPORATE SOURCE: Dr. S.E. Pascucci, Northeastern Eye Institute, 200 Mifflin Avenue, Scranton, PA 18503, United States.
stevepascucci@ne-eye.com

SOURCE: Clinical and Refractive Optometry, (2004) Vol. 15, No. 3, pp. 96-102. .
Refs: 8
ISSN: 1705-4850 CODEN: CROLA8
COUNTRY: Canada
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 012 Ophthalmology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20 May 2004
Last Updated on STN: 20 May 2004

ABSTRACT: Dry eye is a very widespread ocular condition and is one of the most common reasons patients seek help from eye care professionals. With the increasing acceptance and success of laser vision correction procedures, surgeons will likely be seeing more potential patients with dry eye. If careful patient evaluation for dry eye is performed and preoperative treatment is given, most patients with mild dry eye can successfully undergo laser vision correction surgery. However, some patients with dry eye may never be suitable candidates for this surgery.

CONTROLLED TERM: Medical Descriptors:
***dry eye: CO, complication**
***dry eye: DT, drug therapy**
***dry eye: ET, etiology**
***dry eye: PC, prevention**
***dry eye: TH, therapy**
***visual impairment: SI, side effect**
***visual impairment: SU, surgery**
*keratomileusis
*laser epithelial keratomileusis
surgeon
surgical risk
medical assessment
preoperative care
surgical patient
antibiotic prophylaxis
drug capsule
drug formulation
low drug dose
eyelid closure
human
review
Drug Descriptors:
doxycycline: DT, drug therapy
doxycycline: PO, oral drug administration
tetracycline: DT, drug therapy
tetracycline: PO, oral drug administration
omega 3 fatty acid: DT, drug therapy
essential fatty acid: DT, drug therapy
essential fatty acid: PR, pharmaceutics
artificial tear: AE, adverse drug reaction
artificial tear: TO, drug toxicity

fluorometholone: DO, drug dose
fluorometholone: DT, drug therapy
fluorometholone: TP, topical drug administration
loteprednol etabonate: DO, drug dose
loteprednol etabonate: DT, drug therapy
loteprednol etabonate: TP, topical drug administration
cyclosporin A: DT, drug therapy
cyclosporin A: TP, topical drug administration
linseed oil: DT, drug therapy
primrose oil: DT, drug therapy
theratears
hydroeyes
refresh liquigel
genteal gel

CAS REGISTRY NO.: (doxycycline) 10592-13-9, 17086-28-1, 564-25-0; (tetracycline) 23843-90-5, 60-54-8, 64-75-5; (essential fatty acid) 11006-87-4; (fluorometholone) 426-13-1; (loteprednol etabonate) 82034-46-6; (**cyclosporin A**) **59865-13-3**, 63798-73-2; (linseed oil) 8001-26-1; (primrose oil) 65546-85-2

CHEMICAL NAME: (1) Theratears; (2) Hydroeyes; (3) Refresh liquigel; (4) Genteal gel; (5) Alrex; **(6) Restasis**

COMPANY NAME: (1) Advance vision; (2) Science based health; (4) Novartis; (5) Pharmos; (6) Allergan

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ACCESSION NUMBER: 2005405102 EMBASE Full-text

TITLE: The effects of LASIK on the ocular surface.

AUTHOR: Solomon R.; Donnenfeld E.D.; Perry H.D.

CORPORATE SOURCE: Dr. E.D. Donnenfeld, Ophthalmic Consultants of Long Island, Rockville Centre, 2000 North Village Avenue, New York, NY 11570, United States. eddoph@aol.com

SOURCE: Ocular Surface, (2004) Vol. 2, No. 1, pp. 34-44. .
Refs: 78
ISSN: 1542-0124

COUNTRY: United States

DOCUMENT TYPE: Journal; General Review

FILE SEGMENT: 005 General Pathology and Pathological Anatomy
012 Ophthalmology
017 Public Health, Social Medicine and Epidemiology
037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 22 Sep 2005
Last Updated on STN: 22 Sep 2005

ABSTRACT: Laser in situ keratomileusis (LASIK) can affect corneal sensation, aqueous tear production, wound healing, and the incidence of corneal erosions. Virtually all patients experience dry eye at least transiently after LASIK. Because intact corneal sensation drives tear production, denervation associated with the LASIK procedure is the most significant cause of post-LASIK dry eye. To prevent symptomatic postoperative dry eye, it is crucial to identify and treat pre-existing dry eye before surgery. This review addresses the pathophysiology and management of dry eye, as well as the relationship between LASIK and corneal erosions, and suggests intra- and post-operative management techniques to minimize complications and maximize the stability of the ocular surface. Contraindications to LASIK and alternative refractive surgical procedures are discussed. .COPYRGT.2004 Ethis Communications, Inc. All rights reserved.

CONTROLLED TERM: Medical Descriptors:
*keratomileusis
***dry eye: CO, complication**
***dry eye: DI, diagnosis**
***dry eye: DT, drug therapy**
***dry eye: ET, etiology**
***dry eye: PC, prevention**
***cornea erosion: CO, complication**
***cornea erosion: ET, etiology**
***cornea erosion: SU, surgery**
***cornea erosion: TH, therapy**
tear film
denervation
postoperative care
treatment contraindication
surgical technique
risk factor
preoperative evaluation
lacrimal fluid
lacrimation
drug response
keratectomy
human
clinical trial
review
Drug Descriptors:
artificial tear: CM, drug comparison
artificial tear: DT, drug therapy
cyclosporin A: CT, clinical trial
cyclosporin A: CM, drug comparison
cyclosporin A: DT, drug therapy
cyclosporin A: TP, topical drug administration
doxycycline: PO, oral drug administration
methylprednisolone: DT, drug therapy
omega 3 fatty acid
icosapentaenoic acid
docosahexaenoic acid
linseed oil: DT, drug therapy
linseed oil: PO, oral drug administration
CAS REGISTRY NO.: **(cyclosporin A) 59865-13-3,** 63798-73-2; (doxycycline) 10592-13-9, 17086-28-1, 564-25-0; (methylprednisolone) 6923-42-8, 83-43-2; (icosapentaenoic acid) 25378-27-2, 32839-30-8; (docosahexaenoic acid) 25167-62-8, 32839-18-2; (linseed oil) 8001-26-1
CHEMICAL NAME: **(1) Restasis**
COMPANY NAME: (1) Allergan

L139 ANSWER 31 OF 73 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2003476197 EMBASE Full-text
TITLE: The potential of chitosam in ocular drug delivery.
AUTHOR: Alonso M.J.; Sanchez A.
CORPORATE SOURCE: M.J. Alonso, Dept. of Pharm./Pharmaceut. Technol., Faculty of Pharmacy, University of Santiago de Compostela, 15782 Santiago de Compostela, Spain. ffmjalon@ucs.es
SOURCE: Journal of Pharmacy and Pharmacology, (2003) Vol. 55, No. 11, pp. 1451-1463. .
Refs: 76
ISSN: 0022-3573 CODEN: JPPMAB
COUNTRY: United Kingdom

DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 037 Drug Literature Index
030 Pharmacology
039 Pharmacy
012 Ophthalmology
052 Toxicology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 4 Dec 2003
Last Updated on STN: 4 Dec 2003

ABSTRACT: This paper presents an overview of the potential of chitosan-based systems for improving the retention and biodistribution of drugs applied topically onto the eye. Besides its low toxicity and good ocular tolerance, chitosan exhibits favourable biological behaviour, such as bioadhesion- and permeability-enhancing properties, and also interesting physico-chemical characteristics, which make it a unique material for the design of ocular drug delivery vehicles. The review summarizes the techniques for the production of chitosan gels, chitosan-coated colloidal systems and chitosan nanoparticles, and describes their mechanism of action upon contact with the ocular mucosa. The results reported until now have provided evidence of the potential of chitosan gels for enhancing and prolonging the retention of drugs on the eye surface. On the other hand, chitosan-based colloidal systems were found to work as transmucosal drug carriers, either facilitating the transport of drugs to the inner eye (chitosan-coated colloidal systems containing indometacin) or their accumulation into the corneal/conjunctival epithelia (chitosan nanoparticles containing ciclosporin). Finally, the tolerance, toxicity and biodegradation of the carriers under evaluation were reviewed.

CONTROLLED TERM: Medical Descriptors:
nonhuman
drug potency
drug delivery system
drug retention
drug distribution
eye disease: DT, drug therapy
drug tolerance
adhesion
drug penetration
physical chemistry
drug design
drug manufacture
gel
colloid
coated particle
nanoparticle
drug mechanism
evidence based medicine
eye
drug transport
drug accumulation
cornea epithelium
conjunctiva epithelium
biodegradation
wound healing: DT, drug therapy
drug dosage form
drug blood level
review
Drug Descriptors:
*chitosan: PD, pharmacology
*chitosan: PR, pharmaceutics

*chitosan: IO, intraocular drug administration
*chitosan: PK, pharmacokinetics
*chitosan: TP, topical drug administration
*chitosan: DT, drug therapy
*chitosan: CB, drug combination
*chitosan: TO, drug toxicity
*chitosan: DO, drug dose
*chitosan: CR, drug concentration
*chitosan: IV, intravenous drug administration
*chitosan: PO, oral drug administration
*chitosan: NA, intranasal drug administration
indometacin: PD, pharmacology
indometacin: PR, pharmaceutics
indometacin: IO, intraocular drug administration
indometacin: PK, pharmacokinetics
indometacin: TP, topical drug administration
indometacin: DT, drug therapy
indometacin: CB, drug combination
indometacin: TO, drug toxicity
indometacin: DO, drug dose
cyclosporin: PD, pharmacology
cyclosporin: PR, pharmaceutics
cyclosporin: IO, intraocular drug administration
cyclosporin: PK, pharmacokinetics
cyclosporin: TP, topical drug administration
cyclosporin: DT, drug therapy
cyclosporin: CB, drug combination
cyclosporin: TO, drug toxicity
cyclosporin: DO, drug dose
n acetylglucosamine: DT, drug therapy
n acetylglucosamine: PD, pharmacology
n acetylglucosamine: CB, drug combination
n acetylglucosamine: PR, pharmaceutics
oligomer: DT, drug therapy
oligomer: PD, pharmacology
oligomer: CB, drug combination
oligomer: PR, pharmaceutics
tobramycin: DT, drug therapy
tobramycin: PR, pharmaceutics
tobramycin: CB, drug combination
microsphere: CB, drug combination
microsphere: PR, pharmaceutics
aciclovir: CB, drug combination
aciclovir: PR, pharmaceutics
drug carrier: PD, pharmacology
drug carrier: PR, pharmaceutics
drug carrier: IO, intraocular drug administration
drug carrier: PK, pharmacokinetics
drug carrier: TP, topical drug administration
drug carrier: DT, drug therapy
drug carrier: CB, drug combination
drug carrier: TO, drug toxicity
drug carrier: DO, drug dose
macrogol: CB, drug combination
macrogol: PR, pharmaceutics
ofloxacin: CB, drug combination
ofloxacin: PR, pharmaceutics
ofloxacin: CR, drug concentration
liposome: CB, drug combination
liposome: PR, pharmaceutics

idoxuridine: DT, drug therapy
idoxuridine: CB, drug combination
idoxuridine: PR, pharmaceutics
idoxuridine: PD, pharmacology
polycaprolactone: CB, drug combination
polycaprolactone: PR, pharmaceutics
diazepam: CB, drug combination
diazepam: PR, pharmaceutics
diazepam: PD, pharmacology
polylysine: CB, drug combination
polylysine: PR, pharmaceutics
polylysine: PD, pharmacology

CAS REGISTRY NO.: (chitosan) 9012-76-4; (indometacin) 53-86-1, 74252-25-8, 7681-54-1; (cyclosporin) 79217-60-0; (n acetylglucosamine) 7512-17-6; (tobramycin) 32986-56-4; (aciclovir) 59277-89-3; (macrogol) 25322-68-3; (ofloxacin) 82419-36-1; (idoxuridine) 54-42-2; (polycaprolactone) 24980-41-4, 25248-42-4; (diazepam) 439-14-5; (polylysine) 25104-18-1, 25988-63-0, 33960-24-6, 38000-06-5, 73565-56-7

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ACCESSION NUMBER: 2002182844 EMBASE Full-text
TITLE: Current issues in Sjogren's syndrome.
AUTHOR: Jonsson R.; Moen K.; Vestrheim D.; Szodoray P.
CORPORATE SOURCE: Dr. R. Jonsson, Broegelmann Research Laboratory, Amauer Hansen Building, N-5021 Bergen, Norway.
roland.jonsson@gades.uib.no
SOURCE: Oral Diseases, (2002) Vol. 8, No. 3, pp. 130-140. .
Refs: 132
ISSN: 1354-523X CODEN: ORDIFD
COUNTRY: Denmark
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 011 Otorhinolaryngology
026 Immunology, Serology and Transplantation
031 Arthritis and Rheumatism
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 6 Jun 2002
Last Updated on STN: 6 Jun 2002

ABSTRACT: Sjogren's syndrome is a chronic autoimmune and rheumatic disorder with prominent sicca complaints from the mucous membranes because of lack of proper exocrine secretions. There is no straightforward and simple diagnostic test for Sjogren's syndrome, although several classification criteria have been designed including several oral diagnostic tests. A new set of classification criteria in a joint effort by research groups in Europe and USA has recently been presented. A large number of autoantibodies have been reported in Sjogren's syndrome where, in some cases, the antibodies are correlated with the extent and severity of disease. The finding of serum autoantibodies directed against the muscarinic M3 receptor is an important advance in understanding the pathogenesis of not only the impaired glandular function but also associated features of autonomic dysfunction in some patients. The treatment of primary Sjogren's syndrome is still mainly symptomatic.

CONTROLLED TERM: Medical Descriptors:
***Sjoegren syndrome: DI, diagnosis**
***Sjoegren syndrome: DT, drug therapy**
***Sjoegren syndrome: EP, epidemiology**

***Sjoegren syndrome: ET, etiology**
***Sjoegren syndrome: TH, therapy**
genetics
environmental factor
immunopathology: ET, etiology
autoimmunity
disease classification
antibody titer
palliative therapy
virus infection: ET, etiology
bacterial infection: ET, etiology
histopathology
animal model
symptomatology
diagnostic test
saliva analysis
serodiagnosis
biopsy
dry eye: CO, complication
dry eye: DT, drug therapy
dry eye: TH, therapy
xerostomia: CO, complication
xerostomia: DT, drug therapy
side effect: SI, side effect
disease course
human
nonhuman
review
priority journal
Drug Descriptors:
autoantibody
muscarinic receptor
artificial tear
ointment base
saliva substitute
toothpaste
fluoride
pilocarpine: DT, drug therapy
pilocarpine: PO, oral drug administration
alpha interferon: DT, drug therapy
quinuclidine derivative: AE, adverse drug reaction
quinuclidine derivative: DT, drug therapy
cemiveline: AE, adverse drug reaction
cemiveline: DT, drug therapy
hydroxychloroquine: DT, drug therapy
azathioprine: DT, drug therapy
cyclosporin A: DT, drug therapy
cyclophosphamide: DT, drug therapy
nonsteroid antiinflammatory agent: DT, drug therapy
steroid: DT, drug therapy
unclassified drug
CAS REGISTRY NO.: (fluoride) 16984-48-8; (pilocarpine) 148-72-1, 54-71-7, 92-13-7; (hydroxychloroquine) 118-42-3, 525-31-5; (azathioprine) 446-86-6; (**cyclosporin A**) **59865-13-3**, 63798-73-2; (cyclophosphamide) 50-18-0

L139 ANSWER 33 OF 73 EMBASE
ACCESSION NUMBER: 2002194457 EMBASE Full-text

TITLE: Management of dry eye syndrome.
AUTHOR: Lee G.A.
CORPORATE SOURCE: Dr. G.A. Lee, Royal Brisbane Hospital, Brisbane, QLD, Australia
SOURCE: Medicine Today, (2002) Vol. 3, No. 5, pp. 87-90. .
ISSN: 1443-430X CODEN: MTNBCV
COUNTRY: Australia
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 012 Ophthalmology
037 Drug Literature Index
LANGUAGE: English
ENTRY DATE: Entered STN: 13 Jun 2002
Last Updated on STN: 13 Jun 2002
CONTROLLED TERM: Medical Descriptors:
***dry eye: DT, drug therapy**
***dry eye: ET, etiology**
***dry eye: SU, surgery**
***dry eye: TH, therapy**
tear film
symptomatology
lacrimation
medical assessment
anamnesis
visual acuity
visual system examination
Schirmer test
conservative treatment
lacrimal duct occlusion
cauterization
diet supplementation
ointment
human
article
Drug Descriptors:
eye drops: DT, drug therapy
eye drops: TP, topical drug administration
lubricating agent: DT, drug therapy
lubricating agent: TP, topical drug administration
carboxymethylcellulose: DT, drug therapy
carboxymethylcellulose: TP, topical drug administration
artificial tear: DT, drug therapy
artificial tear: TP, topical drug administration
bion tears: DT, drug therapy
bion tears: TP, topical drug administration
hydroxypropylmethylcellulose: DT, drug therapy
hydroxypropylmethylcellulose: TP, topical drug administration
methylcellulose: DT, drug therapy
methylcellulose: TP, topical drug administration
tears naturale: DT, drug therapy
tears naturale: TP, topical drug administration
hydroxypropylcellulose: DT, drug therapy
hydroxypropylcellulose: TP, topical drug administration
omega 3 fatty acid: PD, pharmacology
omega 6 fatty acid: PD, pharmacology
retinol: DT, drug therapy
retinol: PR, pharmaceutics
cyclosporin: DT, drug therapy
cyclosporin: PR, pharmaceutics
povidone: DT, drug therapy

povidone: TP, topical drug administration
hydroxyethylcellulose: DT, drug therapy
hydroxyethylcellulose: TP, topical drug administration
hyaluronic acid: DT, drug therapy
hyaluronic acid: TP, topical drug administration
polyvinyl alcohol: DT, drug therapy
polyvinyl alcohol: TP, topical drug administration
dextran 70: DT, drug therapy
dextran 70: TP, topical drug administration
carbomer: DT, drug therapy
carbomer: TP, topical drug administration
paraffin: DT, drug therapy
paraffin: TP, topical drug administration
lanolin: DT, drug therapy
lanolin: TP, topical drug administration
clerz moisturizing drops
in a wink moisturizing eyedrops
minims artificial tears
vismed
refresh
refresh tears plus
genteal lubricant eye drops
poly tears
liquifilm tears
liquifilm forte
murine revital eyes
murine tears for eyes
tears plus
poly gel lubricating eye gel
geltears
viscotears
genteal moisturizing eye gel
duratears lubricating eye ointment
poly visc
lacri lube

CAS REGISTRY NO.: (carboxymethylcellulose) 8050-38-2, 9000-11-7, 9004-32-4, 9050-04-8; (hydroxypropylmethylcellulose) 9004-65-3; (methylcellulose) 79484-92-7, 9004-67-5; (hydroxypropylcellulose) 9004-64-2; (retinol) 68-26-8, 82445-97-4; (**cyclosporin**) 79217-60-0; (povidone) 9003-39-8; (hydroxyethylcellulose) 9004-62-0; (hyaluronic acid) 31799-91-4, 9004-61-9, 9067-32-7; (polyvinyl alcohol) 37380-95-3, 9002-89-5; (carbomer) 9007-20-9, 9062-04-8; (lanolin) 70321-63-0, 8006-54-0, 8020-84-6, 8031-44-5, 8038-28-6; (lacri lube) 78200-24-5

CHEMICAL NAME: Cellufresh; Clerz moisturizing drops; In a wink moisturizing eyedrops; Minims artificial tears; Bion tears; Vismed; Refresh; Refresh tears plus; Genteal lubricant eye drops; Isopto tears; Methopt; Poly tears; Tears naturale; Liquifilm tears; Liquifilm forte; Murine revital eyes; Murine tears for eyes; Tears plus; Celluvisc; Poly gel lubricating eye gel; Geltears; Viscotears; Genteal moisturizing eye gel; Duratears lubricating eye ointment; Poly visc; Lacri lube; Lacrisert

L139 ANSWER 34 OF 73 EMBASE

ACCESSION NUMBER: 2001319104 EMBASE Full-text

TITLE: Can we still suggest the topical cyclosporin treatment in cutaneous disorders?.

AUTHOR: Vena G.A.; Cassano N.
CORPORATE SOURCE: G.A. Vena, Istituto Dermopatico dell'Immacolata, I.D.I., IRCCS, via Monti di Creta 104, 00167 Rome, Italy. g.vena@dermatologia.uniba.it
SOURCE: Journal of the European Academy of Dermatology and Venereology, (2001) Vol. 15, No. 1, pp. 18-19. .
Refs: 12
ISSN: 0926-9959 CODEN: JEAVEQ
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Editorial
FILE SEGMENT: 012 Ophthalmology
013 Dermatology and Venereology
036 Health Policy, Economics and Management
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
ENTRY DATE: Entered STN: 4 Oct 2001
Last Updated on STN: 4 Oct 2001
CONTROLLED TERM: Medical Descriptors:
*skin disease: DM, disease management
*skin disease: DT, drug therapy
immunomodulation
antiinflammatory activity
psoriasis: DT, drug therapy
atopic dermatitis: DT, drug therapy
contact dermatitis: DT, drug therapy
guinea pig
drug formulation
pyoderma gangrenosum: DT, drug therapy
relapse
drug blood level
eye disease: DT, drug therapy
drug absorption
side effect: SI, side effect
drug cost
human
nonhuman
animal experiment
animal model
editorial
priority journal
Drug Descriptors:
*cyclosporin A: AE, adverse drug reaction
*cyclosporin A: AD, drug administration
*cyclosporin A: CR, drug concentration
*cyclosporin A: DT, drug therapy
*cyclosporin A: PE, pharmacoeconomics
*cyclosporin A: PR, pharmaceutics
*cyclosporin A: PK, pharmacokinetics
*cyclosporin A: IL, intralesional drug administration
*cyclosporin A: PO, oral drug administration
***cyclosporin A: TP, topical drug administration**
petrolatum
CAS REGISTRY NO.: (cyclosporin A) 59865-13-3, 63798-73-2; (petrolatum) 8009-03-8

L139 ANSWER 35 OF 73 EMBASE
ACCESSION NUMBER: 2000389759 EMBASE Full-text
TITLE: Mooren's ulcer in China: A study of clinical

characteristics and treatment.

AUTHOR: Chen J.; Xie H.; Wang Z.; Yang B.; Liu Z.; Chen L.; Gong X.; Lin Y.
CORPORATE SOURCE: Dr. J. Chen, Zhongshan Ophthalmic Center, Sun Yat-sen Univ. of Medical Sci., Guangzhou 510060 PR, China.
zoc@gzsums.edu.cn

SOURCE: British Journal of Ophthalmology, (2000) Vol. 84, No. 11, pp. 1244-1249. .
Refs: 17
ISSN: 0007-1161 CODEN: BJOPAL
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 012 Ophthalmology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 27 Nov 2000
Last Updated on STN: 27 Nov 2000

ABSTRACT: Aims-To investigate the clinical characteristics and compare the effects of several methods of treatment of Mooren's corneal ulcer. Methods-550 consecutive cases of Mooren's corneal ulcer were analysed in patients, including age, sex, laterality of eye, ulcer location, perforative rate, cure rate of surgeries, recurrent rate, the effects of conjunctiva excision, lamellar keratoplasty (LKP), and LKP plus 1% **cyclosporin A** eye drops. Results-The average age of onset was 48.4 years of age. The ratio of males to females was 1:0.74. 165 (30%) cases had the disease bilaterally, of which 52 (31.5%) occurred in the young age group and 113 (68.5%) in the old age group. Ulcers of 501 eyes (70.1%) were located at the limbus of the palpebral fissure. The perforation rate was 13.3%, with perforation of 41 eyes (43.2%) occurring in the young age group and 54 (56.8%) in the old age group. Post-operative recurrence rate was 25.6%. The cure rate of the first procedure of LKP plus 1% **cyclosporin A** eye drops was 73.7%. The final cure rate was 95.6%, and the postoperative preservation rate of the eye globe was 99.7%. Conclusion-This primary study provided the clinical characteristics of patients with Mooren's corneal ulcer in China. LKP plus 1% ***cyclosporin.*** A eye drops was an effective treatment.

CONTROLLED TERM: Medical Descriptors:
***cornea rodent ulcer: DT, drug therapy**
***cornea rodent ulcer: SU, surgery**
China
clinical feature
cornea ulcer: DT, drug therapy
cornea ulcer: SU, surgery
cornea perforation: DT, drug therapy
cornea perforation: SU, surgery
treatment outcome
recurrence risk
conjunctiva disease: SU, surgery
keratoplasty
onset age
sex difference
age
cornea limbus
eyelid
recurrent disease
drug efficacy
eye surgery
postoperative period

human
male
female
major clinical study
clinical trial
controlled study
human tissue
adolescent
aged
adult
article
priority journal
Drug Descriptors:
***cyclosporin A: CT, clinical trial**
***cyclosporin A: DT, drug therapy**
***cyclosporin A: PD, pharmacology**
***cyclosporin A: TP, topical drug administration**
eye drops: CT, clinical trial
eye drops: DT, drug therapy
eye drops: PD, pharmacology
eye drops: TP, topical drug administration
antistreptolysin: EC, endogenous compound
rheumatoid factor: EC, endogenous compound
antinuclear antibody: EC, endogenous compound
olive oil
prednisolone: CT, clinical trial
prednisolone: DT, drug therapy
prednisolone: PD, pharmacology
prednisolone: TP, topical drug administration
dexamethasone: CT, clinical trial
dexamethasone: DT, drug therapy
dexamethasone: PD, pharmacology
dexamethasone: TP, topical drug administration
antibiotic agent: CT, clinical trial
antibiotic agent: TP, topical drug administration
immunosuppressive agent: CT, clinical trial
immunosuppressive agent: DT, drug therapy
immunosuppressive agent: PD, pharmacology
immunosuppressive agent: TP, topical drug administration

CAS REGISTRY NO.: (**cyclosporin A**) **59865-13-3**, 63798-73-2; (antistreptolysin) 9006-92-2; (rheumatoid factor) 9009-79-4; (olive oil) 8001-25-0; (prednisolone) 50-24-8; (dexamethasone) 50-02-2

COMPANY NAME: Sandoz (Switzerland)

L139 ANSWER 36 OF 73 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 97232229 EMBASE Full-text

DOCUMENT NUMBER: 1997232229

TITLE: [**Cyclosporine** effect in corneal neovascularization].
EFECTO DE LA CICLOSPORINA SOBRE LA NEOVASCULARIZATION CORNEAL.

AUTHOR: OShea C.G.; Cuevas-Cancino O.; Naranjo-Tackman R.; Ozorno-Zarate J.

SOURCE: Revista Mexicana de Oftalmologia, (1997) Vol. 71, No. 2, pp. 41-43. .
Refs: 14
ISSN: 0187-4519 CODEN: RMOFEM

COUNTRY: Mexico

DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 012 Ophthalmology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: Spanish
SUMMARY LANGUAGE: English; Spanish
ENTRY DATE: Entered STN: 4 Sep 1997
Last Updated on STN: 4 Sep 1997

ABSTRACT: Human and animal investigations since the mid 1970's have demonstrated the effectiveness of **cyclosporine** (CsA) as an immunosuppresed agent. We sought to determine if **cyclosporine** could suppress Corneal Neovascularization induced by interleukin-2. Forty laboratory mice were treated with daily IM injections of **cyclosporine** (25 mg/kg in olive oil) for 3 days before and 2 weeks following the intrastromal injections of 0.5/µl (5 IU) mouse interleukin-2. The animals in the control group received IM injections of olive oil. The mean area of corneal neovascularization 4, 8 and 12 weeks after injections was 9.2, 9.1 and 9.2 mm2 respectively, in controls and 4.9, 5.3 and 5.2 mm2 in **cyclosporine** treated mice ($P < 0.02$; T students test). **Cyclosporine** causes a significant reduction in IL-2 induced Corneal Neovascularization that may, in part account for its ability to prolong corneal allograft survival especially in the high risk patient.

CONTROLLED TERM: Medical Descriptors:
***cornea neovascularization: PC, prevention**
animal experiment
animal model
article
controlled study
cornea transplantation
graft survival
intramuscular drug administration
mouse
nonhuman
Drug Descriptors:
***cyclosporin**
*interleukin 2
***olive oil**
CAS REGISTRY NO.: (**cyclosporin**) 79217-60-0; (interleukin 2) 85898-30-2; (olive oil) 8001-25-0

L139 ANSWER 37 OF 73 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 96152238 EMBASE Full-text
DOCUMENT NUMBER: 1996152238
TITLE: Effects of **cyclosporin A** on the induction of oral tolerance.
AUTHOR: Fukushima A.; Whitcup S.M.; Nussenblatt R.B.; Gery I.
CORPORATE SOURCE: Laboratory of Immunology, National Eye Institute,Bethesda, MD 20892-1858, United States
SOURCE: Annals of the New York Academy of Sciences, (1996) Vol. 778, pp. 376-378. .
ISSN: 0077-8923 CODEN: ANYAA
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 012 Ophthalmology
026 Immunology, Serology and Transplantation
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English

ENTRY DATE: Entered STN: 4 Jun 1996
Last Updated on STN: 4 Jun 1996
CONTROLLED TERM: Medical Descriptors:
*immunological tolerance
***uveitis**
animal cell
animal experiment
animal model
article
autoimmunity
controlled study
immunization
lymphocyte proliferation
male
nonhuman
rat
Drug Descriptors:
***cyclosporin a**
*retina s antigen
immunosuppressive agent
olive oil
CAS REGISTRY NO.: **(cyclosporin a) 59865-13-3,** 63798-73-2; (retina s antigen) 113315-03-0; (olive oil) 8001-25-0

L139 ANSWER 38 OF 73 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 94311888 EMBASE Full-text
DOCUMENT NUMBER: 1994311888
TITLE: Topical **cyclosporin** treatment of keratoconjunctivitis sicca in secondary Sjogren's syndrome.
AUTHOR: Gunduz K.; Ozdemir O.
CORPORATE SOURCE: Department of Opthalmology, Faculty of Medicine, University of Ankara,Ankara, Turkey
SOURCE: Acta Ophthalmologica, (1994) Vol. 72, No. 4, pp. 438-442. .
ISSN: 0001-639X CODEN: ACOPAT
COUNTRY: Denmark
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 012 Ophthalmology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 27 Oct 1994
Last Updated on STN: 27 Oct 1994

ABSTRACT: Topical **cyclosporin** 2% in olive oil was investigated for its possible immunoregulatory role on the dry eye state in patients with secondary Sjogren's syndrome. The study was a randomized, double-masked, placebo-controlled trial. Thirty eyes of 15 patients were randomized to undergo treatment with topical cyclospolin in olive oil and 30 eyes of the other 15 patients received a placebo, which was the sterile olive oil used as a vehicle for the **cyclosporin**. The effect of the 2-month long treatment with either medication on the status of the dry eye state was measured by Schirmer-I test, tear film break-up time and rose bengal staining. There was a significant increase in the break-up time and a significant decrease in rose bengal staining score between the **cyclosporin** and control groups at the end of the 2-month study period ($p < 0.01$) Schirmer-I test remained unaffected ($p > 0.05$). These results probably indicate that topical **cyclosporin** modulates the goblet cell function in secondary Sjogren's associated keratoconjunctivitis sicca and through this mucus enhancing action or some other mechanism not yet known, helps to maintain the

structural integrity of the epithelium.

CONTROLLED TERM: Medical Descriptors:
***keratoconjunctivitis sicca: CN, congenital disorder**
***keratoconjunctivitis sicca: ET, etiology**
***keratoconjunctivitis sicca: DT, drug therapy**
***sjoegren syndrome: ET, etiology**
***sjoegren syndrome: CN, congenital disorder**
adult
article
clinical article
clinical trial
controlled study
double blind procedure
dry eye: ET, etiology
dry eye: DT, drug therapy
dry eye: CN, congenital disorder
female
human
immunoregulation
male
randomized controlled trial
staining
tear film
topical drug administration
Drug Descriptors:
***cyclosporin: CT, clinical trial**
***cyclosporin: AD, drug administration**
***cyclosporin: DT, drug therapy**
***cyclosporin: PD, pharmacology**
cyclosporin a: CT, clinical trial
cyclosporin a: AD, drug administration
cyclosporin a: DT, drug therapy
cyclosporin a: PD, pharmacology
olive oil
placebo
rose bengal
CAS REGISTRY NO.: (**cyclosporin**) 79217-60-0; (**cyclosporin a**) **59865-13-3**, 63798-73-2; (olive oil) 8001-25-0; (rose bengal) 11121-48-5, 11139-83-6, 632-68-8

L139 ANSWER 39 OF 73 EMBASE
ACCESSION NUMBER: 94073961 EMBASE Full-text
DOCUMENT NUMBER: 1994073961
TITLE: New approaches to dry-eye therapy.
AUTHOR: Tsubota K.
CORPORATE SOURCE: 5-11-13 Sugano,Ichikawa, Chiba 272, Japan
SOURCE: International Ophthalmology Clinics, (1994) Vol. 34, No. 1, pp. 115-128. .
ISSN: 0020-8167 CODEN: IOPCAV
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 012 Ophthalmology
027 Biophysics, Bioengineering and Medical Instrumentation
037 Drug Literature Index
LANGUAGE: English
ENTRY DATE: Entered STN: 30 Mar 1994

Last Updated on STN: 30 Mar 1994

CONTROLLED TERM: Medical Descriptors:
***dry eye: TH, therapy**
***dry eye: DT, drug therapy**
clinical trial
evaporation
eyelid reflex
human
lacrimal fluid
lacrimation
moisture
priority journal
review
sjoegren syndrome: TH, therapy
sjoegren syndrome: DT, drug therapy
spectacles
Drug Descriptors:
*artificial tear: DT, drug therapy
*artificial tear: PD, pharmacology
5 (3 ethoxy 4 pentyloxyphenyl) 2,4 thiazolidinedione: DT, drug therapy
5 (3 ethoxy 4 pentyloxyphenyl) 2,4 thiazolidinedione: PD, pharmacology
aldehyde reductase: EC, endogenous compound
alpha interferon: DT, drug therapy
alpha interferon: PD, pharmacology
arachis oil: PD, pharmacology
arachis oil: DT, drug therapy
arginylglycylaspartic acid: DT, drug therapy
arginylglycylaspartic acid: PD, pharmacology
cyclosporin a: PD, pharmacology
cyclosporin a: DT, drug therapy
dextran derivative: PD, pharmacology
dextran derivative: DT, drug therapy
epalrestat
epidermal growth factor: PD, pharmacology
epidermal growth factor: DT, drug therapy
fibronectin: EC, endogenous compound
hyaluronic acid: DT, drug therapy
hyaluronic acid: PD, pharmacology
hydroxypropylmethylcellulose: PD, pharmacology
hydroxypropylmethylcellulose: DT, drug therapy
retinoic acid: DT, drug therapy
retinoic acid: PD, pharmacology
retinol: PD, pharmacology
retinol: DT, drug therapy
tsukubaenolide: PD, pharmacology
tsukubaenolide: DT, drug therapy
visco tears
unclassified drug

CAS REGISTRY NO.: (5 (3 ethoxy 4 pentyloxyphenyl) 2,4 thiazolidinedione) 79714-31-1; (aldehyde reductase) 58591-34-7, 9023-11-4, 9028-31-3; (arachis oil) 8002-03-7, 8031-20-7; (arginylglycylaspartic acid) 99896-85-2; (**cyclosporin a**) **59865-13-3**, 63798-73-2; (epalrestat) 82159-09-9; (epidermal growth factor) 62229-50-9; (fibronectin) 86088-83-7; (hyaluronic acid) 31799-91-4, 9004-61-9, 9067-32-7; (hydroxypropylmethylcellulose) 9004-65-3; (retinoic acid) 302-79-4; (retinol) 68-26-8, 82445-97-4; (tsukubaenolide)

104987-11-3
CHEMICAL NAME: (1) Ct 112; (2) Kinedak; (3) Visco tears; Fk 506
COMPANY NAME: (1) Senju pharmaceutical (Japan); (2) Ono (Japan); (3) Alcon (United States)

L139 ANSWER 40 OF 73 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 94116169 EMBASE Full-text
DOCUMENT NUMBER: 1994116169
TITLE: Collagen-based drug delivery and artificial tears.
AUTHOR: Kaufman H.E.; Steinemann T.L.; Lehman E.; Thompson H.W.; Varnell E.D.; Jacob- Labarre J.T.; Gebhardt B.M.
CORPORATE SOURCE: LSU Eye Center, 2020 Gravier Street,New Orleans, LA 70112, United States
SOURCE: Journal of Ocular Pharmacology, (1994) Vol. 10, No. 1, pp. 17-27. .
ISSN: 8756-3320 CODEN: JOPHER
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 012 Ophthalmology
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 18 May 1994
Last Updated on STN: 18 May 1994

ABSTRACT: For patients with conditions requiring chronic rather than acute therapy, the advantages of collagen shields in providing high and sustained levels of drugs and/or lubricants to the cornea are outweighed by the difficulty of insertion of the shield and the problem of blurred vision. We have developed a delivery system in which collagen pieces suspended in a viscous vehicle can be instilled into the lower forniceal space, thereby simplifying application and reducing blurring of vision. The collagen pieces (Collasomes) can be formulated with various constituents such as antibiotics or ***cyclosporine*** , or with chemical alterations such as the inclusion of a lipid (Lacrisomes) for the treatment of dry eyes. In the normal eyes of volunteers, Collasomes hydrated in a solution of sodium fluorescein and suspended in a methylcellulose vehicle as a model for delivery of water-soluble drugs produced fluorescein concentrations 17 to 42 times higher in the cornea and 6 to 8 times higher in the aqueous humor, compared with fluorescein-containing vehicle alone. In a preliminary controlled study, 76% of patients with moderately severe keratoconjunctivitis sicca (KCS) preferred Lacrisomes to the vehicle control because of a more soothing effect and longer duration of comfort. All preparations were well tolerated by all study subjects. Current studies involve improving drug delivery by chemically modifying the collagen molecule to slow diffusion of the drug from the Collasome matrix, as well as varying the amount of cetyl alcohol and combining it with modified collagen in Lacrisomes to maximize comfort in patients with dry eyes.

CONTROLLED TERM: Medical Descriptors:
***dry eye: DT, drug therapy**
***dry eye: DI, diagnosis**
***keratoconjunctivitis sicca: DT, drug therapy**
***keratoconjunctivitis sicca: DI, diagnosis**
adult
aged
clinical article
clinical trial

conference paper
controlled study
double blind procedure
drug bioavailability
drug tolerance
female
foreign body: SI, side effect
human
male
photophobia: SI, side effect
randomized controlled trial
visual impairment: SI, side effect
drug delivery system
Drug Descriptors:
*artificial tear: DT, drug therapy
*artificial tear: PR, pharmaceutics
*artificial tear: AE, adverse drug reaction
*collagen
duolube
eye drops
fluorescein
fluorescein sodium
hexadecanol
methyl paraben
methylcellulose
murocel
petrolatum
propyl paraben
unclassified drug

CAS REGISTRY NO.: (collagen) 9007-34-5; (fluorescein) 2321-07-5, 91316-42-6; (fluorescein sodium) 518-47-8; (hexadecanol) 29354-98-1, 36653-82-4, 51260-59-4; (methyl paraben) 99-76-3; (methylcellulose) 79484-92-7, 9004-67-5; (petrolatum) 8009-03-8; (propyl paraben) 94-13-3
CHEMICAL NAME: (1) Murocel; (2) Duolube
COMPANY NAME: (2) Bausch and lomb (United States)

L139 ANSWER 41 OF 73 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 92021561 EMBASE Full-text
DOCUMENT NUMBER: 1992021561
TITLE: [Sjoegren syndrome: Current therapy].
LA SINDROME DI SJOEGREN: ATTUALITA TERAPEUTICHE.
AUTHOR: Di Giacinto G.; Piergiacomi G.
CORPORATE SOURCE: Cattedra di Reumatologia, Universita degli Studi, Piazza Roma 22, 60128 Ancona, Italy
SOURCE: Clinica Terapeutica, (1991) Vol. 139, No. 3-4, pp. 81-92.
ISSN: 0009-9047 CODEN: CLTEA4
COUNTRY: Italy
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 003 Endocrinology
006 Internal Medicine
011 Otorhinolaryngology
026 Immunology, Serology and Transplantation
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: Italian
SUMMARY LANGUAGE: English; Italian
ENTRY DATE: Entered STN: 20 Mar 1992

Last Updated on STN: 20 Mar 1992

CONTROLLED TERM: Medical Descriptors:

*disease severity

***sjoegren syndrome: DT, drug therapy**

***sjoegren syndrome: TH, therapy**

***sjoegren syndrome: SU, surgery**

anorexia: SI, side effect

chewing gum

diet

drug efficacy

human

intramuscular drug administration

intranasal drug administration

intravenous drug administration

kidney failure: SI, side effect

leukemia: SI, side effect

mouth ulcer: SI, side effect

nausea: SI, side effect

oral drug administration

rash: SI, side effect

rectal drug administration

review

topical drug administration

vomiting: SI, side effect

xerophthalmia

therapy

drug therapy

Drug Descriptors:

*antiinflammatory agent: AE, adverse drug reaction

*antiinflammatory agent: DT, drug therapy

*artificial tear: PR, pharmaceutics

*artificial tear: DT, drug therapy

*corticosteroid: DT, drug therapy

*hydroxychloroquine: DT, drug therapy

*hydroxychloroquine: AE, adverse drug reaction

*immunosuppressive agent: AE, adverse drug reaction

*immunosuppressive agent: DT, drug therapy

acetylcysteine: DT, drug therapy

anethole trithione: AE, adverse drug reaction

anethole trithione: DT, drug therapy

antihistaminic agent: PD, pharmacology

antihistaminic agent: DT, drug therapy

antihypertensive agent: PD, pharmacology

antihypertensive agent: DT, drug therapy

azathioprine: PD, pharmacology

azathioprine: DT, drug therapy

benzalkonium chloride: DT, drug therapy

bromhexine: PD, pharmacology

bromhexine: DT, drug therapy

carbomer: DT, drug therapy

carboxymethylcellulose: DT, drug therapy

chlorambucil: DT, drug therapy

clonidine: PD, pharmacology

clonidine: DT, drug therapy

cortisone: DT, drug therapy

cyclophosphamide: AE, adverse drug reaction

cyclophosphamide: DT, drug therapy

cyclosporin: AE, adverse drug reaction

cyclosporin: DT, drug therapy

cyclosporin a

dacriosol
dextran: DT, drug therapy
fibronectin: DT, drug therapy
gelatin: DT, drug therapy
glycosaminoglycan polysulfate: DT, drug therapy
gold: DT, drug therapy
hydroxymethylcellulose: DT, drug therapy
hydroxypropylcellulose: DT, drug therapy
macrogol: DT, drug therapy
methotrexate: DT, drug therapy
methotrexate: PD, pharmacology
nandrolone decanoate: DT, drug therapy
nonsteroid antiinflammatory agent: DT, drug therapy
penicillamine: DT, drug therapy
penicillamine: AE, adverse drug reaction
pentosan polysulfate
phenothiazine derivative: DT, drug therapy
phenothiazine derivative: PD, pharmacology
polyacrylic acid
polyvinyl alcohol: DT, drug therapy
propyl paraben: DT, drug therapy
retinol: PD, pharmacology
retinol: DT, drug therapy
sorbitol: DT, drug therapy
tricyclic antidepressant agent: DT, drug therapy
tricyclic antidepressant agent: PD, pharmacology
xerotin
unclassified drug

CAS REGISTRY NO.: (hydroxychloroquine) 118-42-3, 525-31-5; (acetylcysteine) 616-91-1; (anethole trithione) 532-11-6; (azathioprine) 446-86-6; (benzalkonium chloride) 66331-30-4, 78244-97-0, 81181-32-0; (bromhexine) 3572-43-8, 611-75-6; (carbomer) 9007-20-9, 9062-04-8; (carboxymethylcellulose) 8050-38-2, 9000-11-7, 9004-32-4, 9050-04-8; (chlorambucil) 305-03-3; (clonidine) 4205-90-7, 4205-91-8, 57066-25-8; (cortisone) 53-06-5; (cyclophosphamide) 50-18-0; (**cyclosporin**) 79217-60-0; (**cyclosporin a**) **59865-13-3**, 63798-73-2; (dextran) 87915-38-6, 9014-78-2; (fibronectin) 86088-83-7; (gelatin) 9000-70-8; (glycosaminoglycan polysulfate) 63449-40-1; (gold) 7440-57-5; (hydroxymethylcellulose) 37353-59-6; (hydroxypropylcellulose) 9004-64-2; (macrogol) 25322-68-3; (methotrexate) 15475-56-6, 59-05-2, 7413-34-5; (nandrolone decanoate) 360-70-3; (penicillamine) 2219-30-9, 52-67-5; (pentosan polysulfate) 116001-96-8, 37300-21-3, 37319-17-8; (polyacrylic acid) 74350-43-9, 87003-46-1, 9003-01-4, 9003-04-7; (polyvinyl alcohol) 37380-95-3, 9002-89-5; (propyl paraben) 94-13-3; (retinol) 68-26-8, 82445-97-4; (sorbitol) 26566-34-7, 50-70-4, 53469-19-5

CHEMICAL NAME: (1) Plaquenil; (2) Pemine; **(3) Sandimmune**; (4) Imuran; (5) Methotrexate; (6) Endoxan asta; (7) Linfolysin; (8) Bisolvon; (9) Lacrinorm; (10) Xerotin; (11) Dacriosol; Elmiron; Deca durabolin

COMPANY NAME: (1) Winthrop; (2) Lilly; (3) Sandoz; (4) Burroughs wellcome; (5) Cyanamid; (6) Schering; (7) Istituto sieroterapico milanese; (8) Boehringer; (9) Farmigea; (11) Alcon

L139 ANSWER 42 OF 73 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN DUPLICATE 1
ACCESSION NUMBER: 2006-284509 [29] WPIX
DOC. NO. CPI: C2006-092768
TITLE: Gel composition for treating ocular disease, includes hydrophilic polymer, hydrophobic ocular agent, and gelling component.
DERWENT CLASS: A18 A23 A25 A96 B07
INVENTOR(S): JASTI, B R; LI, X; MAHALINGAM, R
PATENT ASSIGNEE(S): (FORM-N) FORMUREX INC
COUNTRY COUNT: 112
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
WO 2006039558	A2	20060413	(200629)*	EN	40	A61K009-14

RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IS IT KE LS LT LU LV MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KM KP KR KZ LC LK LR LS LT LU LV LY MA MD MG MK MN MW MX MZ NA NG NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SM SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2006039558	A2	WO 2005-US35311	20050929

PRIORITY APPLN. INFO: US 2004-617453P 20041009
INT. PATENT CLASSIF.:
MAIN: A61K009-14
BASIC ABSTRACT:
WO2006039558 A UPAB: 20060505
NOVELTY - A gel composition comprises a hydrophilic polymer, a hydrophobic ocular agent, and a gelling component. It comprises a gel in an ocular environment and provides a sustained release of the hydrophobic ocular agent from the gel in the ocular environment.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for a method of forming an ocular gel comprising selecting an ocular agent for use in treating an ocular disease; mixing an **oil** in water to create an **oil**-in-water **emulsion** comprising the ocular agent and a non-ionic hydrophilic **emulsifier**; combining the **oil**-in-water **emulsion** with a previously formulated gel comprising a gelling component from hydroxypropylmethylcellulose, hydroxypropylethylcellulose, methylcellulose, sodium carboxymethylcellulose, and hydroxyethylcellulose, sodium alginate, alginic acid, tragacanth, polyacrylic acid, xanthan gum, guar gum, locust bean gum, and/or karaya gum carboxyvinyl polymers.

ACTIVITY - Ophthalmological.

MECHANISM OF ACTION - None given.

USE - The composition is used for treating ocular disease by administering the composition to an ocular environment of a subject (claimed). The ocular disease comprises keratoconjunctivitis sicca, conjunctivitis and other ocular allergic responses, dry **eye**, lysosomal storage diseases, glycogen storage diseases, disorders of collagen, disorders of glycosaminoglycans and proteoglycans, sphinogolipodoses, mucolipidoses, disorders of amino acid metabolism, dysthyroid **eye** diseases, anterior and posterior corneal

dystrophies, retinal photoreceptor disorders, corneal ulceration, and other ocular wounds such as those following surgery.

ADVANTAGE - The invention can improve the precorneal residence of ophthalmic agents, improve the fraction of drug absorbed by the ocular tissues, and minimize the nasolachrymal drainage, systemic absorption of agents, and associated adverse effects. It provides improved agent loading and delivery properties to the corneal surface. It also provides enhanced solubility, stability, and sustained release of desired agents.

DESCRIPTION OF DRAWING(S) - The figure is a scanning electron micrograph showing the physical stability of an **oil** phase containing a pharmaceutical agent in an E-Gel. Dwg.1/4

FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; GI; DCN
MANUAL CODES: CPI: A12-V01; B04-B01C1; B04-C01H; B04-C02A; B04-C02B; B04-C02D; B04-C03; B04-H19; B12-M02G; B12-M10A4; B12-M12H; B14-N03

TECH UPTX: 20060505

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Component: The hydrophobic ocular agent comprises **cyclosporine** A, and/or protein. The composition comprises a molecular dispersion of the hydrophobic ocular agent. The composition comprises a peanut **oil**. The molecular dispersion comprises molecules, microparticles, and/or controlled volumes. Preferred Method: An additional agent is administered to provide a combination therapy for the subject.

TECHNOLOGY FOCUS - POLYMERS - Preferred Component: The hydrophilic polymer comprises a poly(alkylene glycol) or a non-ionic hydrophilic **emulsifier**. The poly(alkylene glycol) comprises poly(ethylene glycol). The non-ionic hydrophilic **emulsifier** comprises polyoxyethylene sorbitan monooleate. The gelling component comprises a component from hydroxypropylmethylcellulose, hydroxypropylethylcellulose, methylcellulose, sodium carboxymethylcellulose, and hydroxyethylcellulose, sodium alginate, alginic acid, tragacanth, polyacrylic acid, xanthan gum, guar gum, locust bean gum, and/or karaya gum carboxyvinyl polymers. It comprises carboxypolymethylene. The hydrophilic polymer comprises a component from poly(ethylene glycol) (PEG); PEG-caprolactone; PEG-D,L-lactide; poly(ethylene glycol-co-propylene oxide); poly(vinyl alcohol); poly((2- hydroxyethyl)methacrylate); poly(vinyl pyrrolidone); poly(butylene terephthalate-co-ethylene glycol); poly(alkylene oxalates); poly(vinyl alcohols); pluronic acid; sulfonated polystyrene; dextran; dextrin; fibrin, fibrinogen, cellulose, starch, collagen, and/or heparin and hyaluronic acid.

L139 ANSWER 43 OF 73 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2006-077857 [08] WPIX
DOC. NO. CPI: C2006-027935
TITLE: Use of an **emulsion** and optionally an active ingredient to treat **eye** disease and intraocular conditions e.g. intraocular inflammation, infection, cancerous growth, tumors, retinal edema, macular edema and diabetic retinopathy.
DERWENT CLASS: B04 B05 D16
INVENTOR(S): BEHAR-COHAN, F; BENITA, S; COUVREUR, P; DE KOZAK, Y; DUBERNET, C; LAMBERT, G; RABINOVICH-GUILLAT, L; BEHAR-COHEN, F; RABINOVICH-GUILATT, L; DE KOSAK, Y
PATENT ASSIGNEE(S): (CNRS) CNRS CENT NAT RECH SCI; (INRM) INSERM INST NAT SANTE & RECH MEDICALE; (NOVA-N) NOVAGALI PHARMA SA; (YISS) YISSUM RES DEV CO HEBREW UNIV JERUSALEM; (BEHA-I) BEHAR-COHEN F; (BENI-I) BENITA S; (COUV-I) COUVREUR P; (DKOZ-I) DE KOZAK Y; (DUBE-I) DUBERNET C; (LAMB-I)

LAMBERT G; (RABI-I) RABINOVICH-GUILATT L
COUNTRY COUNT: 112
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
US 2006002963	A1	20060105	(200608)*		9	A61K048-00
EP 1611879	A1	20060104	(200608)	EN		A61K009-107
R: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IT LI LT LU LV MC MK NL PL PT RO SE SI SK TR						
WO 2006003519	A2	20060112	(200608)	EN		A61K009-00
RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IS IT KE LS LT LU LV MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW						
W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KM KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NG NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SM SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW						

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 2006002963	A1	US 2004-891452	20040715
EP 1611879	A1	EP 2004-291684	20040702
WO 2006003519	A2	WO 2005-IB2317	20050701

PRIORITY APPLN. INFO: EP 2004-291684 20040702
INT. PATENT CLASSIF.:
MAIN: A61K009-00; A61K009-107; A61K048-00
SECONDARY: A61K031-4738; A61K031-4745; A61K031-70; A61K038-18; A61K038-19; A61K038-20; A61K038-21
BASIC ABSTRACT:

US2006002963 A UPAB: 20060201
NOVELTY - Treating **eye** diseases by injecting intraocularly or periocularly a composition (I) comprising an **emulsion** and optionally at least an active ingredient, is new.

ACTIVITY - Ophthalmological; Antiinflammatory; Cytostatic; Antidiabetic; Virucide.

MECHANISM OF ACTION - None given.

USE - (I) is useful for treating **eye** disease, and intraocular conditions such as intraocular inflammation, infection, cancerous growth, tumors, neo vessel growth originating from the retina and/or from the choroids, retinal edema, macular edema, diabetic retinopathy, retinopathy of prematurity, degenerative diseases of the retina (macular degeneration, retinal dystrophies), **retinal diseases** associated with glial proliferation, ocular conditions such as glaucoma, proliferative **vitreoretinopathy**, diabetic retinopathy, age-related macular degeneration, uveitis, cytomegalovirus retinitis, herpes simplex viral retinal dystrophies, age related macular degeneration (claimed).

The ability of (I) to treat ocular inflammation was assessed. The results showed that (I) exhibited a significant probability value of less than 0.05.

Dwg.0/2

FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; DCN
MANUAL CODES: CPI: B02-A; B02-B; B02-C01; B02-C02; B02-D; B02-E; B02-M; B02-N; B02-P; B02-R; B02-T; B04-B01B; B04-B03C; B04-C01H; B04-C02E1; B04-E01; B04-E07A; B04-E07C;

B04-E08; B04-G01; B04-G21; B04-G22; B04-H01; B04-H02B; B04-H05; B04-H06; B04-H07; B04-H08; B04-J03A; B04-J04B; B04-L04C; B04-L05C; B04-N04; B04-N06; B05-A03B; B05-B01J; B06-H; B07-H; B08-D01; B10-A09B; B10-A10; B10-A12C; B10-A13D; B10-A19; B10-B01A; B10-B02A; B10-B02B; B10-B03B; B10-C03; B10-C04C; B10-D03; B10-G02; B10-H02E; B12-M02G; **B12-M03**; B12-M12C; B14-A01; B14-A02; B14-A04; B14-H01L; B14-N03; D05-H11

TECH UPTX: 20060201

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Components: The **emulsion** is an **oil**/water type **emulsion** or hydrogels. The active ingredient is anaesthetics. The **emulsion** is anionic or cationic **emulsions**. The cationic/anionic **emulsion** is an **oil**/water type **emulsion** comprising colloid particles having an oily core surrounded by an interfacial film comprising surface active agents and/or lipids; where in the **emulsions** at least part of the surface active agents or lipids in the interfacial film have positively/negatively charged polar groups and the colloid particles have a positive/negative zeta potential respectively). The cationic/anionic **emulsion** comprises (in %w/w): oily carrier (0.5-20 (preferably 0.5-10)%), cationic surfactants or lipids (0.01-2 preferably (0.02-0.4)%) and optionally a non-ionic surfactant (0.05-3 (preferably 0.1-2)%). The **emulsion** comprises phospholipids (0.05-3 (preferably 0.1-2)%). The pH of the **emulsion** is 4-8.5 (preferably 6-8).

The **emulsion** further comprises additive such as osmotic pressure regulators, anti-oxidants, preservatives, dextrose, carriers, stabilizing agents, wetting agents, viscosity enhancersnalgesics, cell transport/mobility impending agents such as colchicines, vincristine, cytochalasin B and related compounds; carbonic anhydrase inhibitors such as acetazolamide, methazolamide, dichlorphenamide, diamox and neuroprotectants such as nimodipine and related compounds; antibiotics such as tetracycline, chlortetracycline, bacitracin, neomycin, polymyxin, gramicidin, cephalexin, oxytetracycline, chloramphenicol, rifampicin, ciprofloxacin, aminosides, gentamycin, erythromycin and penicillin, quinolone, ceftazidime, vancomycine imipeneme; antifungals such as amphotericin B, fluconazole, ketoconazole and miconazole; antibacterials such as sulfonamides, sulfadiazine, sulfacetamide, sulfamethizole and sulfisoxazole, nitrofurazone and sodium propionate; antivirals such as idoxuridine, trifluorothymidine, trifluorouridine, acyclovir, ganciclovir, cidofovir, interferon, didanosine (DDI), zidovudine (AZT), foscamet, vidarabine, irbavirin, protease inhibitors and anti-cytomegalovirus agents; antiallergenics such as sodium cromoglycate, antazoline, methapyriline, chlorpheniramine, cetirizine, pyrilamine and prophenpyridamine; synthetic gluocorticoids and mineralocorticoids, hormones forms derivating from the cholesterol metabolism (dehydroepiandrosterone (DHEA), progesterone, estrogens); non-steroidal anti-inflammatories such as salicylate, indomethacin, ibuprofen, diclofenac, flurbiprofen, piroxicam and cyclooxegenase 2 (COX2) inhibitors; antineoplastics such as carmustine, cisplatin, fluorouracil; adriamycin, asparaginase, azacitidine, azathioprine, bleomycin, busulfan, carboplatin, carmustine, chlorambucil, cyclophosphamide, **cyclosporine**, cytarabine, dacarbazine, dactinomycin, daunorubicin, doxorubicin, estramustine, etoposide, etretinate, filgrastin, floxuridine, fludarabine, fluorouracil, florxymesterone, flutamide, goserelin, hydroxyurea, ifosfamide, leuprolide, levamisole, limustine, nitrogen mustard, melphalan, mercaptopurine, methotrexate, mitomycin, mitotane, pentostatin, pipobroman, plicamycin, procarbazine, sargramostin, streptozocin, tamoxifen, taxol, teniposide, thioguanine, uracil mustard,

vinblastine, vincristine and vindesine; immunological drugs such as vaccines and immune stimulants; insulin, calcitonin, parathyroid hormone and peptide and vasopressin hypothalamus releasing factor; beta adrenergic blockers such as timolol, levobunolol and betaxolol; cytokines, interleukines and growth factors epidermal growth factor, fibroblast growth factor, platelet derived growth factor, transforming growth factor beta, ciliary neurotrophic growth factor, glial derived neurotrophic factor, nerve growth factor (NGF), erythropoietin (EPO), placenta growth factor (PLGF), brain nerve growth factor (BNGF), vascular endothelial growth factor (VEGF) and monoclonal antibodies directed against such growth factors; anti-inflammatories such as hydrocortisone, dexamethasone, fluocinolone, prednisone, prednisolone, methylprednisolone, fluorometholone, betamethasone and triamcinolone; decongestants chosen from the group comprising phenylephrine, naphazoline and tetrahydrazoline; miotics and anti-cholinesterases chosen from the group comprising pilocarpine, carbachol, di-isopropyl fluorophosphate, phospholine iodine and demecarium bromide; mydriatics such as atropine sulfate, cyclopentolate, homatropine, scopolamine, tropicamide, eucatropine; sympathomimetics such as epinephrine and vasoconstrictors and vasodilators; anticlotting agents such as heparin, antifibrinogen, fibrinolysin, anticlotting activase, antidiabetic agents such as acetohexamide, chlorpropamide, glipizide, glyburide, tolazamide, tolbutamide, insulin and aldose reductase inhibitors, hormones, peptides, nucleic acids, saccharides, lipids, glycolipids, glycoproteins and other macromolecules include endocrine hormones such as pituitary, insulin, insulin-related growth factor, thyroid, growth hormones; heat shock proteins; immunological response modifiers such as muramyl dipeptide, **cyclosporins**, interferons (including alpha-, beta- and gamma-interferons), interleukin-2, cytokines, FK506 (an epoxy-pyrido-oxaazcyclotricosine-tetrone, also known as Tacrolimus), tumor necrosis factor, pentostatin, thymopentin, transforming factor beta-.sub.2, erythropoetin; antineogenesis proteins (e.g. anti VEGF, Interferons); antibodies (monoclonal or polyclonal) or antibodies fragments, oligoaptamers, aptamers and gene fragments (oligonucleotides, plasmids, ribozymes, small interference RNA (SiRNA), nucleic acid fragments, peptides); immunomodulators such as endoxan, thalidomide, tamoxifene; antithrombolytic and vasodilator agents such as recombinant tissue plasminogen activator (rtPA), urokinase, plasmin, nitric oxide donors; nucleic acids optionally expressed to produce a protein that may have a variety of pharmacological, physiological or immunological activities.

L139 ANSWER 44 OF 73 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2005-152322 [16] WPIX
CROSS REFERENCE: 2004-389738 [36]; 2005-151639 [16]; 2005-232906 [24]; 2005-271944 [28]
DOC. NO. CPI: C2005-049322
TITLE: Non-translucent **oil** in water **emulsion** , useful to treat e.g. dermatitis, bacterial infections and dermatological disorders, comprises non-volatile hydrophobic solvent, surface-active agent, gelling agent and liquefied gas propellant.
DERWENT CLASS: A96 A97 B05 B07 C03 C07
INVENTOR(S): EINI, M; FRIEDMAN, D; TAMARKIN, D
PATENT ASSIGNEE(S): (FOAM-N) FOAMIX LTD
COUNTRY COUNT: 109
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC

WO 2005011567 A2 20050210 (200516)* EN 68 A61K000-00
RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG 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 MZ NA NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
AU 2004261063 A1 20050210 (200570) A61K007-00
EP 1670435 A2 20060621 (200643) EN A61K009-12
R: AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LU MC NL PL PT RO SE SI SK TR

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2005011567	A2	WO 2004-IB2583	20040804
AU 2004261063	A1	AU 2004-261063	20040804
EP 1670435	A2	EP 2004-786401	20040804
		WO 2004-IB2583	20040804

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2004261063	A1 Based on	WO 2005011567
EP 1670435	A2 Based on	WO 2005011567

PRIORITY APPLN. INFO: US 2003-492385P 20030804
INT. PATENT CLASSIF.:
MAIN: A61K000-00; A61K007-00; A61K009-12
BASIC ABSTRACT:
WO2005011567 A UPAB: 20060906
NOVELTY - Non-translucent **oil** in water **emulsion** (A) (that is stable in its pre-dispensed state) for use as an alcohol-free foamable carrier, comprises:
(1) non-volatile hydrophobic solvent (a) (10-75 weight% of (A));
(2) surface-active agent (b) (0.1-5 weight%), having an HLB value of at least 9);
(3) gelling agent (c) (0.1-5 weight%) comprising an amphiphilic copolymer and;
(4) a liquefied gas propellant (d) (3-18 weight% of (A)).
ACTIVITY - Antibacterial; Fungicide; Virucide; Antiparasitic; Antiinflammatory; Gastrointestinal-Gen.; Immunosuppressive; Antiallergic; Endocrine-Gen.; Dermatological; Ophthalmological; Auditory; Gynecological; Antiseborrheic; Cytostatic; Vulnerary; Anesthetic; Keratolytic.
MECHANISM OF ACTION - None given.
USE - (A) is useful in the treatment of diseases having an etiology of bacterial, fungal, viral, parasitic, inflammatory, autoimmune, allergic, hormonal and/or malignant. (A) is useful in the treatment of bio-abnormality, superficial condition or disorders of the skin, mucosal membrane, **eye**, ear, vagina or rectum. (A) is useful in the treatment of a disorder such as dermatosis, dermatitis, bacterial infections, fungal infections, parasitic infections, viral infections, disorders of hair follicles and sebaceous glands, acne, rosacea, scaling papular diseases, benign tumors, malignant tumors, reactions to sunlight, bullous diseases, pigmentation disorders, disorders of cornification, pressure sores, disorders of sweating, inflammatory reactions, xerosis, ichthyosis, allergy, burn, wound, cut and non-dermatological disorders that respond to transdermal delivery of the drug. (A) is useful to treat, alleviate or prevent dermatological disorder. (A) is

useful to prevent skin cancer or skin hyperpigmentation. (A) enhances hair growth and substantially limits or prevents hair growth. (A) is useful as local anesthetic agent or keratolytic agents. (All claimed.) No biological data given.

ADVANTAGE - (A) is stable in its pre-dispensed state and is a breakable therapeutic foam (claimed). (A) is alcohol free cosmetic or pharmaceutical foam. (A) is lightweight and thus economical. (A) contains a hydrophobic solvent, in any desirable concentration, which provides a refatting and skin soothing effect. (A) contains silicone **oil** in a therapeutically effective concentration and includes both water-soluble and **oil**-soluble active agents. (A) is easily spreadable, allowing treatment of large areas such as the arms, back, legs and the breast, and due to flow properties of (A) that spreads effectively into folds and wrinkles, by providing uniform distribution and absorption of the active agent without the need of extensive rubbing. Dwg.0/0

FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; DCN
MANUAL CODES: CPI: A12-V01; B01-B02; B01-C02; B01-C03; B03-F; B03-H; B04-A04; B04-A06; B04-A07C; B04-A08; B04-A10; B04-B01C; B04-B03D; B04-C02; B04-C03; B04-H05; B04-L03D; B05-A01A; B05-A01B; B05-B01M; B05-B01P; B05-C05; B05-C07; B06-H; B07-H; B09-D01; B10-A04; B10-A09A; B10-A10; B10-A17; B10-A22; B10-B01A; B10-B02; B10-B03B; B10-B04B; B10-C02; B10-C03; B10-C04; B10-D03; B10-E02; B10-E04; B10-H02; B10-J02; B14-A01; B14-A02; B14-A04; B14-B02; B14-C03; B14-C08; B14-G02A; B14-G02D; B14-H01; B14-H01W; B14-N02; B14-N03; B14-N07; B14-N14; B14-N17; B14-R01; B14-R02; C01-B02; C01-C02; C01-C03; C03-F; C03-H; C04-A04; C04-A06; C04-A07C; C04-A08; C04-A10; C04-B01C; C04-B03D; C04-C02; C04-C03; C04-H05; C04-L03D; C05-A01A; C05-A01B; C05-B01M; C05-B01P; C05-C05; C05-C07; C06-H; C07-H; C09-D01; C10-H02; C10-J02

TECH UPTX: 20050308

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Composition: (a) comprises 10-20 wt.% (preferably 20-75 wt.%) of (A).

(a) comprises a mixture of mineral **oil** and an emollient in a ratio of 2:8-8:2 on a weight basis.

(b) is a mixture of a non-ionic surfactant and an ionic surfactant in a ratio of 1:1-20:1 or 100:1-6:1.

(b) consists essentially of at least one non-ionic surfactant comprising a sucrose ester.

The amphiphilic copolymer is a cross linked copolymer of acrylic acid and a hydrophobic comonomer, amphiphilic starch derivatives, amphiphilic silicon polyols or copolyols, amphiphilic block polymers, pemulen polymeric surfactants, acrylates/10-30C alkyl acrylate crosspolymer, cetyl hydroxyethyl cellulose, acrylates /steareth-20 methacrylate copolymer, acrylates/ laureth-25 methacrylate copolymer, acrylates /beheneth-25 methacrylate copolymer, PRG-150/stearyl alcohol/SMDI copolymer, acrylates/vinyl isodecanoate, acrylates/steareth-20 itaconate copolymer, acrylates/ceteth-20 itaconate copolymer and acrylates/aminoacrylates/10-30C alkyl PEG 20 itaconate copolymer, amphiphilic silicone polymers, alkyl dimethicon copolyol, cetyl dimethicon copolyol, dimethicone copolyol PPG-3 oleyl ether, acetylated starch derivatives, amphiphilic modified starches or amphiphilic block copolymers of ethylene oxide, propylene oxide and/or propylene glycol.

(b) further comprises a thickening agent of locust bean gum, sodium alginate, sodium caseinate, egg albumin, gelatin agar, carrageenin gum sodium alginate, xanthan gum, quince seed extract, tragacanth gum, starch, chemically modified starches, cellulose ethers, polyvinylpyrrolidone,

polyvinylalcohol, guar gum, hydroxypropyl guar gum, soluble starch, cationic celluloses, cationic guars, carboxyvinyl polymers, polyvinyl alcohol polyacrylic acid polymers, polymethacrylic acid polymers, polyvinyl acetate polymers, polyvinyl chloride polymers or polyvinylidene chloride polymers.
(A) further comprises a concentration of a drug.
(a) is a vegetable **oil**, a marine **oil**, a mineral **oil**, an emollient, a silicone **oil** and/or a plant-derived therapeutic **oil** at any proportion.
(b) and (c) comprises less than about 8% (preferably less than 5%) (w/w) of (A).
The active agent is a drug (cosmetically effective agent), insecticide, insect repellant, antiparasite (hexachlorobenzene, carbamate, naturally occurring pyrethroids, permethrin, allethrin, malathion, piperonyl butoxide and/or any terpenol and derivatives), antiallergic agent (corticosteroids, non-steroidal antiinflammatory drugs, antihistamines, immunosuppressants and/or immunomodulating agent (preferably diphenhydramine, doxepin, phrilamine maleate, chlorpheniramine and tripelennamine, phenothiazines, promethazine hydrochloride, dimethindene maleate)), antiinflammatory agent (clobetasol proprionate, halobetasol proprionate, betamethasone diproprionate, betamethasone valerate, fluocinolone acetonide, halcinonide, betamethasone valerate, fluocinolone acetonide, hydrocortisone valerate, triamcinolone acetonide, hydrocortisone (preferably oxicams, piroxicam, isoxicam, tenoxicam, sudoxicam, salicylates, aspirin, disalcid, benorylate, trilisate, safapryn, solprin, diflunisal, fendosal, diclofenac, fenclofenac, indomethacin, sulindac, tolmetin, isoxepac, furofenac, tiopinac, zidometacin, acematacin, fentiazac, zomepirac, clindanac, oxepinac, felbinac, ketorolac, fenamates, mefenamic, meclofenamic, flufenamic, niflumic, tolfenamic acids, propionic acid derivatives, ibuprofen, naproxen, benoxaprofen, flurbiprofen, ketoprofen, fenoprofen, fenbufen, indopropfen, pirprofen, carprofen, oxaprozin, pranoprofen, miroprofen, tioxaprofen, suprofen, alminoprofen, tiaprofenic, pyrazoles, phenylbutazone, oxyphenbutazone, feprazone, azapropazone and trimethazone)), anticancer agent, retinoid (retinol, retinal, retinoic acid, etretinate, actiretin, isotretinoin, adapalene or tazarotene), an anti-wrinkle agent, sulfur-containing amino acids, thiol compounds, alpha hydroxy acids, lactic acid and lactic acid derivatives and salts, glycolic acid, glycolic acid derivatives and glycolic acid salts, beta-hydroxy acids, salicylic acid and salicylic acid salts and derivatives, phytic acid, lipoic acid, lysophosphatidic acid, skin peel agents, phenol, resorcinol, vitamin B3 compounds, niacinamide, nicotinic acid and nicotinic acid salts and esters, tocopheryl nicotinate, nicotinyl amino acids, nicotinyl alcohol esters of carboxylic acids, nicotinic acid N-oxide and niacinamide N-oxide, retinoids, retinol, retinal, retinoic acid, retinyl acetate, retinyl palmitate and retinyl ascorbate, caffeine, theophilline, pentoxyphilline, dihydroxy acetone kojic acid, arbutin, nicotinic acid and nicotinic acid precursors, nicotinic acid salts, nicotinic acid derivatives, ascorbic acid, ascorbic acid salts or ascorbic acid derivatives, radical scavenger, herbal extract, ascorbyl esters of fatty acids, magnesium ascorbyl phosphate, sodium ascorbyl phosphate, ascorbyl sorbate, tocopherol, tocopherol sorbate, tocopherol acetate, other esters of tocopherol, butylated hydroxy benzoic acids and their salts, 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid, gallic acid and gallic acid alkyl esters, propyl gallate, uric acid, uric acid salts and alkyl esters, sorbic acid and sorbic acid salts, lipoic acid, N,N-diethylhydroxylamine, aminoguanidine, sulfhydryl compounds, glutathione, dihydroxy fumaric acid and fumaric acid salts, lycine pidolate, arginine pilolate, nordihydroguaiaretic acid, bioflavonoids, curcumin, lysine, methionine, proline, superoxide dismutase, silymarin,

tea extract, grape skin/seed extract, melanin, rosemary extract, self-tanning agent, anti-acne active agent (further comprising retinoid, a keratolytically active agent and an antiinflammatory agent), resorcinol, sulfur, salicylic acid, salicylate salts, benzoyl peroxide, retinoic acid, isotretinoin, adapalene, tazarotene, azelaic acid and azelaic acid derivatives, antibiotic agents, erythromycin and clyndamycin and zinc salts and complexes, skin whitening agents, exfoliant, epilating agent or depilating agent.

The active agent further comprises a screening agent which provides SFP value of at least about 30 (UVA absorber and a UVB absorber), decontaminating agent (oxidizing agent, iodine, iodine compounds, chlorohexidine, bleaching agent or surface-active agent).

The anti-inflammatory agent reduces the occurrence of pro-inflammatory cytokines or inhibits the effect of pro-inflammatory cytokines. The drug is an antibacterial drug (chloramphenicol, tetracyclines, synthetic and semi-synthetic penicillins, beta-lactams, quinolones, fluoroquinolnes, macrolide antibiotics, peptide antibiotics, **cyclosporines**, metronidazole, free radical generating agents, iodine, chlorohexidine, benzoyl peroxide and/or hydrogen peroxide), an antifungal drug (azoles, diazoles, triazoles, miconazole, fluconazole, ketoconazole, clotrimazole, itraconazole griseofulvin, ciclopirox, amorolfine, terbinafine, amphotericin B, potassium iodide and/or flucytosine (5FC)) which is active against dermatophytes or candida, antiviral (vidarabine, acyclovir, gancyclovir, nucleoside-analog reverse transcriptase inhibitors, zidovudine, didanosine, zalcitabine, stavudine, lamivudine, nonnucleoside reverse transcriptase inhibitors, nevirapine, delavirdine, protease inhibitors, saquinavir, ritonavir, indinavir, nelfinavir, ribavirin, amantadine, rimantadine and interferon), photodynamic therapy agent, local anesthetic agent (benzocaine, lidocaine, bupivacaine, chlorprocaine, dibucaine, etidocaine, mepivacaine, tetracaine, dyclonine, hexylcaine, procaine, cocaine, ketamine, pramoxine or phenol), nonsteroidal antiinflammatory drug, retinoid, alpha hydroxy acid, beta hydroxy acid, keratolytic, antiproliferative, anticancer or antipigmentation drugs.

The active agent enhances hair growth and substantially limits or prevents hair growth.

L139 ANSWER 45 OF 73 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2005-271944 [28] WPIX
CROSS REFERENCE: 2004-389738 [36]; 2005-151639 [16]; 2005-152322 [16]; 2005-232906 [24]
DOC. NO. CPI: C2005-085070
TITLE: Alcohol-free foamable carrier, useful for treating e.g. dermatological disorder, comprises non-volatile hydrophobic solvent, surface-active agent, gelling agent comprising amphiphilic copolymer and liquefied gas propellant.
DERWENT CLASS: A96 B05 C03 D21
INVENTOR(S): EINI, M; FRIEDMAN, D; TAMARKIN, D
PATENT ASSIGNEE(S): (FOAM-N) FOAMIX LTD
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
US 2005069566	A1	20050331	(200528)*		18	A61K007-00

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE

US 2005069566 A1 Provisional US 2003-492385P 20030804
US 2004-911367 20040804

PRIORITY APPLN. INFO: US 2003-492385P 20030804; US 2004-911367 20040804
INT. PATENT CLASSIF.:
MAIN: A61K007-00
BASIC ABSTRACT:
US2005069566 A UPAB: 20060906
NOVELTY - A non-translucent, **oil** in water **emulsion** comprises (weight%): liquid, non-volatile hydrophobic solvent (10 - 75, preferably 10 - 20 or 20 - 75); a surface-active agent (0.1 - 5) having an HLB of 9; a gelling agent (0.1 - 5) comprising an amphiphilic copolymer; and a liquefied gas propellant (3 - 18).

ACTIVITY - Dermatological; Cytostatic; Antiseborrheic; Anti-HIV; Virucide; Antibacterial; Fungicide; Antiparasitic; Antipsoriatic; Vulnerary; Keratolytic; Antiulcer.

MECHANISM OF ACTION - None given.

USE - As an alcohol-free foamable carrier useful for treating dermatological disorder and preventing skin cancer or skin hyperpigmentation (claimed). Also useful for treating contact dermatitis, seborrheic dermatitis, bacterial, fungal, parasitic and viral infections, psoriasis, Kaposi's sarcoma, sunburn, pemphigus, vitiligo, Melasma, Ichthyosis, actinic keratosis, ulcers and disorders of sweating.

ADVANTAGE - The composition is alcohol free; stable in pre-dispensed state; and is lightweight. The composition contains a hydrophobic solvent in any desirable concentration, that provides a refatting and skin soothing effect; and contains silicone **oil** in therapeutically effective concentrating and also both water-soluble and **oil** -soluble active agents. The foam composition is easily spreadable, allowing treatment of large areas e.g. arms, back, legs and breast. Due to flow properties of the foam, the foam spreads effectively into folds and wrinkles, thereby provides uniform distribution and absorption of the active agent without the need of extensive rubbing. The foam cleanses, beautifies, promotes or alters the appearance without affecting the body structure or function.

Dwg.0/0
FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; DCN
MANUAL CODES: CPI: A12-V04C; B01-B02; B01-B03; B02-E; B02-G; B03-A; B03-F; B03-H; B04-A06; B04-A07C; B04-A10; B04-B01C; B04-B03B; B04-B03D; B04-C02; B04-C03; B04-N02; B05-A01A; B05-B01P; B05-C06; B05-C08; B06-H; B07-H; B09-D01; B10-A04; B10-A10; B10-A17; B10-B01; B10-B02; B10-B03B; B10-C02; B10-C03; B10-C04; B10-D03; B10-E02; B14-A01; B14-A02; B14-A04; B14-B02; B14-C03; B14-C07; B14-G02; B14-H01; B14-N02; B14-N03; B14-N07; B14-N17; B14-R01; B14-R02; B14-S15; C01-B02; C01-B03; C02-E; C02-G; C03-A; C03-F; C03-H; C04-A06; C04-A07C; C04-A10; C04-B01C; C04-B03D; C04-C02; C04-C03; C04-N02; C05-A01A; C05-B01P; C05-C06; C05-C08; C06-H; C07-H; C09-D01; C10-A04; C10-A10; C10-A17; C10-B01; C10-B03B; C10-C02; C10-C03; C10-C04; C10-D03; C10-E02; C14-A01; C14-A02; C14-A04; C14-B02; C14-C03; C14-C07; C14-G02; C14-H01; C14-N02; C14-N03; C14-N07; C14-N17; C14-R01; C14-R02; C14-S15; D08-B09A
TECH UPTX: 20050504
TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Composition: The

emulsion additionally comprises a thickening agent, therapeutically effective concentration of a drug that is cosmetically effective agent, a sunscreen agent (preferably UVA absorber or UVB absorber) providing SPF value of at least 30, a decontaminating agent and at least one agent selected from retinoid, keratolytically active agent and anti-inflammatory agent.
Preferred Components: The hydrophobic solvent comprises a mixture of mineral **oil** and an emollient in a weight ratio of 2:8 - 8:2. The surface-active agent is mixture of a non-ionic surfactant and an ionic surfactant in a ratio of 1:1 - 20:1 or 100:1 - 6:1 or at least one non-ionic surfactant. The hydrophobic solvent is selected from vegetable **oil**, marine **oil**, mineral **oil**, an emollient, silicone **oil** and/or plant-derived therapeutic **oil**. The non-ionic surfactant comprises a sucrose ester.

TECHNOLOGY FOCUS - POLYMERS - Preferred Components: The amphiphilic copolymer is selected from cross linked copolymer of acrylic acid and hydrophobic comonomer, amphiphilic starch derivatives, amphiphilic silicon polyol or copolyol and amphiphilic block polymer (preferably Pemulen polymeric surfactant, acrylate/10-30C alkyl acrylate crosspolymer, cetyl hydroxyethyl cellulose, acrylate/steareth-20 methacrylate copolymer, acrylate/laureth-25 methacrylate copolymer, acrylate/beheneth-25 methacrylate copolymer, PRG-150/stearyl alcohol/4,4-methylene-bis-(cyclohexylisocyanate) (SMDI) copolymer, acrylate/vinyl isodecanoate, acrylate/steareth-20 itaconate copolymer, acrylate/ceteth-20 itaconate copolymer, acrylate/aminoacrylate/10-30C alkyl polyethylene glycol-20 itaconate copolymer, amphiphilic silicone polymer, alkyl dimethicon copolyol, cetyl dimethicon copolyol, dimethicone copolyol polypropylene-3 oleyl ether, acetylated starch derivatives, amphiphilic modified starch, and amphiphilic block copolymers of ethylene oxide, propylene oxide and/or propylene glycol). The thickening agent is locust bean gum, sodium alginate, sodium caseinate, egg albumin, gelatin agar, carrageenan gum sodium alginate, xanthan gum, quince seed extract, tragacanth gum, starch, chemically modified starch, cellulose ether, polyvinylpyrrolidone, polyvinyl alcohol, guar gum, hydroxypropyl guar gum, soluble starch, cationic cellulose, cationic guar, carboxyvinyl polymer, polyvinyl alcohol polyacrylic acid polymer, polymethacrylic acid polymer, polyvinyl acetate polymer, polyvinyl chloride polymer or polyvinylidene chloride polymer.
TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Components: The drug is selected from those for the treatment of bio-abnormality, superficial condition, disorder of the skin, mucosal membrane, **eye**, ear, vagina or rectum, disease having etiology selected from bacterial, fungal, viral, parasitic, inflammatory, autoimmune, allergic, hormonal and/or malignant, or disorders e.g. dermatosis, dermatitis, bacterial, fungal, parasitic and viral infections, acne, rosacea, scaling popular diseases, benign tumor, malignant tumor, reactions of sunlight, bullous disease, pigmentation disorder, pressure sore, disorders of hair follicles and sebaceous glands, disorders of cornification and sweating, inflammatory reactions, xerosis, ichthyosis, allergy, burn, wound, cut and non-dermatological disorders responding to transdermal delivery of the drug. The drug is an antibacterial material, antifungal material, antiviral, insecticide and insect repellent, anti-allergic agent, anti-inflammatory agent, anticancer agent, photodynamic therapy agent, local anesthetic agent, retinoid, anti-wrinkle agent, radical scavenger, herbal extract, self-tannin agent, anti-acne active agent, skin whitening agent, hair growth enhancer, an exfoliant, an epilating agent or depilating agent.
The antibacterial material is chloramphenicol, tetracycline, synthetic and semi-synthetic penicillin, beta-lactam, quinolone, fluoroquinolone, macrolide antibiotic, peptide antibiotic, **cyclosporines**,

metronidazole, free radical generating agent, iodine, chlorohexidine, benzoyl peroxide and/or hydrogen peroxide.
The antifungal drug is active against dermatophytes or Candida and selected from azoles, diazoles, triazoles, miconazole, fluconazole, ketoconazole, clotrimazole, itraconazole, griseofulvin, ciclopirox, amorolfine, terbinafine, amphotericin B, potassium iodide and/or flucytosine (5FC).
The antiviral drug is vidarabine, acyclovir, gancyclovir, nucleoside-analog reverse transcriptase inhibitors, AZT (zidovudine), ddI (didanosine), ddC (zalcitabine), d4T (stavudine), 3TC (lamivudine), non-nucleoside reverse transcriptase inhibitors, nevirapine, delavirdine, protease inhibitors, saquinavir, ritonavir, indinavir, nelfinavir, ribavirin, amantadine, rimantadine or interferon.
The antiparasite is selected from hexachlorobenzene, carbamate, naturally occurring pyrethroids, permethrin, allethrin, malathion, piperonyl butoxide, any terpenol and/or their derivatives.
The antiallergic agent is corticosteroid, non-steroidal antiinflammatory drug, antihistamine, immunosuppressant and/or immunomodulating agent. The antiallergic agent is doxepin, diphenhydramine, phrilamine maleate, chlorpheniramine, tripelennamine, phenothiazines, promethazine hydrochloride and/or dimethindene maleate.
The anti-inflammatory agent is corticosteroid, non-steroidal antiinflammatory drug, immunosuppressant and/or immunomodulator (preferably clobetasol proprionate, halobetasol proprionate, betamethasone diproprionate, betamethasone valerate, fluocinolone acetonide, halcinonide, betamethasone valerate, fluocinolone acetonide, hydrocortisone valerate, triamcinolone acetonide and/or hydrocortisone or oxicams, piroxicam, isoxicam, tenoxicam, sudoxicam, salicylate, aspirin, disalcid, benorylate, trilisate, safapryn, solprin, diflunisal, fendosal, diclofenac, fenclofenac, indomethacin, sulindac, tolmetin, isoxepac, furofenac, tiopinac, zidometacin, acematacin, fentiazac, zomepirac, clindanac, oxepinac, felbinac, ketorolac, fenamates, mefenamic, meclofenamic, flufenamic, niflumic, tolfenamic acids, propionic acid derivatives, ibuprofen, naproxen, benoxaprofen, flurbiprofen, ketoprofen, fenoprofen, fenbufen, indopropfen, pirprofen, carprofen, oxaprozin, pranoprofen, miroprofen, tioxaprofen, suprofen, alminoprofen, tiaprofenic, pyrazoles, phenylbutazone, oxyphenbutazone, feprazone, azapropazone or trimethazone).
The anesthetic is selected from benzocaine, lidocaine, bupivacaine, chlorprocaine, dibucaine, etidocaine, mepivacaine, tetracaine, dyclonine, hexylcaine, procaine, ketamine, pramoxine and phenol. The retinoid is retinol, retinal, retinoic acid, etretinate, actiretin, isotretinoin, adapalene or tazarotene.
The active agent is selected from sulfur-containing amino acid, thiol compound, alpha hydroxy acid, lactic acid and lactic acid derivatives and salts, glycolic acid, glycolic acid derivatives and glycolic acid salts, beta-hydroxy acid, salicylic acid and salicylic acid salts and derivatives, phytic acid, lipoic acid, lysophosphatidic acid, skin peel agent, phenol, resorcinol, vitamin B3 compounds, niacinamide, nicotinic acid and nicotinic acid salts and esters, tocopheryl nicotinate, nicotinyl amino acids, nicotinyl alcohol esters of carboxylic acids, nicotinic acid N-oxide, niacinamide N-oxide, retinoid, retinol, retinal, retinoic acid, retinyl acetate, retinyl palmitate, retinyl ascorbate, caffeine, theophilline, pentoxyphilline, dihydroxy acetone kojic acid, arbutin, nicotinic acid or its precursors, salts or derivatives, ascorbic acid or its salts or derivatives, ascorbyl ester of fatty acids, magnesium ascorbyl phosphate, sodium ascorbyl phosphate, ascorbyl sorbate, tocopherol, tocopherol sorbate, tocopherol acetate, other esters of tocopherol, butylated hydroxy benzoic acids or their salts, 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid, gallic acid or its

alkyl esters, propyl gallate, uric acid or its salts or alkyl esters, sorbic acid or its salts, lipoic acid, N,N-diethylhydroxylamine, aminoguanidine, sulfhydryl compounds, glutathione, dihydroxy fumaric acid or its salts, lycine pidolate, arginine pilolate, nordihydroguaiaretic acid, bioflavonoids, curcumin, lysine, methionine, proline, superoxide dismutase, silymarin, tea extract, grape skin/seed extract, melanin, rosemary extract, sulfur, salicylic acid, salicylate salts, benzoyl peroxide, retinoic acid, isotretinoin, adapalene, tazarotene, azelaic acid or its derivatives, antibiotic agent, erythromycin, clyndamycin and zinc salts or complexes.

The anti-inflammatory agent or anti-allergic agent reduces the occurrence of pro-inflammatory cytokines or inhibits the effect of proinflammatory cytokines.

TECHNOLOGY FOCUS - INORGANIC CHEMISTRY - Preferred Components: The decontaminating agent is selected from an oxidizing agent, iodine, iodine compound, chlorohexidine, bleaching agent and surface-active agent.

L139 ANSWER 46 OF 73 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2004-689154 [67] WPIX
CROSS REFERENCE: 2004-717813 [70]; 2005-699632 [72]
DOC. NO. CPI: C2004-244217
TITLE: Self-**emulsifying** composition useful with therapeutic drug used in making therapeutic composition, e.g. ophthalmic composition, comprises **oil** globules containing surfactant and polar **oil** components.
DERWENT CLASS: B05
INVENTOR(S): HUTH, S; YU, Z; COOK, J N; CRAWFORD, L L; HUTH, S W
PATENT ASSIGNEE(S): (HUTH-I) HUTH S; (YUZZ-I) YU Z; (ADME-N) ADVANCED MEDICAL OPTICS INC
COUNTRY COUNT: 109
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
US 2004185068	A1	20040923	(200467)*		26	A61K007-00
WO 2004082625	A2	20040930	(200467)	EN		A61K000-00
RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW						
W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG 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 MZ NA NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW						
EP 1603607	A2	20051214	(200582)	EN		A61M001-00
R: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LT LU LV MC MK NL PL PT RO SE SI SK TR						
AU 2004222295	A1	20040930	(200612)			A61K009-107
BR 2004008516	A	20060307	(200619)			A61K009-107

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 2004185068	A1	US 2003-392375	20030318
WO 2004082625	A2	WO 2004-US8076	20040317
EP 1603607	A2	EP 2004-757532	20040317
		WO 2004-US8076	20040317
AU 2004222295	A1	AU 2004-222295	20040317
BR 2004008516	A	BR 2004-8516	20040317

WO 2004-US8076 20040317

FILING DETAILS:

PATENT NO	KIND	PATENT NO
EP 1603607	A2 Based on	WO 2004082625
AU 2004222295	A1 Based on	WO 2004082625
BR 2004008516	A Based on	WO 2004082625

PRIORITY APPLN. INFO: US 2003-392375 20030318
INT. PATENT CLASSIF.:
MAIN: A61K000-00; A61K007-00; A61K009-107; A61M001-00
BASIC ABSTRACT:
US2004185068 A UPAB: 20060320
NOVELTY - A self-**emulsifying** composition comprises **oil** globules containing surfactant and polar **oil** components. The **oil** globules have average size of less than 1 micro m dispersed in aqueous phase. The surfactant component comprises one or two surfactants. The polar **oil** and surfactant components are selected to self- **emulsify** when mixed without mechanical homogenization.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is included for preparing self-**emulsifying** composition comprising preparing **oil** phase comprising polar **oil** and surfactant components, preparing aqueous phase at temperature that permits self-**emulsification**, and mixing **oil** phase and aqueous phase to form **emulsion** without mechanical homogenization.

ACTIVITY - Ophthalmological.

MECHANISM OF ACTION - None given.

USE - Useful with therapeutic drug used in making therapeutic composition, e.g. ophthalmic composition (claimed).

ADVANTAGE - The invention is prepared without mechanical homogenization. It provides low weight ratio of **emulsifying** component to **oil** component and fewer chemical toxicity concerns, resulting in comfort and safety advantages over **emulsions** using at least two **emulsifiers**.

DESCRIPTION OF DRAWING(S) - The figure shows a flow chart of the preparation of ophthalmic self-**emulsifying** compositions. Dwg.1/5

FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; GI; DCN
MANUAL CODES: CPI: B02-C01; B03-L; B04-B01C1; B04-C03B; B04-H03; B06-D06; B10-C04E
TECH UPTX: 20041019

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Components: The surfactant component has hydrophobic portion containing two parts. The first part is oriented proximal to the aqueous phase. The first part is larger than the second part of the hydrophobic portion of the surfactant component. The second part is oriented towards the interior of the **oil** globules. The first hydrophobic portion has longer chain length than the second hydrophobic portion. The composition also comprises additional surfactant that does not interfere with self-**emulsification**. The **oil** component comprises castor **oil** or natural **oil**. The surfactant component is a compound with ether(s) formed from ethylene oxide units (1-100) and carbon atom(s), compound with ether(s) formed from ethylene oxide units (1-100) and 12-22C fatty acid(s), and/or compound with ether, ester, and/or amide formed from ethylene oxide units (1-100) and vitamin and/or its derivative. The surfactant component containing one surfactant is Lumulse GHR-40, or TGPS. The **oil** globules has average size of less than 0.25, preferably less than 0.15microm. The ophthalmic composition contains self-**emulsifying** composition and drug that is therapeutic when administered to the **eye**. The therapeutic compound is **cyclosporin**, prostaglandins, or Brimonidine (salt). The polar

oil is castor or natural **oil**.

L139 ANSWER 47 OF 73 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2004-071249 [07] WPIX
DOC. NO. NON-CPI: N2004-057331
DOC. NO. CPI: C2004-029443
TITLE: Drug delivery system for delivery of drug into **eye** comprises a contact lens having ophthalmic drug in form of nanoparticles nanoencapsulated in a material.
DERWENT CLASS: A14 A28 A96 B05 B07 D22 P32
INVENTOR(S): CHAUHAN, A; GULSEN, D
PATENT ASSIGNEE(S): (CHAU-I) CHAUHAN A; (GULS-I) GULSEN D; (UYFL) UNIV FLORIDA
COUNTRY COUNT: 103
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
WO 2003103549	A1	20031218	(200407)*	EN	46	A61F013-00
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW						
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC 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 MZ NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW						
US 2004096477	A1	20040520	(200434)			A61K009-00
AU 2003248624	A1	20031222	(200445)			A61F013-00
US 2004241207	A1	20041202	(200481)			A61K009-00
BR 2003011585	A	20050510	(200533)			A61F013-00
EP 1534202	A1	20050601	(200536)	EN		A61F013-00
R: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LT LU LV MC MK NL PT RO SE SI SK TR						
JP 2005528185	W	20050922	(200563)		23	A61L027-00
CN 1674841	A	20050928	(200610)			A61F013-00
KR 2005037992	A	20050425	(200637)			A61F009-00

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
WO 2003103549	A1		WO 2003-US17736	20030605
US 2004096477	A1	Provisional	US 2002-385571P	20020605
			US 2003-454836	20030605
AU 2003248624	A1		AU 2003-248624	20030605
US 2004241207	A1	Provisional	US 2002-385571P	20020605
		CIP of	US 2003-454836	20030605
			US 2004-802058	20040317
BR 2003011585	A		BR 2003-11585	20030605
			WO 2003-US17736	20030605
EP 1534202	A1		EP 2003-757353	20030605
			WO 2003-US17736	20030605
JP 2005528185	W		WO 2003-US17736	20030605
			JP 2004-510672	20030605
CN 1674841	A		CN 2003-818898	20030605
KR 2005037992	A		WO 2003-US17736	20030605
			KR 2004-719648	20041203

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2003248624	A1	Based on	WO 2003103549
BR 2003011585	A	Based on	WO 2003103549
EP 1534202	A1	Based on	WO 2003103549
JP 2005528185	W	Based on	WO 2003103549
KR 2005037992	A	Based on	WO 2003103549

PRIORITY APPLN. INFO: US 2002-385571P 20020605; US
2003-454836 20030605; US
2004-802058 20040317

INT. PATENT CLASSIF.:
MAIN: A61F009-00; A61F013-00; A61K009-00; A61L027-00
SECONDARY: A61F002-00; A61K009-24; G02C013-00

BASIC ABSTRACT:

WO2003103549 A UPAB: 20040128

NOVELTY - A drug delivery system (S) comprises a contact lens having an ophthalmic drug in form of nanoparticles (particle size less than 50 nM) nanoencapsulated in a material. The ophthalmic drug diffuses into and migrates through contact lens and into post-lens tear film when contact lens is placed in **eye**.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following:

(1) a kit containing a first components which comprises (S), and a second components which comprises at least one storage container for the first component, where the storage container additionally comprises a material which prevents the diffusion and migration of the drug during storage;

(2) preparation of (S) involving preparing the contact lens from material which incorporates the nanoencapsulated ophthalmic drug such that the nanoencapsulated drug is uniformly dispersed throughout the contact lens; and

(3) an article of manufacture comprising a packaging material and (S) or the kit.

ACTIVITY - Opthalmological.

MECHANISM OF ACTION - None given.

USE - For directly delivery of drug into **eye** (claimed).

ADVANTAGE - The drug has particle size of 50 nM. (S) reduces drug loss, eliminates systemic side effects, improves drug efficacy and ameliorates symptoms associated with pathologic conditions of the **eye**.

Dwg.0/21

FILE SEGMENT: CPI GMPI
FIELD AVAILABILITY: AB; DCN
MANUAL CODES: CPI: A12-V01; A12-V02A; B02-C01; B04-B04D2; B04-B04E; B04-C02C; B04-C02D; B04-C02E; B04-C03; B06-A03; B06-D02; B06-D04; B07-A02A; B07-A02B; B07-D09; B07-D12; B07-E03; B07-F03; B10-B02A; B10-B02F; B12-M11E; B14-N03; D09-C01A

TECH UPTX: 20040128

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Components: The nanoparticles (1 - 5 wt.%) are dispersed within the contact lens such that the lens is optically transparent. The contact lens is a soft contact lens. The ophthalmic drug is selected from lidocaine, timolol, ciproflaxin, **cyclosporin** A, pilocarpine, antiparasitic or anti-protozoal drugs (e.g. ivermectin, pyrimethamine), non-steroids (e.g. acular and voltaren), steroids (e.g. prednisilone acetate), antibiotics (e.g. ciloxan), gentamycin and/or cephlosporins. The ophthalmic drug is nanoencapsulated in an **oil**-in-water **emulsion**. The encapsulation material is microemulsion nanodroplets, tocopherol derivatives stabilized nano-sized **emulsion** particles, gelatin, agarose hydrogel, PMMA, carboxylmethyl dextran magnetic nanoparticles and/or biotinylated pullulan acetate. The material is saturated aqueous

solution of ophthalmic drug.

TECHNOLOGY FOCUS - POLYMERS - Preferred Components: The contact lens comprises poly-2-hydroxyethylmethacrylate. The encapsulation material is biodegradable poly(alkylcyanoacrylates), polybutylcyanoacrylate, polyhexylcyanoacrylate, polyethylcyanoacrylate, (polyisobutylcyanoacrylate), polycyanoacylate, silica nanospheres, PEG'ylated core-shell nanoparticles, biodegradable PLGA (poly(D,L-lactide-co-glycolide)) particles, (poly lactic acid), PGA, PLG (poly(D,L-glycolide))polymeric nanoparticles, low pH sensitive PEG stabilized plasmid-lipid nanoparticles, polysaccharides grafted with polyesters (amphiphilic copolymers), PLA-PEG nanoparticles, nanoparticles composed of hydrophilic proteins coupled with apolipoprotein E, biodegradable poly(vepsiln-caprolactone)nanoparticles, poly(methylidene malonate), poly(E-caprolactone), sodium alginate, biotinylated poly(ethylene glycol) conjugated with lactobionic acid, poly(vinyl alcohol)hydrogel, and/or diblock copolymers.

TECHNOLOGY FOCUS - BIOLOGY - Preferred Components: The encapsulation material is chitosan nanoparticles, human serum albumin nanoparticles, liposomes, biocompatible gliadin nanoparticles and/or nanoparticles composed of hydrophilic proteins coupled with apolipoprotein E.

TECHNOLOGY FOCUS - INORGANIC CHEMISTRY - Preferred Components: The encapsulation material is silica nanospheres, and/or biodegradable calcium phosphate legumin.

L139 ANSWER 48 OF 73 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2004-031226 [03] WPIX
DOC. NO. CPI: C2004-010317
TITLE: **Emulsion** for forming tear film on **eye** surface, for preventing dry **eye**, comprises mixture containing non-polar phospholipid, non-polar **oil**, non-toxic **emulsifying** agent and cationic lipid dispersed in water.
DERWENT CLASS: A96 B04 B05
INVENTOR(S): BENITA, S; LAMBERT, G
PATENT ASSIGNEE(S): (NOVA-N) NOVAGALI SAS; (YISS) YISSUM RES DEV CO HEBREW UNIV JERUSALEM; (NOVA-N) NOVAGALI PHARMA SA; (YISS) YISSUM RES & DEV CO
COUNTRY COUNT: 99
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
US 2003108626	A1	20030612	(200403)*		5	A61K035-78
WO 2003053405	A1	20030703	(200403)#	EN		A61K009-107
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW						
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC 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 MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW						
US 6656460	B2	20031202	(200404)			A61K031-74
AU 2002214233	A1	20030709	(200428)#			A61K009-107
EP 1441696	A1	20040804	(200452)#	EN		A61K009-107
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR						
CN 1558751	A	20041229	(200524)#			A61K009-107
JP 2005513097	W	20050512	(200532)		20	A61K009-107

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 2003108626	A1	US 2001-985185	20011101
WO 2003053405	A1	WO 2001-IL1015	20011101
US 6656460	B2	US 2001-985185	20011101
AU 2002214233	A1	WO 2001-IL1015	20011101
		AU 2002-214233	20011101
EP 1441696	A1	EP 2001-982692	20011101
		WO 2001-IL1015	20011101
CN 1558751	A	CN 2001-823757	20011101
		WO 2001-IL1015	20011101
JP 2005513097	W	WO 2001-IL1015	20011101
		JP 2003-554164	20011101

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2002214233	A1 Based on	WO 2003053405
EP 1441696	A1 Based on	WO 2003053405
JP 2005513097	W Based on	WO 2003053405

PRIORITY APPLN. INFO: US 2001-985185 20011101; WO 2001-IL1015 20011101; AU 2002-214233 20011101; EP 2001-982692 20011101; CN 2001-823757 20011101; JP 2003-554164 20011101

INT. PATENT CLASSIF.:

MAIN: A61K009-107; A61K031-74; A61K035-78

SECONDARY: A61K031-355; A61K031-436; A61K031-4366; A61K031-685; A61K031-706; A61K038-00; A61K038-13; A61K038-133; A61K047-10; A61K047-18; A61K047-24; A61K047-44; A61P027-02; A61P027-022; A61P027-04

BASIC ABSTRACT:

US2003108626 A UPAB: 20040112

NOVELTY - An **emulsion** comprises a mixture containing non-polar phospholipid, non-polar **oil**, non-toxic **emulsifying** agent and cationic lipid dispersed in water. The **emulsion** imparts a net positive charge to the tear film, hence gets entrostatically attracted to the anionic **eye** surface and inhibits evaporation of fluids from the **eye** surface. The **emulsion** is applied to the anionic surface of **eyes**.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for treatment of dry **eye**, which involves preparing the above **emulsion** by dispersing the mixture in water; and applying the obtained **emulsion** to the **eye** surfaces to form a tear film, which is entrostatically attracted/adhered to the anionic surface of **eyes**.

ACTIVITY - Ophthalmological.

No test details are given.

MECHANISM OF ACTION - None given.

USE - For treating dry **eye** (claimed).

ADVANTAGE - The **emulsion** composition effectively treats dry **eye** condition, when applied topically on the **eye** surface. The **emulsion** forms tear film that lubricate the **eyes** and inhibit fluid loss from the **eye** surface. The film formed on the **eye** surface is not washed away easily, hence the effect is maintained for prolonged period. The tear film coating the **eye** surface does

not produce adverse effects. The ingredients in the mixture improves the **emulsion** stability. Dwg.0/0

FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; DCN
MANUAL CODES: CPI: A12-V04C; B02-C01; B02-S; B02-T; B04-B01B; B04-C03C; B05-B01P; B06-A01; B10-A22; B10-B04B; B10-E04C; **B12-M03**; B14-N03
TECH UPTX: 20040112

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Composition: The mixture comprises castor **oil**, 0.1-0.5% of Lipoid E-80 (phospholipid), cationic lipid such as stearylamine or oleylamine, 0.5-2.0% of poloxamer as **emulsifying** agent. The mixture further comprises vitamin E, glycerol, cationic preservative/antiseptic agent e.g. benzalkonium chloride and water-insoluble medicaments such as **cyclosporin**, tacrolimus or sirolimus. The size of the ingredients are made into submicron droplets by formulating as an **emulsion**.

L139 ANSWER 49 OF 73 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2003-186117 [19] WPIX
DOC. NO. CPI: C2003-049221
TITLE: Stable, well tolerated gel-**emulsion** for use in the **eye**, containing mixture of polyacrylate with polyvinyl alcohol, polyvinyl pyrrolidone, dextran or cellulose derivative and optionally ophthalmological drug.
DERWENT CLASS: A11 A14 A96 B04 B07
INVENTOR(S): KREITMEIER, P; MUGGENTHALER, M; POLZER, H; POLZER,
PATENT ASSIGNEE(S): (MEDP-N) MEDPROJECT PHARMA-ENTWICKLUNGS
COUNTRY COUNT: 26
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
EP 1275376	A2	20030115	(200319)*	GE	12	A61K009-10
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR						
DE 10132876	A1	20030130	(200319)			C08L033-08
EP 1275376	B1	20060419	(200630)	GE		A61K009-10
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR						
DE 50109549	G	20060524	(200635)			A61K009-10

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
EP 1275376	A2	EP 2001-124148	20011010
DE 10132876	A1	DE 2001-10132876	20010706
EP 1275376	B1	EP 2001-124148	20011010
DE 50109549	G	DE 2001-00109549	20011010
		EP 2001-124148	20011010

FILING DETAILS:

PATENT NO	KIND		PATENT NO
DE 50109549	G	Based on	EP 1275376

PRIORITY APPLN. INFO: DE 2001-10132876 20010706
INT. PATENT CLASSIF.:

MAIN: A61K009-10; C08L033-08
SECONDARY: A61K009-00; A61K009-107; A61K031-375; A61K031-566; A61K038-13; A61K047-00; A61K047-32; A61K047-34; A61K047-38; C08J003-075; C08L005-02; C08L029-04; C08L039-06

BASIC ABSTRACT:

EP 1275376 A UPAB: 20030320

NOVELTY - A droppable gel-**emulsion** (A), especially for use in the **eye**, contains a polymer mixture of polyacrylate (I) with polyvinyl alcohol, polyvinyl pyrrolidone, dextran or a cellulose derivative (II).

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for the preparation of (A).

ACTIVITY - Ophthalmological. No biological test data provided.

MECHANISM OF ACTION - None Given. No biological test data provided.

USE - The use (I) is claimed in the production of a medicament for use in the **eye**, where (A) optionally contains at least one ophthalmological drug, specifically estradiol or **cyclosporin** A.

ADVANTAGE - (I) has a suitable starting viscosity (1000-50000 mPa.s) to be droppable from a conventional **eye**-drop bottle; has an adjustable residual viscosity in the **eye**, to provide tolerance and the required residence time; and can incorporate all types of water- or **oil**-soluble active agents and preservatives conventionally used in ophthalmology. The gel-forming combination of polymers (I) and (II) is effective in relatively small amounts, and provides stable, sterilzable, well tolerated gels.

Dwg.0/0

FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; DCN
MANUAL CODES: CPI: A04-F06E5; A12-V01; B01-A02; B02-C01; B04-C02A; B04-C02C; B04-C03B; B10-A07; B10-A22; B10-B01B; B10-E04C; **B12-M03**; B14-N03

TECH UPTX: 20030320

TECHNOLOGY FOCUS - POLYMERS - Preferred Composition: The polyacrylate (I) has a molecular weight of 1000000-4000000. (I) additionally contains salts (specifically sodium acetate) to adjust the initial viscosity. (II) is preferably polyvinyl pyrrolidone, in which case (I) specifically contains 0.05-3 (especially 0.05-1)% (I) and 0.05-10 (especially 1-7)% (II). Alternatively (II) is hydroxypropyl methyl cellulose, polyvinyl alcohol or dextran. (I) optionally contains glycerol, sorbitol or mannitol as additive, a preservative (specifically benzalkonium chloride) and/or a base (specifically trometamol or lysine). Preparation: Claimed preparation of (I) involves:

(i) preparing an aqueous dispersion of the polyacrylate (I), containing an isotonic agent and optionally preservatives, then forming a gel (optionally with addition of base and salts);

(ii) finely dispersing the **oil** phase (optionally containing ophthalmological drug(s)) in an aqueous solution of the polymer (II) (optionally containing at least part of the preservative), using a homogenizer; and

(iii) homogeneous incorporating the mixture from (ii) in the gel from (i) under stirring.

L139 ANSWER 50 OF 73 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2003-523923 [50] WPIX
DOC. NO. CPI: C2003-141115
TITLE: An **emulsion** for topical application to the **eye** for the treatment of dry **eye** comprises water, a non-polar phospholipid, a non-polar **oil**, an **emulsifying** agent and a cationic lipid..
DERWENT CLASS: A96 B02 B04 B07 D22

INVENTOR(S): BENITA, S; LAMBERT, G
PATENT ASSIGNEE(S): (NOVA-N) NOVAGALI SAS; (YISS) YISSUM RES DEV CO HEBREW UNIV JERUSALEM; (NOVA-N) NOVAGALI PHARMA SA
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
AU 2001087320	A	20030508	(200350)*		17	A61P027-04
AU 782913	B2	20050908	(200568)			A61P027-04

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
AU 2001087320	A	AU 2001-87320	20011102
AU 782913	B2	AU 2001-87320	20011102

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 782913	B2 Previous Publ.	AU 2001087320

PRIORITY APPLN. INFO: AU 2001-87320 20011102
INT. PATENT CLASSIF.:
MAIN: A61P027-04
SECONDARY: A61K009-107
BASIC ABSTRACT:
AU 200187320 A UPAB: 20030805
NOVELTY - An **emulsion** for topical application to the **eye** comprises water and a mixture including a non-polar phospholipid, a non-polar **oil**, a non-toxic **emulsifying** agent and a cationic lipid.
DETAILED DESCRIPTION - An **emulsion** for topical application to the **eye** to form a tear film which lubricates the **eye** and inhibits the evaporation of fluid therefrom which comprises water and a mixture dispersed in the water including a non-polar phospholipid, a non-polar **oil**, a non-toxic **emulsifying** agent and a cationic lipid which imparts a net positive charge to the tear film, causing it to be entrostatically attracted to the anionic **eye** surface and to adhere there and so inhibit evaporation.
ACTIVITY - Ophthalmological.
MECHANISM OF ACTION - None given.
USE - The composition is used for the treatment of dry **eye** forming an artificial tear film on the surface of the **eye**, providing lubrication and preventing evaporation therefrom, it may also be used to treat **eye** disease.
ADVANTAGE - The composition has a net positive charge and so causes the film to adhere electrostatically to the entire anionically charged **eye** surface, giving even distribution. Dwg.0/0
FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; DCN
MANUAL CODES: CPI: A12-V01; B02-C; B02-S; B03-H; B04-B01B; B04-B01C; B05-B01P; B06-E05; B10-A22; B10-E04C; B12-M02B; B14-N03; D09-A01C
TECH UPTX: 20030805
TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Composition: The **oil** is castor **oil**, the phospholipid is Lipoid E-80, the cationic lipid is stearylamine or oleylamine and the **emulsifying** agent is poloxamer. The composition may further comprise one or more of the following: vitamin E, glycerol, a cationic antiseptic agent such as benzalkonium chloride, a water-insoluble medicament to treat **eye**

disease e.g. **cyclosporin**, tacrolimus or sirolimus. The relative percentage of the phospholipid in the **emulsion** is in the range 0.1-2 %, the castor **oil** 0.5-10 %, the cationic lipid 0.1-0.5 % and the **emulsifying** agent 0.5-2 %.

L139 ANSWER 51 OF 73 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2002-139762 [18] WPIX
CROSS REFERENCE: 2002-139764 [12]
DOC. NO. CPI: C2002-043031
TITLE: Stable, well tolerated composition for topical drug administration to the **eye**, comprises solution of water-insoluble drug in a neutral **oil**, preferably medium chain triglyceride.
DERWENT CLASS: B05 B07
INVENTOR(S): KLOECKER, N
PATENT ASSIGNEE(S): (AUDI-N) AUDIT INST MEDICAL SERVICES & QUALITY AS
COUNTRY COUNT: 96
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
WO 2001097774	A2	20011227	(200218)*	GE	12	A61K009-00

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC 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 MZ 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

DE 10030378	A1	20020314	(200226)	A61K047-44
AU 2001083876	A	20020102	(200230)	A61K009-00

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2001097774	A2	WO 2001-EP7036	20010621
DE 10030378	A1	DE 2000-10030378	20000621
AU 2001083876	A	AU 2001-83876	20010621

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2001083876	A	Based on	WO 2001097774

PRIORITY APPLN. INFO: DE 2000-10030378 20000621
INT. PATENT CLASSIF.:
MAIN: A61K009-00; A61K047-44
SECONDARY: A61K031-565
BASIC ABSTRACT:
WO 200197774 A UPAB: 20020513
NOVELTY - A composition (A) for topical application to the **eye** comprises one water-insoluble or sparingly water-soluble active agent (I) dissolved in a neutral **oil** (II).
ACTIVITY - Ophthalmological.
No biological data given.
MECHANISM OF ACTION - None given.
USE - For topical administration of drugs to the **eye**.
ADVANTAGE - (A) is well tolerated by the **eye**; adheres well to the **eye** surface to provide good resorption via the cornea or ocular mucosa; is stable;

can be sterile filtered; requires no addition of (potentially allergenic) preservatives or **emulsifiers**; is easily administered in exact doses; and can be prepared rapidly and inexpensively.

Dwg.0/0

FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; DCN
MANUAL CODES: CPI: B01-A02; B01-B02; B01-C05; B03-F; B03-H; B04-A01; B04-B01B; B04-B01C; B04-C01C; B04-N01A; B05-B01P; B06-A02; B06-D04; B06-D09; B07-B03; B07-D09; B10-A06; B10-B01B; B10-B02A; B10-B02E; B10-B03A; B10-C03; B10-E04; B10-J01; B12-M05; B12-M06; B14-N03; B14-S08

L139 ANSWER 52 OF 73 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2002-035685 [05] WPIX
DOC. NO. CPI: C2002-010255
TITLE: **Cyclosporin**-containing topical ophthalmological formulations, e.g. for treating dry **eye** kerato-conjunctivitis or Sjoegren syndrome, contain hyaluronic acid and polysorbate 80 to improve bioavailability and tolerance.
DERWENT CLASS: A96 B03 B04
INVENTOR(S): DI NAPOLI, G; DIENABORY, G; NAPOLI, G D
PATENT ASSIGNEE(S): (MEDI-N) LAB MEDIDOM SA; (MEDI-N) LAB MEDIDOM CO LTD; (NAPO-I) NAPOLI G D
COUNTRY COUNT: 35
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
EP 1142566	A1	20011010	(200205)*	FR	15	A61K009-08
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR						
AU 2001033404	A	20011011	(200205)			A61P027-04
BR 2001001332	A	20011106	(200205)			A61K038-13
CA 2342133	A1	20011007	(200205)	EN		A61K038-13
CZ 2001001229	A3	20011114	(200205)			A61K009-08
SK 2001000460	A3	20011106	(200205)			A61K009-08
US 2001041671	A1	20011115	(200205)			A61K038-13
JP 2001316284	A	20011113	(200207)		10	A61K038-00
ZA 2001002769	A	20011224	(200212)		27	A61K000-00
CN 1317342	A	20011017	(200213)			A61K038-13
EP 1142566	B1	20031001	(200365)	FR		A61K009-08
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU MC NL PT RO SE SI TR						
DE 60100866	E	20031106	(200381)			A61K009-08
US 6677304	B2	20040113	(200405)			A61K038-00
ES 2206363	T3	20040516	(200434)			A61K009-08
US 2004106546	A1	20040603	(200436)			A61K038-13
CZ 294385	B6	20041215	(200501)			A61K009-08
AU 778858	B2	20041223	(200510)			A61K038-18
US 6953776	B2	20051011	(200567)			A61K038-13
CN 1185009	C	20050119	(200620)			A61K038-13
SK 285220	B6	20060907	(200662)			A61K009-08

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
EP 1142566	A1	EP 2001-107223	20010323

AU 2001033404	A	AU 2001-33404	20010404
BR 2001001332	A	BR 2001-1332	20010406
CA 2342133	A1	CA 2001-2342133	20010327
CZ 2001001229	A3	CZ 2001-1229	20010404
SK 2001000460	A3	SK 2001-460	20010405
US 2001041671	A1	US 2001-818213	20010327
JP 2001316284	A	JP 2001-109077	20010406
ZA 2001002769	A	ZA 2001-2769	20010404
CN 1317342	A	CN 2001-112484	20010406
EP 1142566	B1	EP 2001-107223	20010323
DE 60100866	E	DE 2001-00100866	20010323
		EP 2001-107223	20010323
US 6677304	B2	US 2001-818213	20010327
ES 2206363	T3	EP 2001-107223	20010323
US 2004106546	A1 Div ex	US 2001-818213	20010327
		US 2003-721007	20031121
CZ 294385	B6	CZ 2001-1229	20010404
AU 778858	B2	AU 2001-33404	20010404
US 6953776	B2 Div ex	US 2001-818213	20010327
		US 2003-721007	20031121
CN 1185009	C	CN 2001-112484	20010406
SK 285220	B6	SK 2001-460	20010405

FILING DETAILS:

PATENT NO	KIND	PATENT NO
DE 60100866	E Based on	EP 1142566
ES 2206363	T3 Based on	EP 1142566
US 2004106546	A1 Div ex	US 6677304
CZ 294385	B6 Previous Publ.	CZ 2001001229
AU 778858	B2 Previous Publ.	AU 2001033404
US 6953776	B2 Div ex	US 6677304
SK 285220	B6 Previous Publ.	SK 2001000460

PRIORITY APPLN. INFO: CH 2000-694 20000407

INT. PATENT CLASSIF.:

MAIN: A61K000-00; A61K009-08; A61K038-00; A61K038-13; A61K038-18; A61P027-04

SECONDARY: A61K031-715; A61K031-728; A61K038-12; A61K047-26; A61K047-34; A61K047-36; A61P027-00; A61P027-02; A61P029-00; A61P037-06

BASIC ABSTRACT:

EP 1142566 A UPAB: 20020123

NOVELTY - Topical ophthalmological formulations (I) comprise aqueous solutions containing a **cyclosporin** (a), hyaluronic acid or its salt (b) and polysorbate 80 (c).

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is included for the use of (a) in combination with (b) and (c) for the preparation of f(I).

ACTIVITY - Ophthalmological; immunosuppressive; antiinflammatory.

A composition contained (by weight): **cyclosporin** A (0.20 %), sodium hyaluronate (0.10 %), Tween 80 (RTM; polysorbate 80) (5.00 %), disodium hydrogen phosphate dodecahydrate (0.08%), sorbitol (5.16%) and purified water. The pH was 7.0-7.4 and the osmolality was 295-305. The composition showed good ocular tolerance in the Draize test and formed no precipitate when stored at room temperature for 12 months. In tests for bioavailability in the conjunctiva, the composition gave an area-under-the curve value of 12483 ng/g.hour compared with 7378 ng/g.hour for Cycloil (RTM; water-in-**oil emulsion** formulation of **cyclosporin** A as described in WO9531211).

MECHANISM OF ACTION - None given.

USE - The use of (I) is claimed for treating dry kerato- conjunctivitis, Sjoegren's syndrome, dry **eye** syndrome or chronic vernal kerato-conjunctivitis, or post-operative prophylaxis in kerato-plastic surgery. The active agents (a) have immunosuppressive and antiinflammatory activity.

ADVANTAGE - Inclusion of (b) and (c) solubilizes the active agent (a), improves the bioavailability in the conjunctiva, cornea and lachrymal gland and improves the ocular tolerance. Dwg.0/0

FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; DCN
MANUAL CODES: CPI: A03-A00A; A05-H01B; A12-V01; B02-C01; B04-C02E; B04-C03D; B14-C03; B14-G02; B14-N03
TECH UPTX: 20020123

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Components: (a) is **cyclosporin** A. (b) has average molecular weight at least 1300000 (preferably 1300000-3000000) Daltons, and is in the form of an alkali metal or alkaline earth metal salt, especially the sodium salt.

L139 ANSWER 53 OF 73 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2002-011896 [02] WPIX
DOC. NO. CPI: C2002-003137
TITLE: High water content water-in-**oil** **emulsion** creams containing e.g. pharmaceuticals together with lecithin and short-chain di- or tri-ols are sterile filtered to give stable products with reduced secondary effects.
DERWENT CLASS: B04 D21 E11
INVENTOR(S): HEIDE, P E
PATENT ASSIGNEE(S): (UYTU-N) UNIV TUEBINGEN EBERHARD-KARLS
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
DE 10015463	A1	20011018 (200202)*			4	A61K009-06

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
DE 10015463	A1	DE 2000-10015463	20000329

PRIORITY APPLN. INFO: DE 2000-10015463 20000329
INT. PATENT CLASSIF.:
MAIN: A61K009-06
SECONDARY: A61K007-48; A61K031-573; A61K038-13
BASIC ABSTRACT:

DE 10015463 A UPAB: 20020109

NOVELTY - A cream in the form of a high water content water-in-**oil** (W/O) **emulsion** consisting of:

(a) lecithin with a content of phosphatidyl-choline and -ethanolamine,
(b) a short-chain di- or tri-ol, (c) an **oil**,
(d) water and
(e) an active component
is sterile filtered.

ACTIVITY - Antiallergenic; Immunosuppressive; Ophthalmological

MECHANISM OF ACTION - None given in the source material.

USE - E.g. for application **cyclosporin** to the skin as an immunodepressive, or to the **eyes** to treat them after corneal grafting. Other preferred actives include hydrocortisone acetate and betamethason, while creams containing other

glucocorticosteroids or antimycotics, antiseptics, thiocarbamates, hormones or cytostats are disclosed.

ADVANTAGE - The cream is easily made and does not show the secondary activity associated with the preservatives used in the prior-art to improve cream stability. Component (a) forms stable hydrate shells in water. The cream is also non-allergenic. Dwg.0/0

FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; DCN
MANUAL CODES: CPI: B01-C01; B04-B01B; B04-C01C; B05-B01P; B10-C04E; B10-E04C; B14-G02; B14-G02A; B14-N03; D08-B09A; E01; E05-G09D; E10-C04H; E10-E04H

TECH UPTX: 20020109

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Composition: The composition comprises:
(a) (especially soya) lecithin made up of 60-80 wt.% phosphatidyl-choline at 5-20 wt.%;
(b) propanediol or glycerol at 10-20 wt.%;
(c) natural **oils** with high linoleic or linolenic acid content (especially maize germ-, sunflower-, thistle- or neutral-**oil**) at 30-50 wt.%; (d) water at 40-50 wt.%; and
(d) **cyclosporin**, hydrocortisone acetate or betamethasone at up to 2 wt.%.
Also present is an antioxidant at up to 0.05 wt.%, especially 0.02% vitamin E and 0.01% ascorbyl palmitate.
Preferred Process: The filter has a pore size of 0.45 microns.

L139 ANSWER 54 OF 73 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2000-037292 [03] WPIX
DOC. NO. CPI: C2000-009539
TITLE: Alleviating dry **eye** related symptoms in dry **eye** patients and contact lens wearers.
DERWENT CLASS: A96 B04
INVENTOR(S): DING, S; OLEJNIK, O; REIS, B L
PATENT ASSIGNEE(S): (ALLR) ALLERGAN
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
US 5981607	A	19991109	(200003)*		13	A61K047-12

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 5981607	A	US 1998-8924	19980120

PRIORITY APPLN. INFO: US 1998-8924 19980120
INT. PATENT CLASSIF.:
MAIN: A61K047-12
SECONDARY: A61K047-14; A61K047-34
BASIC ABSTRACT:

US 5981607 A UPAB: 20000118
NOVELTY - Alleviating dry **eye** related symptoms in dry **eye** patients and contact lens wearers comprises ocular administration of an **emulsion** of a higher fatty acid glyceride (FAG), polysorbate 80 and Pemulen (RTM: polymeric **emulsifier**, carbomer 1342) in water, with no **cyclosporin**.

ACTIVITY - Antiinflammatory; antiallergic.

MECHANISM OF ACTION - None given.

USE - The method is used for alleviating dry **eye** related symptoms, e.g. in patients having immune mediated keratoconjunctivitis sicca or dry **eye** disease or dry **eye** symptoms of contact lens wearers.

ADVANTAGE - The composition is non-irritating with high comfort level and low irritation potential.

DESCRIPTION OF DRAWING(S) - The drawing shows a bar graph of subjective reports of Ocular dryness as a function of time following instillation of the **emulsion**.

Dwg.6/7

FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; GI; DCN
MANUAL CODES: CPI: A12-V02A; B04-B01B; B04-B01C; B04-C03B; B04-C03D; B10-E04C; **B12-M03**; B14-C03; B14-G02A; B14-N03

TECH UPTX: 20000118

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Composition: The weight ratio of FAG to polysorbate 80 is 0.3 to 30. The FAG is castor **oil** or corn **oil**. A preferred composition comprises: castor **oil** 0.6255%, polysorbate 80 1%, Pemulen 0.05%, and glycerine 2.2%.

L139 ANSWER 55 OF 73 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 1999-519544 [44] WPIX
DOC. NO. CPI: C1999-151959
TITLE: Pharmaceutical composition containing **cyclosporin** A suitable for topical administration for treating disorders of skin, mucosa and **eyes**.
DERWENT CLASS: B03 B04
INVENTOR(S): HEIDE, P E
PATENT ASSIGNEE(S): (UYTU-N) UNIV TUEBINGEN EBERHARD-KARLS; (HEID-I) HEIDE P E
COUNTRY COUNT: 25
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
DE 19810655	A1	19990916	(199944)*		6	A61K038-13
EP 945136	A1	19990929	(199945)	GE		A61K038-13
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI						
EP 945136	B1	20051116	(200576)	GE		A61K038-13
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE						
DE 59912782	G	20051222	(200603)			A61K038-13
ES 2248935	T3	20060316	(200622)			A61K038-13
EP 945136	B9	20060524	(200635)	GE		A61K038-13
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE						

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
DE 19810655	A1	DE 1998-1010655	19980312
EP 945136	A1	EP 1999-104009	19990312
EP 945136	B1	EP 1999-104009	19990312
DE 59912782	G	DE 1999-512782	19990312
		EP 1999-104009	19990312
ES 2248935	T3	EP 1999-104009	19990312
EP 945136	B9	EP 1999-104009	19990312

FILING DETAILS:

PATENT NO	KIND	PATENT NO
DE 59912782	G Based on	EP 945136
ES 2248935	T3 Based on	EP 945136

PRIORITY APPLN. INFO: DE 1998-19810655 19980312
INT. PATENT CLASSIF.:
MAIN: A61K038-13
SECONDARY: A61K009-107; A61P017-00; A61P037-08
BASIC ABSTRACT:
DE 19810655 A UPAB: 19991026
NOVELTY - Pharmaceutical composition containing **cyclosporin** A (I) is in the form of an **oil**-in-water nano **emulsion**.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:
(1) use of a pharmaceutical composition containing (I) in a form suitable for topical administration for treating skin disorders;
(2) use of a pharmaceutical composition containing (I) in a form suitable for topical administration for treating allergies;
(3) preparation of the nano **emulsion** composition by dissolving (I) in an **oil** phase, adding part of the aqueous phase, stirring, adding the rest of the aqueous phase, sonicating the mixture, and sterilizing the product by filtration.
ACTIVITY - Immunosuppressant.
MECHANISM OF ACTION - Inhibitor of interleukin release.
USE - The composition is useful for (a) treating disorders of the skin, oral mucosa or genital mucosa; lichen ruber; neurodermatitis, especially in the region of the **eyes**; allergies, especially in the region of the **eyes**; (b) prophylactic and/or therapeutic treatment of the **eyes**; (c) inhibiting transplant rejection, preferably in the region of the **eyes** (e.g. corneal transplant rejection).
ADVANTAGE - The nanoemulsion contains (I) in highly dispersed form, is readily distributed over tissues and absorbed into tissues, has good compatibility with skin and **eyes**, and contains non organic solvents.
Dwg.0/0
FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; DCN
MANUAL CODES: CPI: B02-C01; B04-B01B; B05-B01P; B10-E04C; **B12-M03**; B14-G02; B14-L07; B14-N03; B14-N05; B14-N17
TECH UPTX: 19991026
TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Composition: The nanoemulsion has a droplet size below 500 nm. The composition comprises 0.1-10 (preferably 1-3, especially 2) wt.% (I); 0.1-20 (preferably 1-10, especially 5) wt.% phospholipid, especially lecithin; 10-40 (preferably 20-30, especially 23) wt.% triglycerides, preferably medium-chain triglycerides; and physiological saline, optionally containing preservatives and thickeners. The total lipid content is 1-50 (preferably 20-30) wt.%.

L139 ANSWER 56 OF 73 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 1990-134228 [18] WPIX
DOC. NO. CPI: C1990-058873
TITLE: Topical ophthalmic compsn. - contains **cyclosporin** with a vegetable **oil** and a petroleum jelly.
DERWENT CLASS: B03 P32
INVENTOR(S): PEEPLES, R E
PATENT ASSIGNEE(S): (SANO) SANDOZ SA; (PEEP-I) PEEPLES R E; (SANO) SANDOZ LTD; (SANO) SANDOZ AG

COUNTRY COUNT: 21
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
GB 2224205	A	19900502	(199018)*		28	
DE 3935517	A	19900503	(199019)			
PT 92120	A	19900430	(199022)			
NL 8902657	A	19900516	(199023)			
AU 8943715	A	19900503	(199024)			
FR 2638089	A	19900427	(199024)			
CA 2001502	A	19900426	(199025)			
NO 8904266	A	19900521	(199026)			
SE 8903583	A	19900427	(199026)			
DK 8905312	A	19900427	(199028)			
JP 02164830	A	19900625	(199031)			
FI 8905064	A	19900427	(199032)			
HU 52394	T	19900730	(199035)			
LU 87613	A	19910507	(199127)			
ZA 8908140	A	19910626	(199131)			
ES 2020032	A	19910716	(199133)			
CH 679210	A	19920115	(199208)			
GB 2224205	B	19920415	(199216)			
BE 1003578	A4	19920428	(199224)		30	A61K
IT 1237824	B	19930618	(199347)			A61K000-00
IL 92120	A	19940227	(199419)			A61K037-02
PH 28428	A	19940905	(199838)			A61K031-195

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
GB 2224205	A	GB 1988-24040	19881025
DE 3935517	A	DE 1989-3935517	19891025
NL 8902657	A	NL 1989-2657	19891026
FR 2638089	A	FR 1989-14023	19891024
JP 02164830	A	JP 1989-276174	19891025
ZA 8908140	A	ZA 1989-8140	19891026
ES 2020032	A	ES 1989-3619	19891026
GB 2224205	B	GB 1989-24040	19891025
BE 1003578	A4	BE 1989-1138	19891024
IT 1237824	B	IT 1989-48485	19891026
IL 92120	A	IL 1989-92120	19891025
PH 28428	A	PH 1989-39416	19891026

PRIORITY APPLN. INFO: US 1988-262866 19881026
INT. PATENT CLASSIF.:
MAIN: A61K000-00; A61K013-40; A61K031-195; A61K037-02
SECONDARY: A61F009-00; A61K009-06; A61K031-39; A61K047-00
ADDITIONAL: C07K007-64
BASIC ABSTRACT:
GB 2224205 A UPAB: 19930928
Topical ophthalmic compsns comprise a **cyclosporin**, a vegetable **oil** (1) and a petroleum jelly (2) (pref white petrolatum). Compsn may also cont **emulsifiers** (3) and preserving/antimicrobial agents (4).
USE/ADVANTAGE - Compsns are used for treatment of conditions of the **eye** and surrounding area, esp autoimmune diseases, uveitis, corneal transplant, keratoconjunctivitis sicca. Compsns have rapid delivery to anterior and

posterior regions of the **eye**, cause little discomfort to patients, have convenient application rate, and low systemic involvement.
0/7

FILE SEGMENT: CPI GMPI
FIELD AVAILABILITY: AB; DCN
MANUAL CODES: CPI: B04-B01C1; B04-B01C3; B04-C01C; B12-D07; B12-L04
ABEQ GB 2224205 B UPAB: 19930928
An ophthalmic compsn. comprising a **cyclosporin** as active ingredient and comprising (1) an ophthalmically acceptable vegetable **oil** and (2) an ophthalmically acceptable petroleum jelly as carrier medium. *** ()

L139 ANSWER 57 OF 73 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 1986-335072 [51] WPIX
DOC. NO. CPI: C1986-145258
TITLE: **Eye** drops - composed of lipid microspheres containing remedies for **eye** troubles.
DERWENT CLASS: B05
PATENT ASSIGNEE(S): (MIZU-I) MIZUSHIMA H
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
JP 61249918	A	19861107	(198651)*		4	

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
JP 61249918	A	JP 1985-90426	19850426

PRIORITY APPLN. INFO: JP 1985-90426 19850426
INT. PATENT CLASSIF.: A61K009-10
BASIC ABSTRACT:
JP 61249918 A UPAB: 19930922
Any remedy for an **eye** trouble can be used, i.e., corticosteroid, **cyclosporin**, antibiotics, non-steroid anti-inflammatory drugs, remedies for cataract, remedies for glancoma, etc..
LMS is produced conventionally except that the remedies are added in the course of production. Soy bean **oil** is pref. as the **oil** . Lecithin is pref. as the **emulsifier**. The **oil**, the **emulsifier** and the remedy are mixed and heated at 30-80 deg.C. The mixture is homogenised with homogeniser, sterilised water is added and the mixt.is homogenised again. Thus obtained LMS is 0.1-1.0 micron in radius and is very stable for a long time. The **eye** drops are used several times a day. The **eye** drops have no toxicity other tahn the side effect specific to the remedies contained in the them.
USE/ADVANTAGE - Continuous absorption and action to **eye** tissues without side effect is possible. 0/0
FILE SEGMENT: CPI
FIELD AVAILABILITY: AB
MANUAL CODES: CPI: B12-L04; B12-M07; B12-M10A; B12-M11

L139 ANSWER 58 OF 73 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2006:606158 HCAPLUS Full-text
DOCUMENT NUMBER: 145:130749

TITLE: Ophthalmic preparation containing tetrandrine and use thereof in treating ophthalmic diseases
INVENTOR(S): Hu, Shixing; Xu, Yangui
PATENT ASSIGNEE(S): Peop. Rep. China
SOURCE: Faming Zhuanli Shenqing Gongkai Shuomingshu, 25 pp.
CODEN: CNXXEV
DOCUMENT TYPE: **Patent**
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 1785192	A	20060614	CN 2004-10093862	20041208
PRIORITY APPLN. INFO.:			CN 2004-10093862	20041208

ED Entered STN: 23 Jun 2006

AB The ophthalmic prepns. (eyedrop, ointment) is composed of tetrandrine 0.001-2, synergistic drugs 0-5, excipient 93-99.999, metal ion complexing agent (disodium edetate) 0-5, isotonic regulator (sodium chloride) 0-10%, solubilizer (0.1-2 M HCl) 0.05-50 mL, thickening agent (hydroxymethyl cellulose) 0-5, cuticle lytic agent (borneol) 0-5, and antioxidant (sodium pyrosulfite) 0-5%, resp. Excipient in eyedrop is injection water; excipient in ointment is wool grease 0-20, paraffin oils 0-20, sodium Et cellulose 0.1-10, and addnl. vaseline to 1000 g. The synergistic drug is antimicrobial, such as erythrocin, kanamycin, gentamicin, amikacin, tobramycin, sisomycin, netilmicin, micronomicin, isepamicin, astromicin, etimicin, neomycin, spectinomycin, tetracycline, paromomycin, doxycycline, minocycline, sulfacetamide sodium, norfloxacin, ofloxacin, enoxacin, ciprofloxacin, lomefloxacin, pefloxacin, rufloxacin, sparfloxacin, fleroxacin, moxifloxacin, rifampicin, metronidazole, tinidazole or cefoperazone; antiviral drugs, such as acyclovir, ganciclovir, valaciclovir or ribavirin; hormone drugs, such as dexamethasone phosphate, fluocinolone, beclometasone, etc.; vitamin, such as vitamin B1, vitamin B2, vitamin B6, vitamin B12 or vitamin C, niacinamide or folic acid; anti-inflammatory drug, such as indometacin, ibuprofen, meloxicam, piroxicam, diclofenac sodium, paracetamol or nimesulide; antianaphylactic drug, such as chlorphenamine, diphenhydramine, tripelennamine, etc.; immunoregulatory drug, such as ****, **ciclosporin**, Tripterygium glycosides, tacrolimus, etc.; amino acids; microcirculation-improving nicotinic acid, inositol hexanicotinate or vinpocetine; Chinese medicine active ingredient, such as dipyridamole, puerarin, ligustrazine, allitridin, berberine, isatisroot, fibrauretin, houttuynine, andrographolidume or Sophora flavescens alkaloids. The antioxidant is sodium sulfite, sodium thiosulfate, methionine, thiourea, BHA, BHT, CDGA, tocopherol; isotonic regulator is boric acid, sodium dihydrogen phosphate, disodium hydrogen phosphate or glucose; thickening agent is Me cellulose, Et cellulose, etc.; cuticle lytic agent is menthol; tetrandrine is tetrandrine hydrochloride, tetrandrine sulfate, tetrandrine nitrate, tetrandrine phosphate, etc. Chlorhexidine, benzalkonium bromide, phenylhydrargyric nitrate, phenylhydrargyric acetate, chlorbutol, thiomersalate, mercuric oxycyanide, paraben, benzyl carbinol, sorbic acid, benzoic acid or domiphen are added in medical formulation while using non-antibiotic drugs. The ophthalmic preparation is used for treating chorioretinitis, ceratitis, anaphylactic ophthalmic disease, glaucoma and cataract, proliferative lesion of retinal vitreous body, etc.

L139 ANSWER 59 OF 73 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:1355515 HCAPLUS Full-text
DOCUMENT NUMBER: 144:74885
TITLE: Pharmaceutical compositions containing polyunsaturated fatty acid in combination with immunosuppressive

agents and antineoplastic agents
INVENTOR(S): Mittmann, Ulrich; Sachetto, Jean-Pierre
PATENT ASSIGNEE(S): Tillotts Pharma AG, Switz.
SOURCE: PCT Int. Appl., 33 pp.
CODEN: PIXXD2
DOCUMENT TYPE: **Patent**
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005123061	A1	20051229	WO 2005-EP6413	20050615

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: GB 2004-13730 A 20040618
ED Entered STN: 30 Dec 2005
AB Polyunsatd. fatty acid ("PUFA") or a pharmacol. acceptable salt or derivative thereof (such as EPA and/or DHA) is used in combination with at least one of an immunosuppressive agent or an antineoplastic agent or a pharmacol. acceptable salt or derivative thereof in the treatment of conditions involving acutely or chronically inadequate immune response by topical application of said active agents to at least a portion of the intestinal mucosa. Specific conditions that may be treated include chronic inflammatory disease (e.g. Chrohn's disease and ulcerative colitis) and tumor disease (e.g. bowel cancer and prostate cancer). One advantage of preferred embodiments of the invention is that bioavailability of immunosuppressive or antineoplastic agents is increased. For example, capsules contained fish oil (over 60% of DHA and Incromega 3F60 EPA), Eudragit NE 30D coating, polysorbate 80.
REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L139 ANSWER 60 OF 73 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:1355507 HCAPLUS Full-text
DOCUMENT NUMBER: 144:74884
TITLE: A pharmaceutical compositions containing polyunsaturated fatty acids in combination with immunosuppressive agents and antineoplastic agents
INVENTOR(S): Mittmann, Ulrich; Sachetto, Jean-Pierre
PATENT ASSIGNEE(S): Tillotts Pharma AG, Switz.
SOURCE: PCT Int. Appl., 33 pp.
CODEN: PIXXD2
DOCUMENT TYPE: **Patent**
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005123060	A1	20051229	WO 2005-EP6412	20050615

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: GB 2004-13729 A 20040618

ED Entered STN: 30 Dec 2005

AB Polyunsatd. fatty acid ("PUFA") or a pharmacol. acceptable salt or derivative thereof (such as EPA and/or DHA) is used in combination with at least one of an immunosuppressive agent or an antineoplastic agent or a pharmacol. acceptable salt or derivative thereof in the treatment of conditions involving acutely or chronically inadequate immune response by topical application of said active agents to at least a portion of the intestinal mucosa. Specific conditions that may be treated include chronic inflammatory disease (e.g. Chrohn's disease and ulcerative colitis) and tumor disease (e.g. bowel cancer and prostate cancer). One advantage of preferred embodiments of the invention is that bioavailability of immunosuppressive or antineoplastic agents is increased. For example, capsules contained fish oil (over 60% of DHA and Incromega 3F60 EPA), Eudragit NE 30D coating, polysorbate 80.

REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L139 ANSWER 61 OF 73 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2005:1223775 HCAPLUS Full-text

DOCUMENT NUMBER: 143:483122

TITLE: Methods and articles for the delivery of drugs to the eye for the treatment of posterior segment diseases

INVENTOR(S): Schultz, Clyde

PATENT ASSIGNEE(S): Directcontact LLC, USA

SOURCE: U.S. Pat. Appl. Publ., 11 pp., Cont.-in-part of U.S. Ser. No. 971,997.
CODEN: USXXCO

DOCUMENT TYPE: **Patent**

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2005255144	A1	20051117	US 2005-102454		20050409
US 2005208102	A1	20050922	US 2004-821718		20040409
US 2005074497	A1	20050407	US 2004-971997		20041022
PRIORITY APPLN. INFO.:			US 2003-461354P	P	20030409
			US 2004-821718	A2	20040409
			US 2004-971997	A2	20041022

ED Entered STN: 18 Nov 2005

AB This invention provides articles and methods for drug delivery including a hydrogel containing one or more drugs for the treatment of a posterior segment disease and/or dry eye conditions. Exemplary drugs are anti-angiogenesis compds. for the treatment of macular degeneration. Allowing passive transference of this drug from a dilute solution into the hydrogel produces the delivery system. The hydrogel, when placed in contact with the eye, delivers the drug. The delivery of the drug is sustained over an extended

period of time, which is of particular utility in the eye, which is periodically flushed with tears. This sustained delivery accelerates the treatment process while avoiding potential damaging effects of localized delivery of high concns. of compds., e.g., from eye drops.

L139 ANSWER 62 OF 73 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:983601 HCAPLUS Full-text
DOCUMENT NUMBER: 143:272523
TITLE: Stable ophthalmic oil-in-water emulsions containing sodium hyaluronate for alleviating dry eye
INVENTOR(S): Yu, Zhi-Jian; Huth, Stanley W.; Crawford, Lauren L.; Cook, James N.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 18 pp., Cont.-in-part of U.S. Ser. No. 802,153.
CODEN: USXXCO
DOCUMENT TYPE: **Patent**
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005196370	A1	20050908	US 2005-98827	20050404
US 2004185068	A1	20040923	US 2003-392375	20030318
US 2004191284	A1	20040930	US 2004-802153	20040317
PRIORITY APPLN. INFO.:			US 2003-392375	A2 20030318
			US 2004-802153	A2 20040317

ED Entered STN: 09 Sep 2005
AB Stable oil-in-water emulsions are described which contain a demulcent for the treatment of dry eye such as sodium hyaluronate. The oil-in-water emulsions are stable and have anti-microbial activity sufficient for use as contact lens disinfecting solns. Thus, an emulsion contained sodium chlorite 65 and WSCP 3 ppm, sodium hyaluronate 0.1, castor oil 1.25, ethoxylated hydrogenated castor oil 1, boric acid 0.6, sodium borate decahydrate 0.035, calcium chloride dihydrate 0.006, MgCl2.6H2O 0.006, KCl 0.14, NaCl 3.5, and water qs to 100%.

L139 ANSWER 63 OF 73 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:902155 HCAPLUS Full-text
DOCUMENT NUMBER: 141:384286
TITLE: Novel encochleation methods, cochleates and methods of use
INVENTOR(S): Mannino, Raphael J.; Gould-Fogerite, Susan; Krause-Elsmore, Sara L.; Delmarre, David; Lu, Ruying
PATENT ASSIGNEE(S): Biodelivery Sciences International, Inc., USA; University of Medicine and Dentistry of New Jersey
SOURCE: PCT Int. Appl., 195 pp.
CODEN: PIXXD2
DOCUMENT TYPE: **Patent**
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004091578	A2	20041028	WO 2004-US11026	20040409
WO 2004091578	C1	20050127		
WO 2004091578	A3	20050331		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, 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, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2005013854	A1	20050120	US 2004-822230		20040409
EP 1624858	A2	20060215	EP 2004-759375		20040409
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK					
PRIORITY APPLN. INFO.:			US 2003-461483P	P	20030409
			US 2003-463076P	P	20030415
			US 2003-499247P	P	20030828
			US 2003-502557P	P	20030911
			US 2003-532755P	P	20031224
			US 2004-537252P	P	20040115
			US 2004-556192P	P	20040324
			WO 2004-US11026	W	20040409

ED Entered STN: 28 Oct 2004

AB The invention generally relates to cochleate drug delivery vehicles. Disclose are novel methods for making cochleates and cochleate compns. that include introducing a cargo moiety to a liposome in the presence of a solvent. Also disclosed are cochleates and cochleate compns. that include an aggregation inhibitor, and optionally, a cargo moiety. Addnl., anhydrous cochleates that include a protonized cargo moiety, a divalent metal cation and a neg. charge lipid are disclosed. Methods of using the cochleate compns. of the invention, including methods of administration, are also disclosed.

L139 ANSWER 64 OF 73 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:100508 HCAPLUS Full-text
DOCUMENT NUMBER: 140:157440
TITLE: Methods for treating an autoimmune disease using a soluble CTLA4 molecule in combination with a DMARD or NSAID
INVENTOR(S): Cohen, Robert; Carr, Suzette; Hagerty, David; Peach, Robert J.; Becker, Jean-Claude
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 189 pp., Cont.-in-part of U.S. Ser. No. 898,195.
CODEN: USXXCO
DOCUMENT TYPE: **Patent**
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2004022787	A1	20040205	US 2003-419008		20030418
US 2003083246	A1	20030501	US 2001-898195		20010702
PRIORITY APPLN. INFO.:			US 2000-215913P	P	20000703
			US 2001-898195	A2	20010702

ED Entered STN: 08 Feb 2004

AB The present invention relates to compns. and methods for treating immune system diseases such as rheumatic disease, by administering to a subject

soluble CTLA4 (cytotoxic T lymphocyte antigen 4) mols. that block endogenous B7 (CD80) mols. from binding their ligands, alone, or in conjunction with other agents including disease modifying anti-rheumatic drugs (DMARDs) or non-steroidal anti-inflammatory drugs (NSAIDs). The soluble CTLA4 mol. comprises the extracellular domain (residues 1-124) of full-length human CTLA4, which may be fused at the N-terminus with the signal peptide of oncostatin M and at the C-terminal end with an Igγ1 constant region. Single-site and double-site CTLA4 mutant sequences are also constructed, including L104E/A29Y-CTLA4/Ig, L104E/A29L-CTLA4/Ig, L104E/A29T-CTLA4/Ig, and L104E/A29W-CTLA4/Ig. CTLA4/Ig administered at 10 mg/kg (plus methotrexate) has superior efficacy in treatment of rheumatoid arthritis compared to placebo (plus methotrexate) based on efficacy parameters of the American Collage of Rheumatol. Core Data Set and Response Definitions (ACR). Binding kinetics to CD86 and CD80, pharmacokinetics, and pharmacodynamics of C-reactive protein, rheumatoid factor, interleukin-2 receptor, interleukin -6, and tumor necrosis factor α are provided.

L139 ANSWER 65 OF 73 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:9767 HCAPLUS Full-text
DOCUMENT NUMBER: 136:74627
TITLE: Drug compositions containing **cyclosporin** and their application as topical systems
INVENTOR(S): Wohlrab, Johannes; Neubert, Reinhard; Jahn, Konstanze
PATENT ASSIGNEE(S): Germany
SOURCE: Ger. Offen., 14 pp.
CODEN: GWXXBX
DOCUMENT TYPE: **Patent**
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 10029404	A1	20020103	DE 2000-10029404	20000615
CA 2470230	AA	20030626	CA 2001-2470230	20011214
WO 2003051385	A1	20030626	WO 2001-EP14749	20011214
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, 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, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2002231703	A1	20030630	AU 2002-231703	20011214
EP 1455810	A1	20040915	EP 2001-991845	20011214
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
BR 2001017197	A	20041214	BR 2001-17197	20011214
CN 1582161	A	20050216	CN 2001-823950	20011214
US 2005106189	A1	20050519	US 2003-498656	20011214
JP 2005516931	T2	20050609	JP 2003-552318	20011214
NZ 534061	A	20060127	NZ 2001-534061	20011214
NO 2004003001	A	20040914	NO 2004-3001	20040713
PRIORITY APPLN. INFO.:			DE 2000-10029404 A	20000615
			WO 2001-EP14749 W	20011214

ED Entered STN: 04 Jan 2002

AB The invention concerns emulsions containing **cyclosporin** for the treatment of diseases of the skin and the mucosa of the digestion and urogenital tracts, bronchi, eye: and for the prophylaxis of organ transplant rejection. The compns. can also contain other drugs, e.g. corticosteroids. The emulsions are composed of (weight/weight%): lipophilic phase 1-10; surfactants 1-50; hydrophilic phase 40-80; **cyclosporin** and other drugs 0.1-20. . Thus an emulsion contained (weight/weight%): **cyclosporin A** 2.0; Tagat O2 8.0; Synperonic PE/L101 12.0; isopropylpalmitate 5.0; propylene glycol 48.7; water 24.3.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L139 ANSWER 66 OF 73 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:741944 HCAPLUS Full-text
DOCUMENT NUMBER: 133:301214
TITLE: Eye disorders treatment with **cyclosporin-A** derivatives
INVENTOR(S): Garst, Michael E.
PATENT ASSIGNEE(S): Allergan Sales, Inc., USA
SOURCE: PCT Int. Appl., 32 pp.
CODEN: PIXXD2
DOCUMENT TYPE: **Patent**
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000061168	A1	20001019	WO 2000-US8877	20000404
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, 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, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6254860	B1	20010703	US 1999-290833	19990413
CA 2369457	AA	20001019	CA 2000-2369457	20000404
EP 1169050	A1	20020109	EP 2000-921645	20000404
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002541207	T2	20021203	JP 2000-610500	20000404
AU 759753	B2	20030501	AU 2000-41935	20000404
NZ 514105	A	20050128	NZ 2000-514105	20000404
US 2001036449	A1	20011101	US 2001-870256	20010530
US 6350442	B2	20020226		

PRIORITY APPLN. INFO.: US 1999-290833 A 19990413
WO 2000-US8877 W 20000404

OTHER SOURCE(S): MARPAT 133:301214
ED Entered STN: 20 Oct 2000
AB A method of treating a disorder in an eye, e.g., an aqueous deficient dry eye state, phacoanaphylactic endophthalmitis, or uveitis, is provided. The method generally includes administering a therapeutically effective amount of a **cyclosporin A** derivative topically to the affected eye. The derivative may be administered as a solution, suspension or ointment in a pharmaceutically acceptable excipient. Sixteen rabbits, 32 eyes are injected intravitreally on day 1 with 500 μg of human serum albumin. Eight rabbits receive no treatment. The other rabbits received 10 μL of 2% ((R)-(Cyclo)alkylthio-Sar)3-(4'-

hydroxy-MeLeu)4-**cyclosporin A** in olive oil applied topically to both eyes 4 times daily beginning 1 h after albumin injection. The degree of intraocular inflammation produced was graded clin. 3 times a week for 3 wk. A marked difference in clin. severity of inflammation between eyes treated with the **cyclosporin A** derivative and control eyes was found.

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L139 ANSWER 67 OF 73 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:487224 HCAPLUS Full-text
DOCUMENT NUMBER: 131:125456
TITLE: Method for treating inflammatory diseases using heat shock proteins
INVENTOR(S): Gelfand, Erwin W.; Haczku, Angela Francisca; Lukacs, Katalin Veronika
PATENT ASSIGNEE(S): National Jewish Medical and Research Center, USA
SOURCE: PCT Int. Appl., 69 pp.
CODEN: PIXXD2
DOCUMENT TYPE: **Patent**
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 9937319	A1	19990729	WO 1999-US1421		19990122
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW					
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG					
ZA 9900499	A	19990722	ZA 1999-499		19990122
CA 2318263	AA	19990729	CA 1999-2318263		19990122
AU 9923374	A1	19990809	AU 1999-23374		19990122
BR 9907228	A	20001024	BR 1999-7228		19990122
EP 1049483	A1	20001108	EP 1999-903321		19990122
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO					
TR 200002973	T2	20010221	TR 2000-200002973		19990122
JP 2002509074	T2	20020326	JP 2000-528300		19990122
NO 2000003775	A	20000922	NO 2000-3775		20000721
US 2002006410	A1	20020117	US 2001-932483		20010817
PRIORITY APPLN. INFO.:			US 1998-12330	A	19980123
			WO 1999-US1421	W	19990122

ED Entered STN: 06 Aug 1999
AB A method is provided to protect a mammal from a disease associated with an inflammatory response and in particular from an inflammatory disease characterized by eosinophilia, airway hyperresponsiveness, and/or a Th2-type immune response. The method includes administration of a heat shock protein to a mammal having such a disease. Formulations useful in the present method are also disclosed.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L139 ANSWER 68 OF 73 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:278763 HCAPLUS Full-text
DOCUMENT NUMBER: 126:255503

TITLE: Ophthalmic compositions containing hydrocarbonaceous carrier
INVENTOR(S): Kang, Meng-Che
PATENT ASSIGNEE(S): Kang, Meng-Che, Taiwan
SOURCE: Brit. UK Pat. Appl., 12 pp.
CODEN: BAXXDU
DOCUMENT TYPE: **Patent**
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
GB 2302018	A1	19970108	GB 1995-11983	19950613
GB 2302018	B2	19990825		
US 5698533	A	19971216	US 1994-280827	19940726
PRIORITY APPLN. INFO.:			US 1994-280827 A	19940726

ED Entered STN: 01 May 1997
AB Compns. contain 0.01-20% drug and 80-99.99% of a hydrocarbonaceous carrier which is a semisolid at room temperature and melts at 30-100°. Typical carriers are petrolatum or lanolin. An emulsifier is optionally present. Suitable drugs for inclusion in the compns. are also listed. Delivery to the eye is particularly in nebulized form. Compns. containing vitamin A and vitamin B12 as active ingredients are exemplified. An ophthalmic composition contained petrolatum 94, camphor 5, menthol 1 g, vitamin A 500,000 IU.

L139 ANSWER 69 OF 73 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1996:359823 HCAPLUS Full-text
DOCUMENT NUMBER: 125:19006
TITLE: Improved topical carriers for mucosal applications
INVENTOR(S): Osborne, David W.
PATENT ASSIGNEE(S): Virotex Corporation, USA
SOURCE: PCT Int. Appl., 11 pp.
CODEN: PIXXD2
DOCUMENT TYPE: **Patent**
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9609829	A1	19960404	WO 1995-US12288	19950926
W: AU, CA, JP, KR				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9537263	A1	19960419	AU 1995-37263	19950926
PRIORITY APPLN. INFO.:			US 1994-313418 A	19940927
			WO 1995-US12288 W	19950926

ED Entered STN: 21 Jun 1996
AB A topical semisolid composition is claimed for use on mucosal membranes which comprises one or more hydrophilic polymers suspended in a nonaq. matrix. The composition may be combined with a therapeutic agent to assist in healing mucosal lesions. The active agent may be a local anesthetic suitable for treatment of canker sores or Behcet's syndrome, a corticosteroid for treatment of lichen planus, or **cyclosporin A**, or an antimicrobial or antifungal agent. Thus, a formulation can be prepared which contains 4-10% Carbopol, 4-10% Gantrez MS-955, 4-10% cellulose gum, and 70-88% white petrolatum.

L139 ANSWER 70 OF 73 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1996:377098 HCAPLUS Full-text
DOCUMENT NUMBER: 125:26262
TITLE: Eicosapentaenoic acid and/or docosahexaenoic acid for immunosuppressive therapy of autoimmune eye diseases
INVENTOR(S): Yazawa, Kazuyoshi; Oono, Shigeaki; Ishioka, Misaki; Nakamura, Satoshi
PATENT ASSIGNEE(S): Kanagawa Kagaku Kenkyusho Kk, Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 4 pp.
CODEN: JKXXAF
DOCUMENT TYPE: **Patent**
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 08092129	A2	19960409	JP 1993-275999	19931008
PRIORITY APPLN. INFO.:			JP 1993-275999	19931008

ED Entered STN: 29 Jun 1996
AB Eicosapentaenoic acid and/or docosahexaenoic acid are claimed for immunosuppressive therapy of autoimmune eye diseases. Thus, patients with uveitis were treated with the oral immunosuppressant FK 506 or **cyclosporin A** combined with fish oil containing 6% eicosapentaenoic acid and 25% docosahexaenoic acid with satisfactory results.

L139 ANSWER 71 OF 73 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1996:209937 HCAPLUS Full-text
DOCUMENT NUMBER: 124:242363
TITLE: Stable pharmaceutical lipid emulsions containing oils and emulsifiers and lecithins
INVENTOR(S): Suzuki, Hidekazu; Yamazaki, Satoshi; Naito, Yoshikazu; Endo, Kenji; Oguma, Touru; Maeda, Makoto
PATENT ASSIGNEE(S): Wakamoto Pharmaceutical Co., Ltd., Japan
SOURCE: Can. Pat. Appl., 77 pp.
CODEN: CPXXEB
DOCUMENT TYPE: **Patent**
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CA 2153553	AA	19960114	CA 1995-2153553	19950710
US 5693337	A	19971202	US 1995-500087	19950710
EP 700678	A1	19960313	EP 1995-110923	19950712
R: DE, FR, GB, IT				
JP 08081360	A2	19960326	JP 1995-197896	19950712
PRIORITY APPLN. INFO.:			JP 1994-183045 A	19940713

ED Entered STN: 12 Apr 1996
AB A lipid emulsion which comprises (A) an oil component, (B) an emulsifying agent containing yolk lecithin and/or soybean lecithin, and (C) water, wherein the lipid emulsion further comprises citric acid or a pharmaceutically acceptable salt thereof and at least one member selected from the group consisting of methionine, phenylalanine, serine, histidine and pharmaceutically acceptable salts thereof, provided that is does not simultaneously contain methionine and phenylalanine. The emulsion does not change of color and formation of oil drops associated with the conventional natural lecithin-containing lipid emulsions due to the synergistic effect of the foregoing additives. The drug containing lipid emulsion is also excellent

in storage stability and thus the foregoing lipid emulsion can be applied to drugs such as injections, eye drops, nasal drips, lotions or liniments, inhalants and drugs for oral administration or cosmetics such as humectants. A solution of 0.012 g of fluorometholone in 20 mL of ethanol was added to a solution of 20 mL hexane:ethanol (10:1) containing 0.54 g of yolk lecithin and 0.06 g of yolk phosphatidylethanolamine and mixed, followed by evaporation of solvent to obtain a lipid film. To the lipid film was added 5.4 g of soybean oil and 94 mL of 2% glycerin aqueous solution followed by vigorous stirring through shaking to carry out preliminary emulsification. The preliminarily emulsified liquid was passed through microfluidizer 10 times under a pressure of 750 kg/cm2 to emulsify the liquid, the pH value of the emulsified liquid was adjusted to 6.5-7.5 to give a milk white stock lipid emulsion.

L139 ANSWER 72 OF 73 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1996:38846 HCAPLUS Full-text
DOCUMENT NUMBER: 124:66660
TITLE: Lacrimal gland-specific emulsions for topical application to ocular tissue
INVENTOR(S): Ding, Shulin; Tien, Walter L.; Olejnik, Orest
PATENT ASSIGNEE(S): Allergan, Inc., USA
SOURCE: PCT Int. Appl., 27 pp.
CODEN: PIXXD2
DOCUMENT TYPE: **Patent**
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9531211	A1	19951123	WO 1995-US6302	19950517
W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ				
RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5474979	A	19951212	US 1994-243279	19940517
CA 2190485	AA	19951123	CA 1995-2190485	19950517
CA 2190485	C	20030415		
CA 2309033	AA	19951123	CA 1995-2309033	19950517
CA 2309033	C	20030826		
AU 9526409	A1	19951205	AU 1995-26409	19950517
AU 693213	B2	19980625		
EP 759773	A1	19970305	EP 1995-921294	19950517
EP 759773	B1	20010808		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
CN 1152876	A	19970625	CN 1995-194078	19950517
BR 9507664	A	19971007	BR 1995-7664	19950517
JP 10500414	T2	19980113	JP 1995-529895	19950517
JP 3441462	B2	20030902		
EP 1044678	A1	20001018	EP 2000-202069	19950517
EP 1044678	B1	20030312		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE				
AT 203911	E	20010815	AT 1995-921294	19950517
ES 2161895	T3	20011216	ES 1995-921294	19950517
PT 759773	T	20020228	PT 1995-921294	19950517
AT 234076	E	20030315	AT 2000-202069	19950517
JP 2003231646	A2	20030819	JP 2003-63234	19950517

PT 1044678	T	20030829	PT 2000-202069		19950517
ES 2194670	T3	20031201	ES 2000-202069		19950517
CN 1288722	A	20010328	CN 2000-120126		20000714
HK 1034190	A1	20051209	HK 2001-104710		20010709
GR 3036945	T3	20020131	GR 2001-401814		20011018
PRIORITY APPLN. INFO.:			US 1994-243279	A	19940517
			CA 1995-2190485	A3	19950517
			EP 1995-921294	A3	19950517
			JP 1995-529895	A3	19950517
			WO 1995-US6302	W	19950517

ED Entered STN: 20 Jan 1996

AB A pharmaceutical composition is disclosed in the form of a nonirritating emulsion which includes at least one **cyclosporin** in admixt. with a higher fatty acid glyceride and polysorbate 80. More particularly, the **cyclosporin** may be **cyclosporine A** and the higher fatty acid glyceride may be castor oil. The composition allows a high comfort level and low irritation potential suitable for delivery of medications to sensitive areas such as ocular tissues with enhanced absorption in the lacrimal gland. In addition, the composition has stability for up to 9 mo without crystallization of **cyclosporin**. For example, an ophthalmic emulsion containing **cyclosporin A** 0.2, castor oil 2.5, Polysorbate-80 1.0, Pemulen 0.05, glycerol 2.2, NaOH q.s., and purified water to 100% was formulated to treat keratoconjunctivitis sicca.

L139 ANSWER 73 OF 73 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1993:140090 HCAPLUS Full-text

DOCUMENT NUMBER: 118:140090

TITLE: Effects of steroids and immunosuppressive drugs on endotoxin-uveitis in rabbits

AUTHOR(S): Ohia, Ekanem O.; Mancino, Michael; Kulkarni, Prasad S.

CORPORATE SOURCE: Sch. Med., Univ. Louisville, Louisville, KY, USA

SOURCE: Journal of Ocular Pharmacology (1992), 8(4), 295-307
CODEN: JOPHER; ISSN: 8756-3320

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 13 Apr 1993

AB Anti-inflammatory actions of dexamethasone (DEXA), **cyclosporin A** (CSA) and rapamycin (RAPA) were assessed on uveitis induced by intravitreal E. coli endotoxin (100 ng) in rabbits at 24 h. In this model, endotoxin caused a breakdown of the blood-aqueous barrier (BAB) and polymorphonuclear neutrophils (PMN) infiltration into the aqueous humor (AH) and iris-ciliary body (ICB). DEXA given i.m. (2 mg/kg), but not topical DEXA (0.1% 6 + daily), inhibited AH leukocytes and protein level. However, both routes caused an inhibition of AH PGE2 and LTB4. In the ICB, i.m. DEXA inhibited PGE2 synthesis and myeloperoxidase (MPO) activity. Both i.m. CSA (25 mg/kg) and i.m. RAPA (10 mg/kg) inhibited the AH leukocytes and protein content and MPO activity in the ICB. RAPA also inhibited protein and eicosanoid (except AH LTB4) levels in both the AH and ICB. Interestingly, castor oil, a vehicle of CSA, also inhibited AH leukocytes and the release of PGE2 into AH and from ICB. In summary, systemic administration of DEXA and other immunosuppressive drugs (CSA and RAPA) inhibited endotoxin-induced uveitis in rabbits.

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     FILE 'BIOSIS' ENTERED AT 16:26:29 ON 02 OCT 2006
                ACT GAR857BI1AU/A
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L1   (         1)SEA ABB=ON  PLU=ON  CYCLOSPORIN A/CN
L2   (        44)SEA ABB=ON  PLU=ON  ACHEAMPONG A?/AU
L3   (       117)SEA ABB=ON  PLU=ON  TANG LIU D?/AU
L4   (      4672)SEA ABB=ON  PLU=ON  CHANG J?/AU
L5   (       446)SEA ABB=ON  PLU=ON  POWER D?/AU
L6   (    213487)SEA ABB=ON  PLU=ON  EYE OR  ASTHENOPIA OR CONJUNCTIVAL
                DISEASES OR CORNEAL DISEASES OR EYELID DISEASES OR LACRIMAL
                APPARATUS DISEASES  OR LENS DISEASES OR OCULAR HYPERTENSION
L7   (      7948)SEA ABB=ON  PLU=ON  OCULAR HYPOTENSION  OR OCULAR MOTILITY
                DISORDERS OR OPTIC NERVE DISEASES OR ORBITAL DISEASES OR PUPIL
                DISORDERS  OR REFRACTIVE ERRORS OR RETINAL DISEASES OR
                SCLERAL DISEASES OR UVEAL DISEASES OR VISION DISORDERS OR
                VITREORETINOPATHY OR VITREOUS DETACHMENT
L8   (    124285)SEA ABB=ON  PLU=ON  OIL
L9   (     23151)SEA ABB=ON  PLU=ON  EMULSI?
L10             SEL PLU=ON  L1 1- CHEM :      38 TERMS
L11  (     46884)SEA ABB=ON  PLU=ON  L10
L12  (         0)SEA ABB=ON  PLU=ON  ((L2 OR L3 OR L4 OR L5)) AND ((L6 OR L7))
                AND L8 AND L9 AND L11
L13  (         9)SEA ABB=ON  PLU=ON  ((L2 OR L3 OR L4 OR L5)) AND ((L6 OR L7))
                AND L11
L14             9 SEA ABB=ON  PLU=ON  L12 OR L13
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     FILE 'EMBASE' ENTERED AT 16:26:35 ON 02 OCT 2006
                ACT GAR857EM1AU/A
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L15  (         1)SEA ABB=ON  PLU=ON  CYCLOSPORIN A/CN
L16  (        21)SEA ABB=ON  PLU=ON  ACHEAMPONG A?/AU
L17  (        63)SEA ABB=ON  PLU=ON  TANG LIU D?/AU
L18  (      3346)SEA ABB=ON  PLU=ON  CHANG J?/AU
L19  (       272)SEA ABB=ON  PLU=ON  POWER D?/AU
L20             SEL PLU=ON  L15 1- CHEM :      38 TERMS
L21  (     74476)SEA ABB=ON  PLU=ON  L20
L22  (    301867)SEA ABB=ON  PLU=ON  EYE DISEASE+NT/CT
L23  (      8415)SEA ABB=ON  PLU=ON  EMULSION+NT/CT
L24  (      5657)SEA ABB=ON  PLU=ON  OIL/CT
L25  (     46238)SEA ABB=ON  PLU=ON  D3.60.650./CT
L26  (         0)SEA ABB=ON  PLU=ON  ((L16 OR L17 OR L18 OR L19)) AND L21 AND
                L22 AND L23 AND ((L24 OR L25))
L27  (         2)SEA ABB=ON  PLU=ON  ((L16 OR L17 OR L18 OR L19)) AND L21 AND
                L22 AND L23
L28  (         5)SEA ABB=ON  PLU=ON  ((L16 OR L17 OR L18 OR L19)) AND L21 AND
                L22
L29  (         0)SEA ABB=ON  PLU=ON  ((L16 OR L17 OR L18 OR L19)) AND L21 AND
                L22 AND ((L24 OR L25))
L30             5 SEA ABB=ON  PLU=ON  L26 OR (L27 OR L28 OR L29)
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     FILE 'HCAPLUS' ENTERED AT 16:26:39 ON 02 OCT 2006
                ACT GAR857HC1AU/A
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L31  (        25)SEA ABB=ON  PLU=ON  ACHEAMPONG A?/AU
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L33 (      7140)SEA ABB=ON  PLU=ON  CHANG J?/AU
L34 (       227)SEA ABB=ON  PLU=ON  POWER D?/AU
L35 (         1)SEA ABB=ON  PLU=ON  CYCLOSPORIN A/CN
L36 (     36733)SEA ABB=ON  PLU=ON  EYE, DISEASE+OLD,NT/CT
L37 (     24550)SEA ABB=ON  PLU=ON  EMULSIFYING AGENTS/CT
L38 (    388102)SEA ABB=ON  PLU=ON  OILS+OLD,NT/CT
L39             SEL PLU=ON  L35 1- CHEM :      38 TERMS
L40 (     23233)SEA ABB=ON  PLU=ON  L39
L41 (         1)SEA ABB=ON  PLU=ON  ((L31 OR L32 OR L33 OR L34)) AND L40 AND
                L36 AND L37 AND L38
L42 (        29)SEA ABB=ON  PLU=ON  ((L31 OR L32 OR L33 OR L34)) AND L40
L43 (         4)SEA ABB=ON  PLU=ON  L42 AND ((L36 OR L37 OR L38))
L44           4 SEA ABB=ON  PLU=ON  L41 OR L43
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     FILE 'MEDLINE' ENTERED AT 16:26:46 ON 02 OCT 2006
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L45 (        24)SEA ABB=ON  PLU=ON  ACHEAMPONG A?/AU
L46 (        63)SEA ABB=ON  PLU=ON  TANG LIU D?/AU
L47 (      3663)SEA ABB=ON  PLU=ON  CHANG J?/AU
L48 (       322)SEA ABB=ON  PLU=ON  POWER D?/AU
L49 (         1)SEA ABB=ON  PLU=ON  CYCLOSPORIN A/CN
L50 (      9221)SEA ABB=ON  PLU=ON  EMULSIONS+NT/CT
L51 (       124)SEA ABB=ON  PLU=ON  EMULSIFYING AGENTS/CT
L52 (     34652)SEA ABB=ON  PLU=ON  OILS+NT/CT
L53 (         0)SEA ABB=ON  PLU=ON  L45 AND L46 AND L47 AND L48
L54             SEL PLU=ON  L49 1- CHEM :      38 TERMS
L55 (     39885)SEA ABB=ON  PLU=ON  L54
L56 (    320609)SEA ABB=ON  PLU=ON  EYE DISEASES+NT/CT
L57 (         0)SEA ABB=ON  PLU=ON  ((L45 OR L46 OR L47 OR L48)) AND L56 AND
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L58 (         2)SEA ABB=ON  PLU=ON  ((L45 OR L46 OR L47 OR L48)) AND L56 AND
                L55 AND ((L50 OR L51))
L59 (         0)SEA ABB=ON  PLU=ON  ((L45 OR L46 OR L47 OR L48)) AND L56 AND
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L60 (         5)SEA ABB=ON  PLU=ON  ((L45 OR L46 OR L47 OR L48)) AND L56 AND
                L55
L61 (         5)SEA ABB=ON  PLU=ON  (L57 OR L58 OR L59 OR L60)
L62           5 SEA ABB=ON  PLU=ON  L61 OR L53
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L65 (         7)SEA ABB=ON  PLU=ON  TANG LIU D?/AU
L66 (      3666)SEA ABB=ON  PLU=ON  CHANG J?/AU
L67 (        57)SEA ABB=ON  PLU=ON  POWER D?/AU
L68             SEL PLU=ON  L63 1- CHEM :      38 TERMS
L69 (      2231)SEA ABB=ON  PLU=ON  L68
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               D QUE L14

     FILE 'BIOSIS' ENTERED AT 16:29:16 ON 02 OCT 2006
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     FILE 'EMBASE' ENTERED AT 16:29:36 ON 02 OCT 2006
               D QUE L30

     FILE 'HCAPLUS' ENTERED AT 16:29:47 ON 02 OCT 2006
               D QUE L44

     FILE 'MEDLINE' ENTERED AT 16:30:01 ON 02 OCT 2006
               D QUE L62

     FILE 'WPIX' ENTERED AT 16:30:10 ON 02 OCT 2006
               D QUE L71

     FILE 'MEDLINE, BIOSIS, EMBASE, WPIX, HCAPLUS' ENTERED AT 16:31:07 ON 02
     OCT 2006
L72          19 DUP REM L62 L14 L30 L71 L44 (10 DUPLICATES REMOVED)
                     ANSWERS '1-5' FROM FILE MEDLINE
                     ANSWERS '6-11' FROM FILE BIOSIS
                     ANSWERS '12-13' FROM FILE EMBASE
                     ANSWERS '14-19' FROM FILE WPIX
                D IALL 1-5
                D IALL 6-11
                D IALL 12-13
                D IALL ABEQ TECH 14-19

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                DISORDERS  OR REFRACTIVE ERRORS OR RETINAL DISEASES OR
                SCLERAL DISEASES OR UVEAL DISEASES OR VISION DISORDERS OR
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L78               SEL PLU=ON  L73 1- CHEM :      38 TERMS
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L85 (     301867)SEA ABB=ON  PLU=ON  EYE DISEASE+NT/CT
L86 (       5657)SEA ABB=ON  PLU=ON  OIL/CT
L87 (      46238)SEA ABB=ON  PLU=ON  D3.60.650./CT
L88 (     225955)SEA ABB=ON  PLU=ON  L85/MAJ
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L97 (     24550)SEA ABB=ON  PLU=ON  EMULSIFYING AGENTS/CT
L98 (    388102)SEA ABB=ON  PLU=ON  OILS+OLD,NT/CT
L99              SEL PLU=ON  L95 1- CHEM :      38 TERMS
L100(     23233)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L99
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L103(        17)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L96 AND L100 AND L98
L104(     28869)SEA FILE=HCAPLUS ABB=ON  PLU=ON  EMULSIONS/CT
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L125(       650)SEA FILE=WPIX ABB=ON  PLU=ON  OCULAR HYPOTENSION/BI,ABEX  OR OC
L126(    444197)SEA FILE=WPIX ABB=ON  PLU=ON  OIL/BI,ABEX
L127(    169370)SEA FILE=WPIX ABB=ON  PLU=ON  EMULSI?/BI,ABEX OR (A10-B03 OR B1
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L129             SEL PLU=ON  L123 1- CHEM :      38 TERMS
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L131(       959)SEA FILE=WPIX ABB=ON  PLU=ON  RA0135/DCN OR 90981-1-0-0/DCRE
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     FILE 'HCAPLUS' ENTERED AT 16:37:21 ON 02 OCT 2006
                D QUE L111
L136         17 SEA ABB=ON  PLU=ON  L111 NOT L44

     FILE 'MEDLINE' ENTERED AT 16:37:49 ON 02 OCT 2006
                D QUE L122
L137         14 SEA ABB=ON  PLU=ON  L122 NOT L62

     FILE 'WPIX' ENTERED AT 16:38:39 ON 02 OCT 2006
                D QUE L133
L138         16 SEA ABB=ON  PLU=ON  L133 NOT L71

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     OCT 2006
L139         73 DUP REM L137 L134 L135 L138 L136 (3 DUPLICATES REMOVED)
                      ANSWERS '1-14' FROM FILE MEDLINE
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                      ANSWERS '22-41' FROM FILE EMBASE
                      ANSWERS '42-57' FROM FILE WPIX
                      ANSWERS '58-73' FROM FILE HCAPLUS
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                   D IALL 22-41
                   D IALL ABEQ TECH 42-57
                   D IBIB ED ABS 58-73


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UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/927,857	08/27/2004	Andrew Acheampong	D-3111	2409

33197 7590 10/13/2006

STOUT, UXA, BUYAN & MULLINS LLP
4 VENTURE, SUITE 300
IRVINE, CA 92618

EXAMINER	
CORDERO GARCIA, MARCELA M	
ART UNIT	**PAPER NUMBER**
1654	

DATE MAILED: 10/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 10/03)

Office Action Summary	Application No.	Applicant(s)	
	10/927,857	ACHEAMPONG ET AL.	
	Examiner	Art Unit	
	Marcela M. Cordero Garcia	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-36* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-20, drawn to a method of treating an eye of a human or animal, classified, e.g., in class 514, subclass 11.

II. Claims 21-36, drawn to a composition for treating an eye of a human or animal, classified, e.g., in class 530, subclass 317.

The inventions are distinct, each from the other because of the following reasons:

Inventions II and I are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product. See MPEP § 806.05(h). In the instant case the instantly claimed compositions may also be used, e.g., to treat skin infections.

The search for each of the above inventions is not co-extensive particularly with regard to the literature search. Further, a reference which would anticipate the invention of one Group would not necessarily anticipate or even make obvious another Group. Finally, the consideration for patentability is different in each case. Thus, it would be an undue burden to examine all of the above inventions in one application.

Because these inventions are distinct for the reasons given above and the search required for each Group is not necessarily required for the other Groups, restriction for examination purposes as indicated is proper.

Applicant is advised that the response to this requirement, to be complete, must include an election of the invention to be examined even though the requirement be traversed.

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and the product claims are subsequently found allowable, withdrawn process claims that depend from or otherwise require all the limitations of the allowable product claim will be considered for rejoinder. All claims directed to a nonelected process invention must require all the limitations of an allowable product claim for that process invention to be rejoined.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until all claims to the elected product are found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowable product claim will not be rejoined. See MPEP § 821.04(b). Additionally, in order to retain the right to rejoinder in accordance with the above policy, applicant is advised that the process claims should be amended during prosecution to require the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder**. Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

In addition, this application contains claims directed to the following patentably distinct species: the many and multiple compositions encompassed by the instant claims (e.g. claim 21), the many and multiple diseases to be treated (e.g., claim 2) and methods thereof. The species are independent or distinct because each composition

has a different ratio of components and/or chemically different hydrophobic components.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species [i.e., elect a single composition indicating all its components: the cyclosporin used (e.g., claims 23-24), the % per weight of the cyclosporin component, the hydrophobic component (e.g., claim 28), and the weight ratio of the cyclosporin component to the hydrophobic component. In addition, if Group I is elected, please also elect a single type of condition to be treated (see e.g., claim 2)] for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, claims 1 and 21 are generic.

Applicant is advised that a reply to this requirement must include an identification of the species that is elected consonant with this requirement, and a listing of all claims readable thereon, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species or invention to be examined even though the requirement be traversed (37 CFR 1.143) and (ii) identification of the claims encompassing the elected invention.

The election of an invention or species may be made with or without traverse. To reserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse.

Should applicant traverse on the ground that the inventions or species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions or species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C.103(a) of the other invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

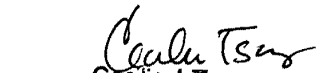
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marcela M. Cordero Garcia whose telephone number is (571) 272-2939. The examiner can normally be reached on M-Th 7:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia J. Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Marcela M Cordero Garcia, Ph.D.
Patent Examiner
Art Unit 1654

MMMCG 09/06



Cecilia J. Tsang
Supervisory Patent Examiner
Technology Center 1600

TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Application Number	10/927,857
Filing Date	8/27/2004
First Named Inventor	Acheampong
Group Art Unit	1654
Examiner Name	Cordero Garcia, M.M.
Total Number of Pages in This Submission	
Attorney Docket Number	D-3111

ENCLOSURES (*check all that apply*)

- ☐ Fee Transmittal Form *(in duplicate)*
- ☐ Fee Attached
- ☒ Amendment/Reply
- ☐ After Final
- ☐ Affidavits/declaration(s)
- ☐ Extension of Time Request
- ☐ Express Abandonment Request
- ☐ Information Disclosure Statement
- ☐ Certified Copy of Priority Document(s)
- ☐ Response to Missing Parts/ Incomplete Application
- ☐ Response to Missing Parts under 37 CFR 1.52 or 1.53
- ☐ Drawing(s)
- ☐ Licensing-related Papers
- ☐ Petition
- ☐ Petition to Convert to a Provisional Application
- ☐ Power of Attorney, Revocation Change of Correspondence Address
- ☐ Terminal Disclaimer
- ☐ Request for Refund
- ☐ CD, Number of CD(s) ____
- ☐ Landscape Table on CD
- ☐ After Allowance Communication to TC
- ☐ Appeal Communication to Board of Appeals and Interferences
- ☐ Appeal Communication to TC *(Appeal Notice, Brief, Reply Brief)*
- ☐ Proprietary Information
- ☐ Status Letter
- ☐ Other Enclosure(s) *(please identify below)*

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	Stout, Uxa, Buyan & Mullins, LLP		
Signature	Frank J. Uxa		
Printed Name	Frank J. Uxa		
Date	11/10/2006	Reg. No.	25,612

CERTIFICATE OF TRANSMISSION/MAILING

I hereby certify that this correspondence is being facsimile transmitted to the USPTO at fax number 571-273-8300, or deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date shown below.

Signature	Janet McGhee		
Typed or printed name	Janet McGhee	Date	11/10/2006

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.	: 10/927,857	Confirmation No. 2409
Applicant	: Acheampong	
Filed	: 08/27/2004	
Title	: METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORINE COMPONENTS	
TC/A.U.	: 1654	
Examiner	: CORDERO GARCIA, M.M.	
Docket No.	: D-3111	
Customer No.	: 33197	

CERTIFICATE OF FACSIMILE TRANSMISSION

I hereby certify that this correspondence is being transmitted via facsimile to Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, to fax number 571-273-8300, on the date indicated below.

November 10, 2006 / Janet McGhee

RESPONSE TO RESTRICTION REQUIREMENT AND ELECTION OF SPECIES REQUIREMENT

Commissioner for Patents
Po Box 1450
Alexandria, VA 22313-1450

Sir:

This is in response to the Examiner's communication mailed October 13, 2006, which included a Restriction Requirement and an Election of Species Requirement.

The Examiner has required restriction between the Group I Claims, that is Claims 1-20, drawn to a method of treating an eye of a human or animal, and Group II Claims, that is Claims 21-36, drawn to a composition for treating an eye of a human or animal.

Applicant provisionally elects the Group II claims, that is claims 21-36.

The Examiner has also required election of a single disclosed composition species indicating the cyclosporine, the percent by weight of the cyclosporine component, the hydrophobic component and the weight ratio of the cyclosporine component to the hydrophobic component.

Applicant provisionally elects the species comprising cyclosporin A, a cyclosporine component concentration of less than 0.1% by weight, vegetable oils as the hydrophobic component and a weight ratio of the cyclosporine component to the hydrophobic component of less than 0.08.

The claims which read on this elected species include claims 21-36.

Applicant traverses the restriction requirement and the election of species requirement.

Independent method claim 1 appears to include all the limitations of independent composition claim 21. The present method claims and the present composition claims are thus closely related so that the Patent and Trademark Office is placed under no undue burden in considering and examining all the present claims in the above-identified application.

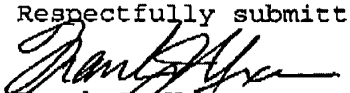
With regard to the election of species requirement, the definitions of a cyclosporine component and a hydrophobic component are clearly set forth in the present specification. The cyclosporine component concentration and weight ratio of cyclosporine component to hydrophobic component are set forth in the independent claims. The different species identified by the Examiner are closely related and can be considered and examined

together without placing an undue burden on the Patent and Trademark Office.

In view of the above, applicant respectfully requests that the restriction requirement and the election of species requirement be withdrawn.

Applicant respectfully requests early and favorable action in the above-identified application.

Respectfully submitted,



Frank J. Uxa
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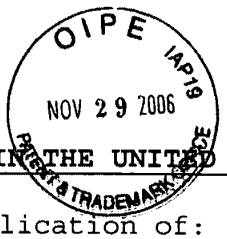
D-3111



IFW

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

PATENT

In re application of:
Acheampong et al.) Group Art Unit: 1654
)
Serial No. 10/927,857) Examiner: Unknown
)
Filed: August 27, 2004)
)
For: METHODS OF PROVIDING)
THERAPEUTIC EFFECTS USING)
CYCLOSPORIN COMPONENTS)

I hereby certify that this correspondent is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, PO Box 1450, Alexandria, VA 22313-1450, on or before

November 27, 2006
Date

Alicia Curran

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

Dear Sir:

Applicant wishes to call to the attention of the Examiner the documents cited on the accompanying Form PTO-1449. No concession is made that these documents are prior art, and applicant expressly reserves the right to antedate the documents as may be appropriate. Applicant requests that each of these documents be made of record in the above-identified application.

Respectfully submitted,

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Irvine, CA 92618
(949) 450-1750
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FJUxa/ac

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE
FORM PTO-1449

LIST OF ART CITED BY APPLICANT

ATTY. DOCKET: D-3111	SERIAL NO.: 10/927,857
APPLICANT: Acheampong et al	TITLE: Methods of Providing Therapeutic Effects Using Cyclosporine Components
FILING DATE: August 27, 2004	GROUP: 1654

U.S. PATENT DOCUMENTS

*EXAMINER INITIAL		DOCUMENT NO.	DATE	NAME	CLASS	SUB-CLASS	FILING DATE (if applicable)
	AA	2003/0055028 A1	03/2003	Stergiopoulos et al.			
	AB	5,368,854	11/1994	Rennick			
	AC	4,614,736	09/1986	Delevallee et al.			
	AD						

FOREIGN PATENT DOCUMENTS

		DOCUMENT NO.	DATE	COUNTRY	CLASS	SUB-CLASS	TRANSLATION (yes/no)
	BA	DE 19810655	09/1999	Germany			
	BB	WO 03/030834	04/2003	PCT			
	BC						

OTHER ART

(Including Author, Title, Date, Pertinent Pages, etc.)

	CA	T.A. Winter, et al. Scand J Gastroenterol. (1993), 28(8), pages 701-704
	CB	M. Schwab and U. Klotz, Clin. Pharmacokinet. (2001), 40(10), pages 723-751
	CC	J. Rudinger. In: Peptide Hormones, JA Parsons, Ed. (1976) pages 1-7
	CD	D.E. Smilek, et al. Proc. Natl. Acad. Sci. USA (1991) 88, pages 9633-9637
	CE	MBanić, et al. Dig. Dis. Sci. (2002), 47(6), pages 1362-1368
	CF	The Online Medical Dictionary, accessed 7/7/05 and 7/13/05. 6 pages
	CG	W.J. Sandborn, et al. Am. J. Gastroenterol. (1993), 88(5), pages 640-645
	CH	D.H. Present. Am. J. Gastroenterol. (1993) 88(5), pages 627-630
	CI	S. Ardizzone and G.B. Porro. Drugs. (1998), 55(4), pages 519-542
	CJ	W.J. Sandborn, et al. Gastroenterology. (1994), 106(6), pages 1429-1435
	CK	K. Tsubota, et al. Invest. Ophthalmol. Vis. Sci. (1998), 39(9), pages 1551-1559
	CL	A.A. Drosos and N.M. Moutsopoulos. Ter. Arkh. (1998), 60(4), pages 77-80
	CM	A.A. Drosos, et al. Scand. J. Rheumatology (1986) Suppl. 61, pages 246-249
	CN	W.A. van der Reijden, et al. Ann. Rheum. Dis. (1999), 58, pages 465-473
	CO	N.A. Robinson and D. Wray. Australian Dental Journal (2003), 48(4), pages 206-211
	CP	A.M. Pedersen and B. Nauntofte. Expert Opin Pharmacother (2001), 2(9), pages 1415-1436
	CQ	D.E. Lopatin. Chemical compositions and functions of Saliva. 8/24/2001, 31 pages

EXAMINER_____ DATE CONSIDERED _____

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

LIST OF ART CITED BY APPLICANT

ATTY. DOCKET: D-3111	SERIAL NO.: 10/927,857
APPLICANT: Acheampong et al	TITLE: Methods of Providing Therapeutic Effects Using Cyclosporine Components
FILING DATE: August 27, 2004	GROUP: 1654

	CR	Gunduz et al, "Topical Cyclosporin Treatment of Keratoconjunctivitis Sicca in Se condary Sjogren's Syndrome", Acta Ophthalmologica, Vol. 72, No. 4, 1994, pp 438-442, XP009063039
	CS	Phillips et al, "Cyclosporine Has A Direct Effect on the Differentiation of a Mucin-Secreting Cell Line", Journal of Cellular Physiology, Vol. 184, No. 3, Sept. 2000, pp 400-408, XP009063023
	CT	Gipson et al, "Character of Ocular Surface Mucins and Their Alteration in Dry Eye Disease", The Ocular Surface, Vol. 2, No. 2, April 2004, pp 131-148, XP001208377
	CU	Akpek et al, "A Randomized Trial of Topical Cyclosporin 0.05% in Topical Steroid-Resistant Atopic Keratoconjunctivitis", Ophthalmology, Vol. III, No. 3, March 2004, pp 476-482, XP00906021
	CV	Eisen et al, "Topical Cyclosporine for Oral Mucosal Disorders", Journal of the American Academy of Dermatology, Vol. 23, No. 6, Part 2, Dec. 1990, pp 1259-1264, XP009063043
	CW	Epstein et al, "Topical Cyclosporine in a Bioadhesive for Treatment of Oral Lichenoid Mucosal Reactions. An Open Label Clinical Trial", Oral Surgery, Oral Medicine..., Vol. 82, No. 5, 1996, pp 532-536, XP009063045
	CX	Erdmann et al, "Pemphigus Vulgaris Der Mund-Und Kehlopfschleimhaut Pemphigus Vulagris of the Oral Mucosa and the Larynx", H+G Zeitschrift Fuer Hautkrankheiten, Vol. 72. No. 4, 1997, pp 283-296, XP009063042
	CY	Brinkmeier et al, "Pyodermatitis-Pyostomatitis Vegetans: A Clinical Course of Two Decades with Response to Cyclosporine and Low-Dose Prednisolone", Acta Dermato-Venereologica, Vol. 81, No. 2, May 2001, pp 134-136
	CZ	Gremse et al, "Ulcerative Colitis in Children. Medical Management", Pediatric Drugs, Vol. 4, No. 12, 2002, pp 807-815, XP009063025
	CAA	Gaeta G.M. et al, "Cyclosporin bioadhesive gel in the topical treatment of erosive lichen planus" International Journal of Immunopathology and Pharmacology, Vol. 7, No. 2, 1994, pages 125-132.

EXAMINER_____ DATE CONSIDERED _____

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

EAST Search History

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L2	1919	cyclosporine.clm. or cyclosporin.clm.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2006/12/27 18:27
L3	384	l2 and (hydrophobic.clm. or oil.clm.)	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2006/12/27 18:28
L4	12	l2 and (hydrophobic.clm. or oil.clm.) and allergan	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2006/12/27 18:52

EAST Search History

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L10	47	cyclosporine near3 oil	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2006/12/27 19:28

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/927,857	08/27/2004	Andrew Acheampong	D-3111	2409

33197 7590 01/17/2007
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EXAMINER	
CORDERO GARCIA, MARCELA M	
ART UNIT	**PAPER NUMBER**
1654	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/17/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/927,857	ACHEAMPONG ET AL.	
	Examiner	Art Unit	
	Marcela M. Cordero Garcia	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-36* is/are pending in the application.

4a) Of the above claim(s) *1-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/04, 3/05, 11/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is in response to the reply received on November 10, 2006. Claims 1-36 are pending in the application.

Applicant elected with traverse Group II, claims 21-36, drawn to a composition for treating an eye of a human or animal. In addition, Applicant elected with traverse the species comprising "cyclosporin A, a cyclosporine component concentration of less than 0.1%, vegetable oils as the hydrophobic component, and a weight ratio of the cyclosporine component to the hydrophobic component of less than 0.08".

Applicant argues that the independent method claim 1 appears to include all the limitations of independent composition claim 21 and therefore it would not be undue burden in considering and examining all claims. Applicant also argues that the definitions of the hydrophobic component are clearly set forth in the present specification and that the concentration and weight ratios of the cyclosporine component are set forth in the independent claims. Applicant's arguments have been considered but not deemed persuasive for the reasons of record and because of the following arguments: The instant restriction is between the product (Group II) and a process of using thereof (Group I). The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product. See MPEP § 806.05(h). In the instant case, the claimed cyclosporine compositions may also be used to

study, e.g., the stability of emulsions, emulsion particle size and/or tandem mass spectrometric fragmentation patterns of cyclosporine compounds. The search for each of the above inventions is not co-extensive particularly with regard to the literature search. Further, a reference which would anticipate the invention of one Group would not necessarily anticipate or even make obvious another Group. Finally, the consideration for patentability is different in each case. Because these inventions are independent or distinct for the reasons given above and there would be a serious burden on the examiner if restriction is not required because the inventions require a different field of search (see MPEP § 808.02), restriction for examination purposes as indicated is proper. Thus, it would be an undue burden to examine all of the above inventions in one application and therefore, the restriction requirement is still deemed proper and is therefore made FINAL.

Please note that, as set forth in the previous Office Action, pursuant to the procedures set forth in MPEP § 821.04(B), the claims directed to the process of making or using an allowable product, and previously withdrawn from consideration as a result of a restriction requirement, would be rejoined and fully examined for patentability under 37 CFR 1.104 after the elected product (as in this instant case) has found to be allowable.

In regards to the species requirement traversal, Applicant's arguments have been carefully considered but not deemed persuasive because as set forth in the previous Office Action, this application contains claims directed to patentably distinct species: the many and multiple compositions encompassed by

the instant claims and methods thereof. The species are independent or distinct because the instant compositions are drawn to a multitude of compositions (and methods thereof) encompassing cyclosporin A and derivatives and functional analogs thereof (or mixtures thereof) in combination with a hydrophobic component encompassing vegetable oils, animal oils, mineral oils, synthetic oils, non-oily hydrophobic components and mixtures thereof combined so that the weight of the cyclosporine component to the weight of the hydrophobic component is less than 0.08. The instant compositions (and methods thereof) are drawn to a large number of combinations, e.g., (cyclosporin A/castor oil) in a ratio of 0.02, (cyclosporine derivative/corn oil) in a ratio of 0.03, (cyclosporin A+cyclosporine derivative/castor oil+mineral oil) in a ratio of 0.007, (cyclosporin Analog/non-oily hydrophobe) in a ratio of 0.001; and so forth. The cyclosporine component encompasses cyclosporine, any derivatives thereof and any functional analogs thereof, which are drawn to a plethora of different chemical formulas. The hydrophobic component encompasses, e.g., vegetable oils, animal oils, mineral oils, synthetic oils and mixtures thereof, non-oily hydrophobic substances and so forth. The combinations of cyclosporine/hydrophobic components and the ratios variations for the combinations above encompass countless different and distinct compositions thereby meeting the species requirement. Therefore, the election requirement is still deemed proper and is therefore made FINAL.

Claims 1-20 are withdrawn as not drawn to the elected invention.

Claims 21-36 are presented for examination on the merits as they read upon the instantly elected species, i.e., "a composition comprising cyclosporin A, a cyclosporine component concentration of less than 0.1%, vegetable oils as the hydrophobic component, and a weight ratio of the cyclosporine component to the hydrophobic component of less than 0.08".

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 21-36 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

> "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is

> claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966." Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." MPEP 2163.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In Regents of the University of California v. Eli Lilly & Co., the court stated:

> "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials. Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606; In re Smythe, 480 F.2d 1376, 1383, 178 USPQ 279, 284-85 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus. . . ."). Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. The MPEP does state that for generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP 2163. Although the MPEP does not define what constitute a sufficient number of representative, the Courts have indicated what do not constitute a representative number species to adequately describe a broad generic. In Gostelli, the Court determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. In re Gostelli, 872 F.2d at 1012, 10 USPQ2d at 1618.

In the instant case, the claims are drawn to a composition for treating an eye of a human or an animal, comprising an emulsion comprising water, a hydrophobic component, and a cyclosporine component in a therapeutically effective amount of less than 0.1% by weight, the weight ratio of the cyclosporine component to the hydrophobic component being less than 0.08. The "hydrophobic component" is not limited to any compound with hydrophobicity including any type of oils, fatty acid glycerides and any other hydrophobic-type compounds (e.g., pages 15-16) and the "cyclosporine component" is not limited to cyclosporine but to any cyclosporin A derivatives and mixtures thereof having similar functionality to cyclosporine (e.g., pages 11-12). As stated earlier, the MPEP states that written description for a genus can be achieved by a representative number of species within a

broad generic. It is unquestionable claim 21 is a broad generic with respect all possible compounds encompassed by the claims. The possible structural variations are limitless to any class of polymer with any biomolecule. It must not be forgotten that the MPEP states that if a biomolecule is described only by a functional characteristic (e.g., hydrophobic), without any disclosed correlation between function and structure of the sequence, it is not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed compound (see MPEP 2163). Here, though the claims may recite some functional characteristics, the claims lack written description because there is no disclosure of a correlation between function and structure of the hydrophobic component beyond compounds disclosed in the examples in the specification (see, e.g., page 26). In addition, one of skill in the art would not know how to find and use all the instantly claimed derivatives of cyclosporine based on the guidance presented, since it basically provides a guidance in terms of functionality, but the functionality is disclosed, i.e., is the functionality of the cyclosporine derivatives that functionality depending on its physical, chemical, bonding, spectrometric, biological, antibiotic or any other properties? The recitation of a few chemical modifications is not sufficient in light of the examples presented (i.e., a single example with cyclosporin A and a comparison formulation). Moreover, the specification lack sufficient variety of species to reflect this variance in the genus since the specification provides examples only one single example of a composition encompassed by the instant claims: with cyclosporin A (as the cyclosporine compound) and castor oil (as the hydrophobic component) and does not encompass any other species from the very broad genus that is claimed in Claim 21. The description requirement of the patent statute requires a description of an invention, not an indication of a result that

one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 21-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 21 is rendered vague and indefinite because it is unclear as what kind of derivatives of cyclosporine. The instant disclosure teaches that the term derivatives refers to compounds having structures sufficiently similar to the cyclosporine so as to function in a manner substantially similar to, or substantially identical to cyclosporine. However, the metes and bounds for such derivatives are not clearly delineated since it is unclear what kind of specific functionality one would look at in order to find the instant derivatives of the molecule cyclosporine.

Claim 21 is also rendered vague and indefinite by the recitation of the term "hydrophobic component". The metes and bounds of this component and therefore of the compositions thereof are not well delineated. The instant disclosure teaches that "any suitable hydrophobic component may be employed", however it is not clear what a suitable hydrophobic component is, e.g., does it encompass any and all compounds that are predominantly hydrophobic such as, e.g., fullerenes, hydrophobic cellulose, polyethylene and so forth. In addition, does this term encompass a hydrophilic compound possessing a hydrophobic area? If so, what size of a molecule needs to be hydrophobic in order to make a compound suitably hydrophobic and therefore usable within the instantly claimed compositions.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 21-36 are rejected under 35 U.S.C. 103(a) as being obvious over Ding et al. (US 5,474,979 cited in the IDS of 12/27/04).

Ding et al. teach a composition for treating an eye of a human or animal comprising an emulsion comprising water, a hydrophobic component, and cyclosporine component in a therapeutically effective amount of less than 0.1% by weight, the weight ratio of the cyclosporine component (cyclosporin A, e.g., Example 1D and column 3, lines 30-37) to the hydrophobic component (castor oil, a vegetable oil) is 0.08. (see, e.g., Example 1D).

Ding et al. do not expressly teach the weight ratio of the cyclosporine component to the hydrophobic component being less than 0.08.

Ding et al. teach that the weight ratio of the cyclosporine component to the hydrophobic component may be preferably varied between 0.12 and 0.02 (see, e.g., column 3, lines 19-20).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the composition of Ding et al. (e.g., Example 1D) by increasing the amount of castor oil in order to reduce the ratio of the cyclosporine component to hydrophobic component from 0.08 to, e.g., 0.02 as taught by Ding et al. (see, e.g., column 3, lines 30-37). The skilled artisan would have been motivated to do so because the compositions encompass castor oil from 0.625% (as in Example 1E) or higher up to 5.0% (see, and Ding et al., claim 8). There would have been a reasonable expectation of success, given that compositions with a higher amount of castor oil are encompassed by the Ding et

al. claims (e.g., claim 8) and because optimizing the ratio of cyclosporine/hydrophobic components to below 0.08 was taught by Ding et al. (e.g., column 3, lines 30-37). Please note that the limitation of claim 22 (wherein the blood of the human has substantially no detectable concentration of the cyclosporine component after application of the composition) would necessarily exist in a composition with the instantly claimed limitations as taught above. The limitation of claim 23 and 24 is taught, e.g., in column 3, lines 30-37; the limitation of claim 25 is taught in column 3, lines 21-27 and 57-67; the limitation of claim 26-27 is taught by Example 1D, the limitation of claims 28-29 is taught in column 3, lines 5-14; the limitation of claim 30 is taught by Ding et al.'s claim 8; the limitation of claim 31 is taught in column 3, line 38-40; the limitations of claim 32-33 is taught in column 4, lines 12-19; the limitation of claim 34 is taught in column 3, lines 64-67 and column 4, lines 1-12; the limitations of claims 35-36 is taught in Example 1D.

Thus the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Claims 21-36 are rejected under 35 U.S.C. 103(a) as being obvious over Ding et al. (US 5,474,979 cited in the IDS of 12/27/04) in view of Ding et al. (Pharm. Res, 1997).

Ding et al. (US 5,474,979) teach a composition for treating an eye of a human or animal comprising an emulsion comprising water, a hydrophobic component, and cyclosporine component in a therapeutically effective amount of

less than 0.1% by weight, the weight ratio of the cyclosporine component (cyclosporin A, e.g., Example 1D and column 3, lines 30-37) to the hydrophobic component (castor oil, a vegetable oil) is 0.08. (see, e.g., Example 1D).

Ding et al. do not expressly teach the weight ratio of the cyclosporine component to the hydrophobic component being less than 0.08.

Ding et al. (Pharm Res, 1997) teach a composition for treating an eye of a huma comprising an emulsion comprising water, a hydrophobic component, and cyclosporine component the weight ration of the cyclosporine component (cyclosporine) to the hydrophobic component (castor oil, a vegetable oil) is 0.074. The composition is a pH-adjusted, oil-in water emulsion with a polysorbate 80 as primary emulsifier and a polyelectrolyte (such as Pemulen) (see entire abstract, e.g., lines 1-12).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the composition of Ding et al. in US '979 (e.g., Example 1D) by increasing the amount of castor oil in order to reduce the ratio of the cyclosporine component to hydrophobic component from 0.08 to, e.g., 0.074 as taught by Ding et al. in Pharm. Res. (see, e.g., column 3, lines 30-37). The skilled artisan would have been motivated to do so because Ding et al. (Pharm. Res.) teaches that the compositions with 0.074 cyclosporin/castor oil are stable at room temperature for at least 18 months. There would have been a reasonable expectation of success, given that compositions with a higher amount of castor oil are encompassed by the Ding et al. claims (e.g., claim 8) and because optimizing the ratio of cyclosporine/hydrophobic components to below

0.08 was taught by Ding et al. US '979 (e.g., column 3, lines 30-37) and Pharm. Res. (abstract, line 12). Thus the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made. Please note that the limitation of claim 22 (wherein the blood of the human has substantially no detectable concentration of the cyclosporine component after application of the composition) would necessarily exist in a composition with the instantly claimed limitations as taught above. The limitation of claim 23 and 24 is taught, e.g., in column 3, lines 30-37; the limitation of claim 25 is taught, e.g., in column 3, lines 21-27 and 57-67; the limitation of claim 26-27 is taught by Example 1D, the limitation of claims 28-29 is taught in column 3, lines 5-14; the limitation of claim 30 is taught by Ding et al.'s claim 8; the limitation of claim 31 is taught in column 3, line 38-40; the limitations of claim 32-33 is taught in column 4, lines 12-19; the limitation of claim 34 is taught in column 3, lines 64-67 and column 4, lines 1-12; the limitations of claims 35-36 is taught in Example 1D.

Double Patenting

Claims 21-36 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-8 of U.S. Patent No. 5,474,979. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instantly claimed invention and the invention claimed in US '979 are both drawn to a composition for treating an eye of a human or animal comprising an emulsion comprising water, a hydrophobic component, and cyclosporine component in a therapeutically

effective amount of less than 0.1% by weight, the weight ratio of the cyclosporine component to the hydrophobic component being less than 0.08. (See, e.g., Example 1D and column 3, lines 19-20 teaching that the weight ratio of cyclosporin A to castor oil is preferably between 0.12 and 0.02. In addition, see claim 8, encompassing species within the instantly claimed compositions).

Conclusion

No claim is allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marcela M. Cordero Garcia whose telephone number is (571) 272-2939. The examiner can normally be reached on M-Th 7:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia J. Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Marcela M Cordero Garcia, PhD
Patent Examiner
Art Unit 1654

MMCG 12/06

1/8/07
ANISH GUPTA
PRIMARY EXAMINER

Form PTO-1449 — INFORMATION DISCLOSURE CITATION IN AN APPLICATION (Use several sheets if necessary)

DEC 27 2006 — U.S. PATENT AND TRADEMARK OFFICE

Docket No.: D-3111	Application No.: 10/927,857
Applicant: Acheampong et al.	
Filing Date: August 27, 2004	Group Art Unit: 1636

U. S. PATENT DOCUMENTS

EXAMINER INITIAL	DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
MMCG	3,278,447	10/1966	McNicholas			
	4,388,307	06/1983	Cavanak			
	4,649,047	03/1987	Kaswan			
	4,814,323	3/1989	Andrieu			
	4,839,342	06/1989	Kaswan			
	4,970,076	11/1990	Horrobin			
	4,990,337	02/1991	Kurihara et al.			
	4,996,193	02/1991	Hewitt et al.			
	5,286,730	02/1994	Caufield et al.			
	5,286,731	02/1994	Caufield et al.			
	5,342,625	08/1994	Hauer et al.			
MMCG	5,411,952	05/1995	Kaswan			

FOREIGN PATENT DOCUMENTS

	DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

MMCG	AA	Acheampong et al,"Cyclosporine Distribution into the Conjunctiva, Cornea, Lacrimal Gland, and Systemic Blood Following Topical Dosing of Cyclosporine to Rabbit, Dog, and Human Eyes," *Lacrimal Gland, Tear Film, and Dry Eye Syndromes 2 - Basic Science and Clinical Relevance, Plenum Press, New York & London, ©1998, pp. 1001-1004.*
	AB	Acheampong et al, "Distribution of Cyclosporin A in Ocular Tissues After Topical Administration to Albino Rabbits and Beagle Dogs," *Curr Eye Res, Feb 1999, 18(2):91-103b.*
	AC	Angelov et al, "Preclinical Safety Studies of Cyclosporine Ophthalmic Emulsion," *Lacrimal Gland, Tear Film, and Dry Eye Syndromes 2 - Basic Science and Clinical Relevance, Plenum Press, New York & London, ©1998, pp. 991-5.*
	AD	Brewster et al, "Enhanced Delivery of Ganciclovir to the Brain through the Use of Redox Targeting," *Antimicrobial Agents and Chemotherapy, April 1994, 38(4):817-823.*
MMCG	AE	Brewster et al, "Intravenous and Oral Pharmacokinetic Evaluation of a 2-Hydroxypropyl-β-cyclodextrin-Based Formulation of Carbamazepine in the Dog: Comparison with Commercially Available Tablets and Suspensions, " *J Pharm Sci, March 1997, 86(3):335-9.*

EXAMINER	DATE CONSIDERED
/Marcela M Cordero Garcia/	12/26/2006

EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP § 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to the applicant.

Form PTO-1449	Docket No.: D-3111	Application No.: 10/927,857
INFORMATION DISCLOSURE CITATION IN AN APPLICATION (Use several sheets if necessary)	Applicant: Acheampong et al.	
	Filing Date: August 27, 2004	Group Art Unit: 1636

U. S. PATENT DOCUMENTS

EXAMINER INITIAL	DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
MMCG	5,474,979	12/1995	Ding et al.			
	5,504,068	04/1996	Komiya et al.			
	5,540,931	07/1996	Hewitt et al.			
	5,719,123	02/1998	Morley et al.			
	5,739,105	04/1998	Kim et al.			
	5,807,820	09/1998	Elias			
	5,843,452	12/1998	Wiedmann et al.			
	5,843,891	12/1998	Sherman			
	5,858,401	01/1999	Bhalani et al.			
	5,866,159	02/1999	Hauer et al.			
	5,891,846	04/1999	Ishida et al.			
MMCG	5,916,589	06/1999	Hauer et al.			

FOREIGN PATENT DOCUMENTS

	DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

MMCG	AA	Brewster et al, "Preparation, Characterization, and Anesthetic Properties of 2-Hydroxypropyl-β-cyclodextrin Complexes of Pregnanolone and Pregnenolone in Rat and Mouse," *J Pharm Sci, October 1995, 84(10):1154-9.*
	AB	Sall et al, "Two Multicenter, Randomized Studies of the Efficacy and Safety of Cyclosporine Ophthalmic Emulsion in Moderate to Severe Dry Eye Disease. CsA Phase 3 Study Group," *Ophthalmology, April 2000, 107(4):631-9.*
	AC	Small et al,"Blood Concentrations of Cyclosporin A During Long-Term Treatment With Cyclosporin A Ophthalmic Emulsions in Patients With Moderate to Severe Dry Eye Disease," *J Ocul Pharmacol Ther, Oct 2002, 18(5):411-8.*
MMCG	AD	Stevenson et al., "Efficacy and Safety of Cyclosporin A Ophthalmic Emulsion in the Treatment of Moderate-to-severe Dry Eye Disease," *Ophthalmology, May 2000, 107(5):967-74.*
	AE	
	AF	

EXAMINER	DATE CONSIDERED
/Marcela M Cordero Garcia/	12/26/2006

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U. S. PATENT DOCUMENTS

EXAMINER INITIAL	DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
MMCG	5,951,971	09/1999	Kawashima et al.			
	5,962,017	10/1999	Hauer et al.			
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	5,998,365	12/1999	Sherman			
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	6,046,163	04/2000	Stuchlik et al.			
	6,159,933	12/2000	Sherman			
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MMCG	6,323,204	11/2001	Burke et al.			

FOREIGN PATENT DOCUMENTS

	DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION	

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

	AA	
	AB	
	AC	
	AD	
	AE	
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	AG	
	AH	

EXAMINER	DATE CONSIDERED
/Marcela M Cordero Garcia/	12/26/2006

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Form PTO-1449

INFORMATION DISCLOSURE CITATION IN AN APPLICATION
(Use several sheets if necessary)

Docket No.: D-3111	Application No.: 10/927,857
Applicant: Acheampong et al.	
Filing Date: August 27, 2004	Group Art Unit: 1636

U. S. PATENT DOCUMENTS

EXAMINER INITIAL	DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
MMCG	6,346,511	02/2002	Singh et al.			
	6,350,442	02/2002	Garst			
	6,413,547	07/2002	Bennett et al.			
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	2003/0021816	01/2003	Kang et al.			
	2003/0044452	03/2003	Ueno			
	2003/0060402	03/2003	Cavanak et al.			
	2003/0087813	05/2003	Or et al			
	2003/0104992	06/2003	Or et al			
	2003/0109425	06/2003	Or et al			
	2003/0109426	06/2003	Or et al.			
MMCG	2003/0143250	07/2003	Hauer et al.			

FOREIGN PATENT DOCUMENTS

	DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

	AA	
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Form PTO-1449

INFORMATION DISCLOSURE CITATION IN AN APPLICATION

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Applicant: Acheampong et al.	
Filing Date: August 27, 2004	Group Art Unit: 1636

U. S. PATENT DOCUMENTS

EXAMINER INITIAL	DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
MMCG	2001/0036449 A1	11/2001	Garst			

FOREIGN PATENT DOCUMENTS

	DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

	AA	
	AB	
	AC	
	AD	
	AE	
	AF	
	AG	
	AH	

EXAMINER	DATE CONSIDERED
/Marcela M Cordero Garcia/	12/26/2006

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U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE
FORM PTO-1449

LIST OF ART CITED BY APPLICANT

ATTY. DOCKET: D-3111	SERIAL NO.: 10/927,857
APPLICANT: Acheampong et al	TITLE: Methods of Providing Therapeutic Effects Using Cyclosporine Components
FILING DATE: August 27, 2004	GROUP: 1654

U.S. PATENT DOCUMENTS

*EXAMINER INITIAL		DOCUMENT NO.	DATE	NAME	CLASS	SUB-CLASS	FILING DATE (if applicable)
MMCG	AA	2003/0055028 A1	03/2003	Stergiopoulos et al.			
	AB	5,368,854	11/1994	Rennick			
	AC	4,614,736	09/1986	Delevallee et al.			
MMCG	AD						

FOREIGN PATENT DOCUMENTS

		DOCUMENT NO.	DATE	COUNTRY	CLASS	SUB-CLASS	TRANSLATION (yes/no)
MMCG	BA	DE 19810655	09/1999	Germany			
	BB	WO 03/030834	04/2003	PCT			
MMCG	BC						

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(Including Author, Title, Date, Pertinent Pages, etc.)

MMCG	CA	T.A. Winter, et al. Scand J Gastroenterol. (1993), 28(8), pages 701-704
	CB	M. Schwab and U. Klotz, Clin. Pharmacokinet. (2001), 40(10), pages 723-751
	CC	J. Rudinger. In: Peptide Hormones, JA Parsons, Ed. (1976) pages 1-7
	CD	D.E. Smilek, et al. Proc. Natl. Acad. Sci. USA (1991) 88, pages 9633-9637
	CE	MBanić, et al. Dig. Dis. Sci. (2002), 47(6), pages 1362-1368
	CF	The Online Medical Dictionary, accessed 7/7/05 and 7/13/05. 6 pages
	CG	W.J. Sandborn, et al. Am. J. Gastroenterol. (1993), 88(5), pages 640-645
	CH	D.H. Present. Am. J. Gastroenterol. (1993) 88(5), pages 627-630
	CI	S. Ardizzone and G.B. Porro. Drugs. (1998), 55(4), pages 519-542
	CJ	W.J. Sandborn, et al. Gastroenterology. (1994), 106(6), pages 1429-1435
	CK	K. Tsubota, et al. Invest. Ophthalmol. Vis. Sci. (1998), 39(9), pages 1551-1559
	CL	A.A. Drosos and N.M. Moutsopoulos. Ter. Arkh. (1998), 60(4), pages 77-80
	CM	A.A. Drosos, et al. Scand. J. Rheumatology (1986) Suppl. 61, pages 246-249
	CN	W.A. van der Reijden, et al. Ann. Rheum. Dis. (1999), 58, pages 465-473
	CO	N.A. Robinson and D. Wray. Australian Dental Journal (2003), 48(4), pages 206-211
	CP	A.M. Pedersen and B. Nauntofte. Expert Opin Pharmacother (2001), 2(9), pages 1415-1436
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EXAMINER /Marcela M Cordero Garcia/ DATE CONSIDERED 12/26/2006

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE
FORM PTO-1449

LIST OF ART CITED BY APPLICANT

ATTY. DOCKET: D-3111	SERIAL NO.: 10/927,857
APPLICANT: Acheampong et al	TITLE: Methods of Providing Therapeutic Effects Using Cyclosporine Components
FILING DATE: August 27, 2004	GROUP: 1654

MMCG	CR	Gunduz et al, "Topical Cyclosporin Treatment of Keratoconjunctivitis Sicca in Se condary Sjogren's Syndrome", Acta Ophthalmologica, Vol. 72, No. 4, 1994, pp 438-442, XP009063039
	CS	Phillips et al, "Cyclosporine Has A Direct Effect on the Differentiation of a Mucin-Secreting Cell Line", Journal of Cellular Physiology, Vol. 184, No. 3, Sept. 2000, pp 400-408, XP009063023
	CT	Gipson et al, "Character of Ocular Surface Mucins and Their Alteration in Dry Eye Disease", The Ocular Surface, Vol. 2, No. 2, April 2004, pp 131-148, XP001208377
	CU	Akpek et al, "A Randomized Trial of Topical Cyclosporin 0.05% in Topical Steroid-Resistant Atopic Keratoconjunctivitis", Ophthalmology, Vol. III, No. 3, March 2004, pp 476-482, XP00906021
	CV	Eisen et al, "Topical Cyclosporine for Oral Mucosal Disorders", Journal of the American Academy of Dermatology, Vol. 23, No. 6, Part 2, Dec. 1990, pp 1259-1264, XP009063043
	CW	Epstein et al, "Topical Cyclosporine in a Bioadhesive for Treatment of Oral Lichenoid Mucosal Reactions. An Open Label Clinical Trial", Oral Surgery, Oral Medicine..., Vol. 82, No. 5, 1996, pp 532-536, XP009063045
	CX	Erdmann et al, "Pemphigus Vulgaris Der Mund-Und Kehlopfschleimhaut Pemphigus Vulagris of the Oral Mucosa and the Larynx", H+G Zeitschrift Fuer Hautkrankheiten, Vol. 72. No. 4, 1997, pp 283-296, XP009063042
	CY	Brinkmeier et al, "Pyodermatitis-Pyostomatitis Vegetans: A Clinical Course of Two Decades with Response to Cyclosporine and Low-Dose Prednisolone", Acta Dermato-Venereologica, Vol. 81, No. 2, May 2001, pp 134-136
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EXAMINER /Marcela M Cordero Garcia/ DATE CONSIDERED 12/26/2006

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Notice of References Cited	Application/Control No. 10/927,857	Applicant(s)/Patent Under Reexamination ACHEAMPONG ET AL.	
	Examiner Marcela M. Cordero Garcia	Art Unit 1654	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-6,872,705	03-2005	Lyons, Robert T.	514/13
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Kuwano et al. Cyclosporine A Formulation Affects Its Ocular Distribution in Rabbits. Pharm Res January 2002. Vol. 19 No. 1, pages 108-111
	V	Ding et al. Cyclosporine Ophthalmic o/w Emulsion: Formulation and Emulsion Characterization. Pharmaceutical Resaerch 1997. 14(11, suppl):S41 (2 pages).
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

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Bib Data Sheet

CONFIRMATION NO. 2409

SERIAL NUMBER	FILING OR 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
10/927,857	08/27/2004 RULE	514	1654	D-3111

APPLICANTS

Andrew Acheampong, Irvine, CA; MMC6
Diane Tang-Liu, Newport Beach, CA; MMC6
James N. Chang, Newport Beach, CA; MMC6
David F. Power, Trabuco Canyon, CA; MMC6

**** CONTINUING DATA ***************************

This appln claims benefit of 60/503,137 09/15/2003 MMC6

**** FOREIGN APPLICATIONS *********************

-NONE-

IF REQUIRED, FOREIGN FILING LICENSE GRANTED
** 10/21/2004

Foreign Priority claimed	STATE OR COUNTRY	SHEETS DRAWING	TOTAL CLAIMS	INDEPENDENT CLAIMS
☐ yes ☑ no	CA	0	36	2

35 USC 119 (a-d) conditions met: ☐ yes ☑ no ☐ Met after Allowance

Verified and Acknowledged: Examiner's Signature MMC6 Initials

ADDRESS
33197

TITLE

Methods of providing therapeutic effects using cyclosporin components

FILING FEE RECEIVED	FEES: Authority has been given in Paper	
1058	No. _____ to charge/credit DEPOSIT ACCOUNT No. _____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

Search Notes	Application/Control No.	Applicant(s)/Patent under Reexamination	
	10/927,857	ACHEAMPONG ET AL.	
	Examiner	Art Unit	
	Marcela M. Cordero Garcia	1654	

SEARCHED			
Class	Subclass	Date	Examiner
none	none		

INTERFERENCE SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES (INCLUDING SEARCH STRATEGY)		
	DATE	EXMR
STN searched by STIC (attached)	10/2/2006	MMCG
EAST searched (attached)	12/27/2006	MMCG
also ran PALM inventor search	12/27/2006	MMCG

TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

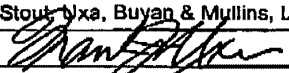
Application Number	11/927,857
Filing Date	8/27/2004
First Named Inventor	Acheampong
Group Art Unit	1654
Examiner Name	Cordero Garcia, M.M.
Total Number of Pages in This Submission: 20	Attorney Docket Number: D-3111

ENCLOSURES (*check all that apply*)

- ☐ Fee Transmittal Form *(in duplicate)*
- ☐ Fee Attached
- ☒ Amendment/Reply
- ☐ After Final
- ☐ Affidavits/declaration(s)
- ☐ Extension of Time Request
- ☐ Express Abandonment Request
- ☐ Information Disclosure Statement
- ☐ Certified Copy of Priority Document(s)
- ☐ Response to Missing Parts/ Incomplete Application
- ☐ Response to Missing Parts under 37 CFR 1.52 or 1.53
- ☐ Drawing(s)
- ☐ Licensing-related Papers
- ☐ Petition
- ☐ Petition to Convert to a Provisional Application
- ☐ Power of Attorney, Revocation Change of Correspondence Address
- ☐ Terminal Disclaimer
- ☐ Request for Refund
- ☐ CD, Number of CD(s) ____
- ☐ Landscape Table on CD
- ☐ After Allowance Communication to TC
- ☐ Appeal Communication to Board of Appeals and Interferences
- ☐ Appeal Communication to TC *(Appeal Notice, Brief, Reply Brief)*
- ☐ Proprietary Information
- ☐ Status Letter
- ☐ Other Enclosure(s) *(please identify below)*

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	Stout, Uxa, Buyan & Mullins, LLP		
Signature			
Printed Name	Frank J. Uxa		
Date	3/23/07	Reg. No.	25,612

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Typed or printed name	Alicia Curran	Date	3/27/07

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FEE TRANSMITTAL for FY 2005

Patent fees are subject to annual revision.

☐ Application claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($)

Complete if Known	
Application Number	11/927,857
Filing Date	8/27/2004
First Named Inventor	Acheampong
Examiner Name	Cordero Garcia, M.M.
Art Unit	1654
Attorney Docket No.	D-3111

METHOD OF PAYMENT *(check all that apply)*

☐ Check ☐ Credit Card ☐ Money Order ☐ None ☐ Other (please identify): ____

☒ Deposit Account Deposit Account Number 01-0885 Deposit Account Name Frank J. Uxa

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FEE CALCULATION

1. BASIC FILING, SEARCH, AND EXAMINATION FEES

	FILING FEES		SEARCH FEES		EXAMINATION FEES		
		Small Entity		Small Entity		Small Entity	
Application Type	Fee ($)	Fee ($)	Fee ($)	Fee ($)	Fee ($)	Fee ($)	Fees Paid ($)
Utility	300	150	500	250	200	100	
Design	200	100	100	50	130	65	
Plant	200	100	300	150	160	80	
Reissue	300	150	500	250	600	300	
Provisional	200	100	0	0	0	0	

Subtotal (1) 0

2. EXCESS CLAIM FEES

Fee Description	Fee ($)	Small Entity Fee ($)
Each claim over 20 or, for Reissues, each claim over 20 and more than in the original patent	50	25
Each independent claim over 3 or, for Reissues, each independent claim more than in the original patent	200	100
Multiple Dependent Claims	360	180

Total Claims	Extra Claims	Fee ($)	Fee Paid ($)
____ -20 or HP =	____ x	____	____

HP = highest number of total claims paid for, if greater than 20

Indep. Claims	Extra Claims	Fee ($)	Fee Paid ($)
____ -3 or HP =	____ x	____	____

HP = highest number of independent claims paid for, if greater than 3

Multiple Dependent Claims	
Fee ($)	Fee Paid ($)
____	____

Subtotal (2) 0

3. APPLICATION SIZE FEE

If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

Total Sheets	Extra Sheets	Number of each additional 50 or fraction thereof	Fee ($)	Fee Paid ($)
____ -100 =	____ /50=	____ (round up to a whole number)	x ____	= ____

Subtotal (3) 0

4. OTHER FEE(S) Fee Paid ($)

- ☐ Surcharge - Late filing fee or oath/declaration: $130 fee ($65 small entity discount)
- ☐ Non-English Specification: $130 fee (no small entity discount)
- ☐ 1-month extension of time: $120 fee ($60 small entity discount)
- ☐ 2-month extension of time: $450 fee ($225 small entity discount)
- ☐ 3-month extension of time: $1020 fee ($510 small entity discount)
- ☐ 4-month extension of time: $1590 fee ($795 small entity discount)
- ☐ 5-month extension of time: $2160 fee ($1080 small entity discount)
- ☐ Information Disclosure Statement Fee: $180 fee (no small entity discount)
- ☐ Notice of Appeal: $500 fee ($250 small entity discount)
- ☐ Filing a Brief in Support of Appeal: $500 fee ($250 small entity discount)
- ☐ Request for Oral Hearing: $1000 fee ($500 small entity discount)
- ☐ Utility Issue Fee: $1400 fee ($700 small entity discount)
- ☐ Recording each patent assignment per property (times number of properties): $40 fee (no small entity fee discount)
- ☐ Request for Continued Examination: $790 fee ($395 small entity discount)
- ☐ Other: ____

Subtotal (4) 0

SUBMITTED BY

Name (Print/Type)	Frank J. Uxa	Registration No. (Attorney/Agent)	25,612	Telephone	949-450-1750
Signature	Frank J. Uxa			Date	3/23/07

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No. : 10/927,857 Confirmation No. 2409
Applicant : ACHEAMPONG ET AL.
Filed : August 27, 2004
Title : METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS

TC/A.U. : 1654
Examiner : Cordero Garcia, Marcela M.

Docket No. : D-3111
Customer No. : 33197

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Date: March 27, 2007
Name: Alicia Curran

Mail Stop AMENDMENT
Commissioner for Patents
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Alexandria, VA 22313-1450

AMENDMENT A

Sir:

In response to the Office Action mailed January 17, 2007, please amend the above-identified application as follows:

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 7 of this paper.

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims

1. (Withdrawn) A method of treating an eye of a human or animal comprising:

administering to an eye of a human or animal a composition in the form of an emulsion comprising water, a hydrophobic component and a cyclosporin component in a therapeutically effective amount of less than 0.1% by weight of the composition, the weight ratio of the cyclosporin component to the hydrophobic component is less than 0.08.

2. (Withdrawn) The method of claim 1 wherein the administering step is effective in treating a condition selected from the group consisting of dry eye syndrome, phacoanaphylactic endophthalmitis, uveitis, vernal conjunctivitis, atopic keratoconjunctivitis and corneal graft rejection.

3. (Withdrawn) The method of claim 1 wherein the administering step is effective in treating dry eye syndrome.

4. (Withdrawn) The method of claim 1 wherein the blood of the human or animal has substantially no detectable concentration of the cyclosporin component.

5. (Withdrawn) The method of claim 1 wherein the blood of the human or animal has substantially no detectable concentration of the cyclosporin component as measured using a

validated liquid chromatography/mass spectrometry-mass spectrometry analytical method.

6. (Withdrawn) The method of claim 1 wherein the blood of the human or animal has a concentration of the cyclosporin component of 0.1 ng/ml or less.

7. (Withdrawn) The method of claim 1 wherein the cyclosporin component comprises a material selected from cyclosporin A, derivatives of cyclosporin A and mixtures thereof.

8. (Withdrawn) The method of claim 1 wherein the cyclosporin component comprises cyclosporin A.

9. (Withdrawn) The method of claim 1 wherein the cyclosporin component is solubilized in the hydrophobic component present in the composition.

10. (Withdrawn) The method of claim 1 wherein the hydrophobic component is present in the composition in an amount greater than 0.625% by weight of the composition.

11. (Withdrawn) The method of claim 1 wherein the hydrophobic component comprises an oily material.

12. (Withdrawn) The method of claim 1 wherein the hydrophobic component comprises an ingredient selected from the group consisting of vegetable oils, animal oils, mineral oils, synthetic oils and mixtures thereof.

13. (Withdrawn) The method of claim 1 wherein the hydrophobic component comprises castor oil.

14. (Withdrawn) The method of claim 1 wherein the administering step comprises topically administering the composition to the eye of the human.

15. (Withdrawn) The method of claim 1 wherein the composition comprises an effective amount of an emulsifier component.

16. (Withdrawn) The method of claim 1 wherein the composition comprises an effective amount of a tonicity component.

17. (Withdrawn) The method of claim 1 wherein the composition comprises an effective amount of an organic tonicity component.

18. (Withdrawn) The method of claim 1 wherein the composition comprises a polyelectrolyte component in an amount effective in stabilizing the composition.

19. (Withdrawn) The method of claim 1 wherein the composition has a pH in the range of about 7.0 to about 8.0.

20. (Withdrawn) The method of claim 1 wherein the composition has a pH in the range of about 7.2 to about 7.6.

21. (Currently Amended) A composition for treating an eye of a human or animal comprising an emulsion comprising water,

~~a hydrophobic component~~ castor oil, and ~~a cyclosporin component~~ cyclosporin A in a therapeutically effective amount of less than 0.1% by weight, the weight ratio of the ~~cyclosporin component~~ cyclosporin A to the ~~hydrophobic component~~ castor oil being less than 0.08.

22. (Currently Amended) The composition of claim 21 having a make-up so that when the composition is administered to an eye of a human in an effective amount in treating dry eye syndrome, the blood of the human has substantially no detectable concentration of the ~~cyclosporin component~~ cyclosporin A.

23. (Canceled)

24. (Canceled)

25. (Original) The composition of claim 21 in the form of an emulsion.

26. (Currently Amended) The composition of claim 21 wherein the ~~hydrophobic component~~ castor oil is present in an amount greater than 0.625% by weight of the composition.

27. (Canceled)

28. (Canceled)

29. (Canceled)

30. (Currently Amended) The composition of claim 21 ~~wherein the administering step comprises topically administering~~

~~the composition to the eye of the human~~ having a make-up so that when the composition is topically administered to an eye of a human in an effective amount in treating dry eye syndrome, the blood of the human has substantially no detectable concentration of the cyclosporin A.

31. (Original) The composition of claim 21 wherein the composition comprises an effective amount of an emulsifier component.

32. (Original) The composition of claim 21 wherein the composition comprises an effective amount of a tonicity component.

33. (Original) The composition of claim 21 wherein the composition comprises an effective amount of an organic tonicity component.

34. (Original) The composition of claim 21 wherein the composition comprises a polyelectrolytic component in an amount effective in stabilizing the composition.

35. (Original) The composition of claim 21 wherein the composition includes water and has a pH in the range of about 7.0 to about 8.0.

36. (Original) The composition of claim 21 wherein the composition includes water and has a pH in the range of about 7.2 to about 7.6.

37. (New) The composition of claim 21 which includes 1.25% by weight of castor oil.

38. (New) The composition of claim 21 which includes 0.05% by weight of cyclosporin A.

39. (New) The composition of claim 38 which includes 1.25% by weight of castor oil.

40. (New) A composition for treating an eye of a human or animal comprising an emulsion comprising water, 1.25% by weight of castor oil and 0.05% by weight of cyclosporin A, the weight ratio of the cyclosporin A to the castor oil being 0.04.

Remarks

The above-identified application has been carefully reviewed in light of the Office Action mailed January 17, 2007.

Without conceding the correctness of any of the Examiner's rejections, applicant has amended certain of the present claims to facilitate prosecution of the above-identified application to an early allowance. Applicant expressly reserves the right to seek patent protection for the original claims and for any other claims supported by the above-identified application in one or more related applications.

Specifically, claim 21 has been amended to refer to castor oil rather than a hydrophobic component; and to cyclosporin A instead of a cyclosporin component. Claims 22 and 26 have been amended to be consistent with the amendments to claim 21. Claim 30 has been amended to read more clearly. Claims 23, 24 and 27-29 have been canceled in view of the amendments to claim 21. New claims 37-40 have been added and are directed to embodiments for which patent protection is sought.

Each of the amendments and the new claims is fully supported by the present specification and the claims as originally filed.

Claims 1-20 have been withdrawn as being directed to a non-elected invention. Applicant hereby requests rejoinder of these method of use claims when the composition claims are found to be allowable.

Claims 21-36 have been rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. Claims 21-36 have been rejected under 35 U.S.C. 112, second paragraph.

In view of the above-noted amendments, applicant submits that the present claims 21, 22, 25, 26 and 30-40 satisfy the

requirements of 35 U.S.C. 112, first and second paragraphs. Therefore, applicant respectfully requests that both these rejections under 35 U.S.C. 112 be withdrawn.

Claims 21-36 have been rejected under 35 U.S.C. 103(a) as being obvious over Ding et al U.S. Patent No. 5,474,979 (hereinafter Ding et al Patent). Claims 21-36 have been rejected under 35 U.S.C. 103(a) as being obvious over Ding et al Patent in view of Ding et al (Pharm. Res., 1997) (hereinafter Ding et al Publication). Applicant traverses each of these rejections as it pertains to the present claims 21, 22, 25, 26 and 30-40.

Independent claim 21 is directed to a composition for treating an eye of a human or animal. The composition comprises an emulsion comprising castor oil and cyclosporin A in a therapeutically effective amount of less than 0.1% by weight. In addition, as recited in claim 21, the weight ratio of the cyclosporin A to the castor oil is less than 0.08.

New independent claim 40 is directed to a composition for treating an eye of a human or animal comprising an emulsion comprising water, 1.25% by weight of castor oil and 0.05% by weight of cyclosporin A, and the weight ratio of the cyclosporin to the castor oil is 0.04.

The present compositions provide substantial advantages. For example, as illustrated in Example 1 of the present specification, Composition II, a composition in accordance with the present invention, and Composition I, a composition having a higher concentration of cyclosporin A, are tested in use for the

treatment of dry eye disease. In relevant part, the make-ups of these two compositions are as follows[1]:

	Composition I wt%	Composition II wt%
Cyclosporin A	0.1	0.05
Castor Oil	1.25	1.25
Weight Ratio of Cyclosporin A to Castor Oil	0.08	0.04

[1]Each composition includes the same weight percent of Polysorbate 80, Premulen®, and Glycerin; and includes sodium hydroxide and water, and has a pH of 7.2-7.6.

Each of these compositions are employed in a Phase 3, double-masked, randomized, parallel group study for the treatment of dry eye disease.

The results of this study indicate that Composition II, in accordance with the present invention, which has a reduced concentration of cyclosporin A and a cyclosporin A to castor oil ratio of less than 0.08, provides overall efficacy in treating dry eye disease substantially equal to that of Composition I. This is surprising for a number of reasons. For example, the reduced concentration of cyclosporin A in Composition II would have been expected to result in reduced overall efficacy in treating dry eye disease.

Using relatively large amounts of castor oil, with reduced amounts of cyclosporin component, as in Composition II, is believed to take advantage of the benefits, for example the ocular lubrication benefits, of castor oil, as well as the presence of ricinoleic acid in the castor oil, to at least

assist in treating dry eye syndrome in combination with cyclosporin A.

In addition, it is found that the high concentration of castor oil relative to cyclosporin component, as in Composition II, provides the advantage of more quickly or rapidly (for example, relative to a composition which includes only 50% as much castor oil) breaking down or resolving the emulsion in the eye; for example, as measured by slit-lamp techniques to monitor the composition in the eye for phase separation. Such rapid break down of the emulsion in the eye reduces vision distortion as the result of the presence of the emulsion in the eye, as well as facilitating the therapeutic effectiveness of the composition in treating dry eye disease.

Using reduced amounts of cyclosporin A, as in Composition II, to achieve therapeutic effectiveness mitigates even further against undesirable side effects and potential drug interactions. Prescribing physicians can prescribe Composition II to more patients and/or with fewer restrictions and/or with reduced risk of the occurrence of adverse events, e.g., side effects, drug interactions and the like, relative to Composition I.

Ding et al Patent discloses a composition comprising cyclosporin A in admixture with an emulsifying amount of castor oil and polysorbate 80. Ding et al Patent discloses that preferably the composition has a weight ratio of castor oil to polysorbate 80 between about 0.3 and about 30 and a weight ratio of cyclosporin A to castor oil of below 0.16. Ding et al Patent discloses that more preferably the weight ratio of castor oil to polysorbate 80 is between 0.5 and 12.5, and the weight ratio of cyclosporin to castor oil is between 0.12 and 0.02. See Ding et al Patent, column 3, lines 15-20. In Example 1, Ding et al

Patent discloses a series of five (5) cyclosporin A-containing emulsions. In relevant part, the make-ups of these five (5) emulsions are as follows[(2)]:

	Composition, wt%				
	A	B	C	D	E
Cyclosporin A	0.40%	0.20%	0.20%	0.10%	0.05%
Castor Oil	5.00%	5.00%	2.50%	1.25%	0.625%
Weight Ratio of Cyclosporin A to Castor Oil	0.08	0.04	0.08	0.08	0.08

[(2)]Each composition includes the same weight percent of Polysorbate 80, Premulen®, and Glycerin; and includes sodium hydroxide and water, and has a pH of 7.2-7.6.

Each of the above-noted emulsions of Ding et al Patent has a weight ratio of cyclosporin A to castor oil of 0.08, except for Composition B, which includes a relatively large amount of cyclosporin A (0.2%) outside the range of cyclosporin A concentrations recited in the present claims, and has a cyclosporin A to castor oil weight ratio of 0.04. Ding et al Patent placed no significance on Composition B relative to Compositions A, C and D of Example 1. Moreover, Composition D, specifically cited by the Examiner, includes more cyclosporin A than in the presently claimed compositions, as well as having a weight ratio of cyclosporin A to castor oil outside the range recited in the present claims.

Claim 8 of Ding et al Patent discloses compositions having make ups similar to those of Example 1 of Ding et al Patent.

The Examiner's citation of Ding et al Patent column 3, lines 30-37 is not understood.

Ding et al Patent does not specifically disclose, teach or suggest the present invention. For example, Ding et al Patent does not specifically disclose, teach or even suggest a composition comprising an emulsion comprising water, castor oil and cyclosporin A in an amount of less than 0.1% by weight, for example, 0.05% by weight, with the weight ratio of cyclosporin A to castor oil being less than 0.08 and/or the castor oil being 1.25% by weight of the composition, as recited in the present claims. Moreover, Ding et al Patent does not specifically disclose, teach or even suggest the substantial, even surprising advantages of the present compositions, for example, in terms of efficacy in treating dry eye disease, more rapid breaking down or resolving the emulsion in the eye and mitigation against undesirable side effects and potential drug interactions, obtained in accordance with the present invention.

Contrary to the Examiner's contention, Ding et al Patent does not teach or even suggest optimizing the weight ratio of cyclosporin A/castor oil to below 0.08. In fact, since four of the five compositions tested in Example 1 of Ding et al Patent have such a weight ratio of 0.08, Ding et al Patent appears to consider 0.08 the optimum weight ratio of cyclosporin A to castor oil. As noted above, Ding et al Patent does not specifically distinguish between compositions having relatively wide variations in cyclosporin A concentrations and castor oil concentrations, such as Compositions A, B, C and D of Example 1 of this reference. Thus, applicant submits that Ding et al Patent actually teaches away from the presently claimed compositions and the substantial, surprising advantages of such compositions obtained by applicant.

Simply put, Ding et al Patent provides no motivation nor any other proper basis to one of ordinary skill in the art to extend the teachings of Ding et al Patent to make obvious the present compositions having the compositional parameters recited in the present claims, let alone obtaining the substantial, surprising advantages of the present compositions obtained by applicant.

Therefore, applicant submits that claims 21, 22, 25, 26 and 30-40 are unobvious from and patentable over Ding et al Patent under 35 U.S.C. 103(b).

The Examiner relies on Ding et al Publication to supplement the teachings of Ding et al Patent.

The disclosure and deficiencies of Ding et al Patent are discussed above and are resubmitted here.

Ding et al Publication discloses a stable, pH-adjusted, oil-in-water emulsion using castor oil as the internal phase to solubilize cyclosporine, polysorbate 80 as the primary emulsifier and a polyelectrolyte as a stabilizer. Ding et al Publication discloses that the concentration of cyclosporin in the oil globule is formulated at a level of 7.4% w/w, meaning that the weight ratio of the cyclosporine to castor oil is 0.074/0.926 or 0.08.

Ding et al Publication does not disclose, teach or suggest the present invention. For example, Ding et al Publication does not disclose a composition with any specific cyclosporin A concentration, let alone a composition having a cyclosporin A concentration of less than 0.1% by weight, for example, 0.05% by weight, as recited in the present claims. In addition, Ding et al Publication does not disclose, teach or even suggest a composition in which the weight ratio of cyclosporin A to castor oil is less than 0.08 and/or the castor oil is 1.25% by weight

of the composition, as recited in the present claims. By disclosing only a composition having a weight ratio of cyclosporin to castor oil of 0.08, Ding et al Publication reinforces the apparent teaching of Ding et al Patent that the optimum weight ratio of cyclosporin A to castor oil is 0.08. To a large extent, Ding et al Publication actually teaches away from the present claims.

The combination of Ding et al Patent and Ding et al Publication does not disclose, teach or suggest the present invention. For example, this combination of references does not disclose, teach or suggest compositions comprising less than 0.1% by weight, for example 0.05% by weight, of cyclosporin A and castor oil in which the weight ratio of cyclosporin A to castor oil is less than 0.08 and/or the castor oil is 1.25% by weight of the composition, let alone the substantial and even surprising advantages of such compositions obtained by applicant.

As noted above, both Ding et al Patent and Ding et al Publication actually teach away from the present invention. These references provide no motivation nor any other proper basis to one of ordinary skill in the art to make obvious the compositions recited in the present invention, let alone obtain the substantial surprising advantages of the present compositions obtained by applicant. Simply put, Ding et al Publication does not supply the deficiencies apparent in the teachings of Ding et al Publication with respect to the present claims.

In view of the above, applicant submits that claims 21, 22, 25, 26 and 30-40 are unobvious from and patentable over Ding et al Patent in view of Ding et al Publication under 35 U.S.C. 103(a).

Claims 21-36 have been rejected on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 1-8 of Ding et al Patent. Applicant traverses these rejections as it pertains to claims 21, 22, 25, 26 and 30-40.

For substantially the same reasons, as stated above, that the present claims are patentable over Ding et al Patent, so too are the present claims patentable over claims 1-8 of Ding et al Patent.

For example, none of claims 1-8 of Ding et al Patent specifically disclose, teach or suggest the present invention. To illustrate, none of claims 1-8 of Ding et al Patent specifically disclose, teach or even suggest a composition comprising less than 0.1% by weight, for example, 0.05% by weight, of cyclosporin A, and castor oil in which the weight ratio of cyclosporin A to castor oil is less than 0.08 and/or the castor oil is 1.25% by weight of the composition, as recited in the present claims, let alone the substantial, surprising advantages of such compositions, discussed above, obtained by applicant.

The Examiner states that claim 8 of Ding et al Patent encompasses species within the instantly claimed compositions. Applicant disagrees.

Claim 8 does not specifically disclose compositions including less than 0.1% by weight of cyclosporin A in which the weight ratio of cyclosporin A to castor oil is less than 0.08, as in the presently claimed compositions. Moreover, the relatively wide ranges of cyclosporin A and castor oil concentrations recited in claim 8 of Ding et al Patent actually lead away from the present claims, and the substantial and

surprising advantages of the presently claimed compositions obtained by applicant.

To a large extent, the disclosure of claim 8 of Ding et al Patent is similar to that of Example 1 of Ding et al Patent, which has been discussed previously. Claim 8, like Example 1, of Ding et al Patent does not distinguish one composition from the other compositions. Neither does column 3, lines 19-20 of Ding et al Patent, cited by the Examiner. As noted previously, Ding et al Patent does not teach optimizing the weight ratio of cyclosporin A to castor oil to below 0.08. Rather, since four of the five compositions tested in Example 1 of Ding et al Patent have such a weight ratio of 0.08, Ding et al Patent appears to consider 0.08 the optimum weight ratio of cyclosporin A to castor oil.

None of the Compositions A, B, C, D and E of Ding et al Patent specifically disclose, teach or suggest the presently claimed compositions. As noted previously, Ding et al Patent does not distinguish the Compositions of Example 1, one from the other. In effect, the claims, including claim 8, of Ding et al Patent discloses that compositions with relatively wide ranges of concentrations of cyclosporin A and castor oil have similar properties. Such teaching actually leads away from the presently claimed compositions and the substantial, surprising advantages, discussed previously, obtained by applicant relative to compositions encompassed by the claims of Ding et al Patent.

In view of the above, applicant submits that claims 21, 22, 25, 26 and 30-40 are patentable over the claims of Ding et al Patent, and respectfully requests that the obviousness-type double patenting rejection based on claims 1-8 of Ding et al Patent be withdrawn.

Each of the present dependent claims is separately patentable over the prior art. For example, none of the prior art, taken single or in any combination, disclose, teach or even suggest the present compositions including the additional feature or features recited in any of the present dependent claims. Therefore, applicant submits that all of the present claims are separately patentable over the prior art.

In conclusion, applicant has shown that the present claims satisfy the requirements of 35 U.S.C. 112, first and second paragraphs; are unobvious from and patentable over the prior art; and are not subject to obviousness type double patenting based on claims 1-8 of Ding et al Patent. Therefore, applicant submits that the present claims, that is claims 21, 22, 25, 26 and 30-40, are allowable and respectfully requests the Examiner to pass the above-identified application to issuance at an early date. Should any matters remain unresolved, applicant requests the Examiner to telephone applicant's attorney at the telephone number given below.

Respectfully submitted,

Date: 3/23/07

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PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
10/927,857	08/27/2004	

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)	SMALL ENTITY ☐		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	03/27/2007	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 35	Minus	** 36	= 0	X $ =		OR	X $50=	0
	Independent (37 CFR 1.16(h))	* 3	Minus	***3	= 0	X $ =		OR	X $200=	0
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	0

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
Rozenia Harmon

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/927,857	08/27/2004	Andrew Acheampong	D-3111	2409

33197 7590 07/02/2007
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EXAMINER	
CORDERO GARCIA, MARCELA M	
ART UNIT	**PAPER NUMBER**
1654	
MAIL DATE	**DELIVERY MODE**
07/02/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/927,857	ACHEAMPONG ET AL.	
	Examiner	Art Unit	
	Marcela M. Cordero Garcia	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 March 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22,25-26, 30-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22,25,26 and 30-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is in response to the reply received on March 27, 2007.

Claims 1-22, 25-26, 30-40 are pending in the application. New claims 37-40 have been added. Any rejection from the previous office action, which is not restated here, is withdrawn.

Claims 1-20 are withdrawn as not drawn to the elected invention. Claims 21-22, 25-26 and 30-36 were originally examined as they read upon the instantly elected species, i.e., "a composition comprising cyclosporin A, a cyclosporine component concentration of less than 0.1%, vegetable oils as the hydrophobic component, and a weight ratio of the cyclosporine component to the hydrophobic component of less than 0.08".

Applicant has now amended claims 21-22, 25-26 substituting the term "cyclosporine component" for "cyclosporin A" and the term "hydrophobic component" for "castor oil". Applicant has also amended claim 30 to include the limitation "having a make-up so that when the composition is topically administered to an eye of a human in an effective amount in treating dry eye syndrome, the blood of the human has substantially no detectable concentration of the cyclosporin A."

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-22, 25-26, 30-40 are rejected under 35 U.S.C. 103(a) as being obvious over Ding et al. (US 5,474,979 cited in the IDS of 12/27/04).

Ding et al. teach a composition for treating an eye of a human or animal comprising an emulsion comprising water, a hydrophobic component, and cyclosporine component in a therapeutically effective amount of less than 0.1% by weight, the weight ratio of the cyclosporine component (cyclosporin A, e.g., Example 1D and column 3, lines 30-37) to the hydrophobic component (castor oil, a vegetable oil) is 0.08. (see, e.g., Example 1D).

Ding et al. do not expressly teach the weight ratio of the cyclosporine component to the hydrophobic component being less than 0.08.

Ding et al. teach that the weight ratio of the cyclosporine component to the hydrophobic component may be preferably varied between 0.12 and 0.02 (see, e.g., column 3, lines 19-20). In addition, Ding et al. teach in claim 8 a pharmaceutical emulsion consisting of between about 0.05% and about 0.40% by weight cyclosporin A (which reads upon the limitation "less than 0.1 % by weight cyclosporin A" of instant

claim 21) and between 0.625 and about 5.0 % castor oil. The corresponding lower and upper rations for the range is 0.05%/5.0% = 0.01 weight ratio of cyclosporin A/castor oil, which reads upon the limitation in claim 21 "the weight ratio of he cyclosporin A to the castor oil being less than 0.08".

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the composition of Ding et al. (e.g., Example 1D) by increasing the amount of castor oil or decreasing the cyclosporine concentration in order to reduce the ratio of the cyclosporine component to hydrophobic component from 0.08 to, e.g., 0.02 as taught by Ding et al. (see, e.g., column 3, lines 18-20). Following the ranges taught by claim 8 of Ding et al. as above one skilled in the art would readily envisage the claimed composition. The skilled artisan would have been motivated to do so because the compositions taught by Ding et al. teach (see claim 8) a pharmaceutical emulsion consisting of between about 0.05% and about 0.40% by weight cyclosporin A (which reads upon the limitation "less than 0.1 % by weight cyclosporin A" of instant claim 21) and between 0.625 and about 5.0 % castor oil. The corresponding lower and upper rations for the range is 0.05%/5.0% = 0.01 weight ratio of cyclosporin A/castor oil, which reads upon the limitation in claim 21 "the weight ratio of he cyclosporin A to the castor oil being less than 0.08" and therefore one skilled in the art would have readily envisaged compositions reading upon the limitations of the instantly claimed compositions. There would have been a reasonable expectation of success, given that compositions with a higher amount of castor oil are encompassed by the Ding et al. claims (e.g., claim 8) and because optimizing the ratio of cyclosporine/hydrophobic

components to below 0.08 (i.e., 0.02 to 0.12, which reads upon the range of ratios of 0.02 to 0.08) was taught by Ding et al. (e.g., column 3, lines 18-20). Please note that the limitation of claim 22 (wherein the blood of the human has substantially no detectable concentration of the cyclosporine component after application of the composition) would necessarily read upon a composition with the instantly claimed limitations as taught above. The limitation of claim 25 is taught in column 3, lines 21-27 and 57-67; the limitation of claim 26 is taught, e.g., in Example 1D, the limitation of claim 30 is taught by Ding et al.'s claim 8; the limitation of claim 31 is taught in column 3, lines 38-40; the limitations of claim 32-33 is taught in column 4, lines 12-19; the limitation of claim 34 is taught in column 3, lines 64-67 and column 4, lines 1-12; the limitations of claims 35-36 are taught, e.g., in Example 1D, column 4, line 43. The limitations of claims 37-40 are not expressly taught, but the claimed species reads upon the instant range as taught with sufficient specificity by the motivation set forth above (0.05% by weight of cyclosporin A, which is the lower limit of the range as claimed in claim 8, 1.25% of castor oil, which is within the range taught by Ding et al. of 0.625% to 5.0% for castor oil, and 0.04 is encompassed by the range of ratios taught at column 3, lines 18-20, 0.02-0.12). The adjustment of particular conventional working conditions (e.g., determining appropriate concentrations and ratios within such compositions) is deemed merely a matter of judicious selection and routine optimization that is well within the purview of the skilled artisan.

Thus the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Applicant's arguments

Applicant argues that Ding et al. Patent discloses a composition comprising cyclosporin A in admixture with an emulsifying amount of castor oil and polysorbate 80. Ding et al. Patent discloses that preferably the composition has a weight ratio of castor oil to polysorbate 80 between about 0.3 and about 30 and a weight ratio of cyclosporin A to castor oil below 0.16. Ding et al. Patent discloses that more preferably the weight ratio of castor oil to polysorbate 80 is between 0.5 and 12.5 and the weight of cyclosporine to castor oil between 0.12 and 0.02. (e.g., column 3, lines 15-20). In example 1, Ding et al. Patent discloses a series of five (5) cyclosporin A-containing emulsions. In relevant part, the make-ups of these five emulsions are as follows, with each composition including the same weight percent of polysorbate 80, Permulen ®, and Glycerin; and includes sodium hydroxide and water, and has a pH of 7.2-7.6::

	A	B	C	D	E
Cyclosporin A	0.40%	0.2%	0.2	0.10%	0.05%
Castor Oil	5.00%	5.00%	2.5%	1.25%	.625%
Weight ratio Cyclosporin A/Castor Oil	0.08	0.04	0.08	0.08	0.08

Each of the above-noted emulsions of Ding et al. Patent has a weight ratio of cyclosporin A to castor oil of 0.08, except for Composition B, which includes a relatively large amount of cyclosporin A (0.2%) outside the range of cyclosporine concentrations recited in the present claims (upper limit 0.1%), and has a cyclosporin A to castor oil

weight ratio of 0.04. Ding et al placed no significance on Composition B relative to Compositions A, C or D of Example 1. Moreover, Composition D, specifically cited by the Examiner, includes more cyclosporin A than in the presently claimed inventions, as well as having a weight ratio of cyclosporin A to castor oil outside the range recited in the present claims.

Claim 8 of Ding et al. Patent discloses compositions having make ups similar to those of Example 1 of Ding et al. Patent. The Examiner's citation of Ding et al. Patent of column 3, lines 30-37 is not understood.

Ding et al. Patent does not specifically disclose, teach or suggest the present invention. For example, Ding et al. Patent does not specifically disclose, teach or even suggest a composition comprising an emulsion comprising water, castor oil and cyclosporin A in an amount of less than 0.1 % by weight, for example, 0.05% by weight, with the weight ratio of cyclosporin A to castor oil being less than 0.08 and/or the castor oil being 1.25 % by weight of the composition, as recited in the present claims. Moreover, Ding et al. Patent does not specifically disclose, teach or even suggest the substantial, even surprising efficacy in treating dry eye disease, more rapid breaking down or resolving the emulsion in the eye and mitigation against undesirable side effects and potential drug interactions, obtained in accordance with the present invention.

Contrary to the Examiner's contention, Ding et al. Patent does not teach or even suggest optimizing the weight ratio of cyclosporin A/castor oil to below 0.08. In fact, since four of the five compositions tested in Example 1 of Ding et al Patent have such a

weight ratio of 0.08, Ding et al Patent appears to consider 0.08 the optimum weight ratio of cyclosporin A to castor oil. As noted above, Ding et al. Patent does not specifically distinguish between compositions having relatively wide variations in cyclosporin A concentrations and castor oil concentrations. Thus, Applicant submits that Ding et al. Patent actually teaches away from the presently claimed compositions and the substantial, surprising advantages of such compositions obtained by Applicant.

Simply put, Ding et al. Patent provides no motivation nor any other proper basis to one of ordinary skill in the art to extend the teachings of Ding et al Patent to make obvious the present compositions having the compositional parameters recited in the present claims, let alone obtaining the substantial, surprising advantages of the present composition.

The Examiner relies on Ding et al. Publication to supplement the teachings of Ding et al. Patent. The disclosure and deficiencies of Ding et al. Patent are discussed above and are resubmitted here.

Ding et al. Publication discloses a stable, pH-adjusted, oil-in-water emulsion using castor oil as the internal phase to solubilize cyclosporine, polysorbate 80 as the primary emulsifier and a polyelectrolyte as a stabilizer. Ding et al. publication discloses that the concentration of cyclosporin in the oil globule is formulated at a level of 7.4% w/w/, meaning that the weight ratio of the cyclosporine to castor oil is 0.074/0.926 or 0.08.

Ding et al. Publication does not disclose, teach or suggest the present invention. For example, Ding et al. Publication does not disclose a composition with any specific

cyclosporin A concentration, let alone a composition having a cyclosporin concentration of less than 0.1% by weight., for example, 0.05% by weight, as recited in the present claims. In addition, Ding et al. Publication does not disclose, teach or even suggest a composition in which the weight ratio of cyclosporin A to castor oil is less than 0.08 and/or the castor oil is 1.25% by weight of the composition, as recited in the present claims. By disclosing only a composition having a weight ratio of cyclosporin to castor oil of 0.08, Ding et al. Publication reinforces the apparent teaching of Ding et al. Patent that the optimum weight ratio of cyclosporin A to castor oil is 0.08. To a large extent, Ding et al. Publication actually teaches away from the present claims.

The combination of Ding et al. Patent and Ding et al. Publication does not disclose, teach or suggest the present invention. For example, this combination of references does not disclose, teach or suggest compositions comprising less than 0.1% by weight, for example 0,05% by weight, of cyclosporin A and castor oil in which the weight ratio of cyclosporin A to castor oil is less than 0.08 and/or the castor oil is 1.25% by weight of the composition, let alone the substantial and even surprising advantages of such compositions obtained by applicant.

Applicant also argues (pages 10 and 11) that the present compositions provide substantial advantages. For example, as illustrated in Example 1 of the present specification, Composition II, a composition in accordance with the present invention, and Composition I, a composition having a higher concentration of cyclosporin A, are

tested in use for the treatment of dry eye disease. In relevant part, the make-ups of these two compositions are as follows:.

	Composition I, wt%	Composition II, wt%
Cyclosporin A	0.1	0.05
Castor Oil	1.25	1.25
Weight Ratio of Cyclosporin A To Castor Oil	0.08	0.04

Note: each composition includes the same weight percent of polysorbate 80, premulen, glycerin and includes sodium hydroxide and water, and has a pH of 7.2 to 7.6

Each of these compositions are employed in a Phase 3 double-masked, randomized, parallel group study for the treatment of dry eye disease. The results of this study indicate that Composition II, in accordance with the present invention, which has a reduced concentration of cyclosporin A and a cyclosporin A to castor oil ratio of less than 0.08, provides overall efficacy in treating dry eye disease substantially equal to that of Composition I. This is surprising for a number of reasons. For example, the reduced concentration of cyclosporin A in Composition II would have been expected to result in reduced efficacy in treating dry eye disease.

Using relatively large amounts of castor oil, with reduced amounts of cyclosporine component, as in Composition II, is believed to take advantage of the benefits, for example the ocular lubrication benefits of castor oil, as well as the presence of ricinoleic acid in the castor oil, to at least assist in treating dry eye syndrome in combination with cyclosporin A.

In addition, it is found that the high concentration of castor oil relative to cyclosporine component, as in Composition II, provides the advantage of more quickly or rapidly (for example, relative to a composition which includes only 50% as much castor oil) breaking down or resolving the emulsion in the eye, for example, as measure by slit-lamp techniques to monitor the composition in the eye for phase separation. Such rapid break down of the emulsion in the eye reduces vision distortion as the result of the presence of the emulsion in the eye, as well as facilitating the therapeutic effectiveness of the composition in treating dry eye disease.

Using reduced amounts of cyclosporin A, as in Composition II, to achieve therapeutic effectiveness mitigates even further against undesirable aide effects and potential drug interactions. Prescribing physicians can prescribe Composition II to more patients and/or with fewer restrictions and/or with reduced risk of the occurrence of adverse effects, drug interactions and the like, relative to Composition I.

Response to Arguments

Applicant's arguments above have been fully considered but they are not persuasive.

According to MPEP 2144.05:

> "In the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a prima facie case of obviousness exists. In re Wertheim, 541 F.2d 257, 191 USPQ 90 (CCPA 1976); In re Woodruff, 919 F.2d 1575, 16 USPQ2d 1934 (Fed.Cir. 1990) (The prior art taught carbon monoxide concentrations of "about 1-5%" while the

> claim was limited to "more than 5%." The court held that "about 1-5%" allowed for concentrations slightly above 5% thus the ranges overlapped.); In re Geisler, 116 F.3d 1465, 1469-71, 43 USPQ2d 1362, 1365-66 (Fed. Cir. 1997) (Claim reciting thickness of a protective layer as falling within a range of "50 to 100 Angstroms" considered prima facie obvious in view of prior art reference teaching that "for suitable protection, the thickness of the protective layer should be not less than about 10 nm [i.e., 100 Angstroms]." The court stated that "by stating that suitable protection' is provided if the protective layer is about' 100 Angstroms thick, [the prior art reference] directly teaches the use of a thickness within [applicant's] claimed range."). Similarly, a prima facie case of obviousness exists where the claimed ranges and prior art ranges do not overlap but are close enough that one skilled in the art would have expected them to have the same properties. Titanium Metals Corp. of America v. Banner, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985) (Court held as proper a rejection of a claim directed to an alloy of "having 0.8% nickel, 0.3% molybdenum, up to 0.1% iron, balance titanium" as obvious over a reference disclosing alloys of 0.75% nickel, 0.25% molybdenum, balance titanium and 0.94% nickel, 0.31% molybdenum, balance titanium.). "[A] prior art reference that discloses a range encompassing a somewhat narrower claimed range is sufficient to establish a prima facie case of obviousness." In re Peterson, 315 F .3d 1325, 1330, 65 USPQ2d 1379, 1382-83 (Fed. Cir. 2003). >See also In re Harris, 409 F.3d 1339, 74 USPQ2d 1951 (Fed. Cir. 2005) (claimed alloy held obvious over prior art alloy that taught ranges of weight percentages overlapping, and in most instances completely encompassing, claimed ranges; furthermore, narrower ranges taught by reference overlapped all but one range in claimed invention."

The Ding et al. Patent does indeed disclose, teaches and suggest the present invention, and it is not deemed to teach away from the present invention (MPEP 2145) because: The skilled artisan would have been motivated to do so because the compositions taught by Ding et al. teach (see claim 8) a pharmaceutical emulsion consisting of between about 0.05% and about 0.40% by weight cyclosporin A (which reads upon the limitation "less than 0.1 % by weight cyclosporin A" of instant claim 21) and between 0.625 and about 5.0 % castor oil. The corresponding lower ratio to the

lower range limit of 0.05%/5.0% = 0.01 weight ratio of cyclosporin A/castor oil, which reads upon the limitation in claim 21 "the weight ratio of the cyclosporin A to the castor oil being less than 0.08" and therefore one skilled in the art would have readily envisaged the instant compositions. There would have been a reasonable expectation of success, given that compositions with a higher amount of castor oil are encompassed by the Ding et al. claims (e.g., claim 8) and because optimizing the ratio of cyclosporine/hydrophobic components to below 0.08 (i.e., 0.02 to 0.12, which reads upon the range of ratios of 0.02 to 0.08) was taught by Ding et al. (e.g., column 3, lines 18-20). In addition, Applicant's arguments with respect to the Examples provided by the disclosure of Ding et al. Patent claiming that such examples teach away from the invention have been carefully considered by Examiner but not deemed persuasive because Ding et al. Patent teaches at column 5, lines 36-43 and column 6, line 1, that:

> "Although there has been hereinabove described a particular pharmaceutical composition in the form of a nonirritating emulsion for the purpose of illustrating the manner in which the invention may be used to advantage, it should be appreciated that the invention is not limited thereto. Accordingly, any and all modifications, variations, or equivalent arrangements, which may occur to those skilled in the art, should be considered to be within the scope of the present invention as defined in the appended claims."

MPEP 2144.05, with regards to Optimization Within Prior Art Conditions or Through Routine Experimentation, states:

> "Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70%

> was held to be prima facie obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.); see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); In re Hoeschele, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969) (Claimed elastomeric polyurethanes which fell within the broad scope of the references were held to be unpatentable thereover because, among other reasons, there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions.). For more recent cases applying this principle, see Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); In re Kulling, 897 F.2d 1147, 14 USPQ2 1056 (Fed.Cir. 1990); and In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997).

Thus, the adjustment of particular conventional working conditions (e.g., determining appropriate concentrations and ratios within such compositions) is deemed merely a matter of judicious selection and routine optimization that is well within the purview of the skilled artisan, based on the teaching set forth in claim 8 and column 3, lines 18-20 as described above.

> .See also MPEP 2145: "Furthermore, "the prior art's mere disclosure of more than one alternative does not constitute a teaching away from any of these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed...." In re Fulton, 391 F.3d 1195, 1201, 73 USPQ2d 1141, 1146 (Fed. Cir. 2004)."

With respect to the unexpected results arguments set in Applicant's response, Examiner notes that the arguments provided for only 2 compositions (Composition I and II), and that they found that both compositions provide substantially equal overall efficacy in treating dry eye disease. The results presented do not actually compare

between the instant invention and the closest prior art as set forth above, including the complete range claimed by Ding et al. In other words, Ding et al. encompasses both Compositions I and II, within its scope. In addition, the arguments and evidence presented are not commensurate in scope with the instant invention, since they are limited to a single point within the concentrations and ranges disclosed.

> According to MPEP 2144.05: Applicants can rebut a prima facie case of obviousness based on overlapping ranges by showing the criticality of the claimed range. "The law is replete with cases in which the difference between the claimed invention and the prior art is some range or other variable within the claims. . . . In such a situation, the applicant must show that the particular range is critical, generally by showing that the claimed range achieves unexpected results relative to the prior art range." In re Woodruff, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990).

> MPEP 716.02(d) [R-2] states:

> "Whether the unexpected results are the result of unexpectedly improved results or a property not taught by the prior art, the "objective evidence of nonobviousness must be commensurate in scope with the claims which the evidence is offered to support." In other words, the showing of unexpected results must be reviewed to see if the results occur over the entire claimed range. In re Clemens, 622 F.2d 1029, 1036, 206 USPQ 289, 296 (CCPA 1980) (Claims were directed to a process for removing corrosion at "elevated temperatures" using a certain ion exchange resin (with the exception of claim 8 which recited a temperature in excess of 100C). Appellant demonstrated unexpected results via comparative tests with the prior art ion exchange resin at 110C and 130C. The court affirmed the rejection of claims 1-7 and 9-10 because the term "elevated temperatures" encompassed temperatures as low as 60C where the prior art ion exchange resin was known to perform well. The rejection of claim 8, directed to a temperature in excess of 100C, was reversed.). See also In re Peterson, 315 F.3d 1325, 1329-31, 65 USPQ2d 1379, 1382-85 (Fed. Cir. 2003) (data showing improved alloy strength with the addition of 2% rhenium did not evidence unexpected results for the entire claimed range of about 1-3% rhenium); In re Grasselli, 713 F.2d 731, 741, 218 USPQ 769, 777 (Fed. Cir. 1983) (Claims were directed to certain catalysts containing an alkali metal. Evidence presented to rebut an obviousness rejection compared catalysts

containing sodium with the prior art. The court held this evidence insufficient to rebut the prima facie case because experiments limited to sodium were not commensurate in scope with the claims.)."

Thus the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 21-22, 25-26 and 30-6 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-8 of U.S. Patent No. 5,474,979. Although the conflicting claims are not identical, they are not patentably

distinct from each other because the skilled artisan would have been motivated to do so because the compositions taught by Ding et al. teach (see claim 8) a pharmaceutical emulsion consisting of between about 0.05% and about 0.40% by weight cyclosporin A (which reads upon the limitation "less than 0.1 % by weight cyclosporin A" of instant claim 21) and between 0.625 and about 5.0 % castor oil. The corresponding lower and upper rations for the range is 0.05%/5.0% = 0.01 weight ratio of cyclosporin A/castor oil, which reads upon the limitation in claim 21 "the weight ratio of he cyclosporin A to the castor oil being less than 0.08" and therefore one skilled in the art would have readily envisaged compositions reading upon the limitations of the instantly claimed. Further, the instantly claimed composition encompasses and/or is encompassed by the claimed composition in US '979.

Applicant's arguments

For substantially the same reasons, as stated above, that the present claims are patentable over Ding et al. Patent, so too are the present claims patentable over claims 1-8 of Ding et al Patent.

For example, none of claims 1-8 of Ding et al. Patent specifically disclose, teach or suggest the present invention. To illustrate, none of the claims 1-8 of Ding et al. Patent specifically disclose, teach or even suggest a composition comprising less than 0.1 % by weight, for example, 0.05% by weight, of cyclosporin A, and castor oil in which the weight ratio of cyclosporin A to castor oil is less than 0.08 and/or the castor oil is 1.25% by weight of the composition, as recited in the present claims, let alone the substantial, surprising advantages of such compositions, discussed above, obtained by applicant.

The Examiner states that claim 8 of Ding et al. Patent encompasses species within the instantly claimed compositions. Applicant disagrees.

Claim 8 does not specifically disclose compositions including less than 0.1% by weight of cyclosporin A in which the weight ratio of cyclosporin A to castor oil is less than 0.08, as in the presently claimed compositions. Moreover, the relatively wide ranges of cyclosporin A and castor oil concentrations recited in claim 8 of Ding et al. actually lead away from the present claims, and the substantial and surprising advantages of the presently claimed compositions obtained by applicant.

To a large extent, the disclosure of claim 8 of Ding et al. Patent is similar to that of Example 1 of Ding et al. Patent, which has been discussed previously. Claim 8, like Example 1, of Ding et al. Patent, does not distinguish one composition from the other compositions. Neither does column 3, lines 19-20 of the Ding et al. Patent, cited by the Examiner. As noted previously, Ding et al. Patent does not teach optimizing the weight ratio of cyclosporin A to castor oil to below 0.08. Rather, since four of the five compositions tested in Example 1 of Ding et al. Patent have such a weight ratio of 0.08, Ding et al. Patent appears to consider 0.08 the optimum weight ratio of cyclosporin A to castor oil.

Response to Arguments

Applicant's arguments have been carefully considered but not deemed persuasive because of the reasons set forth above.

Conclusion

No claim is allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marcela M. Cordero García whose telephone number is (571) 272-2939. The examiner can normally be reached on M-Th 7:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia J. Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Marcela M Cordero García
Patent Examiner
Art Unit 1654

MMCG 06/07

6/25/07
ANISH GUPTA
PRIMARY EXAMINER

Search Notes	Application/Control No.	Applicant(s)/Patent under Reexamination	
	10/927,857	ACHEAMPONG ET AL.	
	Examiner	Art Unit	
	Marcela M. Cordero Garcia	1654	

SEARCHED			
Class	Subclass	Date	Examiner
none	none		

INTERFERENCE SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES (INCLUDING SEARCH STRATEGY)		
	DATE	EXMR
updated	6/20/2007	MMCG

TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Application Number	10/927,857
Filing Date	August 27, 2004
First Named Inventor	Acheampong et al.
Group Art Unit	1654
Examiner Name	cordero Garcia, Marcela M.
Total Number of Pages In This Submission: 19	Attorney Docket Number: D-3111

ENCLOSURES (*check all that apply*)

- ☐ Fee Transmittal Form *(in duplicate)*
- ☐ Fee Attached
- ☒ Amendment/Reply
- ☐ After Final
- ☐ Affidavits/declaration(s)
- ☐ Extension of Time Request
- ☐ Express Abandonment Request
- ☐ Information Disclosure Statement
- ☐ Certified Copy of Priority Document(s)
- ☐ Response to Missing Parts/ Incomplete Application
- ☐ Response to Missing Parts under 37 CFR 1.52 or 1.53
- ☐ Drawing(s)
- ☐ Licensing-related Papers
- ☐ Petition
- ☐ Petition to Convert to a Provisional Application
- ☐ Power of Attorney, Revocation Change of Correspondence Address
- ☐ Terminal Disclaimer
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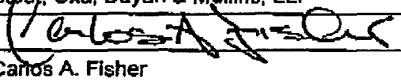
- ☐ Appeal Communication to TC *(Appeal Notice, Brief, Reply Brief)*
- ☐ Proprietary Information
- ☐ Status Letter
- ☐ Other Enclosure(s) *(please identify below)*

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	Stout, Uxa, Buyan & Mullins, LLP		
Signature			
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Date	August 27th 2007	Reg. No.	36,510

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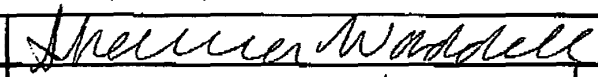
Signature			
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.	: 10/927,857	Confirmation No. 2409
Applicant	: ACHEAMPONG ET AL.	
Filed	: August 27, 2004	
Title	: METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS	
TC/A.U.	: 1654	
Examiner	: Cordero Garcia, Marcela M.	
Docket No.	: D-3111	
Customer No.	: 33197	

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Date: August 27, 2007

Name: Shawnna Waddell

AMENDMENT B

Sir:

In response to the Office Action mailed July 2, 2007, please amend the above-identified application as follows:

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 7 of this paper.

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims

1. (Withdrawn) A method of treating an eye of a human or animal comprising:

administering to an eye of a human or animal a composition in the form of an emulsion comprising water, a hydrophobic component and a cyclosporin component in a therapeutically effective amount of less than 0.1% by weight of the composition, the weight ratio of the cyclosporin component to the hydrophobic component is less than 0.08.

2. (Withdrawn) The method of claim 1 wherein the administering step is effective in treating a condition selected from the group consisting of dry eye syndrome, phacoanaphylactic endophthalmitis, uveitis, vernal conjunctivitis, atopic keratoconjunctivitis and corneal graft rejection.

3. (Withdrawn) The method of claim 1 wherein the administering step is effective in treating dry eye syndrome.

4. (Withdrawn) The method of claim 1 wherein the blood of the human or animal has substantially no detectable concentration of the cyclosporin component.

5. (Withdrawn) The method of claim 1 wherein the blood of the human or animal has substantially no detectable concentration of the cyclosporin component as measured using a

validated liquid chromatography/mass spectrometry-mass spectrometry analytical method.

6. (Withdrawn) The method of claim 1 wherein the blood of the human or animal has a concentration of the cyclosporin component of 0.1 ng/ml or less.

7. (Withdrawn) The method of claim 1 wherein the cyclosporin component comprises a material selected from cyclosporin A, derivatives of cyclosporin A and mixtures thereof.

8. (Withdrawn) The method of claim 1 wherein the cyclosporin component comprises cyclosporin A.

9. (Withdrawn) The method of claim 1 wherein the cyclosporin component is solubilized in the hydrophobic component present in the composition.

10. (Withdrawn) The method of claim 1 wherein the hydrophobic component is present in the composition in an amount greater than 0.625% by weight of the composition.

11. (Withdrawn) The method of claim 1 wherein the hydrophobic component comprises an oily material.

12. (Withdrawn) The method of claim 1 wherein the hydrophobic component comprises an ingredient selected from the group consisting of vegetable oils, animal oils, mineral oils, synthetic oils and mixtures thereof.

13. (Withdrawn) The method of claim 1 wherein the hydrophobic component comprises castor oil.

14. (Withdrawn) The method of claim 1 wherein the administering step comprises topically administering the composition to the eye of the human.

15. (Withdrawn) The method of claim 1 wherein the composition comprises an effective amount of an emulsifier component.

16. (Withdrawn) The method of claim 1 wherein the composition comprises an effective amount of a tonicity component.

17. (Withdrawn) The method of claim 1 wherein the composition comprises an effective amount of an organic tonicity component.

18. (Withdrawn) The method of claim 1 wherein the composition comprises a polyelectrolyte component in an amount effective in stabilizing the composition.

19. (Withdrawn) The method of claim 1 wherein the composition has a pH in the range of about 7.0 to about 8.0.

20. (Withdrawn) The method of claim 1 wherein the composition has a pH in the range of about 7.2 to about 7.6.

21. (Currently Amended) A <u>therapeutically effective</u> composition for treating an eye of a human or animal comprising

an emulsion comprising water, castor oil, and cyclosporin A in a therapeutically effective amount of less than 0.1% by weight, the weight ratio of the cyclosporin A to the castor oil being less than 0.08.

22. (Previously presented) The composition of claim 21 having a make-up so that when the composition is administered to an eye of a human in an effective amount in treating dry eye syndrome, the blood of the human has substantially no detectable concentration of the cyclosporin A.

23. (Canceled)

24. (Canceled)

25. (Original) The composition of claim 21 in the form of an emulsion.

26. (Currently Amended) The composition of claim 21 wherein the castor oil is present in an amount greater than 0.625% by weight of the composition.

27. (Canceled)

28. (Canceled)

29. (Canceled)

30. (Previously presented) The composition of claim 21 having a make-up so that when the composition is topically administered to an eye of a human in an effective amount in

treating dry eye syndrome, the blood of the human has substantially no detectable concentration of the cyclosporin A.

31. (Original) The composition of claim 21 wherein the composition comprises an effective amount of an emulsifier component.

32. (Original) The composition of claim 21 wherein the composition comprises an effective amount of a tonicity component.

33. (Original) The composition of claim 21 wherein the composition comprises an effective amount of an organic tonicity component.

34. (Original) The composition of claim 21 wherein the composition comprises a polyelectrolytic component in an amount effective in stabilizing the composition.

35. (Original) The composition of claim 21 wherein the composition includes water and has a pH in the range of about 7.0 to about 8.0.

36. (Original) The composition of claim 21 wherein the composition includes water and has a pH in the range of about 7.2 to about 7.6.

37. (Previously presented) The composition of claim 21 which includes 1.25% by weight of castor oil.

38. (Previously presented) The composition of claim 21 which includes 0.05% by weight of cyclosporin A.

39. (Previously presented) The composition of claim 38 which includes 1.25% by weight of castor oil.

40. (Previously presented) A composition for treating an eye of a human or animal comprising an emulsion comprising water, 1.25% by weight of castor oil and 0.05% by weight of cyclosporin A, the weight ratio of the cyclosporin A to the castor oil being 0.04.

Remarks

Applicants have the following comments in reply to the Office Action mailed July 2, 2007 (the "Office Action"). The above-identified application has been carefully reviewed in light of the Office Action mailed January 17, 2007.

Rejections Pursuant to 35 USC 103(a)

Claims 1-22, 25-26 and 30-40 have been finally rejected as allegedly obvious over Ding et al., (US Patent Serial No. 5474979). Applicants believe that the Examiner may have intended to specify claims 21-22 (rather than 1-22), 25-26 and 30-40, since claims 1-20 have been withdrawn and are no longer being prosecuted. If Applicants are in error in the regard they ask that the Examiner so indicate in the next communication to Applicants.

Upon a review of the Examiner's comments, Applicants hereby traverse this rejection for the following reasons.

Obviousness is a mixed question of law and fact. The United States Supreme Court's decision in *Graham v. John Deere Co.*, 383 U.S. 1, 148 U.S.P.Q. 459 (1966) sets forth the standards used in determining whether a claimed invention is obvious under 35 U.S.C. §103(a): "the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined." 383 U.S. at 17, 148 U.S.P.Q. at 467.

In applying this test in the case before it, the *Graham* Court found that the differences between the prior art and Graham's invention rendered the invention obvious because "a person having ordinary skill in the prior art . . . would immediately see that the thing to do was what Graham did. . . ." 383 U.S. at 24, 148 U.S.P.Q. at 469 (emphasis added). In other words, when the invention is predictable in light of the prior art in such a way as would permit the person of ordinary skill in the art to "immediately see" the claimed invention, the invention is obvious.

The Supreme Court's recent decision in *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. ___, __ U.S.P.Q.2d___ (2007) affirms in every regard the standards set forth in Graham. Moreover, the *KSR* court indicated that in a proper rejection on obviousness grounds the Examiner must articulate reasoning with some rational underpinning to support the legal conclusion of obviousness, *id.*, slip op. at 14, such as "a reason that would have prompted a person of ordinary skill in the relevant field to combine the [known] elements in the way the claimed new invention does." *Id.*, slip op. at 15.

The presently claimed invention is drawn in claim 21 to a composition for treating an eye of a human or animal comprising an emulsion comprising water, castor oil, and cyclosporin A in a therapeutically effective amount of less than 0.1% by weight, the weight ratio of the cyclosporin A to the castor oil being less than 0.08.

Ding, the reference being applied against the pending claims, is characterized by the Office Action as teaching a composition comprising water, a hydrophobic component and a cyclosporin component in a therapeutically effective amount of less that 0.1% by weight.

Ding et al. disclose that the solubility of cyclosporins (including cyclosporine A) is extremely low have made it practically impossible to prepare a pharmaceutical composition containing cyclosporin in an aqueous medium. Moreover, oil based cyclosporin compositions have generally been limited to oral preparations because of the separation of cyclosporin as a solid immediately after it comes into contact with water, such as in the mouth or eye of a patient.

Ding states that "although it is well known that cycclosporin may be used in combination with castor oil, this combination is irritating to sensitive tissues such as the eye." Ding, column 3, lines 43-45.

The Office Action on pages 3 and 4 argues that the presently claimed invention is obvious because Ding discloses weight ratios of cyclosporin to castor oil of from about 0.12 to about 0.02. The Office Action also points to claim 8 of Ding, which claims from about 0.05% to about 0.4% cyclosporin A and from about 0.625% to about 5.0% castor oil.

However, as acknowledged on page 3 of the Office Action, Ding discloses 5 different cyclosporin-containing compositions in Example 1; none of these compositions has a weight ratio of cyclosporin to castor oil of less than 0.8. Thus, while Ding et

al. disclose amounts of each ingredient that are encompassed by the ranges of ingredients given in Ding et al., in practice Ding et al. teaches away from the present composition having less than 0.1% cyclosporin A and a weight ratio of cyclosporin to castor oil of less than 0.08%.

Furthermore, the present specification provides comparative evidence of surprising results in the use of the claimed compositions. Example 1 of the present specification is drawn to a comparison of two different compositions in which percentages are presented by weight; Composition I, which fall outside the scope of the present claims, contains 0.1% cyclosporin A and 1.25% castor oil. This composition therefore has a weight ratio of cyclosporin to castor oil of 0.08. Composition II contains 0.05% cyclosporin and 1.25% castor oil, and thus has a weight ratio of cyclosporin to castor oil of 0.04%.

It was utterly unpredictable, with reference to Ding, that Composition II, containing half the amount of cyclosporin A as Composition I, would provide substantially equivalent overall efficacy against dry eye diseases such as keratoconjunctivitis sicca when applied topically to the eye. See SPECIFICATION at page 26, lines 8 and 9.

It is therefore completely surprising that an equivalently therapeutically effective composition containing a reduced amount of cyclosporin A (below 0.1%) relative to Composition I (and thus a reduced potential for adverse side effects and drug interactions than Composition I) could be made. Using the currently claimed compositions, prescribing physicians can

prescribe e.g., Composition II to more patients and/or with fewer restrictions and/or with reduced risk of the occurrence of adverse events, e.g., side effects, drug interactions and the like, relative to Composition I.

Moreover, it was utterly unpredictable that the concentration of castor oil (1.25%) present in both Composition I and Composition II of the present specification would be substantially non-irritating in human eyes (and therefore useful as required by 35 USC §101) upon use. See SPECIFICATION at page 26, lines 16 and 17. Although the antibiotic effects of the main component of castor oil, ricinoleic acid, are known, oily ocular topical cyclosporin compositions can lead to irritation or a clouding of visual field. Ding, column 2, lines 6 and 7. Indeed, Ding indicates that in rabbit eyes some discomfort and hyperaemia results from topical application of Compositions A-E disclosed therein.

It is therefore clear in the light of the unpredictability of the present invention that a person of ordinary skill in the art would not only not be able to "immediately see" in light of Ding "that the thing to do was what the Applicants did", Graham, 383 U.S. at 24, 148 U.S.P.Q. at 469, but that such a person would have no basis for even attempting to make the claimed compositions.

Furthermore, since the Office Action admits that Ding et al. does not disclose compositions containing less than 0.1% cyclosporin A and weight ratios of cyclosporin to castor oil of of below 0.08%, the statements that "the limitations" of claims

21, 22, 25 26, and 30-40 are taught in various places in Ding is respectfully submitted to be erroneous.

The Examiner relies on Ding et al Publication PHARM. RES. 1997:14:S41 to supplement the teachings of Ding et al Patent. Thus publication consists of an abstract.

Ding et al Publication discloses a stable, pH-adjusted, oil-in-water emulsion using castor oil as the internal phase to solubilize cyclosporine, polysorbate 80 as the primary emulsifier and a polyelectrolyte as a stabilizer. Ding et al Publication discloses that the concentration of cyclosporin in the oil globule is formulated at a level of 7.4% w/w, meaning that the weight ratio of the cyclosporine to castor oil in the oil globule is 0.074/0.926 or 0.08. Ding et al. Publication does not disclose the concentration of cyclosporin or the amount of castor oil.

Thus, Ding et al. Publication adds nothing to e.g., Example 1 of Ding et al. patent. The Office Action appears to concede that the significance of Ding et al. Publication is that it reinforces that teachis of Ding et al. patent that the op[timal weight ratio of cyclosporin to castor oil is 0.8%.

The Office Action cites the Manual of Patent Examining Procedure (MPEP) §2144.05, which states that if a prima facie case of obviousness exists, such a case is rebutted if, as here, the prior art teaches away from the claimed invention.

Ding et al. patent discloses exemplary compositions, all but one having weight ratios the cyclosporine to castor oil of

0.08%, and all but one having cyclosporin concentrations of 0.1% or above. The clear teaching is that an optimal weight ratio is 0.8%. Thus, Ding et al. teaches away from the present invention. Applicants note that the present claim limitations do not use the term "about" with respect to these limitations, and therefore there is no overlap with the exemplary compositions of Example 1.

The Office Action also appears to hold Applicants to a much higher standard than is permissible regarding the evidence of Example 1 of the present specification demonstrating surprising results. The Office Action seems to indicate that the Applicants must provide such evidence over "the complete range claimed by Ding et al.", and that an experiment using a single composition, such as Composition II, cannot prove such results since it is limited to a single point within the concentrations and ranges claimed. Applicants respectfully disagree with this conclusion.

It is clearly evident to the person of ordinary skill in the art that lower concentrations of cyclosporin than 0.1% would result in a reduced potential for adverse side effects and drug interactions than a composition containing higher concentrations of cyclosporin A. Moreover, regarding therapeutic effectiveness, it is not required that a patent application provide evidence that all embodiments of an invention are operative; the Court of Appeals for the Federal Circuit has ruled that even if some of the claimed combinations were inoperative, the claims are not necessarily invalid." *Atlas Powder Co. v. E.I. DuPont de Nemours & Co.*, 750 F2d. 1569, 204 USPQ 409 (Fed. Cir. 1984). In the present case, the utility of the invention depends upon its

therapeutic effectiveness, and the fact that there is some concentration of cyclosporin at which the claimed composition may not be therapeutically effective does not make these claims obvious.

Furthermore, Applicants point out that the Office Action's reasoning regarding surprising results can in no event pertain to claims 37-40, which are drawn to preferred specific embodiments comprising a single concentration of cyclosporin (0.05%) and/or castor oil (1.25%). Any such conclusion can only be improperly reached from a prior knowledge of and a hindsight analysis of the claims in light of the Applicants' own specification.

In view of the above, Applicants submit that claims 21, 22, 25, 26 and 30-40 are unobvious from and patentable over Ding et al Patent in view of Ding et al Publication under 35 U.S.C. 103(a).

Double Patenting

Claims 21-36 have been rejected on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 1-8 of Ding et al Patent. Applicant traverses these rejections as it pertains to claims 21, 22, 25, 26 and 30-40.

For substantially the same reasons as stated above showing that the present claims are patentable over Ding et al Patent, so too are the present claims patentable over claims 1-8 of Ding et al Patent.

For example, none of claims 1-8 of Ding et al Patent specifically disclose, teach or suggest the present invention. To illustrate, none of claims 1-8 of Ding et al Patent specifically disclose, teach or even suggest a composition comprising less than 0.1% by weight, for example, 0.05% by weight, of cyclosporin A, and castor oil in which the weight ratio of cyclosporin A to castor oil is less than 0.08 and/or the castor oil is 1.25% by weight of the composition, as recited in the present claims, let alone the substantial, surprising advantages of such compositions, discussed above, obtained by Applicants.

The Examiner states that claim 8 of Ding et al Patent encompasses species within the instantly claimed compositions. Applicant disagrees.

Claim 8 does not specifically disclose compositions including less than 0.1% by weight of cyclosporin A in which the weight ratio of cyclosporin A to castor oil is less than 0.08, as in the presently claimed compositions. Moreover, the wide ranges of cyclosporin A and castor oil concentrations recited in claim 8 of Ding et al Patent actually lead away from the present claims, and the substantial and surprising advantages of the presently claimed compositions obtained by Applicants.

To a large extent, the disclosure of claim 8 of Ding et al Publication is similar to that of Example 1 of Ding et al Patent, which has been discussed previously. Claim 8, like Example 1, of Ding et al Patent does not distinguish one composition from the other compositions. Neither does column 3, lines 19-20 of Ding et al Patent, cited by the Examiner. As

noted previously, Ding et al Patent does not teach optimizing the weight ratio of cyclosporin A to castor oil to below 0.08. Rather, since four of the five compositions tested in Example 1 of Ding et al Patent have such a weight ratio of 0.08, Ding et al Patent appears to consider 0.08 the optimum weight ratio of cyclosporin A to castor oil.

None of the Compositions A, B, C, D and E of Ding et al Patent specifically disclose, teach or suggest the presently claimed compositions. As noted previously, Ding et al Patent does not distinguish the Compositions of Example 1, one from the other. In effect, the claims, including claim 8, of Ding et al Patent discloses that compositions with relatively wide ranges of concentrations of cyclosporin A and castor oil have similar properties. Such teaching actually leads away from the presently claimed compositions and the substantial, surprising advantages, discussed previously, obtained by Applicants relative to compositions encompassed by the claims of Ding et al Patent.

Further, nothing in the claims of Ding suggest the specific concentrations and ratios recited in claims 37-40 of the present application.

In view of the above, Applicants submits that claims 21, 22, 25, 26 and 30-40 are patentable over the claims of Ding et al Patent, and respectfully requests that the obviousness-type double patenting rejection based on claims 1-8 of Ding et al Patent be withdrawn.

Each of the present dependent claims is separately patentable over the prior art. For example, none of the prior art, taken single or in any combination, disclose, teach or even suggest the present compositions including the additional feature or features recited in any of the present dependent claims. Therefore, Applicants submits that all of the present claims are separately patentable over the prior art.

In conclusion, Applicants have shown that the present claims satisfy the requirements of 35 U.S.C. 112, first and second paragraphs; are unobvious from and patentable over the prior art; and are not subject to obviousness type double patenting based on claims 1-8 of Ding et al Patent. Therefore, Applicants submits that the present claims, that is claims 21, 22, 25, 26 and 30-40, are allowable and respectfully requests the Examiner to pass the above-identified application to issuance at an early date. Should any matters remain unresolved, Applicants requests the Examiner to telephone Applicants's attorney at the telephone number given below.

Respectfully submitted,

Date: August 27th, 2007

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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 10/927,857	Filing Date 08/27/2004	☐ To be Mailed

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)	SMALL ENTITY ☐		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (l), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	03/27/2007	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 35	Minus	** 36	= 0	X $ =		OR	X $50=	0
	Independent (37 CFR 1.16(h))	* 3	Minus	*** 3	= 0	X $ =		OR	X $200=	0
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	0

8/27/07

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 35	Minus	** 36	=	X $ =		OR	X $ =	
	Independent (37 CFR 1.16(h))	* 3	Minus	*** 3	=	X $ =		OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
Rozenia Harmon

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/927,857	08/27/2004	Andrew Acheampong	D-3111	2409

33197 7590 09/27/2007

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EXAMINER	
CORDERO GARCIA, MARCELA M	
ART UNIT	**PAPER NUMBER**
1654	
MAIL DATE	**DELIVERY MODE**
09/27/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/927,857	**Applicant(s)** ACHEAMPONG ET AL.	
	Examiner Marcela M. Cordero Garcia	**Art Unit** 1654	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 27 August 2007 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires _____ months from the mailing date of the final rejection.
   b) ☒ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☒ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: *See Continuation Sheet*. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *21,22,25,26 and 30-40*.
   Claim(s) withdrawn from consideration: *1-20*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☐ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: _____.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

Cecilia J. Tsang
Supervisory Patent Examiner
Technology Center 1600

Marcela M Cordero Garcia
Patent Examiner
Art Unit 1654

Continuation of 3. NOTE: As noted by Applicant, there was a typo in the final rejection and claim 1 should read as claim 21. Claims 1-20 were withdrawn by restriction since they are drawn to a method of using rather than a product. Therefore, the 103 rejection over Ding is over claims 21-22, 25-26 and 30-40 (see the ODP rejection which encompasses the correct claims). Examiner thanks Applicants for clarifying this point. With respect to applicants arguments: 1) Ding et al. discloses that the solubility of cyclosporins is extremely low and that oil based cyclosporin compositions have generally been limited to oral preparations because of the separation of cyclosporin as a solid when it comes into contact with water. Response to 1): Ding et al. teach operative conditions for the eye emulsions which encompass the instant ranges. Moreover, Ding et al. teaches that the compositions are found to be physically stable upon long term storage and that the drug had reasonably high thermodynamic activity yet without crystallization problems (e.g. column 3, lines 20-28). Moreover, Ding et al. teach that the "present invention achieves a stable solution state of cyclosporin. This stable solution state is another important performance characteristic differentiating the present invention from the conventional oil systems. cyclosporin is notorious for its tendency to precipitate out in conventional oil systems in which it is fully dissolved initially." (column 3, lines 57-63). 2) Ding states that "although it is well known that cyclosporin may be used in combination with castor oil, this combination is irritating to sensitive tissues such as the eye." (Ding column 3, lines 43-45). Response to 2) Ding et al. teach in abstract that the compositions have high comfort level and low irritation potential suitable for delivery of medications to sensitive areas such as ocular tissues. In addition, the compositions of Examples 1-4, encompassing up to 5% castor oil (much larger than the instant Composition II of disclosure which has 1.25% of castor oil) were found to cause only slight to mild discomfort and slight hyperemia (e.g., column 5, lines 15-20). The compositions encompassed by the teachings of the Ding et al. patent are non-irritant as taught by the title of the patent "Nonirritating emulsions for sensitive tissue". 3) According to Apliccants, none of the compositions in Example 1 has a weight ration of cyclosporin to castor oil of less than 0.8, therefore Ding et al. teach away for the present composition. Answer to 3). Example 1A is 0.4% cyclosporin / 5.00 % castor oil, which has a ratio of 0.08; Example 1D is 0.1 % cyclosporin and 1.25% castor oil, which also has a ratio of 0.08. In addition the ratios 0.02 to 0.12 are "more preferred" ratios of cyclosporin to castor oil (column 3, lines 17-20), therefore it does not teach away but instead provides ample motivation to make the instantly claimed compositions. 4) Applicants argue unexpected results because when comparing composition 1D of Ding et al. (named composition I in the instant application, comprising 0.1 % cyclosporin and 1.25% castor oil) and composition II which has 0.05% cyclosporin (half as much as composition I) and 1.25% castor oil, composition II provides substantially equivalent overall efficacy against dry eye diseases such as keratoconjunctivitis sicca when applied topically to the eye. Response to 4) The statement that both compositions provide "substantially equivalent overall efficacy" is not unexpected since both compositions are encompassed by the invention of Ding et al. and all the embodiments described therein are considered operative. Moreover, no data is presented to substantiate the arguments besides the statement that the composition II and composition I have substantially overall efficacy. 5) Applicants allege unexpected result encompassing less adverse effects due to the use of a lower amount of cyclosporin. Response to 5) a lower amount of cyclosporin is taught, e.g., at claim 8, which teaches cyclosporin A at 0.05% and therefore the result is not unexpected. Additionally, the less adverse results would be dependent on the lower concentration and are not unexpected and encompassed by the invention of Ding et al. 6) Applicants allege that "it was utterly unpredictable that the concnetration of castor oil (1.25%) present in both composition I and composition II of the present specification would be substantially non-irritating in human eyes upon use. Although the antibiotic effects of the main component of castor oil, ricinoleic acid, are known, oily ocular topical cyclosporin compositions can lead to irritation or a colduing of visual field. Ding , column 2, lines 6 and 7. Indeed Ding indicates that in rabbit eyes some discomfort and hyperaemia results from topical application of compositions A-E disclosed therein. Response to 6) Ding et al. teach in abstract that the compositions have high comfort level and low irritation potential suitable for delivery of medications to sensitive areas such as ocular tissues. In addition, the compositions of Examples 1-4, encompassing up to 5% castor oil (much larger than the instant Composition II of disclosure which has 1.25% of castor oil) were found to cause only slight to mild discomfort and slight hyperemia (e.g., column 5, lines 15-20). The compositions encompassed by the teachings of the Ding et al. patent are non-irritant as taught by the title of the patent "Nonirritating emulsions for sensitive tissue". 7) Applicants allege that the limitations as pointed out in claims 21, 22, 25, 26 and 30-40 are taught erroneously. Response to 7) Applicants have not specifically pointed out in each claim and limitation, why they are erroneous. The disclosure of Ding et al. is relied upon for all that it teaches and therefore, not only the Examples are considered when making an art rejection. 8) Examiner relies of Ding et al. (Pharm Res, 1997) tosupplement the teachings of Ding et al. Response to 8) Examiner agrees that the ratio of cyclosporine to castor oil is 0.074/0.926 or 0.08. Please note that the ratio is 0.08 and not 0.8% as pointed out by Applicants in page 13, paragraph 4 of the after final arguments. 9) Ding et al. patent discloses exemplary compositions, all but one having weight ratios of the cyclosporine to castor oil of 0.08%, and all but one having cyclosporin concentrations of 0.1% or above. The clear teaching is that an optimal weight ratio is 0.8%. Thus Ding et al. teaches away from the present invention. Response to 9) First of all, Examiner points out that the limitations of claim 21 are "cyclosporin in a therapeutically effective amount of less than 0.1 % by weight" and "the weight ratio of the cyclosporin A to the castor oil being less less than 0.08". It is unclear to Examiner how is the 0.8% optimal ratio being obtained. Ding et al. teaches in claim 7, that the cyclosporin is present in the amount of between about 0.05 to and about 0.40%, which clearly encompasses 0.1 %, and castor oil at 0.625-5.0%, e.g., 0.1/5.0 = 0.02 (which is less than 0.08). In addition, the limitation "the weight ratio of the cyclosporin A to the castor oil being less less than 0.08" is taught as within the more preferred ratio of cyclosporin to castor oil of 0.12 and 0.02 (e.g., column 3, lines 17-20). 10) Furthermore, Applicants point out that the Office Action's reasoning regarding surprising results can in no event pertain to claims 37-40 which are drawn to preferred specific embodiments comprising a single concentration of cyclosporin (0.05%) and/or castor oil (1.25%). Any such conclusion can only be improperly reached from a prior knowledge of and a hindsight analysis of the claims in light of the Applicants' own specification. Response to 10) Claim 37 is drawn to claim 21 wherein castor oil is 1.25% by weight, which is encompassed by the teachings of Ding et al. (e.g., claim 7, which encompasses 0.05 % of cyclosporin and 1.25% of castor oil to make a ratio of 0.04). 11) For substantially the same reasons above, the present claims are patentable over Ding et al. Specifically, claims 8 discloses compositions with relatively wide ranges of concentrations of clyclosporin A and castor oil teaching away from the present unexpected advantages. Response to 11). It would have been obvious to one of ordinary skill in the art to at once envisage the embodiments encompassed by the ranges, e.g., in claim 8, which are 0.05-0.4 of cyclosporin (encompassing less than 0.1% and specifically 0.05%) and castor oil between 1.0-5.0% weight (which encompass 1.25% of castor oil).

AF/ IFW

TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Application Number	10/927,857
Filing Date	August 27, 2004
First Named Inventor	Acheampong et al.
Group Art Unit	1654
Examiner Name	cordero Garcia, Marcela M.
Total Number of Pages in This Submission	6
Attorney Docket Number	D-3111

ENCLOSURES (*check all that apply*)

- [X] Fee Transmittal Form
- [X] Fee Attached
- [ ] Amendment/Reply
- [ ] After Final
- [ ] Affidavits/declaration(s)
- [X] Extension of Time Request
- [ ] Express Abandonment Request
- [ ] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Response to Missing Parts/ Incomplete Application
- [ ] Response to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
- [ ] Terminal Disclaimer
- [ ] Request for Refund
- [ ] CD, Number of CD(s) ____
- [ ] Landscape Table on CD
- [ ] After Allowance Communication to TC
- [ ] Appeal Communication to Board of Appeals and Interferences
- [X] Appeal Communication to TC *(Appeal Notice, Brief, Reply Brief)*
- [ ] Proprietary Information
- [ ] Status Letter
- [X] Other Enclosure(s) *(please identify below)*

Return Self Addressed Postcard

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	Stout, Uxa, Buyan & Mullins, LLP		
Signature			
Printed Name	Carlos A. Fisher		
Date	November 16 2007	Reg. No.	36,510

CERTIFICATE OF TRANSMISSION/MAILING

I hereby certify that this correspondence is being facsimile transmitted to the USPTO at fax number 571-273-8300, or deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: **Mail Stop** Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date shown below.

Signature			
Typed or printed name	Shawnna Waddell	Date	Nov. 16, 2007

Fees Pursuant to the Consolidated Appropriations Act 2005 (H.R. 4818).

FEE TRANSMITTAL For FY 2008

Patent fees are subject to annual revision.

☐ Application claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 970.00

Complete if Known	
Application Number	10/927,857
Filing Date	August 27, 2004
First Named Inventor	Andrew Acheampong
Examiner Name	Cordero Garcia, Marcela M
Art Unit	1654
Attorney Docket No.	D-3111

METHOD OF PAYMENT *(check all that apply)*

☒ Check ☐ Credit Card ☐ Money Order ☐ None ☐ Other (please identify): PLEASE USE CHECK FOR 2 MONTH EXTENSION FEE $460.00, AND THE DEPOSIT ACCOUNT FOR THE APPEAL FEE $510.00.

☒ Deposit Account Deposit Account Number 01-0885 Deposit Account Name Allergan, Inc.

For the above-identified deposit account, the Director is hereby authorized to: *(check all that apply)*

☒ Charge fee(s) indicated below ☐ Charge fee(s) indicated below, **except for the filing fee**

☒ Charge any additional fee(s) associated with this communication ☒ Credit any overpayments

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

FEE CALCULATION

1. BASIC FILING, SEARCH, AND EXAMINATION FEES

	FILING FEES		SEARCH FEES		EXAMINATION FEES		
		Small Entity		Small Entity		Small Entity	
Application Type	Fee ($)	Fee ($)	Fee ($)	Fee ($)	Fee ($)	Fee ($)	Fees Paid ($)
Utility	310	155	510	255	210	105	
Design	210	105	100	50	130	65	
Plant	210	105	310	155	160	80	
Reissue	310	155	510	255	620	310	
Provisional	210	105	0	0	0	0	
						Subtotal (1)	0

2. EXCESS CLAIM FEES

Fee Description	Fee ($)	Small Entity Fee ($)
Each claim over 20 or , for Reissues, each claim over 20 and more than in the original patent	50	25
Each independent claim over 3 or, for Reissues, each independent claim more than in the original patent	210	105
Multiple Dependent Claims	370	185

Total Claims ____ -20 or HP = ____ x Fee ($) ____ Fee Paid ($) ____

HP = highest number of total claims paid for, if greater than 20

Indep. Claims ____ -3 or HP = ____ x Fee ($) ____ Fee Paid ($) ____

HP = highest number of independent claims paid for, if greater than 3

Multiple Dependent Claims: Fee ($) ____ Fee Paid ($) ____

Subtotal (2) 0

3. APPLICATION SIZE FEE

If the specification and drawings exceed 100 sheets of paper, the application size fee due is $260 ($130 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

Total Sheets	Extra Sheets	Number of each additional 50 or fraction thereof	Fee ($)	Fee Paid ($)
____	-100 = ____	/50= ____(round up to a whole number)	x ____	=
			Subtotal (3)	0

4. OTHER FEE(S)

	Fee Paid ($)
☐ Surcharge - Late filing fee or oath/declaration: $130 fee ($65 small entity discount)	
☐ Non-English Specification: $130 fee (no small entity discount)	
☐ 1-month extension of time: $120 fee ($60 small entity discount)	
☒ 2-month extension of time: $460 fee ($230 small entity discount)	460.00
☐ 3-month extension of time: $1050 fee ($525 small entity discount)	
☐ 4-month extension of time: $1640 fee ($820 small entity discount)	
☐ 5-month extension of time: $2230 fee ($1115 small entity discount)	
☐ Information Disclosure Statement Fee: $180 fee (no small entity discount)	
☒ Notice of Appeal: $510 fee ($255 small entity discount)	510.00
☐ Filing a Brief in Support of Appeal: $510 fee ($255 small entity discount)	
☐ Request for Oral Hearing: $1030 fee ($515 small entity discount)	
☐ Utility Issue Fee: $1440 fee ($720 small entity discount)	
☐ Recording each patent assignment per property (times number of properties): $40 fee (no small entity fee discount)	
☐ Request for Continued Examination: $810 fee ($405 small entity discount)	
☐ Other: ____	
Subtotal (4)	970.00

SUBMITTED BY

Name (Print/Type)	Carlos Fisher	Registration No. (Attorney/Agent)	36,510	Telephone	949-450-1750
Signature				Date	11/16/07

The PTO did not receive the following listed item(s) A check for $970.00 but we got $460.00

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.	: 10/927,857	Confirmation No. 2409
Applicant	: ACHEAMPONG ET AL.	
Filed	: August 27, 2004	
Title	: METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS	
TC/A.U.	: 1654	
Examiner	: Cordero Garcia, Marcela M.	
Docket No.	: D-3111	
Customer No.	: 33197	

CERTIFICATE OF MAILING OR FACSIMILE TRANSMISSION

I hereby certify that this paper is being facsimile transmitted to the Patent and Trademark Office fax number 571-273-8300, or mailed by first class mail to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date shown below.

Date: November 16, 2007

Name: Sharon Waddell

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

PETITION FOR TWO MONTH EXTENSION OF TIME

Dear Sir:

Applicants hereby request a two-month extension of time to respond to the Final Office Action mailed July 2, 2007. A check for $460 is enclosed for the payment of this fee. If any other fee is due in connection with this communication please use Deposit Account 01-0885.

Sincerely yours,

Date: November 16, 2007

Carlos A. Fisher
Reg. No. 36, 510
Stout, Uxa, Buyan & Mullins, LLP
4 Venture, Suite 300
Irvine, California 92618
Telephone: 949-450-1750

11/23/2007 EHAILE1 00000028 10927857
01 FC:1252
460.00 OP

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No. : 10/927,857 Confirmation No. 2409
Applicant : ACHEAMPONG ET AL.
Filed : August 27, 2004
Title : METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS

TC/A.U. : 1654
Examiner : Cordero Garcia, Marcela M.

Docket No. : D-3111
Customer No. : 33197

CERTIFICATE OF MAILING OR FACSIMILE TRANSMISSION

I hereby certify that this paper is being facsimile transmitted to the Patent and Trademark Office fax number 571-273-8300, or mailed by first class mail to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date shown below.

Date: November 16, 2007
Name: Shawnna Waddell

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

NOTICE OF APPEAL

11/27/2007 EHAILE1 00000020 010885 10927857
01 FC:1401 510.00 DA

Dear Sir,

In reply to the Advisory Action mailed September 27, 2007, 2007, Applicants hereby appeal from the rejection of claims 1-22, 25-26, and 30-40 pursuant to 35 U.S.C. §103.

Applicants hereby enclose a check in the amount $460.00 in payment of the extension fee associated with a two-month extension of time to reply to the Final Office Action mailed September 27, 2007. Kindly utilize Deposit Account 01-0885 for the payment of

the fee associated with filing the Notice of Appeal and any other fee now due.

Respectfully submitted,

Carlos A. Fisher
Attorney for Applicant
Reg. No. 36, 510
4 Venture, Suite 300
Irvine, CA 92618
(949) 450-1750
Facsimile (494) 450-1764

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.	: 10/927,857	Confirmation No.	2409
Applicant	: Andrew Acheampong		
Filed	: August 27, 2004		
Title	: METHODS OF PROVIDING HERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS		
TC/A.U.	: 1654		
Examiner	: Cordero Garcia, Marcela M.		
Docket No.	: D-3111		
Customer No.	: 33197		

Mail Stop Appeal Brief - Patent
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

EXPRESS MAIL CERTIFICATE

EXPRESS MAIL MAILING LABEL NO. EV 516292512 US

Date of Deposit: **January 15, 2008**

I hereby certify that the following documents as identified below are being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and are addressed to the Mail Stop Appeal Brief - Patent, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450:

- ☒ Appeal Brief (30 pages)
- ☒ Stamped, self-addressed postcard
- ☒ Transmittal Form
- ☒ Fee Transmittal Form
- ☐
- ☐
- ☐
- ☐ Other: _____

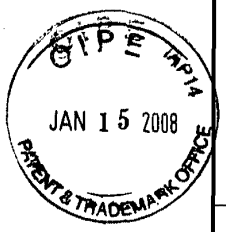
Each of the 4 above-identified documents are enclosed herewith.

Respectfully submitted,

Date: January 15, 2008

Shawnna Waddell
Assistant to Carlos A. Fisher
Stout, Uxa, Buyan & Mullins, LLP
4 Venture, Suite 300
Irvine, California 92618
Telephone: 949-450-1750

01-17-08



TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Application Number	10/927,857
Filing Date	August 27, 2004
First Named Inventor	Andrew Acheampong
Group Art Unit	1654
Examiner Name	Cordero Garcia, Marcela M.
Total Number of Pages in This Submission	37
Attorney Docket Number	D-3111

ENCLOSURES (*check all that apply*)

- [x] Fee Transmittal Form
- [ ] Fee Attached
- [ ] Amendment/Reply
- [ ] After Final
- [ ] Affidavits/declaration(s)
- [ ] Extension of Time Request
- [ ] Express Abandonment Request
- [ ] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Response to Missing Parts/ Incomplete Application
- [ ] Response to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
- [ ] Terminal Disclaimer
- [ ] Request for Refund
- [ ] CD, Number of CD(s) ____
- [ ] Landscape Table on CD
- [ ] After Allowance Communication to TC
- [ ] Appeal Communication to Board of Appeals and Interferences
- [x] Appeal Communication to TC *(Appeal Notice, Brief, Reply Brief)* 30 pages
- [ ] Proprietary Information
- [ ] Status Letter
- [x] Other Enclosure(s) *(please identify below)*

Express Mail Certificate

Self Addressed Postcard

- U.S. Patent 5,124,979

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	Stout, Uxa, Buyan & Mullins, LLP		
Signature	Carlos A. Fisher		
Printed Name	Carlos A. Fisher		
Date	January 15, 2008	Reg. No.	36,510

CERTIFICATE OF TRANSMISSION/MAILING

I hereby certify that this correspondence is being facsimile transmitted to the USPTO at fax number 571-273-8300, or deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: **Mail Stop** Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date shown below.

Signature	Shawnna Waddell		
Typed or printed name	Shawnna Waddell	Date	Jan. 15 2008

Fees Pursuant to the Consolidated Appropriations Act 2005 (H.R. 4818).

FEE TRANSMITTAL For FY 2008

Patent fees are subject to annual revision.

☐ Application claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 510.00

Complete if Known	
Application Number	10/927,857
Filing Date	August 27, 2004
First Named Inventor	Andrew Acheampong
Examiner Name	Codero Garcia, Marcela M.
Art Unit	1654
Attorney Docket No.	D-3111

METHOD OF PAYMENT *(check all that apply)*

☐ Check ☐ Credit Card ☐ Money Order ☐ None ☐ Other (please identify): ____

☒ Deposit Account Deposit Account Number 01-0885 Deposit Account Name Allergan, Inc.

For the above-identified deposit account, the Director is hereby authorized to: *(check all that apply)*

☒ Charge fee(s) indicated below ☐ Charge fee(s) indicated below, **except for the filing fee**

☐ Charge any additional fee(s) associated with this communication ☒ Credit any overpayments

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

FEE CALCULATION

1. BASIC FILING, SEARCH, AND EXAMINATION FEES

	FILING FEES		SEARCH FEES		EXAMINATION FEES		
Application Type	**Fee ($)**	**Small Entity Fee ($)**	**Fee ($)**	**Small Entity Fee ($)**	**Fee ($)**	**Small Entity Fee ($)**	**Fees Paid ($)**
Utility	310	155	510	255	210	105	
Design	210	105	100	50	130	65	
Plant	210	105	310	155	160	80	
Reissue	310	155	510	255	620	310	
Provisional	210	105	0	0	0	0	

Subtotal (1) **0**

2. EXCESS CLAIM FEES

Fee Description	Fee ($)	Small Entity Fee ($)
Each claim over 20 or , for Reissues, each claim over 20 and more than in the original patent	50	25
Each independent claim over 3 or, for Reissues, each independent claim more than in the original patent	210	105
Multiple Dependent Claims	370	185

Total Claims ____ -20 or HP = ____ x Fee ($) ____ Fee Paid ($) ____

HP = highest number of total claims paid for, if greater than 20

Indep. Claims ____ -3 or HP = ____ x Fee ($) ____ Fee Paid ($) ____

HP = highest number of independent claims paid for, if greater than 3

Multiple Dependent Claims Fee ($) ____ Fee Paid ($) ____

Subtotal (2) **0**

3. APPLICATION SIZE FEE

If the specification and drawings exceed 100 sheets of paper, the application size fee due is $260 ($130 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

Total Sheets ____ -100 = Extra Sheets ____ /50= Number of each additional 50 or fraction thereof ____(round up to a whole number) x Fee ($) ____ = Fee Paid ($) ____

Subtotal (3) **0**

4. OTHER FEE(S)

	Fee Paid ($)
☐ Surcharge - Late filing fee or oath/declaration: $130 fee ($65 small entity discount)	
☐ Non-English Specification: $130 fee (no small entity discount)	
☐ 1-month extension of time: $120 fee ($60 small entity discount)	
☐ 2-month extension of time: $460 fee ($230 small entity discount)	
☐ 3-month extension of time: $1050 fee ($525 small entity discount)	
☐ 4-month extension of time: $1640 fee ($820 small entity discount)	
☐ 5-month extension of time: $2230 fee ($1115 small entity discount)	
☐ Information Disclosure Statement Fee: $180 fee (no small entity discount)	
☐ Notice of Appeal: $510 fee ($255 small entity discount)	
☒ Filing a Brief in Support of Appeal: $510 fee ($255 small entity discount)	510.00
☐ Request for Oral Hearing: $1030 fee ($515 small entity discount)	
☐ Utility Issue Fee: $1440 fee ($720 small entity discount)	
☐ Recording each patent assignment per property (times number of properties): $40 fee (no small entity fee discount)	
☐ Request for Continued Examination: $810 fee ($405 small entity discount)	
☐ Other: ____	
Subtotal (4)	**510.00**

SUBMITTED BY

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Signature	Carlos A. Fisher			*Date*	January 15, 2008

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.	: 10/927,857	Confirmation No.	2409
Appellant	: ACHEAMPONG ET AL.		
Filed	: August 27, 2004		
Title	: METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS		
TC/A.U.	: 1654		
Examiner	: Cordero Garcia, Marcela M.		
Docket No.	: D-3111		
Customer No.	: 33197		

CERTIFICATE OF EXPRESS MAILING

I hereby certify that this paper is being sent by Express Mail bearing Label No. EV516292512 US to Box Appeal Brief-Patents, Commissioner for Patents, P.O. Box1450, Alexandria, VA 22313-1450 on the date shown below.

Date: January 15, 2008

Name: Shawnna Waddell

Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPEAL BRIEF

01/18/2008 SDENBOB3 00000001 010885 10927857
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TABLE OF CONTENTS

REAL PARTY IN INTEREST

The inventors Andrew Acheampong, Diane Tang-Liu, James N. Chang, and David F. Power assigned their entire interest in this patent application to Allergan, Inc. via an assignment document signed by the inventors on August 12, 2004 and recorded at reel 0157490, frame 0698 on August 27, 2004. Allergan, Inc., is therefore the owner of this patent application and the real party in interest in this appeal.

RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences.

STATUS OF CLAIMS

Claims 1 – 20 are withdrawn.

Claims 23-24 and 27-29 have been cancelled.

Claims 21-22, 25-26, and 30-40 are pending, have been rejected, and are under appeal.

STATUS OF AMENDMENTS

No amendment of any claim has been filed after the date of final rejection.

SUMMARY OF CLAIMED SUBJECT MATTER

Independent claim 21 is drawn to a therapeutically effective composition for treating an eye of a human or animal comprising an emulsion comprising water, castor oil, and cyclosporin A in a therapeutically effective amount of less than 0.1% by weight, the weight ratio of the cyclosporin A to the castor oil being less than 0.08. Support for this claim can be found in the specification, e.g., at Example 1, beginning on page 25 and page 8, lines 2-12.

Dependent claim 22 is drawn to the composition of claim 21 wherein the composition is formed as to result in substantially no detectable concentration of cyclosporin A in a patient's blood when an amount of the composition effective to treat dry eye syndrome is administered to the patient's eye. Support for this claim can be found where indicated for claim 21 and in the specification at, e.g., page 9, line 6 to page 10, line 13.

Dependent claim 25 is drawn to the composition of claim 21 wherein the composition is in the form of an emulsion. Support for this claim can be found where indicated for claim 21 and in the specification at, e.g., page 23, lines 16-19.

Dependent claim 26 is drawn to the composition of claim 21 wherein the castor oil is present in an amount greater than 0.625% by weight of the composition. Support for this claim can be found where indicated for claim 21 and in the specification at, e.g., page 16, lines 1-7.

Dependent claim 30 is drawn to the composition of claim 21 having a make-up so that when the composition is topically administered to an eye of a human in an effective amount in treating dry eye syndrome, the blood of the human has substantially no detectable concentration of the cyclosporin A. Support for this claim can be found where indicated for claim 21 and in the specification at, e.g., page 8, lines 13-23 and page 9, line 6 to page 10, line 13.

Dependent claim 31 is drawn to the composition of claim 21 wherein the composition comprises an effective amount of an emulsifier component. Support for this claim can be found where indicated for claim 21 and in the specification at, e.g., page 17, lines 20-27.

Dependent claim 32 is drawn to the composition of claim 21 wherein the composition comprises an effective amount of a tonicity component. Support for this claim can be found where indicated for claim 21 and in the specification at, e.g., page 20, lines 7-17.

Dependent claim 33 is drawn to the composition of claim 21 wherein the composition comprises an effective amount of an organic tonicity component. Support for this claim can be found where indicated for claim 21 and in the specification at, e.g., page 20, lines 7-17.

Dependent claim 34 is drawn to the composition of claim 21 wherein the composition comprises a polyelectrolytic component in an amount effective in stabilizing the composition. Support for this claim can be found where indicated for claim 21 and in the specification at, e.g., the paragraph bridging pages 19 and 20.

Dependent claim 35 is drawn to the composition of claim 21 wherein the composition includes water and has a pH in the range of about 7.0 to about 8.0. Support for this claim can be found where indicated for claim 21 and in the specification at, e.g., page 7, lines 16-19.

Dependent claim 36 is drawn to the composition of claim 21 wherein the composition includes water and has a pH in the range of about 7.2 to about 7.6. Support for this claim can be found where indicated for claim 21 and in the specification at, e.g., page 7, lines 16-19.

Dependent claim 37 is drawn to the composition of claim 21, which includes 1.25%, by

weight of castor oil. Support for this claim can be found where indicated for claim 21 and in the specification at, e.g., Example 1, beginning on page 25.

Dependent claim 38 is drawn to the composition of claim 21 which includes 0.05% by weight of cyclosporin A. Support for this claim can be found where indicated for claim 21 and in the specification at, e.g., Example 1, beginning on page 25.

Dependent claim 39 is drawn to the composition of claim 38 which includes 1.25% by weight of castor oil. Support for this claim can be found where indicated for claim 38 and in the specification at, e.g., Example 1, beginning on page 25.

Independent claim 40 is drawn to a composition for treating an eye of a human or animal comprising an emulsion comprising water, 1.25% by weight of castor oil and 0.05% by weight of cyclosporin A, the weight ratio of the cyclosporin A to the castor oil being 0.04. Support for this claim can be found e.g., Example 1, beginning on page 25 and page 3, lines 4-6.

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Presently pending claims 1-22, 25-26, and 30-40 have all been rejected pursuant to 35 U.S.C. §103(a) as being allegedly obvious over Ding et al., U.S. Patent Serial No. 5,474,979.

Claims 21-36 have been rejected under the doctrine of non-statutory obviousness-type double patenting over Ding et al., U.S. Patent Serial No. 5,474,979.

ARGUMENT

Rejections pursuant to 35 USC 103(a)

a) Claims 21, 22, 25-26 and 30-39

Claims 21, 22, 25-26 and 30-39 were rejected as allegedly obvious pursuant to 35 USC §103(a) over U.S. Patent Serial No. 5,474,979, to Ding et al. (the "Ding patent"). Appellants respectfully appeal from the Examiner's rejection for the following reasons.

An invention is patentable unless the invention is lacking in utility or novelty, or is obvious. The burden of proving that an invention lacks one of these requirements see 35 USC §101 ("Whoever invents or discovers any new and useful process, machine, manufacture or composition of matter . . . may obtain a patent therefor subject to the conditions and requirements of this title.")

Obviousness is determined from the point of view of a person of ordinary skill in the art at the time the invention was made. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. __, 82 U.S.P.Q.2d 1385 (2007). *Graham v. John Deere Co.*, 383 U.S. 1, 148 U.S.P.Q. 459 (1966) sets forth the standards used in determining whether a claimed invention is obvious under 35 U.S.C. §103(a): "the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined." 383 U.S. at 17, 148 U.S.P.Q. at 467.

The Scope and Content of the Prior Art

Ding et al., U.S. Patent Serial No. 5,474,979 (hereinafter "Ding") is the sole prior art reference alleged by the Examiner to render the present invention obvious. This reference is directed to stable emulsions for the delivery of poorly water-soluble medications to sensitive tissues. Ding, column 1, lines 4-6. Ding states that oils exacerbate the symptoms of certain ocular surface diseases such as dry eye syndrome, that are otherwise effectively treated using cyclosporin, a poorly water-soluble drug. Ding, et al., column 2, lines 46-49. Additionally, ocular formulations containing cyclosporin dissolved in oil (as in an emulsion) limits the bioavailability of cyclosporin to the target tissue. Ding, column 1, lines 45-53.

Ding discloses an emulsion containing cyclosporin (a poorly water soluble drug), castor oil and polysorbate 80 wherein the weight ratio of cyclosporin to castor oil is below 0.16 and preferably between 0.12 and 0.02. The stated advantage of these ratios is that, when so formulated the emulsion resists crystallization of the cyclosporin upon storage at room temperature for at least 9 months. Ding, column 3, lines 21-25 and lines 58-63. Thus, Ding discloses nothing concerning the limits of these ranges of ratios with respect to either efficacy or comfort.

In Example 1, Ding discloses 5 cyclosporin-containing compositions: these compositions include A) 0.4% cyclosporin A and 5% castor oil, B) 0.2% cyclosporin A and 5% castor oil, C) 0.2% cyclosporin A and 2.5% castor oil, D) 0.1% cyclosporin A and 2.5% castor oil, and E) 0.5% cyclosporin A and 0.625% castor oil. The weight ratios of cyclosporin A to castor oil in all these formulations is 0.08, except in composition B, in which case the ratio is 0.04 and the concentration of cyclosporin A is 0.2% by weight. These compositions were applied to rabbit eyes eight times a day for 7 days and found to cause "slight to mild discomfort" and slight hyperemia in rabbit eyes. Significantly, the compositions of only Examples 1A-1D (each having

a concentration of cyclosporin of 0.1% or greater) were indicated as delivering a "therapeutic level of cyclosporin" in ocular tissues. Ding, column 5, lines 19-22.

Very conspicuously absent from Ding's conclusions concerning the delivery of therapeutic levels of cyclosporin to the tissues of interest was Example 1E, which was not indicated in any way as being therapeutically effective.

The Differences Between the Prior Art and the Claims at Issue

Independent claim 21 is drawn to a therapeutically effective composition for treating an eye of a human or animal comprising an emulsion comprising water, castor oil, and cyclosporin A in a therapeutically effective amount of less than 0.1% by weight, the weight ratio of the cyclosporin A to the castor oil being less than 0.08. Thus, not only must the composition itself be therapeutically effective, but the amount of cyclosporin A must also be therapeutically effective and less than 0.1% by weight.

This latter fact alone is sufficient to demonstrate a non-obvious difference between the present invention and the disclosure of Ding. There is absolutely no indication in Ding that a therapeutically effective dosage of cyclosporin can be achieved at a concentration less than 0.1%. Indeed, the apparent failure of Ding to even test the bioavailablity of composition 1E (at 0.05% cyclosporin having less half or less the amount of cyclosporin A as any other of compositions A-D) demonstrates that Ding et al. could not and did not predict that compositions containing cyclosporin A dosages of less than 0.1% would be therapeutically effective, or alternatively, that composition 1E failed to deliver a therapeutic level of cyclosporin to the ocular tissues of interest. Either possibility must lead to the conclusion that therapeutically effective compositions having less than 0.1% cyclosporin A, as required by claim 21 and its dependent claims were unpredictable at the priority date of the present application.

Furthermore, present claim 21 and its dependent claims require that the ratio of cyclosporin A to castor oil must be less than 0.08%. Although it is true that Ding discloses a range of weight ratios of cyclosporin A to castor oil (less than 0.16 and preferably between 0.12 and 0.02), there is absolutely no indication in Ding that a composition having therapeutically effective dosages of cyclosporin less than 0.1% while simultaneously maintaining a ratio of castor oil to cyclosporin less than 0.08 could be made. Such higher relative concentrations of castor oil are thought to facilitate the resolution of "break-down" of the emulsion in the eye following instillation into the eye. See e.g., Specification at page 4, lines 5-11. Additionally, these relatively higher concentrations of castor oil may improve the cyclosporin's bioavailability when present in the composition in small amounts.

The Level of Ordinary Skill in the Art

Appellants submit that a person of ordinary skill in the art could not have predicted the present invention in light of Ding et al. As stated above, Ding that therapeutically effective compositions have a therapeutically effective amount of cyclosporin A above 0.1% by weight. Not only does Ding fail to indicate that cyclosporin A concentrations below this range would be therapeutically effective, but Ding's conspicuous failure to perform bioavailability testing on composition E, the only composition specifically made by Ding that has an amount of cyclosporin less than 0.1%, indicates that Ding et al. (having at least ordinary skill in the art) did not reasonably expect this composition to contain a therapeutically effective amount of cyclosporin A.

The Examiner has responded that all the embodiments encompassed by Ding et al. "are considered operative." Advisory Action of September 27, 2007, page 2.

With respect, this statement is not consistent with a proper reading of the law, and clearly skews the obviousness analysis. First, *Graham* is concerned with the meaning of a prior art reference (i.e., Ding et al.) to a person of ordinary skill in the art, rather than to the Examiner. *Accord KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. __, 82 U.S.P.Q.2d 1385 (2007) (obviousness is determined from the point of view of a person of ordinary skill in the art at the time the invention was made). Appellants submit that a ordinarily skilled drug formulator would recognize that, for example, a ratio of cyclosporin A to castor oil of "less than 0.16", includes a composition containing no cyclosporin A, as well as compositions containing vanishing small traces of the drug. Such a person would clearly not reasonably expect such trace amounts (or lack) of cyclosporin to constitute a "therapeutically effective amount" of the drug.

Secondly, the Examiner has not explained what is meant by the term "operative" in the sentence quoted above. However, the Examiner cannot mean that every embodiment encompassed by the disclosure of Ding is therapeutically effective, for the reasons presented in the previous paragraph. Nowhere in the lengthy Advisory Action does the Examiner address the material fact that the therapeutic effectiveness of the presently claimed composition and the therapeutic effectiveness of the amount of cyclosporin A in the claimed composition are limitations of the appealed claims, and that this effectiveness is in no way suggested or rendered predictable for the claimed compositions based upon the Ding et el. reference. Thus, whatever the meaning to the term "operable" in the Examiner's Advisory Action comments, a person of ordinary skill in the art would not have believed that all compositions having a ratio of cyclosporin A to castor oil within the range of ratios disclosed by Ding would be therapeutically effective. This is the proper legal inquiry, and to the extent the Examiner's statement contends otherwise, Appellants submit that this is error.

A reference teaches away from an invention when a person of ordinary skill in the art, upon reading a reference, would be led in a direction divergent from the path taken by the

inventor of presently claimed subject matter. See, e.g., *In re Gurley*, 27 F.3d 551,553, 31 U.S.P.Q.2d 1130, ____, (Fed. Cir. 1994). As acknowledged by the Examiner in his remarks in the Advisory Action, Ding discloses that the emulsions described therein are effective to prevent the precipitation of cyclosporin from solution, to prevent the deleterious effects on ocular surface disease caused by oil, and to provide a relatively low level of irritation to sensitive tissues including the eye, upon topical administration.

However, Ding is largely silent as to the range of cyclosporin concentrations conferring therapeutic effectiveness to the emulsions it describes. Only when discussing the compositions of Examples 1A-1D (respectively, 0.4%, 0.2%, 0.2% and 0.1% cyclosporin by weight) is any testing done concerning the delivery of cyclosporin to the eye by these emulsions. Ding, column 5. Thees tests were performed in rabbit eyes and only examined the "bioavailability" of cyclosporin in the disclosed emulsions; the "therapeutic level" of cyclosporin A in tissues of interest was determined, presumably by sacrificing the animals and assaying the amount of drug in dissected ocular tissues. Nevertheless, Ding does not indicate that any testing was performed to determine whether these emulsions were in fact effective in the treatment of dry eye syndrome.

Not one of Examples 1A-1D describles compositions falling within present claim 21 or its dependent claims. Despite the fact that "[t]he formulations of Examples 1-4 [all the formulations] were applied to rabbit eyes eight times a day for seven days and found to cause mild to moderate discomfort to ocular tissue, only the cyclosporin composition having less than 0.1% cyclosporin A by weight (Example 1E) was excluded by Ding et al. from bioavailability testing. This fact would clearly indicate to a person of ordinary skill in the art that Ding et al. did not expect that the composition of Example 1E is therapeutically effective, or Ding was aware that composition 1E did not deliver therapeutic levels of cyclodsporin to the tissues of interest. Accordingly, a person of ordinary skill in the art, upon reading Ding et al, would be led in a

direction divergent from the present formulations having a cyclosporin A concentration of less than 0.1% by weight. Indeed, based at least in part upon this, a finding that an ocular composition containing less than 0.1% cyclosporin A is therapeutically effective is surprising. Accordingly, Ding teaches away from the present invention.

Furthermore, even if Ding did not teach away from the invention of the instant application, given the disclosure (or lack of disclosure) of Ding it is clear that the present invention would have been unpredictable to a person of ordinary skill in the art at the time the invention was made. All Ding discloses is that a composition containing less that 0.1% by weight of cyclosporin A can be made, and is slightly or moderately irritating to the eye. Ding also discloses that, although 5 cyclosporin A-containing compositions were made, Ding decided not to even test the composition containing less than 0.1% cyclosporin A for efficiency of therapeutic delivery.

In order to be predictable, one must have a reasonable expectation of success. The word expect has a meaning defined as "to consider probabable or certain"; Miriam-Webster's Online Dictionary, www.m-w.com/dictionary/expecting (accessed January 11, 2008). However, an event that has no greater than a 50% probability of occurring can not give rise to a reasonable expectation of success. To be probable an event must be more likely to occur than simply based upon a flip of a coin; it must be at least "more possible than not".

In the present case, either a given concentration of cyclosporin is therapeutically effective or it is not. But without further information either option is merely a possibility and cannot give rise to a "reasonable expectation". Without a reasonable expectation of success, the present invention cannot be either predictable or obvious over Ding.

For these reasons, Appellants respectfully submit that the Examiner has erred in rejecting claims 21, 22, 25-26 and 30-39 as allegedly obvious over U.S. Patent Serial No. 5,474,979, and ask the Board to reverse this Examiner's rejection and permit the claims to proceed to issue.

b) Claim 40

Appellants hereby incorporate by reference the arguments made above with respect to claims 21, 22, 25-26 and 30-39 in their argument for the reversal of the rejection of claim 40 under 35 U.S.C. §103(a) as being allegedly obvious over Ding et al. In addition, Appellant have the following comments.

Claim 40 is drawn to a composition for treating an eye of a human or animal comprising an emulsion comprising water, 1.25% by weight of castor oil and 0.05% by weight of cyclosporin A, wherein the weight ratio of the cyclosporin A to the castor oil is 0.04. Claim 40 is thus drawn to a composition having specific concentrations of castor oil and cyclosporin A.

The concentration of cyclosporin A in the composition of claim 40 is 0.05% by weight. This is thus half the concentration of cyclosporin A as is present in the composition of Example 1D of Ding et al., the composition having the lowest concentration of cyclosporin (0.1% by weight) disclosed as being able to deliver therapeutic levels of cyclosporin A to tissues of interest. *See* Ding, column 5, lines 18-22.

Additionally, claim 40 defines a composition that has the same concentration of cyclosporin A (0.5% by weight) as was present in the composition of Example 1E in Ding, conspicuously omitted from the evaluation of therapeutic dosages in Ding. *Id.*

As stated above, Ding's omission of the composition of Example 1E from such evaluation is significant. Appellants submit that a person of ordinary skill in the art is not an automaton; such a person would conclude based on the evidence of record that Ding et al. had a reason for failing to report testing this formulation for therapeutic delivery of cyclosporin. This reason could reasonably be one of two things: either Ding et al. did not believe that a composition containing 0.05% cyclosporin A would delivery therapeutically effective dosages of cyclosporin A to the ocular tissues of interest, or the composition of Example 1E was tested and failed to deliver such dosages.

In either event, Ding et al. would dissuade such a person from attempting to employ a composition containing 0.05% cyclosporin for the treatment of ocular conditions. Thus, Ding teaches away from a composition for treating an eye of a human or animal comprising an emulsion comprising water, 1.25% by weight of castor oil and 0.05% by weight of cyclosporin A.

Thus, the disclosure in the present patent application that Composition II in Example 1, which contains 0.05% cyclosporin A and 1.25% castor oil "provides overall efficacy in treating dry eye disease substantially equal" to Composition 1, containing twice as much cyclosporin A, is clearly a surprising and unpredictable result. Specification, at page 26, lines 23-25.

Furthermore, Ding provides absolutely no reasoning for increasing the concentration of castor oil (relative to the concentration of cyclosporin A) to 1.25%. Thus, nothing in Ding or otherwise in the record indicates to the person of ordinary skill in the art that merely increasing the concentration of castor oil in composition of Example 1E would render effective a composition previously thought to be ineffective for the treatment of ocular surface disease.

For this reason, Appellants contend that the Examiner erred in rejecting claim 40 as being obvious over Ding, and respectfully ask the Board to reverse the rejection of this claim and permit it to proceed to issue.

Non-Statutory Obviousness-Type Double Patenting Rejection

a) Claims 21, 22, 25-26 and 30-36

Claims 21, 22, 25-126 and 30-36 stand rejected pursuant to the judicially created doctrine of obviousness-type double patenting over claims 1-8 of Ding et al., U.S. Patent No. 5,474,979.

While obviousness-type double patenting and §103 rejections may be analogous in the sense that an obviousness analysis is performed "the objects of comparison are very different: Obviousness compares claimed subject matter to the prior art; nonstatutory double patenting compares claims in an earlier patent to claims in a later patent or application." *Geneva Pharmaceuticals, Inc. v. GlaxoSmithKline PLC*, 349 F.3d 1373, 68 USPQ2d 1865 (Fed. Cir. 2003). Furthermore, "when considering whether the invention defined in a claim or an application would have been an obvious variation of the invention defined in the claim of a patent, the disclosure of the patent may not be used as prior art." MPEP §804(II)(b)(1) *citing General Foods Corp. v. Studiengesellschaft Hohle mbH*, 972 F.2d 1272, 1279, 23 USPQ2d 1839, 1846 (Fed. Cir. 1992).

Claim 1 of Ding is drawn to a pharmaceutical composition comprising a non-irritating emulsion of at least one cyclosporin in admixture with a higher fatty acid glyceride, polysorbate 80 and an emulsion-stabilizing amount of Pemulin® in water. Claims 2-5 are dependant claims. Claim 2 specifies that the cyclosporin comprises cyclosporin A. Claim 3, which depends from claim 2, indicates that the weight ratio of the higher fatty acid glyceride and polysorbate 80 is between about 0.3 and about 30. Claim 4, which depends from claim 3, indicates that the higher fatty acid glyceride comprises castor oil, and that the weight ratio of cyclosporin to castor oil is

below about 0.16. Claim 5 depends from claim 1, and indicates that the higher fatty acid glyceride and polysorbate 80 are present are present in amounts sufficient to prevent crystallization of cyclosporin for a period of up to about 9 months.

Claim 6 of Ding is an independent claim directed to a pharmaceutical emulsion comprising cyclosporin A, castor oil, Pemulin®, glycerine, polysorbate 80 and water in amounts sufficient to prevent crystallization of cyclosporin A for up to 9 months and suitable for topical ocular administration. As such claim 6 adds nothing to claims 1-5, and does not render the present invention obvious for the same reasons. Claim 7 is drawn to the pharmaceutical emulsion of claim 6 in which the cyclosporin A is present in an amount of from about 0.05% to about 0.4% by weight and the castor oil is present in an amount of from about 0.625% to about 5% by weight, the polysorbate 80 is present in about 1% by weight, the Pemulin® is present in an amount of about 0.05% by weight, and the glycerine is present in an amount of about 2.2% by weight.

Claim 8 is an independent claim drawn to a pharmaceutical emulsion consisting of cyclosporin A is present in an amount of from about 0.05% to about 0.4% by weight and the castor oil is present in an amount of from about 0.625% to about 5% by weight, the polysorbate 80 is present in about 1% by weight, the Pemulin® is present in an amount of about 0.05% by weight, and the glycerin is present in an amount of about 2.2% by weight, with a pH of between about 7.2 and 7.6, suitable for application to ocular tissue.

Each of claims 1-8 of Ding is drawn to a "pharmaceutical" emulsion or composition. In order to constitute a "pharmaceutical composition", the composition of claims 1-8 of Ding must be pharmaceutically active, and must define an pharmaceutically effective amount of the only active ingredient, cyclosporin A. However, none of these claims indicates what an "pharmaceutical" dosage of cyclosporin A would be.

Under the doctrine of obviousness-type double patenting only the claims (rather than the specification) may be used to reject pending claims in a double patenting rejection, however, "those portions of the specification which provide support for the patent claims may also be examined and considered when addressing the issue of whether a claim in the application defines an obvious variation of an invention claimed in the patent." *In re Vogel*, 422 F.2d 438, 441-42, 164 USPQ 619, 622 (CCPA 1970). Since the claims do not tell us what a "pharmaceutical" concentration of cyclosporin A is, the Ding patent's disclosure must be consulted to help explain the meaning of this term to a person of ordinary skill in the art at the time the present patent application was filed.

Ding discloses 5 exemplary compositions (Examples 1A-1E) containing cyclosporin A, present in concentrations of 4%, 2%, 2% 0.1% and 0.5% by weight, respectively. Although each composition appeared to cause slight to moderate discomfort when applied to rabbit eyes, only those compositions (Examples 1A-1D) having a cyclosporin A concentration of 0.1% or greater were reported to deliver therapeutic levels of cyclosporin A to tissues of interest. Not only was the composition of Example 1E not reported to have such efficacy, but Ding et al. are conspicuously silent with respect to the therapeutic efficacy of this composition. See Ding, column 4, lines 32-67 and column 5, lines 18-23.

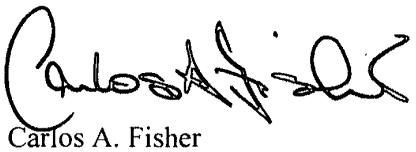
Thus, the specification of Ding, read from the perspective of a person of ordinary skill in the art seeking to define the term "pharmaceutical" as used in the claims, makes clear that a pharmaceutical composition has a cyclosporin A concentration of 0.1% by weight or above. Indeed, such a person would be led by Ding not to believe that a "pharmaceutical composition" is defined by concentrations of cyclosporin less than 0.1%, thus Ding teaches "in a direction divergent from the path taken" by the inventors of presently claimed subject matter. See, e.g., *In re Gurley*, 27 F.3d 551, 553, 31 U.S.P.Q.2d 1130, ___ (Fed. Cir. 1994).

It is therefore clear that a therapeutically active composition comprising water, castor oil, and a therapeutically active amount of cyclodextrin A less than 0.1% by weight cyclosporin A is contrary to the teaching of the claims of Ding et al. and is surprising in light thereof.

Additionally, the fact that a claimed invention may be encompassed by a disclosed generic disclosure does not, without more, render that invention obvious. See e.g., *In re Baird*, 16 F.3d 380, 29 U.S.P.Q.2d 1550 (Fed. Cir. 1994). For example, while claim 4 mentions a range of weight ratios (below about 0.16) of cyclosporin A to castor oil, this range clearly includes a composition wherein the weight ratio is 0 and the composition lacks cyclosporin. Therefore a person of ordinary skill in the art would know based upon this claim that claim 4 contains inoperable embodiments and would not be guided in any way to the therapeutically effective composition of claim 21 and its dependent claims, wherein the therapeutically effective concentration of cyclosporin A is less than 0.1% by weight, and the ratio of cyclosporin A to castor oil is below 0.08.

For these reasons Appellants hereby request that the Board reverse the Examiner's rejection of claims 21, 22, 25-26 and 30-36 over claims 1-8 of Ding et al. and permit the claims to proceed to issue.

Respectfully submitted,



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CLAIM APPENDIX

1. (Withdrawn) A method of treating an eye of a human or animal comprising:

administering to an eye of a human or animal a composition in the form of an emulsion comprising water, a hydrophobic component and a cyclosporin component in a therapeutically effective amount of less than 0.1% by weight of the composition, the weight ratio of the cyclosporin component to the hydrophobic component is less than 0.08.

2. (Withdrawn) The method of claim 1 wherein the administering step is effective in treating a condition selected from the group consisting of dry eye syndrome, phacoanaphylactic endophthalmitis, uveitis, vernal conjunctivitis, atopic keratoconjunctivitis and corneal graft rejection.

3. (Withdrawn) The method of claim 1 wherein the administering step is effective in treating dry eye syndrome.

4. (Withdrawn) The method of claim 1 wherein the blood of the human or animal has substantially no detectable concentration of the cyclosporin component.

5. (Withdrawn) The method of claim 1 wherein the blood of the human or animal has substantially no detectable concentration of the cyclosporin component as measured using a validated liquid chromatography/mass spectrometry-mass spectrometry analytical method.

6. (Withdrawn) The method of claim 1 wherein the blood of the human or animal has a concentration of the cyclosporin component of 0.1 ng/ml or less.

7. (Withdrawn) The method of claim 1 wherein the cyclosporin component comprises a material selected from cyclosporin A, derivatives of cyclosporin A and mixtures thereof.

8. (Withdrawn) The method of claim 1 wherein the cyclosporin component comprises cyclosporin A.

9. (Withdrawn) The method of claim 1 wherein the cyclosporin component is solubilized in the hydrophobic component present in the composition.

10. (Withdrawn) The method of claim 1 wherein the hydrophobic component is present in the composition in an amount greater than 0.625% by weight of the composition.

11. (Withdrawn) The method of claim 1 wherein the hydrophobic component comprises an oily material.

12. (Withdrawn) The method of claim 1 wherein the hydrophobic component comprises an ingredient selected from the group consisting of vegetable oils, animal oils, mineral oils, synthetic oils and mixtures thereof.

13. (Withdrawn) The method of claim 1 wherein the hydrophobic component comprises castor oil.

14. (Withdrawn) The method of claim 1 wherein the administering step comprises topically administering the composition to the eye of the human.

15. (Withdrawn) The method of claim 1 wherein the composition comprises an effective amount of an emulsifier component.

16. (Withdrawn) The method of claim 1 wherein the composition comprises an

effective amount of a tonicity component.

17. (Withdrawn) The method of claim 1 wherein the composition comprises an effective amount of an organic tonicity component.

18. (Withdrawn) The method of claim 1 wherein the composition comprises a polyelectrolyte component in an amount effective in stabilizing the composition.

19. (Withdrawn) The method of claim 1 wherein the composition has a pH in the range of about 7.0 to about 8.0.

20. (Withdrawn) The method of claim 1 wherein the composition has a pH in the range of about 7.2 to about 7.6.

21. (Previously Presented) A therapeutically effective composition for treating an eye of a human or animal comprising an emulsion comprising water, castor oil, and cyclosporin A in a therapeutically effective amount of less than 0.1% by weight, the weight ratio of the cyclosporin A to the castor oil being less than 0.08.

22. (Previously presented) The composition of claim 21 having a make-up so that when the composition is administered to an eye of a human in an effective amount in treating dry eye syndrome, the blood of the human has substantially no detectable concentration of the cyclosporin A.

23. (Canceled)

24. (Canceled)

25. (Original) The composition of claim 21 in the form of an emulsion.

26. (Previously Presented) The composition of claim 21 wherein the castor oil is present in an amount greater than 0.625% by weight of the composition.

27. (Canceled)

28. (Canceled)

29. (Canceled)

30. (Previously presented) The composition of claim 21 having a make-up so that when the composition is topically administered to an eye of a human in an effective amount in treating dry eye syndrome, the blood of the human has substantially no detectable concentration of the cyclosporin A.

31. (Original) The composition of claim 21 wherein the composition comprises an effective amount of an emulsifier component.

32. (Original) The composition of claim 21 wherein the composition comprises an effective amount of a tonicity component.

33. (Original) The composition of claim 21 wherein the composition comprises an effective amount of an organic tonicity component.

34. (Original) The composition of claim 21 wherein the composition comprises a

polyelectrolytic component in an amount effective in stabilizing the composition.

35. (Original) The composition of claim 21 wherein the composition includes water and has a pH in the range of about 7.0 to about 8.0.

36. (Original) The composition of claim 21 wherein the composition includes water and has a pH in the range of about 7.2 to about 7.6.

37. (Previously presented) The composition of claim 21 which includes 1.25% by weight of castor oil.

38. (Previously presented) The composition of claim 21 which includes 0.05% by weight of cyclosporin A.

39. (Previously presented) The composition of claim 38 which includes 1.25% by weight of castor oil.

40. (Previously presented) A composition for treating an eye of a human or animal comprising an emulsion comprising water, 1.25% by weight of castor oil and 0.05% by weight of cyclosporin A, the weight ratio of the cyclosporin A to the castor oil being 0.04.

EVIDENCE APPEENDIX

1. Ding et al., U.S. Patent No. 5,474,979.

RELATED PROCEDINGS APPENDIX

None

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/927,857	08/27/2004	Andrew Acheampong	D-3111	2409

33197 7590 02/07/2008

STOUT, UXA, BUYAN & MULLINS LLP
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EXAMINER	
ART UNIT	PAPER NUMBER

DATE MAILED: 02/07/2008

Please find below and/or attached an Office communication concerning this application or proceeding.

Notification of Non-Compliant Appeal Brief (37 CFR 41.37)	Application No.	Applicant(s)	
	10/927,857	ACHEAMPONG ET AL.	
	Examiner	Art Unit	
	Marcela Cordero Garcia	1654	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

The Appeal Brief filed on *15 January 2008* is defective for failure to comply with one or more provisions of 37 CFR 41.37.

To avoid dismissal of the appeal, applicant must file anamended brief or other appropriate correction (see MPEP 1205.03) within **ONE MONTH or THIRTY DAYS** from the mailing date of this Notification, whichever is longer. **EXTENSIONS OF THIS TIME PERIOD MAY BE GRANTED UNDER 37 CFR 1.136.**

1. ☐ The brief does not contain the items required under 37 CFR 41.37(c), or the items are not under the proper heading or in the proper order.

2. ☐ The brief does not contain a statement of the status of all claims, (e.g., rejected, allowed, withdrawn, objected to, canceled), or does not identify the appealed claims (37 CFR 41.37(c)(1)(iii)).

3. ☐ At least one amendment has been filed subsequent to the final rejection, and the brief does not contain a statement of the status of each such amendment (37 CFR 41.37(c)(1)(iv)).

4. ☐ (a) The brief does not contain a concise explanation of the subject matter defined in each of the independent claims involved in the appeal, referring to the specification by page and line number and to the drawings, if any, by reference characters; and/or (b) the brief fails to: (1) identify, for each independent claim involved in the appeal and for each dependent claim argued separately, every means plus function and step plus function under 35 U.S.C. 112, sixth paragraph, and/or (2) set forth the structure, material, or acts described in the specification as corresponding to each claimed function with reference to the specification by page and line number, and to the drawings, if any, by reference characters (37 CFR 41.37(c)(1)(v)).

5. ☒ The brief does not contain a concise statement of each ground of rejection presented for review (37 CFR 41.37(c)(1)(vi))

6. ☐ The brief does not present an argument under a separate heading for each ground of rejection on appeal (37 CFR 41.37(c)(1)(vii)).

7. ☐ The brief does not contain a correct copy of the appealed claims as an appendix thereto (37 CFR 41.37(c)(1)(viii)).

8. ☐ The brief does not contain copies of the evidence submitted under 37 CFR 1.130, 1.131, or 1.132 or of any other evidence entered by the examiner **and relied upon by appellant in the appeal**, along with a statement setting forth where in the record that evidence was entered by the examiner, as an appendix thereto (37 CFR 41.37(c)(1)(ix)).

9. ☐ The brief does not contain copies of the decisions rendered by a court or the Board in the proceeding identified in the Related Appeals and Interferences section of the brief as an appendix thereto (37 CFR 41.37(c)(1)(x)).

10. ☒ Other (including any explanation in support of the above items):

5.vi Grounds of Rejection :The claims in the Double Patenting rejection contains claims that have been cancelled. The grounds of rejection to be reviewed on appeal should list the same rejections and claims as those set in the final office action. .

/Everett R. Williams /
Everett R. Williams
Patent Appeals Specialist

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.	:	10/927,857	Confirmation No. 2409
Applicant	:	Acheampong et al.	
Filed	:	August 27, 2004	
Title	:	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS	
TC/A.U.	:	1654	
Examiner	:	Cordero Garcia, Marcela M	
Docket No.	:	D-3111	
Customer No.	:	33197	

Mail Stop Appeal Brief - Patent
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

EXPRESS MAIL CERTIFICATE

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Date of Deposit: **March 7, 2008**

I hereby certify that the following documents as identified below are being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and are addressed to the Mail Stop Appeal Brief - Patent, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450:

- ☒ Amended Appeal Brief
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- ☐
- ☐
- ☐
- ☐
- ☐ Other: _____

Each of the 3 above-identified documents are enclosed herewith.

Respectfully submitted,

Date: March 7, 2008

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03-10-08 IFW AF

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.	: 10/927,857	Confirmation No.	2409
Appellant	: ACHEAMPONG ET AL.		
Filed	: August 27, 2004		
Title	: METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS		
TC/A.U.	: 1654		
Examiner	: Cordero Garcia, Marcela M.		
Docket No.	: D-3111		
Customer No.	: 33197		

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Transmittal Letter

Applicants are submitting the attached Amended Appeal Brief in response to the Notice of Non-Compliant Brief, mailed February 7, 2008. As this reply is being filed within the period set for such reply, no fee is thought due in connection with the submission of this Amended Appeal Brief. However, if applicants are in error in this regard, please use Deposit Account 50-4004 for the payment of any fee now due.

Respectfully submitted,

Carlos A. Fisher
Attorney for Appellant

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.	: 10/927,857	Confirmation No.	2409
Appellant	: ACHEAMPONG ET AL.		
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Title	: METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS		
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Docket No.	: D-3111		
Customer No.	: 33197		

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Date: March 7, 2008

Name: Sheena Wallace

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P.O. Box 1450
Alexandria, VA 22313-1450

AMENDED APPEAL BRIEF

Carlos A. Fisher
Attorney for Appellant

TABLE OF CONTENTS

REAL PARTY IN INTEREST

The inventors Andrew Acheampong, Diane Tang-Liu, James N. Chang, and David F. Power assigned their entire interest in this patent application to Allergan, Inc. via an assignment document signed by the inventors on August 12, 2004 and recorded at reel 0157490, frame 0698 on August 27, 2004. Allergan, Inc., is therefore the owner of this patent application and the real party in interest in this appeal.

RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences.

STATUS OF CLAIMS

Claims 1 – 20 are withdrawn.

Claims 23-24 and 27-29 have been cancelled.

Claims 21-22, 25-26, and 30-40 are pending, have been rejected, and are under appeal.

STATUS OF AMENDMENTS

No amendment of any claim has been filed after the date of final rejection.

SUMMARY OF CLAIMED SUBJECT MATTER

Independent claim 21 is drawn to a therapeutically effective composition for treating an eye of a human or animal comprising an emulsion comprising water, castor oil, and cyclosporin A in a therapeutically effective amount of less than 0.1% by weight, the weight ratio of the cyclosporin A to the castor oil being less than 0.08. Support for this claim can be found in the specification, e.g., at Example 1, beginning on page 25 and page 8, lines 2-12.

Dependent claim 22 is drawn to the composition of claim 21 wherein the composition is formed as to result in substantially no detectable concentration of cyclosporin A in a patient's blood when an amount of the composition effective to treat dry eye syndrome is administered to the patient's eye. Support for this claim can be found where indicated for claim 21 and in the specification at, e.g., page 9, line 6 to page 10, line 13.

Dependent claim 25 is drawn to the composition of claim 21 wherein the composition is in the form of an emulsion. Support for this claim can be found where indicated for claim 21 and in the specification at, e.g., page 23, lines 16-19.

Dependent claim 26 is drawn to the composition of claim 21 wherein the castor oil is present in an amount greater than 0.625% by weight of the composition. Support for this claim can be found where indicated for claim 21 and in the specification at, e.g., page 16, lines 1-7.

Dependent claim 30 is drawn to the composition of claim 21 having a make-up so that when the composition is topically administered to an eye of a human in an effective amount in treating dry eye syndrome, the blood of the human has substantially no detectable concentration of the cyclosporin A. Support for this claim can be found where indicated for claim 21 and in the specification at, e.g., page 8, lines 13-23 and page 9, line 6 to page 10, line 13.

Dependent claim 31 is drawn to the composition of claim 21 wherein the composition comprises an effective amount of an emulsifier component. Support for this claim can be found where indicated for claim 21 and in the specification at, e.g., page 17, lines 20-27.

Dependent claim 32 is drawn to the composition of claim 21 wherein the composition comprises an effective amount of a tonicity component. Support for this claim can be found where indicated for claim 21 and in the specification at, e.g., page 20, lines 7-17.

Dependent claim 33 is drawn to the composition of claim 21 wherein the composition comprises an effective amount of an organic tonicity component. Support for this claim can be found where indicated for claim 21 and in the specification at, e.g., page 20, lines 7-17.

Dependent claim 34 is drawn to the composition of claim 21 wherein the composition comprises a polyelectrolytic component in an amount effective in stabilizing the composition. Support for this claim can be found where indicated for claim 21 and in the specification at, e.g., the paragraph bridging pages 19 and 20.

Dependent claim 35 is drawn to the composition of claim 21 wherein the composition includes water and has a pH in the range of about 7.0 to about 8.0. Support for this claim can be found where indicated for claim 21 and in the specification at, e.g., page 7, lines 16-19.

Dependent claim 36 is drawn to the composition of claim 21 wherein the composition includes water and has a pH in the range of about 7.2 to about 7.6. Support for this claim can be found where indicated for claim 21 and in the specification at, e.g., page 7, lines 16-19.

Dependent claim 37 is drawn to the composition of claim 21, which includes 1.25%, by

weight of castor oil. Support for this claim can be found where indicated for claim 21 and in the specification at, e.g., Example 1, beginning on page 25.

Dependent claim 38 is drawn to the composition of claim 21 which includes 0.05% by weight of cyclosporin A. Support for this claim can be found where indicated for claim 21 and in the specification at, e.g., Example 1, beginning on page 25.

Dependent claim 39 is drawn to the composition of claim 38 which includes 1.25% by weight of castor oil. Support for this claim can be found where indicated for claim 38 and in the specification at, e.g., Example 1, beginning on page 25.

Independent claim 40 is drawn to a composition for treating an eye of a human or animal comprising an emulsion comprising water, 1.25% by weight of castor oil and 0.05% by weight of cyclosporin A, the weight ratio of the cyclosporin A to the castor oil being 0.04. Support for this claim can be found e.g., Example 1, beginning on page 25 and page 3, lines 4-6.

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Presently pending claims 1-22, 25-26, and 30-40 have all been rejected pursuant to 35 U.S.C. §103(a) as being allegedly obvious over Ding et al., U.S. Patent Serial No. 5,474,979.

Claims 21,22, 25, 26, and 30-36 have been rejected under the doctrine of non-statutory obviousness-type double patenting over Ding et al., U.S. Patent Serial No. 5,474,979.

ARGUMENT

Rejections pursuant to 35 USC 103(a)

a) Claims 21, 22, 25-26 and 30-39

Claims 21, 22, 25-26 and 30-39 were rejected as allegedly obvious pursuant to 35 USC §103(a) over U.S. Patent Serial No. 5,474,979, to Ding et al. (the "Ding patent"). Appellants respectfully appeal from the Examiner's rejection for the following reasons.

An invention is patentable unless the invention is lacking in utility or novelty, or is obvious. The burden of proving that an invention lacks one of these requirements see 35 USC §101 ("Whoever invents or discovers any new and useful process, machine, manufacture or composition of matter . . . may obtain a patent therefor subject to the conditions and requirements of this title.")

Obviousness is determined from the point of view of a person of ordinary skill in the art at the time the invention was made. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. __, 82 U.S.P.Q.2d 1385 (2007). *Graham v. John Deere Co.,* 383 U.S. 1, 148 U.S.P.Q. 459 (1966) sets forth the standards used in determining whether a claimed invention is obvious under 35 U.S.C. §103(a): "the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined." 383 U.S. at 17, 148 U.S.P.Q. at 467.

The Scope and Content of the Prior Art

Ding et al., U.S. Patent Serial No. 5,474,979 (hereinafter "Ding") is the sole prior art reference alleged by the Examiner to render the present invention obvious. This reference is directed to stable emulsions for the delivery of poorly water-soluble medications to sensitive tissues. Ding, column 1, lines 4-6. Ding states that oils exacerbate the symptoms of certain ocular surface diseases such as dry eye syndrome, that are otherwise effectively treated using cyclosporin, a poorly water-soluble drug. Ding, et al., column 2, lines 46-49. Additionally, ocular formulations containing cyclosporin dissolved in oil (as in an emulsion) limits the bioavailability of cyclosporin to the target tissue. Ding, column 1, lines 45-53.

Ding discloses an emulsion containing cyclosporin (a poorly water soluble drug), castor oil and polysorbate 80 wherein the weight ratio of cyclosporin to castor oil is below 0.16 and preferably between 0.12 and 0.02. The stated advantage of these ratios is that, when so formulated the emulsion resists crystallization of the cyclosporin upon storage at room temperature for at least 9 months. Ding, column 3, lines 21-25 and lines 58-63. Thus, Ding discloses nothing concerning the limits of these ranges of ratios with respect to either efficacy or comfort.

In Example 1, Ding discloses 5 cyclosporin-containing compositions: these compositions include A) 0.4% cyclosporin A and 5% castor oil, B) 0.2% cyclosporin A and 5% castor oil, C) 0.2% cyclosporin A and 2.5% castor oil, D) 0.1% cyclosporin A and 2.5% castor oil, and E) 0.5% cyclosporin A and 0.625% castor oil. The weight ratios of cyclosporin A to castor oil in all these formulations is 0.08, except in composition B, in which case the ratio is 0.04 and the concentration of cyclosporin A is 0.2% by weight. These compositions were applied to rabbit eyes eight times a day for 7 days and found to cause "slight to mild discomfort" and slight hyperemia in rabbit eyes. Significantly, the compositions of only Examples 1A-1D (each having

a concentration of cyclosporin of 0.1% or greater) were indicated as delivering a "therapeutic level of cyclosporin" in ocular tissues. Ding, column 5, lines 19-22.

Very conspicuously absent from Ding's conclusions concerning the delivery of therapeutic levels of cyclosporin to the tissues of interest was Example 1E, which was not indicated in any way as being therapeutically effective.

The Differences Between the Prior Art and the Claims at Issue

Independent claim 21 is drawn to a therapeutically effective composition for treating an eye of a human or animal comprising an emulsion comprising water, castor oil, and cyclosporin A in a therapeutically effective amount of less than 0.1% by weight, the weight ratio of the cyclosporin A to the castor oil being less than 0.08. Thus, not only must the composition itself be therapeutically effective, but the amount of cyclosporin A must also be therapeutically effective and less than 0.1% by weight.

This latter fact alone is sufficient to demonstrate a non-obvious difference between the present invention and the disclosure of Ding. There is absolutely no indication in Ding that a therapeutically effective dosage of cyclosporin can be achieved at a concentration less than 0.1%. Indeed, the apparent failure of Ding to even test the bioavailablity of composition 1E (at 0.05% cyclosporin having less half or less the amount of cyclosporin A as any other of compositions A-D) demonstrates that Ding et al. could not and did not predict that compositions containing cyclosporin A dosages of less than 0.1% would be therapeutically effective, or alternatively, that composition 1E failed to deliver a therapeutic level of cyclosporin to the ocular tissues of interest. Either possibility must lead to the conclusion that therapeutically effective compositions having less than 0.1% cyclosporin A, as required by claim 21 and its dependent claims were unpredictable at the priority date of the present application.

Furthermore, present claim 21 and its dependent claims require that the ratio of cyclosporin A to castor oil must be less than 0.08%. Although it is true that Ding discloses a range of weight ratios of cyclosporin A to castor oil (less than 0.16 and preferably between 0.12 and 0.02), there is absolutely no indication in Ding that a composition having therapeutically effective dosages of cyclosporin less than 0.1% while simultaneously maintaining a ratio of castor oil to cyclosporin less than 0.08 could be made. Such higher relative concentrations of castor oil are thought to facilitate the resolution of "break-down" of the emulsion in the eye following instillation into the eye. See e.g., Specification at page 4, lines 5-11. Additionally, these relatively higher concentrations of castor oil may improve the cyclosporin's bioavailability when present in the composition in small amounts.

The Level of Ordinary Skill in the Art

Appellants submit that a person of ordinary skill in the art could not have predicted the present invention in light of Ding et al. As stated above, Ding that therapeutically effective compositions have a therapeutically effective amount of cyclosporin A above 0.1% by weight. Not only does Ding fail to indicate that cyclosporin A concentrations below this range would be therapeutically effective, but Ding's conspicuous failure to perform bioavailability testing on composition E, the only composition specifically made by Ding that has an amount of cyclosporin less than 0.1%, indicates that Ding et al. (having at least ordinary skill in the art) did not reasonably expect this composition to contain a therapeutically effective amount of cyclosporin A.

The Examiner has responded that all the embodiments encompassed by Ding et al. "are considered operative." Advisory Action of September 27, 2007, page 2.

With respect, this statement is not consistent with a proper reading of the law, and clearly skews the obviousness analysis. First, *Graham* is concerned with the meaning of a prior art reference (i.e., Ding et al.) to a person of ordinary skill in the art, rather than to the Examiner. *Accord KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. __, 82 U.S.P.Q.2d 1385 (2007) (obviousness is determined from the point of view of a person of ordinary skill in the art at the time the invention was made). Appellants submit that a ordinarily skilled drug formulator would recognize that, for example, a ratio of cyclosporin A to castor oil of "less than 0.16", includes a composition containing no cyclosporin A, as well as compositions containing vanishing small traces of the drug. Such a person would clearly not reasonably expect such trace amounts (or lack) of cyclosporin to constitute a "therapeutically effective amount" of the drug.

Secondly, the Examiner has not explained what is meant by the term "operative" in the sentence quoted above. However, the Examiner cannot mean that every embodiment encompassed by the disclosure of Ding is therapeutically effective, for the reasons presented in the previous paragraph. Nowhere in the lengthy Advisory Action does the Examiner address the material fact that the therapeutic effectiveness of the presently claimed composition and the therapeutic effectiveness of the amount of cyclosporin A in the claimed composition are limitations of the appealed claims, and that this effectiveness is in no way suggested or rendered predictable for the claimed compositions based upon the Ding et el. reference. Thus, whatever the meaning to the term "operable" in the Examiner's Advisory Action comments, a person of ordinary skill in the art would not have believed that all compositions having a ratio of cyclosporin A to castor oil within the range of ratios disclosed by Ding would be therapeutically effective. This is the proper legal inquiry, and to the extent the Examiner's statement contends otherwise, Appellants submit that this is error.

A reference teaches away from an invention when a person of ordinary skill in the art, upon reading a reference, would be led in a direction divergent from the path taken by the

inventor of presently claimed subject matter. See, e.g., *In re Gurley*, 27 F.3d 551,553, 31 U.S.P.Q.2d 1130, ____, (Fed. Cir. 1994). As acknowledged by the Examiner in his remarks in the Advisory Action, Ding discloses that the emulsions described therein are effective to prevent the precipitation of cyclosporin from solution, to prevent the deleterious effects on ocular surface disease caused by oil, and to provide a relatively low level of irritation to sensitive tissues including the eye, upon topical administration.

However, Ding is largely silent as to the range of cyclosporin concentrations conferring therapeutic effectiveness to the emulsions it describes. Only when discussing the compositions of Examples 1A-1D (respectively, 0.4%, 0.2%, 0.2% and 0.1% cyclosporin by weight) is any testing done concerning the delivery of cyclosporin to the eye by these emulsions. Ding, column 5. Thees tests were performed in rabbit eyes and only examined the "bioavailability" of cyclosporin in the disclosed emulsions; the "therapeutic level" of cyclosporin A in tissues of interest was determined, presumably by sacrificing the animals and assaying the amount of drug in dissected ocular tissues. Nevertheless, Ding does not indicate that any testing was performed to determine whether these emulsions were in fact effective in the treatment of dry eye syndrome.

Not one of Examples 1A-1D describles compositions falling within present claim 21 or its dependent claims. Despite the fact that "[t]he formulations of Examples 1-4 [all the formulations] were applied to rabbit eyes eight times a day for seven days and found to cause mild to moderate discomfort to ocular tissue, only the cyclosporin composition having less than 0.1% cyclosporin A by weight (Example 1E) was excluded by Ding et al. from bioavailability testing. This fact would clearly indicate to a person of ordinary skill in the art that Ding et al. did not expect that the composition of Example 1E is therapeutically effective, or Ding was aware that composition 1E did not deliver therapeutic levels of cyclodsporin to the tissues of interest. Accordingly, a person of ordinary skill in the art, upon reading Ding et al, would be led in a

direction divergent from the present formulations having a cyclosporin A concentration of less than 0.1% by weight. Indeed, based at least in part upon this, a finding that an ocular composition containing less than 0.1% cyclosporin A is therapeutically effective is surprising. Accordingly, Ding teaches away from the present invention.

Furthermore, even if Ding did not teach away from the invention of the instant application, given the disclosure (or lack of disclosure) of Ding it is clear that the present invention would have been unpredictable to a person of ordinary skill in the art at the time the invention was made. All Ding discloses is that a composition containing less that 0.1% by weight of cyclosporin A can be made, and is slightly or moderately irritating to the eye. Ding also discloses that, although 5 cyclosporin A-containing compositions were made, Ding decided not to even test the composition containing less than 0.1% cyclosporin A for efficiency of therapeutic delivery.

In order to be predictable, one must have a reasonable expectation of success. The word expect has a meaning defined as "to consider probabable or certain"; Miriam-Webster's Online Dictionary, www.m-w.com/dictionary/expecting (accessed January 11, 2008). However, an event that has no greater than a 50% probability of occurring can not give rise to a reasonable expectation of success. To be probable an event must be more likely to occur than simply based upon a flip of a coin; it must be at least "more possible than not".

In the present case, either a given concentration of cyclosporin is therapeutically effective or it is not. But without further information either option is merely a possibility and cannot give rise to a "reasonable expectation". Without a reasonable expectation of success, the present invention cannot be either predictable or obvious over Ding.

For these reasons, Appellants respectfully submit that the Examiner has erred in rejecting claims 21, 22, 25-26 and 30-39 as allegedly obvious over U.S. Patent Serial No. 5,474,979, and ask the Board to reverse this Examiner's rejection and permit the claims to proceed to issue.

b) Claim 40

Appellants hereby incorporate by reference the arguments made above with respect to claims 21, 22, 25-26 and 30-39 in their argument for the reversal of the rejection of claim 40 under 35 U.S.C. §103(a) as being allegedly obvious over Ding et al. In addition, Appellant have the following comments.

Claim 40 is drawn to a composition for treating an eye of a human or animal comprising an emulsion comprising water, 1.25% by weight of castor oil and 0.05% by weight of cyclosporin A, wherein the weight ratio of the cyclosporin A to the castor oil is 0.04. Claim 40 is thus drawn to a composition having specific concentrations of castor oil and cyclosporin A.

The concentration of cyclosporin A in the composition of claim 40 is 0.05% by weight. This is thus half the concentration of cyclosporin A as is present in the composition of Example 1D of Ding et al., the composition having the lowest concentration of cyclosporin (0.1% by weight) disclosed as being able to deliver therapeutic levels of cyclosporin A to tissues of interest. *See* Ding, column 5, lines 18-22.

Additionally, claim 40 defines a composition that has the same concentration of cyclosporin A (0.5% by weight) as was present in the composition of Example 1E in Ding, conspicuously omitted from the evaluation of therapeutic dosages in Ding. *Id.*

As stated above, Ding's omission of the composition of Example 1E from such evaluation is significant. Appellants submit that a person of ordinary skill in the art is not an automaton; such a person would conclude based on the evidence of record that Ding et al. had a reason for failing to report testing this formulation for therapeutic delivery of cyclosporin. This reason could reasonably be one of two things: either Ding et al. did not believe that a composition containing 0.05% cyclosporin A would delivery therapeutically effective dosages of cyclosporin A to the ocular tissues of interest, or the composition of Example 1E was tested and failed to deliver such dosages.

In either event, Ding et al. would dissuade such a person from attempting to employ a composition containing 0.05% cyclosporin for the treatment of ocular conditions. Thus, Ding teaches away from a composition for treating an eye of a human or animal comprising an emulsion comprising water, 1.25% by weight of castor oil and 0.05% by weight of cyclosporin A.

Thus, the disclosure in the present patent application that Composition II in Example 1, which contains 0.05% cyclosporin A and 1.25% castor oil "provides overall efficacy in treating dry eye disease substantially equal" to Composition 1, containing twice as much cyclosporin A, is clearly a surprising and unpredictable result. Specification, at page 26, lines 23-25.

Furthermore, Ding provides absolutely no reasoning for increasing the concentration of castor oil (relative to the concentration of cyclosporin A) to 1.25%. Thus, nothing in Ding or otherwise in the record indicates to the person of ordinary skill in the art that merely increasing the concentration of castor oil in composition of Example 1E would render effective a composition previously thought to be ineffective for the treatment of ocular surface disease.

For this reason, Appellants contend that the Examiner erred in rejecting claim 40 as being obvious over Ding, and respectfully ask the Board to reverse the rejection of this claim and permit it to proceed to issue.

Non-Statutory Obviousness-Type Double Patenting Rejection

a) Claims 21, 22, 25-26 and 30-36

Claims 21, 22, 25-126 and 30-36 stand rejected pursuant to the judicially created doctrine of obviousness-type double patenting over claims 1-8 of Ding et al., U.S. Patent No. 5,474,979.

While obviousness-type double patenting and §103 rejections may be analogous in the sense that an obviousness analysis is performed "the objects of comparison are very different: Obviousness compares claimed subject matter to the prior art; nonstatutory double patenting compares claims in an earlier patent to claims in a later patent or application." *Geneva Pharmaceuticals, Inc. v. GlaxoSmithKline PLC*, 349 F.3d 1373, 68 USPQ2d 1865 (Fed. Cir. 2003). Furthermore, "when considering whether the invention defined in a claim or an application would have been an obvious variation of the invention defined in the claim of a patent, the disclosure of the patent may not be used as prior art." MPEP §804(II)(b)(1) *citing General Foods Corp. v. Studiengesellschaft Hohle mbH*, 972 F.2d 1272, 1279, 23 USPQ2d 1839, 1846 (Fed. Cir. 1992).

Claim 1 of Ding is drawn to a pharmaceutical composition comprising a non-irritating emulsion of at least one cyclosporin in admixture with a higher fatty acid glyceride, polysorbate 80 and an emulsion-stabilizing amount of Pemulin® in water. Claims 2-5 are dependant claims. Claim 2 specifies that the cyclosporin comprises cyclosporin A. Claim 3, which depends from claim 2, indicates that the weight ratio of the higher fatty acid glyceride and polysorbate 80 is between about 0.3 and about 30. Claim 4, which depends from claim 3, indicates that the higher fatty acid glyceride comprises castor oil, and that the weight ratio of cyclosporin to castor oil is

below about 0.16. Claim 5 depends from claim 1, and indicates that the higher fatty acid glyceride and polysorbate 80 are present are present in amounts sufficient to prevent crystallization of cyclosporin for a period of up to about 9 months.

Claim 6 of Ding is an independent claim directed to a pharmaceutical emulsion comprising cyclosporin A, castor oil, Pemulin®, glycerine, polysorbate 80 and water in amounts sufficient to prevent crystallization of cyclosporin A for up to 9 months and suitable for topical ocular administration. As such claim 6 adds nothing to claims 1-5, and does not render the present invention obvious for the same reasons. Claim 7 is drawn to the pharmaceutical emulsion of claim 6 in which the cyclosporin A is present in an amount of from about 0.05% to about 0.4% by weight and the castor oil is present in an amount of from about 0.625% to about 5% by weight, the polysorbate 80 is present in about 1% by weight, the Pemulin® is present in an amount of about 0.05% by weight, and the glycerine is present in an amount of about 2.2% by weight.

Claim 8 is an independent claim drawn to a pharmaceutical emulsion consisting of cyclosporin A is present in an amount of from about 0.05% to about 0.4% by weight and the castor oil is present in an amount of from about 0.625% to about 5% by weight, the polysorbate 80 is present in about 1% by weight, the Pemulin® is present in an amount of about 0.05% by weight, and the glycerin is present in an amount of about 2.2% by weight, with a pH of between about 7.2 and 7.6, suitable for application to ocular tissue.

Each of claims 1-8 of Ding is drawn to a "pharmaceutical" emulsion or composition. In order to constitute a "pharmaceutical composition", the composition of claims 1-8 of Ding must be pharmaceutically active, and must define an pharmaceutically effective amount of the only active ingredient, cyclosporin A. However, none of these claims indicates what an "pharmaceutical" dosage of cyclosporin A would be.

Under the doctrine of obviousness-type double patenting only the claims (rather than the specification) may be used to reject pending claims in a double patenting rejection, however, "those portions of the specification which provide support for the patent claims may also be examined and considered when addressing the issue of whether a claim in the application defines an obvious variation of an invention claimed in the patent." *In re Vogel*, 422 F.2d 438, 441-42, 164 USPQ 619, 622 (CCPA 1970). Since the claims do not tell us what a "pharmaceutical" concentration of cyclosporin A is, the Ding patent's disclosure must be consulted to help explain the meaning of this term to a person of ordinary skill in the art at the time the present patent application was filed.

Ding discloses 5 exemplary compositions (Examples 1A-1E) containing cyclosporin A, present in concentrations of 4%, 2%, 2% 0.1% and 0.5% by weight, respectively. Although each composition appeared to cause slight to moderate discomfort when applied to rabbit eyes, only those compositions (Examples 1A-1D) having a cyclosporin A concentration of 0.1% or greater were reported to deliver therapeutic levels of cyclosporin A to tissues of interest. Not only was the composition of Example 1E not reported to have such efficacy, but Ding et al. are conspicuously silent with respect to the therapeutic efficacy of this composition. See Ding, column 4, lines 32-67 and column 5, lines 18-23.

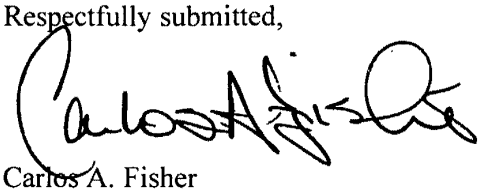
Thus, the specification of Ding, read from the perspective of a person of ordinary skill in the art seeking to define the term "pharmaceutical" as used in the claims, makes clear that a pharmaceutical composition has a cyclosporin A concentration of 0.1% by weight or above. Indeed, such a person would be led by Ding not to believe that a "pharmaceutical composition" is defined by concentrations of cyclosporin less than 0.1%, thus Ding teaches "in a direction divergent from the path taken" by the inventors of presently claimed subject matter. See, e.g., *In re Gurley*, 27 F.3d 551, 553, 31 U.S.P.Q.2d 1130, ___ (Fed. Cir. 1994).

It is therefore clear that a therapeutically active composition comprising water, castor oil, and a therapeutically active amount of cyclodextrin A less than 0.1% by weight cyclosporin A is contrary to the teaching of the claims of Ding et al. and is surprising in light thereof.

Additionally, the fact that a claimed invention may be encompassed by a disclosed generic disclosure does not, without more, render that invention obvious. See e.g., *In re Baird*, 16 F.3d 380, 29 U.S.P.Q.2d 1550 (Fed. Cir. 1994). For example, while claim 4 mentions a range of weight ratios (below about 0.16) of cyclosporin A to castor oil, this range clearly includes a composition wherein the weight ratio is 0 and the composition lacks cyclosporin. Therefore a person of ordinary skill in the art would know based upon this claim that claim 4 contains inoperable embodiments and would not be guided in any way to the therapeutically effective composition of claim 21 and its dependent claims, wherein the therapeutically effective concentration of cyclosporin A is less than 0.1% by weight, and the ratio of cyclosporin A to castor oil is below 0.08.

For these reasons Appellants hereby request that the Board reverse the Examiner's rejection of claims 21, 22, 25-26 and 30-36 over claims 1-8 of Ding et al. and permit the claims to proceed to issue.

Respectfully submitted,



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CLAIM APPENDIX

1. (Withdrawn) A method of treating an eye of a human or animal comprising:

administering to an eye of a human or animal a composition in the form of an emulsion comprising water, a hydrophobic component and a cyclosporin component in a therapeutically effective amount of less than 0.1% by weight of the composition, the weight ratio of the cyclosporin component to the hydrophobic component is less than 0.08.

2. (Withdrawn) The method of claim 1 wherein the administering step is effective in treating a condition selected from the group consisting of dry eye syndrome, phacoanaphylactic endophthalmitis, uveitis, vernal conjunctivitis, atopic keratoconjunctivitis and corneal graft rejection.

3. (Withdrawn) The method of claim 1 wherein the administering step is effective in treating dry eye syndrome.

4. (Withdrawn) The method of claim 1 wherein the blood of the human or animal has substantially no detectable concentration of the cyclosporin component.

5. (Withdrawn) The method of claim 1 wherein the blood of the human or animal has substantially no detectable concentration of the cyclosporin component as measured using a validated liquid chromatography/mass spectrometry-mass spectrometry analytical method.

6. (Withdrawn) The method of claim 1 wherein the blood of the human or animal has a concentration of the cyclosporin component of 0.1 ng/ml or less.

7. (Withdrawn) The method of claim 1 wherein the cyclosporin component comprises a material selected from cyclosporin A, derivatives of cyclosporin A and mixtures thereof.

8. (Withdrawn) The method of claim 1 wherein the cyclosporin component comprises cyclosporin A.

9. (Withdrawn) The method of claim 1 wherein the cyclosporin component is solubilized in the hydrophobic component present in the composition.

10. (Withdrawn) The method of claim 1 wherein the hydrophobic component is present in the composition in an amount greater than 0.625% by weight of the composition.

11. (Withdrawn) The method of claim 1 wherein the hydrophobic component comprises an oily material.

12. (Withdrawn) The method of claim 1 wherein the hydrophobic component comprises an ingredient selected from the group consisting of vegetable oils, animal oils, mineral oils, synthetic oils and mixtures thereof.

13. (Withdrawn) The method of claim 1 wherein the hydrophobic component comprises castor oil.

14. (Withdrawn) The method of claim 1 wherein the administering step comprises topically administering the composition to the eye of the human.

15. (Withdrawn) The method of claim 1 wherein the composition comprises an effective amount of an emulsifier component.

16. (Withdrawn) The method of claim 1 wherein the composition comprises an

effective amount of a tonicity component.

17. (Withdrawn) The method of claim 1 wherein the composition comprises an effective amount of an organic tonicity component.

18. (Withdrawn) The method of claim 1 wherein the composition comprises a polyelectrolyte component in an amount effective in stabilizing the composition.

19. (Withdrawn) The method of claim 1 wherein the composition has a pH in the range of about 7.0 to about 8.0.

20. (Withdrawn) The method of claim 1 wherein the composition has a pH in the range of about 7.2 to about 7.6.

21. (Previously Presented) A therapeutically effective composition for treating an eye of a human or animal comprising an emulsion comprising water, castor oil, and cyclosporin A in a therapeutically effective amount of less than 0.1% by weight, the weight ratio of the cyclosporin A to the castor oil being less than 0.08.

22. (Previously presented) The composition of claim 21 having a make-up so that when the composition is administered to an eye of a human in an effective amount in treating dry eye syndrome, the blood of the human has substantially no detectable concentration of the cyclosporin A.

23. (Canceled)

24. (Canceled)

25. (Original) The composition of claim 21 in the form of an emulsion.

26. (Previously Presented) The composition of claim 21 wherein the castor oil is present in an amount greater than 0.625% by weight of the composition.

27. (Canceled)

28. (Canceled)

29. (Canceled)

30. (Previously presented) The composition of claim 21 having a make-up so that when the composition is topically administered to an eye of a human in an effective amount in treating dry eye syndrome, the blood of the human has substantially no detectable concentration of the cyclosporin A.

31. (Original) The composition of claim 21 wherein the composition comprises an effective amount of an emulsifier component.

32. (Original) The composition of claim 21 wherein the composition comprises an effective amount of a tonicity component.

33. (Original) The composition of claim 21 wherein the composition comprises an effective amount of an organic tonicity component.

34. (Original) The composition of claim 21 wherein the composition comprises a

polyelectrolytic component in an amount effective in stabilizing the composition.

35. (Original) The composition of claim 21 wherein the composition includes water and has a pH in the range of about 7.0 to about 8.0.

36. (Original) The composition of claim 21 wherein the composition includes water and has a pH in the range of about 7.2 to about 7.6.

37. (Previously presented) The composition of claim 21 which includes 1.25% by weight of castor oil.

38. (Previously presented) The composition of claim 21 which includes 0.05% by weight of cyclosporin A.

39. (Previously presented) The composition of claim 38 which includes 1.25% by weight of castor oil.

40. (Previously presented) A composition for treating an eye of a human or animal comprising an emulsion comprising water, 1.25% by weight of castor oil and 0.05% by weight of cyclosporin A, the weight ratio of the cyclosporin A to the castor oil being 0.04.

EVIDENCE APPEENDIX

1. Ding et al., U.S. Patent No. 5,474,979.

RELATED PROCEDINGS APPENDIX

None

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10/927,857		1654	16M1

Correspondence Address / Fee Address Change

The following fields have been set to Customer Number 51957 on 04/17/2008

- Correspondence Address
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The address of record for Customer Number 51957 is:
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/927,857	08/27/2004	Andrew Acheampong	D-3111	2409

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EXAMINER	
CORDERO GARCIA, MARCELA M	
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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/927,857
Filing Date: August 27, 2004
Appellant(s): ACHEAMPONG ET AL.

Carlos A. Fisher
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 7 March 2008 appealing from the Office action mailed 2 July 2008.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

1. Ding et al. U.S. Patent No. 5,474,979

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-22, 25-26, 30-40 are rejected under 35 U.S.C. 103(a) as being obvious over Ding et al. (US 5,474,979 cited in the IDS of 12/27/04).

Ding et al. teach a composition for treating an eye of a human or animal comprising an emulsion comprising water, a hydrophobic component, and cyclosporine component (cyclosporin A, column 3, lines 30-37) in a therapeutically effective amount of less than 0.1% by weight, the weight ratio of the cyclosporin A (See, e.g., Example 1D) to the hydrophobic component (castor oil, a vegetable oil) is 0.08. (see, e.g., Example 1D). Ding et al. also teach that the weight ratio of the cyclosporin component to the hydrophobic component may be preferably varied between 0.12 and 0.02 (see, e.g., column 3, lines 19-20). Example 1E teaches 0.05 % of cyclosporin A; 0.625%

castor oil and a ratio of cyclosporin A to castor oil being 0.08. In addition, Ding et al. teach in claim 8 a pharmaceutical emulsion consisting of between about 0.05% and about 0.40% by weight cyclosporin A (which reads upon the limitation “less than 0.1 % by weight cyclosporin A” of instant claim 21) and between 0.625 and about 5.0 % castor oil. The corresponding lower and upper rations for the range is 0.05%/5.0% = 0.01 weight ratio of cyclosporin A/castor oil, which reads upon the limitation in instant claim 21 “the weight ratio of the cyclosporin A to the castor oil being less than 0.08” and the limitation of claim 40: wherein the weight ratio of cyclosporin to castor oil is 0.04. It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the composition of Ding et al. (e.g., Examples 1D and 1E) by increasing the amount of castor oil or decreasing the cyclosporin concentration in order to reduce the ratio of the cyclosporin component to hydrophobic component from 0.08 to, e.g., 0.04 as taught by Ding et al. (see, e.g., column 3, lines 18-20). The skilled artisan would have been motivated to do so because such ranges were taught in the Ding patent and it would have been obvious to use all the proportions taught therein. There would have been a reasonable expectation of success, given that compositions with a higher amount of castor oil are encompassed by the Ding et al. claims (e.g., claim 8) and because optimizing the ratio of cyclosporine/hydrophobic components to below 0.08 (i.e., 0.02 to 0.12, which reads upon the range of ratios of 0.02 to 0.08) was taught by Ding et al. (e.g., column 3, lines 18-20). Please note that the limitation of claim 22 and claim 30: “wherein the blood of the human has substantially no detectable concentration of the cyclosporin component after application of the composition” would necessarily

read upon a composition with the instantly claimed limitations as taught above. The limitation “emulsion" of claim 25: is taught, e.g., in column 3, lines 21-27 and 57-67; the limitation “wherein the castor oil is present in an amount greater than 0.625 % by weight of the composition" of claim 26 is taught, e.g., in Example 1D (1.25% of castor oil); the limitation “topically administered” of claim 30 is taught by Ding et al.’s claim 8; the limitation “comprising an effective amount of an emulsifier component” of claim 31 is taught in column 3, lines 38-40; the limitations drawn to a “tonicity component” and "organic tonicity component" in claims 32-33 are taught in column 4, lines 12-19; the limitation “polyelectrolytic component in an amount effective in stabilizing the composition” of claim 34 is taught in column 3, lines 64-67 and column 4, lines 1-12; the limitations of claims 35-36: “wherein the pH ranges about 7.0 to about 8.0” and "about 7.2 to about 7.6" are taught, e.g., in Examples 1A-E, column 4, line 43. The limitation of claims 37 and 39: “1.25% by weight of castor oil" is taught e.g., in Example 1D, the limitation “0.05% of cyclosporin A" is taught, e.g., in Example 1E, the limitation of claim 40: "1.25% of castor oil" is taught in Example 1D and 0.05 % by weight of cyclosporin A” is taught in Example 1E. The limitation of claim 40: "wherein the weight ratio of the cyclosporin A to the castor oil being 0.04" is taught, e.g. in Example 1B and is also within the ranges claimed by Ding et al. (e.g., column 3, lines 15-20). The adjustment of particular conventional working conditions (e.g., optimizing the compositions by using the proportions taught by the Ding et al. reference) is deemed merely a matter of judicious selection and routine optimization that is well within the purview of the skilled artisan. As such, it would have been obvious to one skilled in the art at the time of

invention to determine all optimum and operable conditions (e.g., ratios of all the components in the pharmaceutical composition), because such conditions are art-recognized result-effective variables that are routinely determined and optimized in the art through routine experimentation ("[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.". *In re Aller,* 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). See MPEP 2145.05). One would have been motivated to determine all optimum and operable conditions in order to achieve the highest yield of the highest purity product in the most efficient manner. One would have had a reasonable expectation for success because such modifications are routinely determined and optimized in the art through routine experimentation.

From the teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

(10) Response to Argument

Applicant's arguments have been carefully considered by Examiner, but not deemed persuasive for the following reasons:

Rejections pursuant to 35 USC 103(a)

a) Claims 21, 22, 25-26 and 30-39

i) The Scope and Content of the Prior Art section:

First of all, in the page 12 of the Appeal Brief, last paragraph, Examiner would like to point out the typographical error in line 4 of the last paragraph: Example 1D contains 0.05% of cyclosporin A instead of 0.5% as indicated. With regards to the statement that "Ding discloses nothing concerning the limits of these range of ratios with respect to either efficacy of comfort" (page 12, second paragraph), Examiner points out that claim 8 of Ding is drawn to a pharmaceutical emulsion for topical application to ocular tissue and that encompasses compositions within the claimed ranges. Such pharmaceutical compositions including Examples 1A-D have therapeutic activity in treating dry eye (e.g., column 5, lines 15-25) and are therefore "therapeutically effective" (e.g., column 5, lines 23-25). Additionally, such compositions are mentioned to cause "only slight to mild discomfort and slight hyperemia in the rabbit eyes" (column 5, lines 15-18). The disclosure of Ding et al. also teaches that the pharmaceutical compositions are "nonirritating with high comfort level and low irritation potential suitable for delivery to sensitive areas such as ocular tissues" (column 3, lines 6-10) Please also note that the composition of Example 1E was used in applications to rabbit's eyes (column 5, lines 15-17) since the formulations in Examples 1-4 were used. Additionally, the

instantly claimed ranges are encompassed by claim 8 of Ding et al., which is drawn to pharmaceutical compositions which one of skill in the art would have been motivated to make for their therapeutic effectiveness.

ii) The Differences Between the Prior Art and the Claims at Issue

Applicant argues that there is absolutely no indication in Ding et al. that a therapeutically effective dosage of cyclosporin can be achieved at a concentration less than 0.1% and that the apparent failure of Ding to even test the bioavailability of composition 1E at 0.05% cyclosporin demonstrates that Ding et al. could not and did not predict that compositions containing cyclosporin A dosages of less than 0.1% would be therapeutically effective, or alternatively, that composition 1E failed to deliver a therapeutic level of cyclosporine to the ocular tissues of interest. This is not find persuasive as Ding et al. teach pharmaceutical compositions for topical eye administration encompassing such ranges (e.g., claim 8 of Ding et al) and because the conclusory statement "that Ding et al. could not and did not predict that compositions containing cyclosporin A dosages of less than 0.1% would be therapeutically effective, or alternatively, that composition 1E failed to deliver a therapeutic level of cyclosporin to the ocular tissues of interest" is provided without any evidenciary support. MPEP 2164.05 states:

> "Applicant may submit factual affidavits under 37 CFR 1.132 or cite references to show what one skilled in the art knew at the time of filing the application. A declaration or affidavit is, itself, evidence that must be considered. The weight to give a declaration or affidavit will depend upon the amount of factual evidence

the declaration or affidavit contains to support the conclusion of enablement. In re Buchner, 929 F.2d 660, 661, 18USPQ2d 1331, 1332 (Fed. Cir. 1991) ("expert's opinion on the ultimate legal conclusion must be supported by something more than a conclusory statement"); cf. In re Alton, 76F.3d 1168, 1174, 37 USPQ2d 1578, 1583 (Fed. Cir. 1996) (declarations relating to the written description requirement should have been considered)."

Please also note that the composition of Example 1E was used in applications to rabbit's eyes (column 5, lines 15-17) since the formulations in Examples 1-4 were used. It is clear that application of such compositions to the eye indicates that the pharmaceutical composition is expected to be therapeutically effective with respect to e.g., dry eye (column 5, line 25) and because it would not be made into a pharmaceutical composition without having a bioactive function.

Additionally the arguments directed to "less than 0.08" as not being taught by Ding et al. have been considered but have not been found persuasive as the Ding et al. patent teaches ranges between 0.12 and 0.02, which encompass "less than 0.08".

iii) The Level of Ordinary Skill in the Art

Applicant's arguments have been carefully considered but not deemed persuasive for the reasons set forth above. Additionally, the Ding et al. reference does not teach away from the instant invention. The statement that "a person of ordinary skill in the art could not have predicted the present invention in the light of Ding et al." because not only does Ding fail to indicate that cyclosporin A concentrations below this range would be therapeutically effective, but Ding's conspicuous failure to perform

bioavailability testing on composition E, the only composition specifically made by Ding that has an amount of cyclosporin less than 0.1% indicates that Ding et al. (having at least ordinary skill in the art) did not reasonably expect this composition to contain a therapeutically effective amount of cyclosporine A" (page 14, paragraph 2). However, this is a conclusory statement which has not been supported by evidence. (See MPEP 2164.05). Please also note that the composition of Example 1E was used in applications to rabbit's eyes (column 5, lines 15-17) since the formulations in Examples 1-4 were used. It is clear that application of such compositions to the eye indicates that the pharmaceutical composition is expected to be therapeutically effective with respect to e.g., dry eye (column 5, line 25) and because it would not be made into a pharmaceutical composition without having a bioactive function.

With regards to the arguments in pages 15-17 of the Appeal Brief, Examiner has carefully considered applicant's arguments but does not find them persuasive because the Ding et al. patent teaches pharmaceutical compositions which would reasonably be expected to be therapeutically effective in light of the disclosure of Ding teaching that "The formulations in Examples 1-4 (note this would include Example 1E) were applied to rabbit eyes eight times a day..." (column 5, lines 15-17; see also claim 8). It is clear that application of such compositions to the eye indicates that the pharmaceutical composition is expected to be therapeutically effective with respect to e.g., dry eye (column 5, line 25) and because it would not be made into a pharmaceutical composition without having a bioactive function.

b) Claim 40

Applicant's arguments set forth in pages 18-19 of the Appeal Brief have been carefully considered but not deemed persuasive for the reasons of record and because it would be obvious to use the proportions taught by the Ding et al. reference which include the instantly claimed ranges in pharmaceutical compositions which therefore would be reasonably expected to have the bioactivity taught by the Ding et al. patent.

The arguments indicating that Ding teaches away from a composition for treating an eye of a human or animal comprising an emulsion comprising water, 1.25% of castor oil and 0.05% by weight of cyclosporin A is not deemed persuasive because the "reasonable beliefs" assumed to be held by Ding et al. were not supported by any evidence and therefore are mere conclusory statements. Additionally, the range 0.04 is taught both in Examples and in the acceptable proportion ranges for the pharmaceutical compositions for eye treatment. Applicant's arguments stating that a comparison of a composition with 0.1 % cyclosporin, 1.25 % castor oil and 0.08 cyclosporin/ castor oil (corresponding to Example 1D in Ding et al.) and 0.05% cyclosporin, 1.25% castor oil and 0.04 cyclosporin/ castor oil (page 26 of application's disclosure) provide overall efficacy in treating dry eye that is substantially equal and therefore it is a clearly surprising and unexpected result, have been considered but not deemed persuasive because substantially equal is not defined via any specific detection measurements and therefore it is not clear what "substantially equal" is and therefore the extent of the effect measured is not well determined or evidenced. Additionally, the similar eye irritations in the use of both compositions is not an unexpected result as it is taught by Ding et al. at column 3, lines 6-10 which teaches "nonirritating pharmaceutical compositions with high

comfort level and low irritation potential suitable for delivery to sensitive areas such as ocular tissues" and at column 5, lines 14-17: “The formulations in Examples 1-4 were applied to rabbit eyes eight times a day for seven days and were found to cause only slight to mild discomfort and slight hyperemia in the rabbit eyes”.

Non-Statutory Obviousness-Type Double Patenting Rejection

a) Claims 21, 22, 25-26 and 30-36

Applicant argues in pages 22-23 that the disclosure of Ding is require for a person of ordinary skill in the art to see what the term "pharmaceutical" means, and that the specification of Ding teaches that a pharmaceutical composition has a cyclosporin A concentration of 0.1% by weight or above. Examiner has carefully considered this argument but it is not deemed persuasive because claim 8 of Ding is drawn to a “pharmaceutical emulsion consisting of between about 0.05% and about 0.40% by weight, cyclosporin A” (which clearly includes 0.05% and is not limited to 0.1 % or more as Applicant argues).

Additionally, the arguments regarding that a claimed invention may be encompassed by a generic disclosure does not, without more, render that invention obvious, and that the weight ratio of cyclosporin/castor oil would encompass 0 wherein cyclosporin is zero and therefore non-therapeutic have been carefully considered but not deemed persuasive because the Ding patent is also drawn to a genus which encompasses the instantly claimed subgenus of claim 21 and the instantly claimed species of claim 40. One skilled in the art would have been motivated to make therefore

pharmaceutical compositions which were previously taught by Ding to be “nonirritating with high comfort level and low irritation potential suitable for delivery to sensitive areas such as ocular tissues" (column 3, lines 6-10) including those with 0.05% cyclosporin A (as in Example 1E) since such compositions were applied to rabbits for their therapeutic use as set forth above, and since it would have been obvious to one of ordinary skill in the art to have used the proportions taught by Ding et al.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Marcela M Cordero Garcia/

Primary Examiner, Art Unit 1654

Conferees:

/Andrew D Kosar/
Primary Examiner, Art Unit 1654
Acting SPE

/Robert A. Wax/
Robert A. Wax
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Technology Center 1600

MMCG 05/08

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/927,857	08/27/2004	Andrew Acheampong	D-3111	2409

51957 7590 06/12/2008

ALLERGAN, INC.
2525 DUPONT DRIVE, T2-7H
IRVINE, CA 92612-1599

EXAMINER	
ART UNIT	PAPER NUMBER

DATE MAILED: 06/12/2008

Please find below and/or attached an Office communication concerning this application or proceeding.

UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO./ CONTROL NO.	FILING DATE	FIRST NAMED INVENTOR / PATENT IN REEXAMINATION	ATTORNEY DOCKET NO.
10927857	8/27/04	ACHEAMPONG ET AL.	D-3111

ALLERGAN, INC.
2525 DUPONT DRIVE, T2-7H
IRVINE, CA 92612-1599

EXAMINER	
MARCELA M. CORDERO GARCIA	
ART UNIT	**PAPER**
1654	20080605

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner for Patents

The Examiner's Answer mailed on 5/28/08 is missing Heading 11)Related Proceedings Appendix is missing. This section should read: 11)Related Prceedings Appendix. None.
Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARCELA M. CORDERO GARCIA whose telephone number is (571)272-2939. The examiner can normally be reached on M-F 8:30-5:00.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia J. Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.
Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Cecilia Tsang/
Supervisory Patent Examiner, Art Unit 1654

/Marcela M Cordero Garcia/
Examiner, Art Unit 1654

PTO-90C (Rev.04-03)

Attorney's Docket No.: D-2957

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.	: 10/927,857	Confirmation No.	2409
Appellant	: ACHEAMPONG ET AL.		
Filed	: August 27, 2004		
Title	: METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS		
TC/A.U.	: 1654		
Examiner	: Cordero Garcia, Marcela M.		
Docket No.	: D-3111		
Customer No.	: 33197		

Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REPLY BRIEF

Carlos A. Fisher
Stout, Uxa, Buyan & Mullins LLP

For Appellant

Appellants are in receipt of the Examiner's Answer mailed May 28, 2008, and have the following comments.

The Examiner has added no new Grounds of Rejection. The sole basis for rejection of 1-22, 25-26 and 30-40 remains the allegation that the claims are obvious under 35 USC §103(a) in view of Ding et al., U.S. Patent No. 5,474,979.

Reply to Examiner's Response to Argument

The Examiner points out the typographical error in line 4 of page 12 of the Appeal Brief, wherein Example 1D is said to contain 0.5% cyclosporin A rather than the correct amount of 0.05% (w/v). Applicants appreciate the Examiner's courtesy in this regard, and hope that the error has not caused any undue hardship.

The Examiner responds to the detailed arguments made by the Appellants, as follows:

Claims 21, 22, 25-26 and 30-39

1) The Examiner attempts to rebut the Applicants' statement on page 12, second paragraph of the Office action that Ding does not disclose the limits of this range of ratios with respect to efficacy or comfort. Thus, the Examiner states that "claim 8 of Ding is drawn to a pharmaceutical emulsion for topical application to ocular tissue and that [sic] encompasses compositions within the claimed ranges." Reply Brief at page 7,

Paragraph 10(a)(i). The range of ratios of cyclosporin A to castor oil contained in claims 21, 22, 25-26 and 30-39 is "less than 0.08". *See* claim 21.

Claim 8 of Ding is drawn to an emulsion containing, among other ingredients, between about 0.05% and about 0.40% cyclosporin A, and about 0.625% and about 5.0% castor oil, both by weight. Claim 8 does not expressly mention ratios of cyclosporin A to castor oil; however, if ratios are to be calculated from these ingredients, the lowest ratio implied by these concentrations would be about 0.05/5.0 = 0.01, and the highest ratio would be about 0.4/0.625=0.64.

Even if claim 8 were interpreted to implicitly disclose a range of ratios of about 0.01 to about 0.64, the Examiner's statement fails to consider either the pending claims or the prior art (Ding) as a whole, as dictated e.g., by the Manual of Patent Examining Procedure at Section 2141.02. For example, claim 21 is drawn to a therapeutically effective composition containing cyclosporin A in a therapeutically effective amount of less than 0.1% by weight, the weight ratio of the cyclosporin A to the castor oil being less than 0.08. Thus, not only must the composition itself be therapeutically effective, but the amount of cyclosporin A must also be therapeutically effective and less than 0.1% by weight. Claim 8 says nothing about therapeutic effectiveness at all claimed concentrations, nor is it reasonable to assume that it does, since a patent claim need not cover only operative embodiments. *See e.g., Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984). (Holding that the presence of inoperative

embodiments within the scope of a claim does not necessarily render a claim nonenabled).

2) The Examiner, citing Ding, col. 5, lines 15-25, alleges that the compositions of Examples 1A-1D of Ding have therapeutic activity in treating dry eye and are therefore therapeutically effective. However, Applicants note that none of Examples 1A-1D fall within the present claims. None of these compositions contain cyclosporin at a concentration below 0.1% by weight. Only Example 1B has a ratio of cyclosporin A to castor oil below 0.08 - however, this composition (1B) contains 0.2% cyclosporin A. To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 CCPA 1974). This clearly not the case with Examples 1A-1D of Ding.

The Examiner again states "the instantly claimed ranges [of ratios] are encompassed by claim 8 of Ding et al." Ding, pages 7-8, Paragraph 10(a)(i). However, this is respectfully not true. It is true that if ratios of cyclosporin A to castor oil (unmentioned in claim 8) were to be calculated, there is overlap between the range of ratios so obtained (about 0.01 to about 0.64), and the range or ratios present in the pending instant claims ("less than 0.08").

3. However, equally importantly of course, the pending claims contain other limitations (for example, the requirement that the invention be a therapeutically effective composition containing less than 0.1% cyclosporin A). Furthermore, the

Examiner fails to adequately address the fact the Example 1E, which is the only composition in Ding that contains less than 0.1% cyclosporin A, is not listed at all by Ding in column 5, lines 15-25 as a therapeutically effective composition.

With respect, Ding's clearly intentional omission of Example 1E from mention when discussing the results of animal testing of the cyclosporin A compositions cannot simply be ignored, particularly when Examples 1A-1D are mentioned three times in col. 5. It is a matter of black letter law that even a *prima facie* case of obviousness can "be rebutted by showing that the art, in any material respect, teaches away from the claimed invention." MPEP 2144.05, citing *In re Geisler*, 116 F.3d 1465, 1471, 43 USPQ2d 1362, 1366 (Fed. Cir. 1997). In the present case, Applicants submit that a person of ordinary skill in the art would note Ding's intentional failure to mention the composition of Example 1E when mentioning therapeutic efficacy and interpret this omission as a purposeful teaching away from using less than 0.1% cyclosporin to make a therapeutically effective composition.

The Examiner states that this argument is not persuasive because Ding et al. allegedly teaches pharmaceutical compositions for topical eye administration encompassing (actually overlapping) the range "less than 0.1% cyclosporin". *See Examiner's Answer*, page 8, Paragraph 10(a)(ii). However, as stated above, a patent claim need not cover only operative embodiments. *See e.g., Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984). Therefore, while claim 8 of Ding may disclose wide ranges which include

concentrations of cyclosporin below 0.1 within their purview, there is no justification for assuming that all of the compositions included within claim 8's scope are therapeutically effective, as required of the present claims.

The Examiner characterizes as "conclusory" the Applicant's statement in the Appeal Brief that Ding could not and did not predict that compositions containing cyclosporin A of less than 0.1% would be therapeutically effective. Actually, it is simply factually accurate that Ding did not make this prediction; the Examiner has not pointed to one location in the specification of Ding in which such prediction is made.

The statement that Ding "could not" make such prediction is indeed the result of concluding that the omission of Example 1E was not an oversight, but was intended by Ding; the utter reasonableness of this conclusion is evident from the mention by Ding three times of "Examples 1A-1D" (and thus the lack of mention of Example 1E) in column 5 when discussion the therapeutic effectiveness of higher concentrations of cyclosporin A. The Examiner states that the composition of Example 1E was used in applications to rabbit eyes (Examiner's Answer page 9 and page 10). This is true, and only bolsters the reasonableness of the Applicants' position that a person of reasonable skill in the art would conclude that the rabbit results using the Example 1E composition were somehow unfavorable since they were not reported. With respect, the Examiner's interpretation that because this composition was applied it "is expected to be therapeutically effective" is entirely without basis. The person of ordinary skill in the art

is aware that animal tests of this sort are performed to determine a range of effective concentrations, not because every concentration is "expected" to be effective.

Contrary to the Examiner's position on page 8 of the Examiner's Answer, the fact that a person of ordinary skill in the art would reasonably reach the conclusion that a prior art reference teaches away from a claimed invention does not require evidentiary support. No evidence is needed to "show what one of ordinary skill knew at the time of filing" when the question is what a prior art reference teaches.

Applicants again submit that "ascertaining the differences between the claimed invention and the prior art requires interpreting the claim language, see MPEP § 2111, and considering both the invention and the prior art as a whole." Ding, like any prior art reference, must be considered for all it teaches, particularly when, as here, it teaches away from the claimed invention. *See e.g.*, MPEP §2141. Respectfully, to ignore this obvious teaching away is reversible error.

Claim 40

a) The Examiner finds the Applicant's arguments concerning the patentability of claim 40 unpersuasive. Applicants incorporate by reference the remarks made in the Appeal Brief and above, and add the following additional comments.

The Examiner again questions Applicant's whether Ding teaches away from a therapeutically effective composition containing less than 0.1% cyclosporin A. Applicants maintain that the reasonableness of a person of ordinary skill in the art reaching such a conclusion is evidenced by the Ding reference itself, as argued above. On page 11 of the Examiner's Answer the Examiner attempts to argue obviousness of claim 40 from the fact that a ratio of cyclosporin A to castor oil of 0.04 an be found in Example 1B (0.3% cyclosporin A to 5.0% castor oil). However, of course, this composition contains six times the maximum amount of cyclosporin A permitted by claim 40. Therefore, the Examiner is not comparing the claimed invention as a whole to Ding - rather the Examiner is attempting to argue in a piecemeal fashion.

The Examiner does not find the surprising the fact that the present specification discloses that a composition containing half the amount of cyclosporin A (0.5%) as the composition of Example 1D of Ding (0.15) would have substantially equal therapeutic efficacy. However, this fact is surprising for at least two reasons. First, it is surprising in light of the disclosure of Ding that a composition having less than 0.1% (much less one having the same amount of the active agent as the composition of Example 1E) would have therapeutic efficacy at all. Secondly, the fact that the efficacies would be substantially equal is also surprising since the concentrations of active ingredient in the composition having the lower concentration is 50% that of the higher. "Substantial" is defined in the Merriam-Webster on-line dictionary as "being

largely but not wholly that which is specified". "Half" is by any person's measure not "largely" equal.

Obviousness Type-Double Patenting

Applicants incorporate by reference the arguments made herein regarding the non-obviousness of the present invention and those made in the Appeal Brief, particularly on pages 20-23 thereof.

CONCLUSION

For the reasons stated in the Appeal Brief (such statements being hereby incorporated by reference herein) and in the present Reply Brief, Appellants hereby respectfully ask the Board to reverse the Examiner's rejection of the presently pending claims and permit Claims 21, 22, 25-26 and 30-39 to proceed to issue.

Applicants hereby request a two month Extension of Time and include a check in the amount of the corresponding extension fee. If the Appellants have overlooked any other fee, kindly use Deposit Account 21-0890 for the payment of any such fee now due.

Respectfully submitted,

Carlos A. Fisher
Attorney for Appellant
Reg. No. 36,510

09/22/08

IFW AF

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of Acheampong, et al.	Group Art Unit: 1654
Serial No.10/927,857 Conf. No. 2409	Examiner: Cordero Garcia, M.
Filed: August 27, 2004	
For: METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS	

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- ☒ 2 Month Extension of Time
- ☒ Stamped, self-addressed postcard
- ☒ Other: Fee Transmittal
  Check in the amount of $460.00

Each of the 4 above-identified documents are enclosed herewith.

Respectfully submitted,

Date: 9/18/2008

Janet McGhee
Assistant to Carlos A. Fisher
Stout, Uxa, Buyan & Mullins, LLP
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Irvine, California 92618

Fees Pursuant to the Consolidated Appropriations Act 2005 (H.R. 4818).

FEE TRANSMITTAL For FY 2008

Patent fees are subject to annual revision.

☐ Application claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 460.

Complete if Known	
Application Number	10/927,857
Filing Date	8/27/2004
First Named Inventor	Acheampong
Examiner Name	Cordero Garcia, M.M.
Art Unit	1654
Attorney Docket No.	D-3111

METHOD OF PAYMENT *(check all that apply)*

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☒ Deposit Account Deposit Account Number 21-0890 Deposit Account Name Carlos A. Fisher

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FEE CALCULATION

1. BASIC FILING, SEARCH, AND EXAMINATION FEES

	FILING FEES		SEARCH FEES		EXAMINATION FEES		
Application Type	**Fee ($)**	**Small Entity Fee ($)**	**Fee ($)**	**Small Entity Fee ($)**	**Fee ($)**	**Small Entity Fee ($)**	**Fees Paid ($)**
Utility	310	155	510	255	210	105	
Design	210	105	100	50	130	65	
Plant	210	105	310	155	160	80	
Reissue	310	155	510	255	620	310	
Provisional	210	105	0	0	0	0	

Subtotal (1) 0

2. EXCESS CLAIM FEES

Fee Description	**Fee ($)**	**Small Entity Fee ($)**
Each claim over 20 or , for Reissues, each claim over 20 and more than in the original patent	50	25
Each Independent claim over 3 or, for Reissues, each independent claim more than in the original patent	210	105
Multiple Dependent Claims	370	185

Total Claims _____ -20 or HP = _____ x _____ **Extra Claims** **Fee ($)** **Fee Paid ($)**

HP = highest number of total claims paid for, if greater than 20

Indep. Claims _____ -3 or HP = _____ X _____ **Extra Claims** **Fee ($)** **Fee Paid ($)**

HP = highest number of independent claims paid for, if greater than 3

Multiple Dependent Claims **Fee ($)** _____ **Fee Paid ($)** _____

Subtotal (2) 0

3. APPLICATION SIZE FEE

If the specification and drawings exceed 100 sheets of paper, the application size fee due is $260 ($130 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

Total Sheets	**Extra Sheets**	**Number of each additional 50 or fraction thereof**	**Fee ($)**	**Fee Paid ($)**
_____ -100 =	_____ /50=	_____ (round up to a whole number)	x _____ =	

Subtotal (3) 0

4. OTHER FEE(S)

	Fee Paid ($)
☐ Surcharge - Late filing fee or oath/declaration: $130 fee ($65 small entity discount)	
☐ Non-English Specification: $130 fee (no small entity discount)	
☐ 1-month extension of time: $120 fee ($60 small entity discount)	
☒ 2-month extension of time: $460 fee ($230 small entity discount)	460
☐ 3-month extension of time: $1050 fee ($525 small entity discount)	
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☐ Notice of Appeal: $510 fee ($255 small entity discount)	
☐ Filing a Brief in Support of Appeal: $510 fee ($255 small entity discount)	
☐ Request for Oral Hearing: $1030 fee ($515 small entity discount)	
☐ Utility Issue Fee: $1440 fee ($720 small entity discount)	
☐ Recording each patent assignment per property (times number of properties): $40 fee (no small entity fee discount)	
☐ Request for Continued Examination: $810 fee ($405 small entity discount)	
☐ Other: _____	

Subtotal (4) 460

SUBMITTED BY

Name (Print/Type)	Carlos A. Fisher	*Registration No. (Attorney/Agent)*	36,510	*Telephone*	949-450-1750
Signature				*Date*	9/18/2008

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.	: 10/927,857	Confirmation No.	2409
Appellant	: ACHEAMPONG ET AL.		
Filed	: August 27, 2004		
Title	: METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS		
TC/A.U.	: 1654		
Examiner	: Cordero Garcia, Marcela M.		
Docket No.	: D-3111		
Customer No.	: 33197		

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Alexandria, VA 22313-1450

REQUEST FOR EXTENSION OF TIME

Sir:

Applicant requests a two-month extension of time. Enclosed herewith is a check in the amount of $460 for the required fee.

Please charge any deficiency or credit any overpayment to Deposit Account No. 21-0890.

09/22/2008 HDEMESS1 00000064 10927857
01 FC:1252 460.00 OP

Respectfully submitted,

Carlos A. Fisher
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UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/927,857	08/27/2004	Andrew Acheampong	D-3111	2409

51957 7590 12/10/2008

ALLERGAN, INC.
2525 DUPONT DRIVE, T2-7H
IRVINE, CA 92612-1599

EXAMINER	
CORDERO GARCIA, MARCELA M	
ART UNIT	PAPER NUMBER
1654	
MAIL DATE	DELIVERY MODE
12/10/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

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APPLICATION NO./ CONTROL NO.	FILING DATE	FIRST NAMED INVENTOR / PATENT IN REEXAMINATION	ATTORNEY DOCKET NO.
10927857	8/27/04	ACHEAMPONG ET AL.	D-3111

ALLERGAN, INC.
2525 DUPONT DRIVE, T2-7H
IRVINE, CA 92612-1599

EXAMINER
MARCELA M. CORDERO GARCIA

ART UNIT	PAPER
1654	20081202

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner for Patents

The reply brief filed 18 September 2008 is noted and has been entered in the file. The application has been forwarded to the Board of Patent Appeals and Interferences for decision on the appeal.

/Marcela M Cordero Garcia/
Examiner, Art Unit 1654

PTO-90C (Rev.04-03)

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/927,857	08/27/2004	Andrew Acheampong	D-3111	2409

51957 7590 03/19/2009

ALLERGAN, INC.
2525 DUPONT DRIVE, T2-7H
IRVINE, CA 92612-1599

EXAMINER	
CORDERO GARCIA, MARCELA M	
ART UNIT	PAPER NUMBER
1654	

MAIL DATE	DELIVERY MODE
03/19/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

United States Patent and Trademark Office

Under Secretary of Commerce for Intellectual Property and
Director of the United States Patent and Trademark Office
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

ALLERGAN, INC.
2525 DUPONT DRIVE, T2-7H
IRVINE, CA 92612-1599

Appeal No: 2009-5649
Application: 10/927,857
Appellant: Andrew Acheampong et al.

Board of Patent Appeals and Interferences
Docketing Notice

Application 10/927,857 was received from the Technology Center at the Board on December 17, 2008 and has been assigned Appeal No: 2009-5649.

A review of the file indicates that the following documents have been filed by appellant:

Appeal Brief filed on:	March 07, 2008
Reply Brief filed on:	September 18, 2008
Request for Hearing filed on:	NONE

In all future communications regarding this appeal, please include both the application number and the appeal number.

The mailing address for the Board is:

BOARD OF PATENT APPEALS AND INTERFERENCES
UNITED STATES PATENT AND TRADEMARK OFFICE
P.O. BOX 1450
ALEXANDRIA, VIRGINIA 22313-1450

The facsimile number of the Board is 571-273-0052. Because of the heightened security in the Washington D.C. area, facsimile communications are recommended. Telephone inquiries can be made by calling 571-272-9797 and should be directed to a Program and Resource Administrator.

By order of the Board of Patent Appeals and Interferences

PTO/SB/30 (01-08)
Approved for use through 03/31/2008. OMB 0651-0031
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Request for Continued Examination (RCE) Transmittal

Address to:
Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Application Number	10/927,857
Filing Date	August 27, 2004
First Named Inventor	Andrew Acheampong
Art Unit	1654
Examiner Name	Marcela M. Cordero Garcia
Attorney Docket Number	17618(AP)

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. See Instruction Sheet for RCEs (not to be submitted to the USPTO) on page 2.

1. Submission required under 37 CFR 1.114 Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

   a. ☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

      i. ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____

      ii. ☐ Other _____

   b. ☑ Enclosed

      i. ☑ Amendment/Reply

      ii. ☐ Affidavit(s)/ Declaration(s)

      iii. ☑ Information Disclosure Statement (IDS)

      iv. ☐ Other _____

2. Miscellaneous

   a. ☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of _____ months. (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

   b. ☐ Other _____

3. Fees The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.

   a. ☑ The Director is hereby authorized to charge the following fees, any underpayment of fees, or credit any overpayments, to Deposit Account No. 01-0885. I have enclosed a duplicate copy of this sheet.

      i. ☑ RCE fee required under 37 CFR 1.17(e)

      ii. ☑ Extension of time fee (37 CFR 1.136 and 1.17)

      iii. ☐ Other _____

   b. ☐ Check in the amount of $ _____ enclosed

   c. ☐ Payment by credit card (Form PTO-2038 enclosed)

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

Signature	/Joel B. Gerrnary/	Date	June 15, 2009
Name (Print/Type)	Joel B. Gerrnan	Registration No.	48,678

CERTIFICATE OF MAILING OR TRANSMISSION

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop RCE, Commissioner for Patents, P. O. Box 1450, Alexandria, VA 22313-1450 or facsimile transmitted to the U.S. Patent and Trademark Office on the date shown below.

Signature			
Name (Print/Type)		Date	

This collection of information is required by 37 CFR 1.114. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Mail Stop RCE, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Acheampong et al	Examiner: Marcela M. Cordero Garcia
Serial No.: 10/927,857	Group Art Unit: 1654
Filed: August 27, 2004	Confirmation No.: 2409
For: METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS	Customer No.: 051957

Response

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

The Applicants request continued examination of the above-referenced application, thereby withdrawing their pending appeal. They submit with this paper a list of amended claims at page 2. Remarks follow at page 3.

CLAIMS

The following listing of claims will replace all previous versions of claims presented in this application:

1. – 40 (Canceled).

41. (New) A composition for treating an eye of a human or animal comprising cyclosporin A, castor oil, Pemulen, glycerin, and water, wherein

the cyclosporin A is in an amount less than 0.05% by weight;

the Pemulin is in amount equal to or greater than 1.0% by weight;

the glycerin is in amount equal to or less than 1.0% by weight;

and wherein the ratio of cyclosporin A to castor oil is less than 0.04.

REMARKS

The applicants have reviewed the prosecution history of the present application and co-pending application no. 11/897,177, and have found significant errors. The purpose of this request for continued examination is to bring those errors to the attention of the examiner, to file an IDS, and to submit new claims.

The Ding reference and obviousness

The present application describes two compositions at Example 1. Composition II is as follows:

Present Application

	Composition II
Cyclosporin A	0.05 %
Castor Oil	1.25 %
Polysorbate 80	1.00 %
Pemulin®	0.05 %
Glycerine	2.20 %
NaOH	qs
Purified water	qs
pH	7.2-7.6
Ratio cyclosporin to castor oil	0.04

Composition II fell within the scope of the claims that the applicants previously presented for prosecution.

In a final action dated July 2, 2007, the Office rejected the claims under 35 U.S.C. § 103 in view of U.S. Patent No. 5,474,979 (the "Ding reference). The Ding reference discloses at Examples 1B, 1D, and 1E the compositions shown on the following page.

Ding Reference

	Example 1B	Example 1D	Example 1E
Cyclosporin A	0.40 %	0.05 %	0.05 %
Castor Oil	5.00 %	0.625 %	0.625 %
Polysorbate 80	1.00 %	1.00 %	1.00 %
Pemulin®	0.05 %	0.05 %	0.05 %
Glycerine	2.20 %	2.20 %	2.20 %
NaOH	qs	qs	qs
Purified water	qs	qs	qs
pH	7.2-7.6	7.2-7.6	7.2-7.6
Ratio cyclosporin to castor oil	0.08	0.08	0.08

The only difference between Composition II of the present application, and Examples 1D and 1E of the Ding reference, is that Example 1D has more cyclosporin, and Example 1E has less castor oil. The only difference between Composition II and Example 1B, is that Example 1B has less cyclosporin and less castor oil, although both compositions have cyclosporin and castor oil in the same proportion. Stated differently, Composition II has the same amount of cyclosporin as Example 1E, the same amount of castor oil as Example 1D, and the same proportion of cyclosporin to castor oil as Example 1B. As shown on the following page, the compositions are otherwise the same.

Compositions of the Ding reference compared to

Composition II of the present application

	Ding *et al.* Example 1B	Ding *et al.* Example 1D	Ding *et al.* Example 1E	Composition II
Cyclosporin A	0.20 %	0.10 %	**0.05 %**	**0.05 %**
Castor Oil	5.00 %	**1.250 %**	0.625 %	**1.250 %**
Polysorbate 80	1.00 %	1.00 %	1.00 %	1.00 %
Pemulin®	0.05 %	0.05 %	0.05 %	0.05 %
Glycerine	2.20 %	2.20 %	2.20 %	2.20 %
NaOH	qs	Qs	qs	qs
Purified water	qs	Qs	qs	qs
pH	7.2-7.6	7.2-7.6	7.2-7.6	7.2-7.6
cyclosporin : castor oil	**0.04**	0.08	0.08	**0.04**

The Office argued that the differences between the compositions disclosed in the Ding reference and the compositions of the present application were obvious:

> It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the composition of Ding et al. by increasing the amount of castor oil or decreasing the cyclosporine concentration. . . . [O]ne skilled in the art would readily envisage the claimed composition. The skilled artisan would have been motivated to do so because the compositions taught by Ding et al. teach a pharmaceutical emulsion consisting of between about 0.05% an about 0.40% by weight cyclosporin A and between 0.625 and about 5.0% castor oil. . . There would have been a reasonable expectation of success, given that compositions with a higher amount of castor oil are encompassed by the Ding et al. claims and because optimizing the ratio of cyclosporine/hydrophobic components to below 0.08 was taught by Ding et al.

Office action dated July 2, 2007, at 4-5 (parenthetical text omitted).

The applicants concede that it would have been obvious to modify examples 1A-1E of the Ding reference to arrive at Composition II of the present application. The differences are insignificant. One need only use the cyclosporin concentration of Example 1E (0.05%), the castor oil concentration of Example 1D (1.250%), and the remaining ingredients of those examples. As the examiner correctly observes, one of ordinary skill in the art "would readily envisage" such a composition, especially in view of Example 1B: having selected 0.05% as the concentration of cyclosporin, Example 1B (wherein the ratio of cyclosporin to castor oil is 0.04) teaches that the concentration of castor oil should be 1.250% (0.05% / 1.250% = 0.04). The applicants concede that in making this selection (0.05% cyclosporin and 1.250% castor oil) there would have been a reasonable expectation of success; the differences between Examples 1A-1E and Composition II are too small to believe otherwise.

The formulation of Composition II is squarely within the teaching of the Ding reference, and the Office should disregard any statements by the applicants suggesting otherwise, whether in this application or in co-pending application no. 11/897,177.

The Ding reference and 0.05% cyclosporin

Counsel for the applicants attempted to distinguish the Ding reference by arguing that it does not disclose any therapeutically effective compositions comprising less than 0.10% cyclosporin. That argument is in error. It urges an interpretation of the Ding reference that the applicants do not accept.

Below is an example of counsel's argument. It should be disregarded, as should all other statements filed in connection with this application or co-pending application no. 11/897,177 in support of this argument:

> There is absolutely no indication in Ding that a therapeutically effective dosage of cyclosporin can be achieved at a concentration less than 0.1%. Indeed, the apparent failure of Ding to even test the bioavailability of composition 1E (at 0.05% cyclosporin having less

> [than] half or less [than] the amount of cyclosporin A as any other of compositions A-D) demonstrates that Ding et al. could not and did not predict that compositions containing cyclosporin A dosages of less than 0.1% would be therapeutically effective, or alternatively, that composition 1E failed to deliver a therapeutic level of cyclosporin to the ocular tissues of interest. Either possibility must lead to the conclusion that therapeutically effective compositions having less than 0.1% cyclosporin A . . . were unpredictable at the priority date of the present application. . . .

Amended appeal brief filed March 7, 2008 ("Amended Appeal Brief"), at 13 (emphasis omitted).

The examiner thought little of this argument, dismissing it as a "conclusory statement . . . provided without any evidentiary support." Examiner's Answer filed May 28, 2008 ("Examiner's Answer"). The applicants concede that the examiner is correct.

Counsel for the applicants had advanced a case based not on evidence but on speculation: the Ding reference states that Examples 1A-1D were tested for ocular bioavailability; it does not state that Example 1E (cyclosporin 0.05%) was tested for ocular bioavailability; hence, this supposedly

> clearly indicate[s] . . . that Ding et al. did not expect that the composition of Example 1E is therapeutically effective, or Ding was aware that composition 1E did not deliver therapeutic levels of cyclosporin [sic] to the tissues of interest."

Amended Appeal Brief, at 16.

Counsel's argument was based on an unfounded negative implication. It is the equivalent of arguing, for example, that because Ding *et al.* fail to state that their compositions are chemically stable, that one should expect them to explode; that because they fail to state that their compositions are not radioactive, that they are radioactive; or that because nowhere do Ding *et al.* state that the compositions will *not* give a patient x-ray vision, that one may conclude that the compositions will allow

a patient to see through walls. Counsel's logic elevates speculation above evidence, and permits one to draw any conclusion, no matter how incredible.

Counsel for the applicants has not identified any reason to believe that the compositions of the Ding reference would be ineffective using cyclosporin in amounts less than 0.10%. The Ding reference expressly discloses a composition comprising 0.05% cyclosporin; it describes its testing; and it claims its use. As the examiner aptly points out:

> the composition of Example 1E was used in applications to rabbit's eyes since the formulations in Examples 1-4 were used. It is clear that application of such compositions to the eye indicates that the pharmaceutical composition is expected to be therapeutically effective with respect to, e.g., dry eye and because it would not be made into a pharmaceutical composition without having a bioactive function.

Examiner's Answer, at 9 (parenthetical text omitted). The applicants concede that the examiner is correct.

In sum, the notion that that "there is absolutely no indication in Ding that a therapeutically effective dosage of cyclosporin can be achieved at a concentration less than 0.1%" (Amended Appeal Brief, at 13) is incorrect. It improperly characterizes the Ding reference, and the Office should disregard any statements made in support of that characterization, whether in this application or in or co-pending application no. 11/897,177.

Claim amendments

In view of the foregoing, the applicants have amended the claims to recite a composition for treating an eye of a human or animal comprising cyclosporin A, castor oil, Pemulen, glycerin, and water, wherein

> the cyclosporin A is in an amount less than 0.05% by weight;
> the Pemulin is in amount equal to or greater than 1.0% by weight;
> the glycerin is in amount equal to or less than 1.0% by weight;

and wherein the ratio of cyclosporin A to castor oil is less than 0.04.

Information Disclosure Statement

Composition II of Example I of the present application describes the formulation of Restasis®, a treatment for dry eye. Restasis® has been on sale in the United States since approximately April, 2003. The applicants submit with this paper an IDS with the prescribing information that Restasis is sold with.

The Commissioner is hereby authorized to charge any fees required or necessary for the filing, processing or entering of this paper or any of the enclosed papers, and to refund any overpayment, to deposit account 01-0885.

Respectfully submitted,

/JOEL B. GERMAN/

Date: June 15, 2009

JOEL B. GERMAN
Attorney of Record
Registration Number 48,676

Please direct all inquiries and correspondence to:
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17618(AP)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Acheampong et al	Examiner: Marcela M. Cordero Garcia
Serial No.: 10/927,857	Group Art Unit: 1654
Filed: August 27, 2004	Confirmation No.: 2409
For: METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS	Customer No.: 051957

INFORMATION DISCLOSURE STATEMENT

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Dear Sir:

In accordance with the provisions of 37 C.F.R. 1.56, 1.97, and 1.98, the attention of the Patent and Trademark Office is hereby directed to the documents listed on the attached form PTO-SB/08b (formerly 1449). It is respectfully requested that the documents be expressly considered during the prosecution of this application, and that the documents be made of record therein and appear among the "References Cited" on any patent to issue therefrom.

While these documents may be material pursuant to 37 C.F.R. §1.56, their disclosure is not intended to constitute an admission that the documents are prior art in regard to this invention. The filing of this Statement should not be construed to mean that a search has been conducted or that no other material documents or information exists. Please do not hesitate to contact the undersigned should any questions arise regarding this Statement.

The Commissioner is hereby authorized to charge any fees required or necessary for the filing, processing or entering of this paper or any of the enclosed papers, and to refund any overpayment, to deposit account 01-0885.

Respectfully submitted,

/JOEL B. GERMAN/

Date: June 15, 2009

JOEL B. GERMAN
Attorney of Record
Registration Number 48,676

Please direct all inquiries and correspondence to:
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2525 Dupont Drive, T2-7H
Irvine, California 92612
Tel: (714) 246-4920 Fax: (714) 246-4249

FORM PTO-1449 U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTY. DOCKET NO.	SERIAL NO.
INFORMATION DISCLOSURE STATEMENT BY APPLICANT	17618(AP)	10/927,857
(USE SEVERAL SHEETS IF NECESSARY)	APPLICANT: Andrew Acheampong	
	FILING DATE: August 27, 2004	GROUP: 1654

U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE (IF APPROPRIATE)

FOREIGN PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION	
							YES	NO

EXAMINER INITIAL		**OTHER DOCUMENTS** (INCLUDING AUTHOR, TITLE, DATE, PERTINENT PAGES, ETC.)
		Restasis Product Information Sheet - 5 pages

EXAMINER	DATE CONSIDERED

***EXAMINER**: INITIAL IF CITATION CONSIDERED, WHETHER OR NOT CITATION IS IN CONFORMANCE WITH MPEP 609; DRAW LINE THROUGH CITATION IF NOT IN CONFORMANCE AND NOT CONSIDERED, INCLUDE COPY OF THIS FORM WITH NEXT COMMUNICATION TO APPLICANT.

Electronic Patent Application Fee Transmittal

Application Number:	10927857
Filing Date:	27-Aug-2004
Title of Invention:	Methods of providing therapeutic effects using cyclosporin components
First Named Inventor/Applicant Name:	Andrew Acheampong
Filer:	Joel B. German/Bonnie Ferguson
Attorney Docket Number:	17618(AP)

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Request for continued examination	1801	1	810	810
		Total in USD ($)		**810**

Electronic Acknowledgement Receipt

EFS ID:	5514219
Application Number:	10927857
International Application Number:	
Confirmation Number:	2409
Title of Invention:	Methods of providing therapeutic effects using cyclosporin components
First Named Inventor/Applicant Name:	Andrew Acheampong
Customer Number:	51957
Filer:	Joel B. German/Bonnie Ferguson
Filer Authorized By:	Joel B. German
Attorney Docket Number:	17618(AP)
Receipt Date:	15-JUN-2009
Filing Date:	27-AUG-2004
Time Stamp:	13:10:38
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$810
RAM confirmation Number	8198
Deposit Account	010885
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)

1	Request for Continued Examination (RCE)	17618-RCETransmittal.pdf	97684 4d5c7fcb4a0d82d1f95115e5d8edf8029dea8515	no	1
Warnings:					
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2		17618Response061509.pdf	85651 7574bdab3fe4d177ac5a965e4c4d82d58d6b2ca8	yes	9
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Amendment/Argument after Notice of Appeal		1	1	
	Claims		2	2	
	Applicant Arguments/Remarks Made in an Amendment		3	9	
Warnings:					
Information:					
3	Transmittal Letter	17618-IDS-Trans6-15-09.pdf	61819 f288731d605943f65b093d25fd169d4b11e70263	no	2
Warnings:					
Information:					
4	Information Disclosure Statement (IDS) Filed (SB/08)	17618-1449-6-15-09.pdf	64544 e18bf4cb6923fc83eb6c1c5cc9dfb2f768b7dcc7	no	1
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5	NPL Documents	RestasisProductInfoSheetsb.pdf	62345 604160268435ab09d0183919a20f9a4d97bb6f79	no	5
Warnings:					
Information:					
6	Fee Worksheet (PTO-875)	fee-info.pdf	30217 5c9ada3462d7ed1b1a4406fb9e125008e04e6ac4	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	402260		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
10/927,857	08/27/2004	

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)	SMALL ENTITY ☐		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	06/15/2009	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 1	Minus	** 36	= 0	X $ =		OR	X $52=	0
	Independent (37 CFR 1.16(h))	* 1	Minus	***3	= 0	X $ =		OR	X $220=	0
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	0

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/Kim Downing/

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/927,857	08/27/2004	Andrew Acheampong	17618(AP)	2409

51957 7590 06/16/2009

ALLERGAN, INC.
2525 DUPONT DRIVE, T2-7H
IRVINE, CA 92612-1599

EXAMINER	
CORDERO GARCIA, MARCELA M	
ART UNIT	PAPER NUMBER
1654	

MAIL DATE	DELIVERY MODE
06/16/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte ANDREW ACHEAMPONG, DIANE TANG-LIU,
JAMES N. CHANG and DAVID F. POWER

Appeal 2009-005649
Application 10/927,857
Technology Center 1600

Mailed: June 16, 2009

Before STEVEN J. BARTLETT, *Appeals Program Manager.*

ORDER DISMISSING APPEAL

On March 9, 2009, Appeal No. 2009-005649 was assigned and a Docketing Notice was mailed. On June 15, 2009, Appellants filed a Request for Continued Examination (RCE).

Accordingly, it is

ORDERED that the appeal is dismissed.

This application is returned to the Examiner for such further action as may be appropriate.

If there are any questions pertaining to this Order, please contact the Board of Patent Appeals and Interferences at 571-272-9797.

SJB

ALLERGAN, INC.
2525 DUPONT DRIVE, T2-7H
IRVINE CA 92612-1599

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/927,857	08/27/2004	Andrew Acheampong	17618(AP)	2409

51957 7590 09/01/2009

ALLERGAN, INC.
2525 DUPONT DRIVE, T2-7H
IRVINE, CA 92612-1599

EXAMINER	
CORDERO GARCIA, MARCELA M	
ART UNIT	PAPER NUMBER
1654	

MAIL DATE	DELIVERY MODE
09/01/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/927,857	ACHEAMPONG ET AL.	
	Examiner	Art Unit	
	MARCELA M. CORDERO GARCIA	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 June 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *06/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

U.S. Patent and Trademark Office

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on June 15, 2009 has been entered.

2. Applicant's arguments filed with the RCE on June 15, 2009, have been carefully considered by Examiner, however it is noted that these arguments clarify Applicant's response to the previous Examiner Answer, which was based upon different claims than the newly presented claim 41.

3. Claim 41 is pending in the application. Claims 1-40 have been cancelled by Applicant. New claim 41 has been added. Claim 41 is presented for examination on the merits. Any rejection from the previous office action, which is not restated here, is withdrawn

Claim Rejections - 35 USC § 112

4. Claim 41 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 41 contains the trademark/trade name Pemulen ® . Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See Ex parte Simpson, 218 USPQ 1020 (Bd. App. 1982). (see MPEP 2173.05 (u)) The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe acrylate/C10-30 alkyl acrylate cross-polymers, or high molecular weight co-polymers of acrylic acid and a long chain alkyl methacrylate cross-linked with allyl ethers of pentaerythritol (see paragraph bridging pages 19-20 of the disclosure) and, accordingly, the identification/description is indefinite.

Trademarks

5. The use of the trademark Permulen ® has been noted in this application (including in the claims, as noted above). It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Information Disclosure Statement

6. The information disclosure statement (IDS) submitted on 6/15/09 was filed before the mailing of a first Office action after the filing of a request for continued examination under § 1.114. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claim 41 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ding et al. (US 5,474,979, cited in the IDS dated 12/27/2004).

Ding et al. teach compositions for treating an eye of a human or animal comprising cyclosporin A, castor oil, Pemulen ® , glycerin and water (e.g., claims 7-8 of Ding et al.). The compositions are nonirritating pharmaceutical compositions with high comfort level and low irrirtation potential suitable for delivery to sensitive areas such as ocular tissues comprise cyclosporin in admixture with an emulsifying amount of a higher fatty acid glycerol and polysorbate 80. More particularly, the composition may comprise cyclosporin A and castor oil. The Ding et al. patent discloses the 4 required components of the instantly claimed compositions (cyclosporin A, castor oil, Pemulen ® , glycerin and water) and also discloses administering to the eye of an animal or human for the purpose of treating dry eye disease (see, e.g., claim 8 of Ding et al., Examples 1-4).

With respect to the concentrations of the compositions, the Ding et al. patent does not discloses cyclosporin A in a range which encompasses about 0.05% of cyclosporin A (e.g., claim 8 of Ding et al.) and which reasonably reads upon slightly less than 0.05% (see also Example 1E). With respect to the Pemulen ® , which is an emulsifier, the Ding et al. patent discloses emulsifier Polysorbate 80 at 1.0% and Pemulen ® , another emulsifier, at 0.05% (for a total emulsifier ratio of 1.05%). With respect to glycerin, the Ding et al. patent discloses that the tonicity of the emulsions can be further adjusted using glycerin, mannitol or sorbitol if desired (e.g., col. 4, lines 12-13). With respect to the ratio of cyclosporin A/castor oil, the ratio taught by Ding et al. is encompassed between 0.02-0.12 (which encompasses 0.04) [see MPEP 2144.05 (I) regarding overlapping ranges]. With respect to water, Ding et al. discloses water as one of the components (see claim 8 of Ding et al. and Examples).

Ding et al. do not *expressly* teach a composition having Pemulen ® in a concentration equal to 1.0% by weight or greater, nor does it *expressly* disclose less than 1.0% of glycerin.

However, with regards to the emulsifier, the Ding patent does disclose a total emulsifier amount of 1.05% (Pemulen ® + Polysorbate 80, see Examples and claim 8). With regards to glycerin, the Ding patent directs one skilled in the art to adjust the emulsions tonicity with tonicity agents such as glycerin (e.g., col. 4, lines 12-13). With regards to cyclosporine the range cited in claim 8 of the Ding patent is from *about 0.05%* to about 0.40%, which encompasses slightly *less than 0.05%* and reads upon the claimed range of *less than 0.05%* by weight.

One of ordinary skill in the art at the time the invention was made would have been motivated to modify the invention of Ding et al. by making any composition encompassed by Ding et al. and/or by using other functionally equivalent emulsifiers/tonicity agents/solvents within the Ding et al. solutions. One of ordinary skill in the art, at the time the invention was made, would have had a reasonable expectation of success for doing so because such modifications are routinely determined and optimized in the art through routine experimentation [see MPEP 2144.05 (I) regarding optimization of ranges] and because the active ingredient, cyclosporin A was present at overlapping concentrations between the instant invention and the invention of Ding et al. [see MPEP 2144.05 (I) regarding overlapping ranges]. Moreover, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical [see MPEP 2144.05 (II)].

Please note that, in this instant case, the claim is constructed using a “wherein” clause, and that the “wherein" transitional phrase is deemed, in this specific case of claim 41, to affect the scope of the claim since it does limit the claimed composition to a particular structure/composition having the ratios as instantly claimed (see MPEP 211.04 [R-3]).

From the teaching of the reference, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of

ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Double Patenting

9. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

10. Claim 41 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-8 of U.S. Patent No. 5,474,979. Although the conflicting claims are not identical, they are not patentably distinct from each other because Ding et al. (US 5,474,979) claims pharmaceutical emulsions comprising of cyclosporine A, castor oil, Pemulen ®, glycerine and water as instantly claimed (see claims 6-8 of Ding et al.) for topical application comprising to ocular tissue wherein the cyclosporine A is presents in an amount of between about 0.05 to and about 0.40% by weight (which reasonably encompasses slightly less than 0.05%

cyclosporin A), castor oil from about 0.625% to about 5.0% (which reads upon a range of cyclosporin A to castor oil of about 0.08 to about 0.01 when calculated with about 0.05% of cyclosporin A, and which therefore encompasses the instantly claimed "less than 0.04 ratio of cyclosporin A to castor oil"), Pemulen ® at about 0.05%, and glycerin at about 2.2%. (see, e.g., claim 8). Additionally, a different emulsifier, i.e., polysorbate 80, is taught at about 1.0% (see also claim 8) for a total emulsifier at 1.05%). The emulsion contains water as set forth in claims 6-8 of Ding et al. See also claim 6.

Ding et al. do not *expressly* teach a composition having Pemulen ® in a concentration equal to 1.0% by weight or greater, nor does it *expressly* disclose less than 1.0% of glycerin.

However, with regards to the emulsifier, the Ding patent does disclose a total emulsifier amount of 1.05% (Pemulen ® + Polysorbate 80, see claim 8). See also generic claim 6. With regards to glycerin, the Ding patent directs one skilled in the art to adjust the emulsions tonicity with tonicity agents such as glycerin, in general (e.g., col. 4, lines 12-13, see also generic claim 6).

One of ordinary skill in the art at the time the invention was made would have been motivated to modify the invention of Ding et al. by making any composition encompassed by Ding et al. and/or by using other functionally equivalent emulsifiers/tonicity agents/solvents within the Ding et al. solutions. One of ordinary skill in the art, at the time the invention was made, would have had a reasonable expectation of success for doing so because such modifications are routinely determined and optimized in the art through routine experimentation [see MPEP 2144.05 (I) regarding

optimization of ranges] and because the active ingredient, cyclosporin A was present at overlapping concentrations between the instant invention and the invention of Ding et al. [see MPEP 2144.05 (I) regarding overlapping ranges]. Moreover, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical [see MPEP 2144.05 (II)].

Please note that, in this instant case, the claim is constructed using a “wherein” clause, and that the “wherein" transitional phrase is deemed, in this specific case of claim 41, to affect the scope of the claim since it does limit the claimed composition to a particular structure/composition having the ratios as instantly claimed (see MPEP 211.04 [R-3]).

From the teaching of the reference, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

11. No claim is allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARCELA M. CORDERO GARCIA whose telephone number is (571)272-2939. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia J. Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Marcela M Cordero Garcia/
Examiner, Art Unit 1654

MMCG 08/09

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	10927857	ACHEAMPONG ET AL.
	Examiner	Art Unit
	MARCELA M CORDERO GARCIA	1654

SEARCHED			
Class	Subclass	Date	Examiner
none	none	8/26/09	MMCG

SEARCH NOTES		
Search Notes	Date	Examiner
STN searched by STIC (available via SCORE / PAIR)	7/22/09	MMCG
EAST searched (attached)	8/26/09	MMCG
also ran PALM Inventor search	8/26/09	MMCG
class/subclass search in text	8/26/09	MMCG

INTERFERENCE SEARCH			
Class	Subclass	Date	Examiner

FORM PTO-1449 U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTY. DOCKET NO. 17618(AP)	SERIAL NO. 10/927,857
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (USE SEVERAL SHEETS IF NECESSARY)	APPLICANT Andrew Acheampong	
	FILING DATE August 27, 2004	GROUP 1654

U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE (IF APPROPRIATE)

FOREIGN PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION	
							YES	NO

EXAMINER INITIAL		**OTHER DOCUMENTS** (INCLUDING AUTHOR, TITLE, DATE, PERTINENT PAGES, ETC.)
/MMCG/		Restasis Product Information Sheet - 5 pages last updated 01/2009

EXAMINER /Marcela M Cordero Garcia/	DATE CONSIDERED 08/26/2009

***EXAMINER**: INITIAL IF CITATION CONSIDERED, WHETHER OR NOT CITATION IS IN CONFORMANCE WITH MPEP 609; DRAW LINE THROUGH CITATION IF NOT IN CONFORMANCE AND NOT CONSIDERED, INCLUDE COPY OF THIS FORM WITH NEXT COMMUNICATION TO APPLICANT.

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S64	28126	cyclosporin or cyclosporine	US-PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2009/08/26 10:01
S65	67182	castor oil	US-PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2009/08/26 10:01
S66	2410	pemulen	US-PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2009/08/26 10:02
S67	101919	glycerin	US-PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2009/08/26 10:02
S68	18	S64 same S65 same S66 same S67	US-PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2009/08/26 10:02
S69	0	l1and S65 and S66 and S67	US-PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2009/08/26 10:10
S70	54	S64 and S65 and S66 and S67	US-PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2009/08/26 10:10

8/26/09 11:20:18 AM
C:\Documents and Settings\mgarcia\My Documents\EAST\Workspaces\11927857.wsp

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Confirmation No.	**:**	**2409**
Appln. No.	**:**	10/927,857
Applicant	**:**	Andrew Acheampong
Filed	**:**	08/27/2004
TC/A.U.	**:**	1654
Examiner	**:**	Cordero Garcia, Marcela M.
Docket No.	**:**	17618 (AP)
Customer No.	**:**	51957
Title	**:**	Methods of Providing Therapeutic Effects Using Cyclosporin Components

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AMENDMENT AND REMARKS

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

The Applicants submit the following Amendment and Remarks in Response to the Office Action dated September 1, 2009 in the above referenced patent application.

Amendments to the Specification begin on page 2 of this paper.

Amendments to the Claims are reflected in the listing of claims which begins on page 3 of this paper.

Remarks/Arguments begin on page 4 of this paper.

Amendment to the Specification:

Please replace paragraph [0086] with the following amended paragraph:

One particularly useful emulsion stabilizing component includes crosslinked polyacrylates, such as carbomers and PEMULEN® ~~Pemulen®~~ materials. PEMULEN® ~~Pemulen®~~ is a registered trademark of B.F. Goodrich for polymeric emulsifiers and are commercially available from B.F. Goodrich Company, Specialty Polymers & Chemicals Division, Cleveland, Ohio. PEMULEN® ~~Pemulen®~~ materials include acrylate/C10-30 alkyl acrylate cross-polymers, or high molecular weight co-polymers of acrylic acid and a long chain alkyl methacrylate cross-linked with allyl ethers of pentaerythritol.

Please replace paragraph [0096] with the following amended paragraph:

Very useful examples of preservative components in the present invention include, but are not limited to, chlorite components. Specific examples of chlorite components useful as preservatives in accordance with the present invention include stabilized chlorine dioxide (SCD), metal chlorites such as alkali metal and alkaline earth metal chlorites, and the like and mixtures thereof. Technical grade (or USP grade) sodium chlorite is a very useful preservative component. The exact chemical composition of many chlorite components, for example, SCD, is not completely understood. The manufacture or production of certain chlorite components is described in McNicholas U.S. Pat. No. 3,278,447, which is incorporated in its entirety by reference herein. Specific examples of useful SCD products include that sold under the trademark Dura Klor by Rio Linda Chemical Company, Inc., and that sold under the trademark ANTHIUM DIOXIDE® ~~Anthium Dioxide®~~ by International Dioxide, Inc. An especially useful SCD is a product sold under the trademark BIO-CIDE® ~~Bio-Cide®~~ by Bio-Cide International, Inc., as well as a product identified by Allergan, Inc. by the trademark PURITE® ~~Purite®~~.

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1-40. (Canceled)

41. (Currently Amended) A composition for treating an eye of a human or animal comprising cyclosporin A, castor oil, a crosslinked polyacrylate stabilizer ~~Pemulen~~, glycerin, and water, wherein

the cyclosporin A is in an amount less than 0.05% by weight;

the crosslinked polyacrylate stabilizer ~~Pemulen~~, is in amount equal to or greater than 1.0% by weight;

the glycerin is in amount equal to or less than 1.0% by weight; and wherein the ratio of cyclosporin A to castor oil is less than 0.04.

42. (New) The composition of claim 41, wherein the crosslinked polyacrylate stabilizer is an acrylate/C_{10}-C_{30} alkyl acrylate cross polymer.

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REMARKS/ARGUMENTS

In the specification, the paragraphs [0086] and [0096] have been amended to capitalize Trademark references.

Claim 41 is pending in this application. Claims 1-40 have been previously canceled. Claim 41 is amended and claims 42-43 are new.

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Claim 41 is rejected under 35 U.S.C §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regard as the invention. In particular, the Office objects to the use of the trademark Pemulen® in the claim. Applicants have amended claim 1 to recite a crosslinked polyacrylate stabilizer and have removed Pemulen® from the claim. Examples of crosslinked polyacrylate stabilizers are disclosed, for example, in paragraph [0086]. Therefore, claim 41 is in compliance with 35 U.S.C §112, second paragraph, and Applicants respectfully request that the rejection be withdrawn.

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Claim 41 is rejected under 35 U.S.C §103(a) as allegedly unpatentable over Ding (US 5,474,979). Applicants respectfully traverse.

To maintain a proper rejection under 35 U.S.C. §103, the Office must meet four conditions to establish a *prima facie* case of obviousness. First, the Office must show that the prior art suggested to those of ordinary skill in the art that they should make the claimed composition or device or carry out the claimed process. Second, the Office must show that the prior art would have provided one of ordinary skill in the art with a reasonable expectation of success. Both the suggestion and the reasonable expectation of success must be adequately founded in the prior art and not in an applicant's disclosure. Third, the prior art must teach or suggest all the claim limitations. *In re Vaeck,* 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). Fourth, if an obviousness rejection is based on some combination of prior art references, the Office must show a suggestion, teaching, or motivation to combine the prior art references ("the TSM test"). *In re Dembiczak,* 50 U.S.P.Q.2d 1614, 1617 (Fed. Cir. 1999). Following *KSR Int'l Co. v. Teleflex, Inc.*, this fourth prong of the *prima facie* obviousness analysis must not be applied in a rigid or formulaic way such that it becomes inconsistent with the more flexible approach of *Graham v. John Deere*, 383 U.S. 1, 17-18 (1966); 127 S. Ct. 1727 (2007). It must still be applied, however, as the TSM test captures the important insight that "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *Id.* at 1741 (citing *United States v. Adams*, 383 U.S. 39, 50-52 (1966)). It is necessary to "show all of the limitations of the claims arranged or combined in the same way as recited in the claims." *Net Moneyin v. Verisign*, 545 F.3d 1359, 1368 (Fed. Cir. 2008).

As amended herein, claim 41 recites a composition for treating an eye of a human or animal comprising cyclosporin A, castor oil, a crosslinked polyacrylate stabilizer, glycerin, and water, wherein the cyclosporin A is in an amount less than 0.05% by weight; the crosslinked polyacrylate stabilizer, is in amount equal to or greater than 1.0% by weight; the glycerin is in an amount equal to or less than 1.0% by weight; and wherein the ratio of cyclosporin A to castor oil is less than 0.04.

The Office Action states that the composition of Ding renders the claimed composition obvious. Ding discloses the same combination of ingredients. However, Ding discloses those ingredients in different amounts. Ding does not disclose the claimed composition. As indicated in the specification (see paragraphs [0109]-[0110]), achieving therapeutic effectiveness with reduced amounts of cyclosporine A mitigates undesirable side effects and potential drug interactions. Further, a lower dose of cyclosporine A, in this case *less than* 0.05% by weight, can increase the number of patients that can receive the composition for treatment and also reduce the number of restrictions attendant to its administration. Further, the concentration of castor oil relative to cyclosporine A is important to the comfort and ease of use of the composition. The claimed ratio provides the advantage of more rapidly breaking down the emulsion in the eye, which reduces vision distortion that results from the administration, and further facilitates therapeutic effectiveness. There is a clear benefit achieved with a composition that has a reduced concentration of cyclosporine A, less than 0.05% by weight, and also a cyclosporine A to castor oil ratio that is less than 0.04. This benefit is not obvious and it is not disclosed in Ding.

The cited art does not teach each limitation of the claimed invention. Therefore, the Office has failed to establish a *prima facie* case of obviousness and Applicants respectfully request that the rejection be withdrawn.

Double Patenting Rejection

Claim 41 is rejected on the ground of nonstatutory obviousness-type double patenting as allegedly unpatentable over claims 1-8 of US Pat. 5,474,979.

The Office has instructed that a terminal disclaimer in compliance with 37 C.F.R. § 1.321(c) or § 1.321(d) may be used to overcome an actual or provisional rejection based on non-statutory double patenting ground. Without addressing the propriety of the Office's rejection, and specifically the Office's interpretation of what the cited reference teaches or suggests, the Applicants respectfully and properly defer addressing the present rejection until there is otherwise allowable subject matter in the present application. Only then is it proper to assess the propriety of the Office's rejection in view of the potentially allowable claims. Accordingly, the Applicants respectfully request reconsideration and withdrawal of the present rejections or that the rejections be held in abeyance until claims are allowable in the present application.

CONCLUSION

Applicants respectfully request that a timely Notice of Allowance be issued in this case. The Commissioner is authorized to charge any fee which may be required in connection with this Amendment to deposit account No. 01-0885.

Respectfully submitted,

/Joel B. German/

Dated: March 1, 2010

Joel German
Registration No. 48,676
CUSTOMER NUMBER: 51957

ALLERGAN, INC.
LEGAL DEPT. – T2-7H
2525 Dupont Drive
Irvine, California 92612
Telephone: 714.246.4920
Facsimile: 714.246.4249

Electronic Patent Application Fee Transmittal

Application Number:	10927857
Filing Date:	27-Aug-2004
Title of Invention:	Methods of providing therapeutic effects using cyclosporin components
First Named Inventor/Applicant Name:	Andrew Acheampong
Filer:	Joel B. German/Bonnie Ferguson
Attorney Docket Number:	17618(AP)

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Extension - 3 months with $0 paid	1253	1	1110	1110

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
		Total in USD ($)		**1110**

Electronic Acknowledgement Receipt

EFS ID:	7112242
Application Number:	10927857
International Application Number:	
Confirmation Number:	2409
Title of Invention:	Methods of providing therapeutic effects using cyclosporin components
First Named Inventor/Applicant Name:	Andrew Acheampong
Customer Number:	51957
Filer:	Joel B. German/Bonnie Ferguson
Filer Authorized By:	Joel B. German
Attorney Docket Number:	17618(AP)
Receipt Date:	01-MAR-2010
Filing Date:	27-AUG-2004
Time Stamp:	16:09:03
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$1110
RAM confirmation Number	3224
Deposit Account	010885
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)

1		RESPONSETOOADATED9-1-09-17618-3-1-10.pdf	101980 9019f2fbc29ebfdd9d7ce71aa925936eea9f6a83	yes	7

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment/Req. Reconsideration-After Non-Final Reject	1	1
	Specification	2	2
	Amendment Copy Claims/Response to Suggested Claims	3	3
	Applicant Arguments/Remarks Made in an Amendment	4	7

Warnings:

Information:

2	Fee Worksheet (PTO-875)	fee-info.pdf	30101 4f1aa578de2b46d8202c84121baec054cb5e9dd6	no	2

Warnings:

Information:

Total Files Size (in bytes):	132081

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (12-04

Approved for use through 7/31/2006. OMB 0651-003

U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number

PATENT APPLICATION FEE DETERMINATION RECORD
Substitute for Form PTO-875

Application or Docket Number: 10/927,857

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =		x$26		OR	x$52	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	x$110			x$220	
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $260 ($130 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR						
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))			195			390	
			TOTAL			TOTAL	

* If the difference in column 1 is less than zero, enter "0" in column 2.

APPLICATION AS AMENDED – PART II

AMENDMENT A — 3/1/10

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 3	Minus	** 36	=	x =		OR	x =	
Independent (37 CFR 1.16(h))	* 1	Minus	*** 3	=	x =		OR	x =	
Application Size Fee (37 CFR 1.16(s))							OR		
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))					N/A		OR	N/A	
					TOTAL ADD'T FEE		OR	TOTAL ADD'T FEE	

AMENDMENT B

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)	OR	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
Application Size Fee (37 CFR 1.16(s))									
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))					N/A		OR	N/A	
					TOTAL ADD'T FEE		OR	TOTAL ADD'T FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/927,857	08/27/2004	Andrew Acheampong	17618(AP)	2409

51957 7590 05/25/2010

ALLERGAN, INC.
2525 DUPONT DRIVE, T2-7H
IRVINE, CA 92612-1599

EXAMINER	
CORDERO GARCIA, MARCELA M	
ART UNIT	PAPER NUMBER
1654	

MAIL DATE	DELIVERY MODE
05/25/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

UNITED STATES DEPARTMENT OF COMMERCE
U.S. Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450

APPLICATION NO./ CONTROL NO.	FILING DATE	FIRST NAMED INVENTOR / PATENT IN REEXAMINATION	ATTORNEY DOCKET NO.
10927857	8/27/04	ACHEAMPONG ET AL.	17618(AP)

ALLERGAN, INC.
2525 DUPONT DRIVE, T2-7H
IRVINE, CA 92612-1599

EXAMINER
MARCELA M. CORDERO GARCIA

ART UNIT	PAPER
1654	20100522-B

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner for Patents

The reply filed on March 1, 2010 is not fully responsive to the prior Office Action because of the following omission(s) or matter(s):
The claim set filed on March 1, 2010 is not compliant since it contains two claims numbered "Claim 42". See 37 CFR 1.111 and 1.121. Since the above-mentioned reply appears to be bona fide, applicant is given ONE (1) MONTH or THIRTY (30) DAYS from the mailing date of this notice, whichever is longer, within which to supply the omission or correction in order to avoid abandonment. EXTENSIONS OF THIS TIME PERIOD MAY BE GRANTED UNDER 37 CFR 1.136(a).
Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARCELA M. CORDERO GARCIA whose telephone number is (571)272-2939. The examiner can normally be reached on M-F 8:30-5:00.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia J. Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.
Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Cecilia Tsang/
Supervisory Patent Examiner, Art Unit 1654

PTO-90C (Rev.04-03)

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

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1-40. (Canceled)

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Confirmation No.	**:**	**2409**
Appln. No.	**:**	10/927,857
Applicant	**:**	Andrew Acheampong
Filed	**:**	08/27/2004
TC/A.U.	**:**	1654
Examiner	**:**	Cordero Garcia, Marcela M.
Docket No.	**:**	17618 (AP)
Customer No.	**:**	51957
Title	**:**	Methods of Providing Therapeutic Effects Using Cyclosporin Components

---

AMENDMENT AND REMARKS

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

The Applicants submit the correction to the claim set which the Applicants submitted in the Amendment and Remarks to the Office Action dated September 1, 2009 in the above referenced patent application as requested in the Office Communication received June 2, 2010.

Amendments to the Specification begin on page 2 of this paper.

Amendments to the Claims are reflected in the listing of claims which begins on page 3 of this paper.

Remarks/Arguments begin on page 4 of this paper.

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Please replace paragraph [0086] with the following amended paragraph:

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To maintain a proper rejection under 35 U.S.C. §103, the Office must meet four conditions to establish a *prima facie* case of obviousness. First, the Office must show that the prior art suggested to those of ordinary skill in the art that they should make the claimed composition or device or carry out the claimed process. Second, the Office must show that the prior art would have provided one of ordinary skill in the art with a reasonable expectation of success. Both the suggestion and the reasonable expectation of success must be adequately founded in the prior art and not in an applicant's disclosure. Third, the prior art must teach or suggest all the claim limitations. *In re Vaeck,* 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). Fourth, if an obviousness rejection is based on some combination of prior art references, the Office must show a suggestion, teaching, or motivation to combine the prior art references ("the TSM test"). *In re Dembiczak,* 50 U.S.P.Q.2d 1614, 1617 (Fed. Cir. 1999). Following *KSR Int'l Co. v. Teleflex, Inc*., this fourth prong of the *prima facie* obviousness analysis must not be applied in a rigid or formulaic way such that it becomes inconsistent with the more flexible approach of *Graham v. John Deere*, 383 U.S. 1, 17-18 (1966); 127 S. Ct. 1727 (2007). It must still be applied, however, as the TSM test captures the important insight that "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *Id*. at 1741 (citing *United States v. Adams*, 383 U.S. 39, 50-52 (1966)). It is necessary to "show all of the limitations of the claims arranged or combined in the same way as recited in the claims." *Net Moneyin v. Verisign*, 545 F.3d 1359, 1368 (Fed. Cir. 2008).

As amended herein, claim 41 recites a composition for treating an eye of a human or animal comprising cyclosporin A, castor oil, a crosslinked polyacrylate stabilizer, glycerin, and water, wherein the cyclosporin A is in an amount less than 0.05% by weight; the crosslinked polyacrylate stabilizer, is in amount equal to or greater than 1.0% by weight; the glycerin is in an amount equal to or less than 1.0% by weight; and wherein the ratio of cyclosporin A to castor oil is less than 0.04.

The Office Action states that the composition of Ding renders the claimed composition obvious. Ding discloses the same combination of ingredients. However, Ding discloses those ingredients in different amounts. Ding does not disclose the claimed composition. As indicated in the specification (see paragraphs [0109]-[0110]), achieving therapeutic effectiveness with reduced amounts of cyclosporine A mitigates undesirable side effects and potential drug interactions. Further, a lower dose of cyclosporine A, in this case *less than* 0.05% by weight, can increase the number of patients that can receive the composition for treatment and also reduce the number of restrictions attendant to its administration. Further, the concentration of castor oil relative to cyclosporine A is important to the comfort and ease of use of the composition. The claimed ratio provides the advantage of more rapidly breaking down the emulsion in the eye, which reduces vision distortion that results from the administration, and further facilitates therapeutic effectiveness. There is a clear benefit achieved with a composition that has a reduced concentration of cyclosporine A, less than 0.05% by weight, and also a cyclosporine A to castor oil ratio that is less than 0.04. This benefit is not obvious and it is not disclosed in Ding.

The cited art does not teach each limitation of the claimed invention. Therefore, the Office has failed to establish a *prima facie* case of obviousness and Applicants respectfully request that the rejection be withdrawn.

Double Patenting Rejection

Claim 41 is rejected on the ground of nonstatutory obviousness-type double patenting as allegedly unpatentable over claims 1-8 of US Pat. 5,474,979.

The Office has instructed that a terminal disclaimer in compliance with 37 C.F.R. § 1.321(c) or § 1.321(d) may be used to overcome an actual or provisional rejection based on non-statutory double patenting ground. Without addressing the propriety of the Office's rejection, and specifically the Office's interpretation of what the cited reference teaches or suggests, the Applicants respectfully and properly defer addressing the present rejection until there is otherwise allowable subject matter in the present application. Only then is it proper to assess the propriety of the Office's rejection in view of the potentially allowable claims. Accordingly, the Applicants respectfully request reconsideration and withdrawal of the present rejections or that the rejections be held in abeyance until claims are allowable in the present application.

CONCLUSION

Applicants respectfully request that a timely Notice of Allowance be issued in this case. The Commissioner is authorized to charge any fee which may be required in connection with this Amendment to deposit account No. 01-0885.

Respectfully submitted,

/Joel B. German/

Dated: June 8, 2010

Joel German
Registration No. 48,676
CUSTOMER NUMBER: 51957

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Electronic Acknowledgement Receipt

EFS ID:	7772682
Application Number:	10927857
International Application Number:	
Confirmation Number:	2409
Title of Invention:	Methods of providing therapeutic effects using cyclosporin components
First Named Inventor/Applicant Name:	Andrew Acheampong
Customer Number:	51957
Filer:	Joel B. German/Bonnie Ferguson
Filer Authorized By:	Joel B. German
Attorney Docket Number:	17618(AP)
Receipt Date:	08-JUN-2010
Filing Date:	27-AUG-2004
Time Stamp:	18:13:35
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		RESPONSETOCOMMUNICATION-5-25-10-17618-6-8-10pdf.pdf	102071 e99f2e19e4e924de95a4925cf2896f9fb32013ab	yes	7

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Supplemental Response or Supplemental Amendment	1	1
	Specification	2	2
	Amendment Copy Claims/Response to Suggested Claims	3	3
	Applicant Arguments/Remarks Made in an Amendment	4	7
Warnings:			
Information:			
	Total Files Size (in bytes):	102071	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

<u>New Applications Under 35 U.S.C. 111</u>
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

<u>National Stage of an International Application under 35 U.S.C. 371</u>
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

<u>New International Application Filed with the USPTO as a Receiving Office</u>
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
10/927,857	08/27/2004	

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)	SMALL ENTITY ☐		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

		(Column 1)		(Column 2)	(Column 3)	SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
AMENDMENT	06/08/2010	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 3	Minus	** 36	= 0	X $ =		OR	X $52=	0
	Independent (37 CFR 1.16(h))	* 1	Minus	***3	= 0	X $ =		OR	X $220=	0
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	0

		(Column 1)		(Column 2)	(Column 3)					
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/ROSALIND BALL/

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/927,857	08/27/2004	Andrew Acheampong	17618(AP)	2409

51957 7590 09/02/2010

ALLERGAN, INC.
2525 DUPONT DRIVE, T2-7H
IRVINE, CA 92612-1599

EXAMINER	
CORDERO GARCIA, MARCELA M	
ART UNIT	PAPER NUMBER
1654	

MAIL DATE	DELIVERY MODE
09/02/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/927,857	ACHEAMPONG ET AL.	
	Examiner	Art Unit	
	MARCELA M. CORDERO GARCIA	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 June 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *41-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *41-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This Office Action is in response to the reply received on June 8, 2010. Any rejection from the previous office action, which is not restated here, is withdrawn.

2. A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal.

3. Claim 41 was previously pending in the application. Claims 1-40 had been cancelled by Applicant. New claims 42-43 have been added.

Claim Rejections - 35 USC § 112

4. Claim 41 was rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for containing the trademark/trade name Pemulen ® . Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph (see MPEP 2173.05 (u)). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe acrylate/C10-30 alkyl acrylate cross-polymers, or high molecular weight co-polymers of acrylic acid and a long chain alkyl methacrylate cross-linked with allyl ethers of pentaerythritol (see

paragraph bridging pages 19-20 of the disclosure) and, accordingly, the identification/description is indefinite.

The rejection is withdrawn based on applicant's amendment.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 41-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ding et al. (US 5,474,979, cited in the IDS dated 12/27/2004).

Ding et al. teach compositions for treating an eye of a human or animal comprising cyclosporin A, castor oil, a crosslinked polyacrylate stabilizer, glycerin and water (e.g., claims 7-8 of Ding et al.). The compositions are nonirritating pharmaceutical compositions with high comfort level and low irrirtation potential suitable for delivery to sensitive areas such as ocular tissues comprise cyclosporin in admixture with an emulsifying amount of a higher fatty acid glycerol and polysorbate 80. More particularly, the composition may comprise cyclosporin A and castor oil. The Ding et al. patent discloses the 4 required components of the instantly claimed compositions (cyclosporin A, castor oil, Pemulen ® , glycerin and water) and also discloses administering to the eye of an animal or human for the purpose of treating dry eye disease (see, e.g., claim 8 of Ding et al., Examples 1-4).

With respect to the concentrations of the compositions, the Ding et al. patent does disclose cyclosporin A in a range which encompasses *about* 0.05% of cyclosporin A (e.g., claim 8 of Ding et al.) and which reasonably reads upon slightly less than 0.05% (see also Example 1E). The reference anticipates the limitation “less than 0.05%” since it recites "about 0.05%". The propriety of the use of the expression "about" in claims to permit "of some tolerance" is established by long practice in the Patent Office. See W.L. Gore & Associates, Inc. v. Garlock, Inc., 82 U.S.P.Q. (BNA) 303, 306 (Fed. Cir. 1983) and Ex Parte King, 82 U.S.P.Q. (BNA) 450, 451 (Pat. & Trademark Office Bd. App. 1948). The term "about" allows for some tolerance in the ranges disclosed. In In re Ayers, the Federal Circuit held that "at least about 10%" was anticipated by a reference that disclosed "about 8%" because the term "about" allowed for some tolerance. In re Ayers, 154 F.2d 182, 185 (Fed. Cir. 1946). Similarly, in Johnson and Johnson v. W.L. Gore & Associates, Inc., the Court allowed for "about 1.2" to be inclusive of 1.0. See Johnson and Johnson,436 F.Supp. 704, 728-729 (Fed. Cir. 1977). Although about has never been confined to specific percentage of variability, the Johnson and Johnson decision at least implies that 16% variability is permissible when "about" is used (1.0/1.2 = ~16.6% variability). Thus, the term about implicitly discloses some variability even though the specification may not literally cite this variability. Accordingly, "about 0.05%" encompasses less than 0.05%. Furthermore, a composition having 0.05% cyclosporine was used for treating dry eye disease (e.g., Example 1). See MPEP 2144.05: in the case where the claimed ranges “overlap or lie inside ranges disclosed by the prior art” a prima facie case of obviousness exists. In re Wertheim, 541 F.2d 257, 191 USPQ 90

(CCPA 1976); In re Woodruff, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990) (The prior art taught carbon monoxide concentrations of “about 1-5%” while the claim was limited to “more than 5%.” The court held that “about 1-5%” allowed for concentrations slightly above 5% thus the ranges overlapped.)

With respect to the Pemulen ® , which is an emulsifier, the Ding et al. patent discloses emulsifier Polysorbate 80 at 1.0% and Pemulen ® , another emulsifier, at 0.05% (for a total emulsifier ratio of 1.05%). With respect to glycerin, the Ding et al. patent discloses that the tonicity of the emulsions can be further adjusted using glycerin, mannitol or sorbitol if desired (e.g., col. 4, lines 12-13). With respect to the ratio of cyclosporin A/castor oil, the ratio taught by Ding et al. is encompassed between 0.02-0.12 or less thant 0.16 (which encompass 0.04) See MPEP 2144.05 regarding overlapping ranges: "[A] prior art reference that discloses a range encompassing a somewhat narrower claimed range is sufficient to establish a prima facie case of obviousness." With respect to water, Ding et al. discloses water as one of the components (see claim 8 of Ding et al. and Examples).

Ding et al. do not *expressly* teach a composition having a crosslinked polyacrylate stabilizer in a concentration equal to 1.0% by weight or greater, nor does it *expressly* disclose less than 1.0% of glycerin.

However, with regards to the emulsifier, the Ding patent does disclose a total emulsifier amount of 1.05% [Pemulen ® (crosslinked polyacrylate stabilizer) plus Polysorbate 80, see Examples and claim 8]. Further, the disclosure of Ding teaches that the emulsions can be further stabilized using a polyelectrolyte, or polyelectrolytes if

more than one, from the family of cross-linked polyacrylates, such as carbomers and Pemulen ®. Ding goes on to teach that Pemulen ® is a registered trademark of B. F. Goodrich for polymeric emulsifiers and commercially available from B. F. Goodrich Company, Specialty Polymers & Chemicals Division, Cleveland, Ohio. Pemulens are Acrylates/C10-30 Alkyl Acrylate Cross-Polymers, and is not restricted to specific amounts. Further, Ding teaches that Pemulens are high molecular weight co-polymers of acrylic acid and a long chain alkyl methacrylate cross-linked with allyl ethers of pentaerythritol, contain not less than 52.0 percent and not more than 62.0 percent of carboxylic acid groups. The viscosity of a neutralized 1.0 percent aqueous dispersion is between 9,500 and 26,500 centipoises. With regards to glycerin, the Ding patent directs one skilled in the art to adjust the emulsions tonicity with tonicity agents such as glycerin (e.g., col. 4, lines 12-13). Ding expressly teaches that the tonicity of the emulsions can be further adjusted using glycerine, mannitol, or sorbitol if desired. The pH of the emulsions can be adjusted in a conventional manner using sodium hydroxide to a near physiological pH level and while buffering agents are not required, suitable buffers may include phosphates, citrates, acetates and borates.

One of ordinary skill in the art at the time the invention was made would have been motivated to modify the invention of Ding et al. by making any composition encompassed by Ding et al. and/or by using other functionally equivalent emulsifiers/tonicity agents/solvents within the Ding et al. solutions. One of ordinary skill in the art, at the time the invention was made, would have had a reasonable expectation of success for doing so because such modifications are routinely determined and

optimized in the art through routine experimentation [see MPEP 2144.05 (I) regarding optimization of ranges] and because the active ingredients, cyclosporin A and castor oil were present at overlapping concentrations between the instant invention and the invention of Ding et al. [see MPEP 2144.05 (I) regarding overlapping ranges]. Moreover, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical [see MPEP 2144.05 (II)].

From the teaching of the reference, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments

7. To maintain a proper rejection under 35 U.S.C. §103, the Office must meet four conditions to establish a prima facie case of obviousness. First, the Office must show that the prior art suggested to those of ordinary skill in the art that they should make the claimed composition or device or carry out the claimed process. Second, the Office must show that the prior art would have provided one of ordinary skill in the art with a reasonable expectation of success. Both the suggestion and the reasonable expectation of success must be adequately founded in the prior art and not in an applicant's disclosure. Third, the prior art must teach or suggest all the claim limitations. In re Vaeck, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). Fourth, if an obviousness rejection

is based on some combination of prior art references, the Office must show a suggestion, teaching, or motivation to combine the prior art references ("the TSM test"). In re Dembiczak, 50 U.S.P.Q.2d 1614, 1617 (Fed. Cir. 1999). Following KSR Int'l Co. v. Teleflex, Inc., this fourth prong of the prima facie obviousness analysis must not be applied in a rigid or formulaic way such that it becomes inconsistent with the more flexible approach of Graham v. John Deere, 383 U.S. 1, 17-18 (1966); 127 S. Ct. 1727 (2007). It must still be applied, however, as the TSM test captures the important insight that "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." Id. at 1741 (citing United States v. Adams, 383 U.S. 39, 50-52 (1966)). It is necessary to "show all of the limitations of the claims arranged or combined in the same way as recited in the claims." Net Moneyin v. Verisign, 545 F.3d 1359, 1368 (Fed. Cir. 2008).

As amended herein, claim 41 recites a composition for treating an eye of a human or animal comprising cyclosporin A, castor oil, a crosslinked polyacrylate stabilizer, glycerin, and water, wherein the cyclosporin A is in an amount less than 0.05% by weight; the crosslinked polyacrylate stabilizer, is in amount equal to or greater than 1.0% by weight; the glycerin is in an amount equal to or less than 1.0% by weight; and wherein the ratio of cyclosporin A to castor oil is less than 0.04.

The Office Action states that the composition of Ding renders the claimed composition obvious. Ding discloses the same combination of ingredients. However, Ding discloses those ingredients in different amounts. Ding does not disclose the claimed composition. As indicated in the specification (see paragraphs [0109]-[0110]),

achieving therapeutic effectiveness with reduced amounts of cyclosporine A mitigates undesirable side effects and potential drug interactions. Further, a lower dose of cyclosporine A, in this case less than 0.05% by weight, can increase the number of patients that can receive the composition for treatment and also reduce the number of restrictions attendant to its administration. Further, the concentration of castor oil relative to cyclosporine A is important to the comfort and ease of use of the composition. The claimed ratio provides the advantage of more rapidly breaking down the emulsion in the eye, which reduces vision distortion that results from the administration, and further facilitates therapeutic effectiveness. There is a clear benefit achieved with a composition that has a reduced concentration of cyclosporine A, less than 0.05% by weight, and also a cyclosporine A to castor oil ratio that is less than 0.04. This benefit is not obvious and it is not disclosed in Ding.

The cited art does not teach each limitation of the claimed invention. Therefore, the Office has failed to establish a prima facie case of obviousness and Applicants respectfully request that the rejection be withdrawn.

Response to arguments

8. Applicant's arguments have been carefully considered but not deemed persuasive for the reasons pf record, for the reasons set forth above and for following reasons:

Applicant argues that a lower dose of cyclosporine A, in this case less than 0.05% by weight, can increase the number of patients that can receive the composition for treatment and also reduce the number of restrictions attendant to its administration.

Further, the concentration of castor oil relative to cyclosporine A is important to the comfort and ease of use of the composition. The claimed ratio provides the advantage of more rapidly breaking down the emulsion in the eye, which reduces vision distortion that results from the administration, and further facilitates therapeutic effectiveness. There is a clear benefit achieved with a composition that has a reduced concentration of cyclosporine A, less than 0.05% by weight, and also a cyclosporine A to castor oil ratio that is less than 0.04 (e.g., claim 4). However, both the less than 0.05% by weight cyclosporine and the ratio of cyclosporine/castor oil less than 0.04 are taught by Ding and therefore the associated effects and benefits would also be encompassed by the invention of Ding. “[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art’s functioning, does not render the old composition patentably new to the discoverer. […] Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable.” (See MPEP 2112).

Please note that this is a 103 rejection not 102 rejection, therefore all the limitations need not be set forth in the reference. In the instant reference the critical ratios/concentrations were set forth in Ding. The other components (glycerin, stabilizer such as crosslinked polyacrylate stabilizer and water) are not taught at the concentration as instantly taught, however the application does teach that these components may be adjusted to obtain a stable emulsion (e.g., claim 6, col. 3-4). Furthermore, no criticality appears to be associated to these components.

Therefore, based on the guidance of Ding, one of ordinary skill in the art would have had a reasonable expectation of success in obtaining the claimed inventions and therefore the 103 rejection of record is maintained.

Double Patenting

9. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

10. Claims 41-43 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-8 of U.S. Patent No. 5,474,979. Although the conflicting claims are not identical, they are not patentably distinct from each other because Ding et al. (US 5,474,979) claims pharmaceutical emulsions comprising of cyclosporine A, castor oil, Pemulen ® (crosslinked polyacrylate stabilizer), glycerine and water as instantly claimed (see claims 6-8 of Ding et al.) for topical application comprising to ocular tissue wherein the cyclosporine A is presents in an

amount of between about 0.05 to and about 0.40% by weight (which reasonably encompasses slightly less than 0.05% cyclosporin A), castor oil from about 0.625% to about 5.0% (which reads upon a range of cyclosporin A to castor oil of about 0.08 to about 0.01 when calculated with about 0.05% of cyclosporin A, and which therefore encompasses the instantly claimed "less than 0.04 ratio of cyclosporin A to castor oil"), Pemulen ® at about 0.05%, and glycerin at about 2.2%. (see, e.g., claim 8). Additionally, a different emulsifier, i.e., polysorbate 80, is taught at about 1.0% (see also claim 8) for a total emulsifier at 1.05%). The emulsion contains water as set forth in claims 6-8 of Ding et al. See also claim 6.

Ding et al. do not *expressly* teach a composition having Pemulen ® in a concentration equal to 1.0% by weight or greater, nor does it *expressly* disclose less than 1.0% of glycerin.

However, with regards to the emulsifier, the Ding patent does disclose a total emulsifier amount of 1.05% (Pemulen ® + Polysorbate 80, see claim 8). See also generic claim 6. With regards to glycerin, the Ding patent directs one skilled in the art to adjust the emulsions tonicity with tonicity agents such as glycerin, in general (e.g., col. 4, lines 12-13, see also generic claim 6).

One of ordinary skill in the art at the time the invention was made would have been motivated to modify the invention of Ding et al. by making any composition encompassed by Ding et al. and/or by using other functionally equivalent emulsifiers/tonicity agents/solvents within the Ding et al. solutions. One of ordinary skill in the art, at the time the invention was made, would have had a reasonable expectation

of success for doing so because such modifications are routinely determined and optimized in the art through routine experimentation [see MPEP 2144.05 (I) regarding optimization of ranges] and because the active ingredients, cyclosporin A and castor oil were present at overlapping concentrations between the instant invention and the invention of Ding et al. [see MPEP 2144.05 (I) regarding overlapping ranges]. Moreover, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical [see MPEP 2144.05 (II)].

From the teaching of the reference, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments

11. The Office has instructed that a terminal disclaimer in compliance with 37 C.F.R. § 1.321(c) or § 1.321(d) may be used to overcome an actual or provisional rejection based on non-statutory double patenting ground. Without addressing the propriety of the Office's rejection, and specifically the Office's interpretation of what the cited reference teaches or suggests, the Applicants respectfully and properly defer addressing the present rejection until there is otherwise allowable subject matter in the present application. Only then is it proper to assess the propriety of the Office's rejection in view of the potentially allowable claims. Accordingly, the Applicants respectfully

request reconsideration and withdrawal of the present rejections or that the rejections be held in abeyance until claims are allowable in the present application.

Response to arguments

12. Applicant's arguments regarding the obviousness rejection have been carefully considered but not deemed persuasive for the reasons of record, for the reasons set forth above and for following reasons:

Applicant argues that a lower dose of cyclosporine A, in this case less than 0.05% by weight, can increase the number of patients that can receive the composition for treatment and also reduce the number of restrictions attendant to its administration.

Further, the concentration of castor oil relative to cyclosporine A is important to the comfort and ease of use of the composition. The claimed ratio provides the advantage of more rapidly breaking down the emulsion in the eye, which reduces vision distortion that results from the administration, and further facilitates therapeutic effectiveness. There is a clear benefit achieved with a composition that has a reduced concentration of cyclosporine A, less than 0.05% by weight, and also a cyclosporine A to castor oil ratio that is less than 0.04 (e.g., claim 4). However, both the less than 0.05% by weight cyclosporine and the ratio of cyclosporine/castor oil less than 0.04 are taught by Ding and therefore the associated effects and benefits would also be encompassed by the invention of Ding. "[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer. […]

Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable." (See MPEP 2112).

Please note that this is a 103 rejection not 102 rejection, therefore all the limitations need not be set forth in the reference. In the instant reference the critical ratios/concentrations were set forth in Ding. The other components (glycerin, stabilizer such as crosslinked polyacrylate stabilizer and water) are not taught at the concentration as instantly taught, however the application does teach that these components may be adjusted to obtain a stable emulsion (e.g., claim 6, col. 3-4). Furthermore, no criticality appears to be associated to these components.

Therefore, based on the guidance of Ding, one of ordinary skill in the art would have had a reasonable expectation of success in obtaining the claimed inventions and therefore the ODP rejection of record is maintained.

Conclusion

13. No claim is allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARCELA M. CORDERO GARCIA whose telephone number is (571)272-2939. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia J. Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Marcela M Cordero Garcia/
Examiner, Art Unit 1654

MMCG 08/10

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	10927857	ACHEAMPONG ET AL.
	Examiner	Art Unit
	MARCELA M CORDERO GARCIA	1654

SEARCHED

Class	Subclass	Date	Examiner
none	none	8/26/09	MMCG

SEARCH NOTES

Search Notes	Date	Examiner
STN searched by STIC (available via SCORE / PAIR)	7/22/09	MMCG
EAST searched (attached)	8/26/09	MMCG
also ran PALM Inventor search	8/26/09	MMCG
class/subclass search in text	8/26/09	MMCG
EAST updated	8/30/10	MMCG
also ran PALM inventor search	8/30/10	MMCG

INTERFERENCE SEARCH

Class	Subclass	Date	Examiner

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	6	pemulen same cyclosporin same castor same glycerin	US-PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2010/08/30 23:02
L2	9	pemulen same cyclosporin same castor	US-PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2010/08/30 23:03
L3	315	cyclosporin same castor	US-PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2010/08/30 23:05
L4	26	cyclosporin same castor and pemulen and glycerin	US-PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2010/08/30 23:06
S1	2	"5474979".pn.	US-PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2010/08/30 18:30

8/30/10 11:08:33 PM

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	65	pemulen same glycerin same castor	US-PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2010/08/30 15:56
L2	57	"5,474,979"	US-PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2010/08/30 16:00
L3	2	"5,474,979".pn.	US-PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2010/08/30 16:00
L4	1	pemulen near10 "1.05"	US-PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2010/08/30 16:26
L5	832	pemulen near10 "2"	US-PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2010/08/30 16:26
L6	1	pemulen.clm. near10 "ocular"	US-PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2010/08/30 16:26
L7	1	pemulen.clm. near10 castor	US-PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2010/08/30 16:27
L8	65	pemulen same castor same glycerin	US-PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2010/08/30 16:27

8/30/10 5:34:50 PM

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/927,857	08/27/2004	Andrew Acheampong	17618(AP)	2409

51957 7590 04/11/2011

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EXAMINER	
CORDERO GARCIA, MARCELA M	
ART UNIT	**PAPER NUMBER**
1654	

NOTIFICATION DATE	DELIVERY MODE
04/11/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patents_ip@allergan.com

Notice of Abandonment	Application No.	Applicant(s)
	10/927,857	ACHEAMPONG ET AL.
	Examiner	Art Unit
	MARCELA M. CORDERO GARCIA	1654

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

This application is abandoned in view of:

1. ☒ Applicant's failure to timely file a proper reply to the Office letter mailed on *02 September 2010*.
   (a) ☐ A reply was received on _____ (with a Certificate of Mailing or Transmission dated _____), which is after the expiration of the period for reply (including a total extension of time of _____ month(s)) which expired on _____.
   (b) ☐ A proposed reply was received on _____, but it does not constitute a proper reply under 37 CFR 1.113 (a) to the final rejection.
   (A proper reply under 37 CFR 1.113 to a final rejection consists only of: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114).
   (c) ☐ A reply was received on _____ but it does not constitute a proper reply, or a bona fide attempt at a proper reply, to the non-final rejection. See 37 CFR 1.85(a) and 1.111. (See explanation in box 7 below).
   (d) ☒ No reply has been received.

2. ☐ Applicant's failure to timely pay the required issue fee and publication fee, if applicable, within the statutory period of three months from the mailing date of the Notice of Allowance (PTOL-85).
   (a) ☐ The issue fee and publication fee, if applicable, was received on _____ (with a Certificate of Mailing or Transmission dated _____), which is after the expiration of the statutory period for payment of the issue fee (and publication fee) set in the Notice of Allowance (PTOL-85).
   (b) ☐ The submitted fee of $_____ is insufficient. A balance of $_____ is due.
   The issue fee required by 37 CFR 1.18 is $_____. The publication fee, if required by 37 CFR 1.18(d), is $_____.
   (c) ☐ The issue fee and publication fee, if applicable, has not been received.

3. ☐ Applicant's failure to timely file corrected drawings as required by, and within the three-month period set in, the Notice of Allowability (PTO-37).
   (a) ☐ Proposed corrected drawings were received on _____ (with a Certificate of Mailing or Transmission dated _____), which is after the expiration of the period for reply.
   (b) ☐ No corrected drawings have been received.

4. ☐ The letter of express abandonment which is signed by the attorney or agent of record, the assignee of the entire interest, or all of the applicants.

5. ☐ The letter of express abandonment which is signed by an attorney or agent (acting in a representative capacity under 37 CFR 1.34(a)) upon the filing of a continuing application.

6. ☐ The decision by the Board of Patent Appeals and Interference rendered on _____ and because the period for seeking court review of the decision has expired and there are no allowed claims.

7. ☒ The reason(s) below:

Examiner left a message for Applicant's representative inquiring about status of the application. No response was received.

/MARCELA M CORDERO GARCIA/
Primary Examiner, Art Unit 1654

Petitions to revive under 37 CFR 1.137(a) or (b), or requests to withdraw the holding of abandonment under 37 CFR 1.181, should be promptly filed to minimize any negative effects on patent term.

U.S. Patent and Trademark Office