PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patentee: Acheampong, *et al.*	Examiner: Marcela M Cordero Garcia
Patent No.: 9,248,191	Group Art Unit: 1676
Issue Date: February 2, 2016	Confirmation No. 9616
For: METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS	Customer No.: 51957

REQUEST FOR CERTIFICATE OF CORRECTION

Attn: Certificate of Correction Branch
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

It is requested that a Certificate of Correction be issued correcting printing errors appearing in the above-identified United States patent.

Pursuant to 1.20(a), the examiner is authorized to charge the Certificate of Correction fee of $100.00 or any additional fees or credit overpayment to Deposit Account No. 010885.

Issuance of the Certificate of Correction would neither expand nor contract the scope of the claims as properly allowed, and re-examination is not required.

Respectfully submitted,

Date February 16, 2016

By: /Laura L. Wine/
Laura L. Wine
Reg. No.: 68681

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patentee: Acheampong, *et al.*	Examiner: Marcela M Cordero Garcia
Patent No.: 9,248,191	Group Art Unit: 1676
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For: METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS	Customer No.: 51957

Attn: Certificate of Correction Branch
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

We are transmitting herewith the attached:

X Request for Certificate of Correction.
X Certificate of Correction Form - PTO-1050

Please charge any additional fees or credit overpayment to Deposit Account No. 010885.

Respectfully submitted,

/Laura L. Wine/

Date: February 16, 2016

By Laura L. Wine
Reg. No.:68681

PTO/SB/44 (09-07)
Approved for use through 08/31/2013. OMB 0651-0033
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

(Also Form PTO-1050)

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO : 9,248,191

DATED : February 2, 2016

INVENTOR(S) : Andrew Acheampong et al.

It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the first page, in field (63), in column 1, in "Related U.S. Application Data", line 4, delete "and" and insert - - which is - -, therefor.

On the Page 2, in column 2, under "Other Publications", line 9, delete "a" and insert - - A - -, therefor.

On the Page 3, in column 1, under "Other Publications", line 52, delete "a" and insert - - A - -, therefor.

On the Page 3, in column 1, under "Other Publications", line 61, delete "Muscosal" and insert - - Mucosal - -, therefor.

On the Page 3, in column 2, under "Other Publications", line 24, delete "a" and insert - - A - -, therefor.

On the Page 3, in column 2, under "Other Publications", line 28, delete "Polyocyethylene" and insert - - Polyoxyethylene - -, therefor.

On the Page 3, in column 2, under "Other Publications", line 29, delete "PhysicoChemical" and insert - - Physico-Chemical - -, therefor.

On the Page 3, in column 2, under "Other Publications", line 39, delete "a" and insert - - A - -, therefor.

On the Page 4, in column 1, under "Other Publications", line 13, delete "a" and insert - - A - -, therefor.

On the Page 4, in column 1, under "Other Publications", line 35, delete "a" and insert - - A - -, therefor.

On the Page 4, in column 1, under "Other Publications", line 48, after "U.S." insert - - Re-Examination - -.

PTO/SB/44 (09-07)
Approved for use through 08/31/2013. OMB 0651-0033
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO : 9,248,191

DATED : February 2, 2016

INVENTOR(S) : Andrew Acheampong et al.

It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Page 4, in column 2, under "Other Publications", line 10, delete "Allegran," and insert - - Allergan, - -, therefor.

On the Page 4, in column 2, under "Other Publications", line 43, delete "Occular" and insert - - Ocular - -, therefor.

On the Page 5, in column 1, under "Other Publications", line 58, after "Systane" insert - - Products, Systane - -.

On the Page 5, in column 1, under "Other Publications", line 59, delete "http;//" and insert - - http:// - -, therefor.

On the Page 5, in column 2, under "Other Publications", line 22, delete "Waston" and insert - - Watson - -, therefor.

On the Page 5, in column 2, under "Other Publications", line 31, delete "No." and insert - - Nos. - -, therefor.

On the Page 5, in column 2, under "Other Publications", line 33, delete "5050)(2)(13)" and insert - - 505(j)(2)(B) - -, therefor.

On the Page 5, in column 2, under "Other Publications", line 48, delete "5050)(2)(13)" and insert - - 505(j)(2)(B) - -, therefor.

In column 1, line 8, delete "13/961.828" and insert - - 13/961,828 - -, therefor.

In column 1, line 36, delete "a" and insert - - A - -, therefor.

In column 1, line 37, delete "a" and insert - - A - -, therefor.

In column 1, line 39, delete "2002," and insert - - 2002 - -, therefor.

In column 1, line 53, delete "al." and insert - - al, - -, therefor.

PTO/SB/44 (09-07)
Approved for use through 08/31/2013. OMB 0651-0033
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

(Also Form PTO-1050)

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CERTIFICATE OF CORRECTION

PATENT NO : 9,248,191

DATED : February 2, 2016

INVENTOR(S) : Andrew Acheampong et al.

It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In column 2, line 65, delete "kerapoconjunctivitis," and
insert - - keratoconjunctivitis, - -, therefor.

In column 3, line 12, delete "clyclcosporin" and insert - - cyclosporin - -, therefor.

In column 3, line 52, delete "were" and insert - - are - -, therefor.

In column 4, line 23, After "more" insert - - of - -.

In column 5, line 9, delete "kerapoconjunctivitis," and
insert - - keratoconjunctivitis, - -, therefor.

In column 5, line 66, After "with" delete "a".

In column 6, line 3, delete "acetronitrile-based" and insert - - acetonitrile-based - -, therefor.

In column 9, line 20, delete "each" and insert - - such - -, therefor.

In column 9, line 48, delete "extant" and insert - - extent - -, therefor.

In column 9, line 60, delete "benefiting" and insert - - benefitting - -, therefor.

In column 10, line 22, delete "informing" and insert - - in forming - -, therefor.

In column 10, line 35, delete "amphorteric" and insert - - amphoteric - -, therefor.

In column 11, line 7, delete "methylhydroxyethlystarches" and
insert - - methylhydroxyethylstarches - -, therefor.

In column 11, line 10, delete "glucoaminoglycans" and
insert - - glycosaminoglycans - -, therefor.

In column 11, line 28, delete "2-methacrylolyoxyethlysulfonic" and
insert - - 2-methacryloyloxyethylsulfonic - -, therefor.

PTO/SB/44 (09-07)
Approved for use through 08/31/2013. OMB 0651-0033
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

(Also Form PTO-1050)

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PATENT NO : 9,248,191

DATED : February 2, 2016

INVENTOR(S) : Andrew Acheampong et al.

It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In column 11, line 29, delete "2-methacryloyloxethylsulfonates" and insert - - 2-methacryloyloxyethylsulfonates - -, therefor.

In column 11, line 30, delete "2-hydroxyproplysulfonic" and insert - - 2-hydroxypropylsulfonic - -, therefor.

In column 11, line 45, delete "crosslinked" and insert - - cross-linked - -, therefor.

In column 12, line 9, delete "polyvinyl," and insert - - polyvinyl - -, therefor.

In column 13, line 1, delete "Disoxide," and insert - - Dioxide, - -, therefor.

In column 13, line 34, delete "materiel" and insert - - material - -, therefor.

In column 14, line 32, delete "Premulen ®" and insert - - Pemulen® - -, therefor.

In column 15, line 24, in Claim 1, delete "005%" and insert - - 0.05% - -, therefor.

In column 15, line 61, in Claim 11, delete "claim 2," and insert - - claim 6, - -, therefor.

Electronic Patent Application Fee Transmittal

Application Number:	14222478
Filing Date:	21-Mar-2014
Title of Invention:	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS
First Named Inventor/Applicant Name:	Andrew Acheampong
Filer:	Laura Lee Wine/Maria Stein
Attorney Docket Number:	17618CON6CON1 (AP)

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

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:				
Certificate of Correction	1811	1	100	100

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**100**

Electronic Acknowledgement Receipt

EFS ID:	24926019
Application Number:	14222478
International Application Number:	
Confirmation Number:	9616
Title of Invention:	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS
First Named Inventor/Applicant Name:	Andrew Acheampong
Customer Number:	51957
Filer:	Laura Lee Wine/Maria Stein
Filer Authorized By:	Laura Lee Wine
Attorney Docket Number:	17618CON6CON1 (AP)
Receipt Date:	16-FEB-2016
Filing Date:	21-MAR-2014
Time Stamp:	16:41:29
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$100
RAM confirmation Number	3850
Deposit Account	010885
Authorized User	WINE, LAURA L.

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 CFR 1.16 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 CFR 1.17 (Patent application and reexamination processing fees)

Charge any Additional Fees required under 37 CFR 1.19 (Document supply fees)

Charge any Additional Fees required under 37 CFR 1.20 (Post Issuance fees)

Charge any Additional Fees required under 37 CFR 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Request for Certificate of Correction	COCAllergan17618CON6CON1 AP9248191.pdf	164544 896d1a453cf219586794f8fade9fefd8b525c808	no	6
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30499 77d8f5cf7d4c6377f431b5aca5d39b369a6900f5	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	195043		

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.

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.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/222,478	02/02/2016	9248191	17618CON6CON1 (AP)	9616

51957 7590 01/13/2016

ALLERGAN, INC.
2525 DUPONT DRIVE, T2-7H
IRVINE, CA 92612-1599

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

Allergan, Inc., Irvine, CA;
Andrew Acheampong, Irvine, CA;
Diane D. Tang-Liu, Las Vegas, CA;
James N. Chang, Newport Beach, CA;
David F. Power, San Clemente, CA;

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

51957 7590 12/18/2015

ALLERGAN, INC.
2525 DUPONT DRIVE, T2-7H
IRVINE, CA 92612-1599

EXAMINER
CORDERO GARCIA, MARCELA M

ART UNIT	PAPER NUMBER
1676	

DATE MAILED: 12/18/2015

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/222,478	03/21/2014	Andrew Acheampong	17618CON6CON1 (AP)	9616

TITLE OF INVENTION: METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	03/18/2016

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

51957 7590 12/18/2015
ALLERGAN, INC.
2525 DUPONT DRIVE, T2-7H
IRVINE, CA 92612-1599

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/222,478	03/21/2014	Andrew Acheampong	17618CON6CON1 (AP)	9616

TITLE OF INVENTION: METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	03/18/2016

EXAMINER	ART UNIT	CLASS-SUBCLASS
CORDERO GARCIA, MARCELA M	1676	514-020500

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
- ❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.
1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:
- ❑ Issue Fee
- ❑ Publication Fee (No small entity discount permitted)
- ❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
- ❑ A check is enclosed.
- ❑ Payment by credit card. Form PTO-2038 is attached.
- ❑ The director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
- ❑ Applicant certifying micro entity status. See 37 CFR 1.29 — NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
- ❑ Applicant asserting small entity status. See 37 CFR 1.27 — NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
- ❑ Applicant changing to regular undiscounted fee status. — NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

PTOL-85 Part B (10-13) Approved for use through 10/31/2013. OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF C CE

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.
14/222,478	03/21/2014	Andrew Acheampong	17618CON6CON1 (AP)	9616

51957 7590 12/18/2015

ALLERGAN, INC.
2525 DUPONT DRIVE, T2-7H
IRVINE, CA 92612-1599

EXAMINER	
CORDERO GARCIA, MARCELA M	
ART UNIT	PAPER NUMBER
1676	

DATE MAILED: 12/18/2015

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. 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, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. 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.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Applicant-Initiated Interview Summary	Application No.	Applicant(s)	
	14/222,478	ACHEAMPONG ET AL.	
	Examiner	Art Unit	
	MARCELA M. CORDERO GARCIA	1676	

All participants (applicant, applicant's representative, PTO personnel):

(1) *MARCELA M. CORDERO GARCIA*. (3)_____.

(2) *LAURA L.WINE*. (4)_____.

Date of Interview: *11 December 2015*.

Type: ☒ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☒ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☐112 ☐102 ☐103 ☒Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: *All, in general*.

Identification of prior art discussed: *US 9,101,574*.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

See Continuation Sheet.

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☒ Attachment

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews
Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:
1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

Continuation of Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: Applicant's representative contacted Examiner to discuss the outstanding rejection and Applicant's response. During the interview Examiner indicated that, upon consideration of the response, Applicant's arguments mailed on 10/22/2015 are deemed persuasive and the only outstanding rejection (112 2nd 1st paragraph) has been withdrawn. Further, on 12/14/2015, Examiner contacted Applicant's representative to discuss US 9,101,574 with regards to a potential ODP rejection. Applicant's representative argued that the claims in the instant application were non-obvious over those claimed on US '574 because the specific ranges of cyclosporin and castor oil were not taught, and such ranges were associated to unexpected efficacy results (See, e.g., Reasons for Allowance, pages 2-6 of the Notice of Allowance mailed on 1/28/14 for parent U.S. Patent Application No. 13/961,828, and 6/10/15 Non-Final Office Action for the instant application,paragraph 13). Applicant's arguments were deemed persuasive.Thus no ODP rejection over US '574 has been required and the instant application is deemed in condition for allowance. Applicant's representative filed their arguments in a supplemental response dated 12/14/2015 (see also attached electronic communication and copy of the filed arguments).

Notice of Allowability	Application No. 14/222,478	Applicant(s) ACHEAMPONG ET AL.	
	Examiner MARCELA M. CORDERO GARCIA	Art Unit 1676	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *10/22/2015 and 12/14/2015*.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on_____.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are *37-63*. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov .
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some *c) ☐ None of the:
   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)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☒ Notice of References Cited (PTO-892)
2. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 10/22/2015
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
4. ☒ Interview Summary (PTO-413), Paper No./Mail Date _____ .
5. ☒ Examiner's Amendment/Comment
6. ☐ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/MARCELA M CORDERO GARCIA/
Primary Examiner, Art Unit 1676

The present application is being examined under the pre-AIA first to invent provisions.

REASONS FOR ALLOWANCE

The following is an examiner's statement of reasons for allowance: The closest prior art is that of Ding et al. (US 5,474,979). The declaration under 37 CFR 1.132 by Rhett M. Schiffman filed on 12/5/2013 (EXHIBIT 1 comprising EXHIBITS A-F) in parent case Application 13/961,828, of which this case is a CON, is deemed sufficient to overcome a potential 103 rejection of the instant claims over Ding et al. (US 5,474,979, cited in the instant IDS dated 3/28/2014) because: After carefully reviewing exhibits A-F, which compare the instantly claimed embodiment having 0.05%/1.25% castor oil with embodiments E and F of Ding et al. (0.10%/1.25% castor oil and 0.05/.625% cyclosporin/castor oil ratios), Examiner is persuaded that, unexpectedly, the claimed formulation (0.05% cyclosporin A/1.25% castor oil) demonstrated an 8-fold increase in relative efficacy for the Schirmer Tear Test score in the first study of Phase 3 trials compared to the relative efficacy for the 0.05% by weight cyclosporin A/0.625% by weight castor oil formulation disclosed in Example 1E of Ding, tested in Phase 2 trials. The data represents a comparison of the subpopulation of Phase 2 patients using compositions with the same reductions in tear production (5 mm/5 min) as those enrolled in the Phase 3 studies. EXHIBIT 1 at paragraph 8. All of the cyclosporin A-containing formulations as well as the vehicle also included 2.2% by weight glycerine, 1.0% by weight polysorbate, 0.05% Pemulen, sodium hydroxide, and water (see paragraph 6, page 2 of EXHIBIT 1).

Exhibits E and F also illustrate that the claimed formulations comprising 0.05% cyclosporin A/1.25% castor oil also demonstrated a 4-fold improvement in the relative efficacy for the Schirmer Tear Test score for the second study of Phase 3 and a 4-fold increase in relative efficacy for decrease in corneal staining score in both of the Phase 3 studies compared to the 0.05% by weight cyclosporin A/0.625% by weight castor oil formulation tested in Phase 2 and disclosed in Ding (Ding 1E). The excipients were the same in the compared compositions. Given that the compositions comprise the same amount of active agent (0.05 % cyclosporin A) as Ding 1E, the improvements are surprising, unexpected and commensurate in scope with the claimed invention.

The declaration under 37 CFR 1.132 by Mayssa Attar, filed on 12/5/2013 (EXHIBIT 2, comprising EXHIBITS A-D) in parent case Application 13/961,828, of which this case is a CON, is deemed sufficient to overcome a potential rejection of the instant claims based upon Ding et al. (US 5,474,979, cited in the IDS dated 9/12/2013) because: As described in paragraph 7 of the EXHIBIT 2, the chart in EXHIBIT B shows that the amount of cyclosporin A that reaches the cornea and conjunctiva, ocular tissues that are highly relevant for the treatment of dry eye or keratoconjunctivis sicca, is higher for the formulation containing 0.05% by weight cyclosporin A and 0.625% by weight castor oil (Ding et al. 1E) than the formulation containing 0.05% by weight cyclosporin A and 1.25% by weight castor oil (the claimed formulation) relative to the formulation containing 0.1% by weight cyclosporin A and 1.25% by weight castor oil (Ding et al. 1D). According to Dr. Attar, this data teaches that the formulation containing 0.05% by weight cyclosporin A and 1.25% by weight castor oil would be less therapeutically effective

than the formulation containing 0.05% by weight cyclosporin A and 0.625% by weight castor oil or the formulation containing 0.10% by weight cyclosporin A and 1.25% by weight castor oil. EXHIBIT A, paragraph 8. Therefore it would be unexpected that the composition with lower uptake in cornea and conjunctiva would have significantly improved activity.

Taking the results of the studies and data presented in the EXHIBITS 1 and 2 together, it is clear that the specific combination of 0.05% by weight cyclosporin A with 1.25% by weight castor oil is surprisingly critical for therapeutic effectiveness in the treatment of dry eye or keratoconjunctivitis sicca.

Accordingly, the Declarations in EXHIBIT 1 and EXHIBIT 2, together with the data presented in those declarations, provide clear and convincing objective evidence that establishes that the claimed formulations, including 0.05% by weight cyclosporin A and 1.25% by weight castor oil, demonstrate surprising and unexpected results, including improved Schirmer Tear Test scores and corneal staining scores (key objective measures of efficacy for dry eye or keratoconjunctivitis sicca) and improved visual blurring and reduced artificial tear use as compared to the prior art, for example, emulsion formulations disclosed in Ding et al., including formulations with 0.05% by weight cyclosporin A and 0.625% by weight castor oil (Ding et al. 1E) and formulations with 0.10% by weight cyclosporin A and 1.25% by weight castor oil (Ding et al. 1D) which are the closest prior art formulations. The unexpected results are commensurate in scope with the claims (MPEP 716.02(d)).

The same described unexpected results above obviate a potential ODP rejection over US 9,101,574 (see attached interview summary).

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

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, Karlheinz R. Skowronek can be reached on (571)-272-9047. 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/
Primary Examiner, Art Unit 1676

MMCG 12/2015

Applicant-Initiated Interview Summary	Application No.	Applicant(s)	
	14/222,478	ACHEAMPONG ET AL.	
	Examiner	Art Unit	
	MARCELA M. CORDERO GARCIA	1676	

All participants (applicant, applicant's representative, PTO personnel):

(1) *MARCELA M. CORDERO GARCIA*. (3)_____.

(2) *LAURA L.WINE*. (4)_____.

Date of Interview: *11 December 2015*.

Type: ☒ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☒ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☐112 ☐102 ☐103 ☒Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

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Paragraph (b)

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Notice of References Cited	Application/Control No. 14/222,478	Applicant(s)/Patent Under Reexamination ACHEAMPONG ET AL.	
	Examiner MARCELA M. CORDERO [illegible]	Art Unit 1676	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
*	A	US-9,101,574 B2	08-2015	Chang; James N.	A61K9/0048	1/1
	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	CPC Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	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.

Cordero Garcia, Marcela M.

From: Wine_Laura <Wine_Laura@Allergan.com>
Sent: Monday, December 14, 2015 4:27 PM
To: Cordero Garcia, Marcela M.
Cc: Stein_Maria
Subject: US 14/222,478 Courtesy Copy of Supplemental Response and Interview Summary
Attachments: US14-222478_Supplemental_Response.pdf

Dear Examiner Cordero,

Attached please find a courtesy copy of a Supplemental Response and Interview Summary that was filed today for US 14/222,478 (AGN Ref: 17618CON6CON1). Please be advised that I have already filed a communication today under MPEP 502.3 authorizing email communications in this patent application.

Please do not hesitate to contact me if you have any questions.

Best regards,

Laura

Laura Wine
Patent Counsel
Allergan, Inc.
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EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	617	cyclosporin same (keratoconjunctivitis or "dry eye" or tears or tear or lacrimal)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/12/14 11:42
L2	95	cyclosporin near3 (keratoconjunctivitis or "dry eye" or tears or tear or lacrimal)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/12/14 11:43
L3	25	cyclosporin near3 (keratoconjunctivitis or "dry eye" or tears or tear or lacrimal) and ("castor oil" and polysorbate and acrylate)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/12/14 11:43
L9	37	(cyclosporin or cyclosporine) near3 ("keratoconjunctivitis sicca" or "dry eye" or tears or tear or lacrimal) and ("castor oil" and polysorbate and acrylate)	US-PGPUB; USPAT; USOCR; FPRS; EPO; DERWENT	ADJ	ON	2015/12/14 11:51
L10	2	(cyclosporin or cyclosporine) near3 ("keratoconjunctivitis sicca" or "dry eye" or tears or tear or lacrimal) same ("castor oil" and polysorbate and acrylate)	US-PGPUB; USPAT; USOCR; FPRS; EPO; DERWENT	ADJ	ON	2015/12/14 11:52
L11	33	"7288520"	US-PGPUB; USPAT; USOCR; FPRS; EPO; DERWENT	ADJ	ON	2015/12/14 11:56
L12	2	"7288520".pn.	US-PGPUB; USPAT; USOCR; FPRS; EPO; DERWENT	ADJ	ON	2015/12/14 11:56

EAST Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L4	7	cyclosporin near3 (keratoconjunctivitis or "dry eye" or tears or tear or lacrimal) and ("castor oil" and polysorbate and acrylate)	USPAT	ADJ	ON	2015/12/14 11:44
L5	58	"5,578,586"	USPAT	ADJ	ON	2015/12/14 11:46
L6	1	"5,578,586".pn.	USPAT	ADJ	ON	2015/12/14 11:46
L7	12	(cyclosporin or cyclosporine) near3 (keratoconjunctivitis or "dry eye" or tears or tear or lacrimal) and ("castor oil" and polysorbate and acrylate)	USPAT	ADJ	ON	2015/12/14 11:50

L8	12	(cyclosporin or cyclosporine) near3 ("keratoconjunctivitis sicca" or "dry eye" or tears or tear or lacrimal) and ("castor oil" and polysorbate and acrylate)	USPAT	ADJ	ON	2015/12/14 11:51

12/14/2015 12:17:09 PM

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14222478	ACHEAMPONG ET AL.
	Examiner	Art Unit
	MARCELA M CORDERO GARCIA	1676

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner
none	none	6/16/2014	MMCG

SEARCH NOTES		
Search Notes	Date	Examiner
EAST search (attached)	6/14/2014	MMCG
STN search (attached)	6/16/2014	MMCG
also ran PALM Inventor search	6/16/2014	MMCG
EAST updated (attached)	11/6/2014	MMCG
also updated PALM Inventor search	11/6/2014	MMCG
EAST search (attached)	6/4/2015	MMCG
also ran PALM Inventor search	6/4/2015	MMCG
EAST updated (attached)	12/14/2015	MMCG
also updated PALM Inventor search	12/14/2015	MMCG

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner
EAST updated	attached	11/6/2014	MMCG
EAST updated	attached	12/14/2015	MMCG

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	14222478	ACHEAMPONG ET AL.
	Examiner	**Art Unit**
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CPC								
Symbol							**Type**	**Version**
A61K		47	/	02			F	2013-01-01
A61K		9	/	0048			I	2013-01-01
A61K		38	/	13			I	2013-01-01
A61K		47	/	44			I	2013-01-01
A61K		9	/	107			I	2013-01-01
A61K		47	/	10			I	2013-01-01
A61K		47	/	22			I	2013-01-01
A61K		47	/	32			I	2013-01-01
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CPC Combination Sets								
Symbol					**Type**	**Set**	**Ranking**	**Version**
			/					
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NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	27	
/MARCELA M CORDERO GARCIA/ Primary Examiner.Art Unit 1676	12/14/2015	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

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	14222478	ACHEAMPONG ET AL.
	Examiner	**Art Unit**
	MARCELA M CORDERO GARCIA	1676

US ORIGINAL CLASSIFICATION		INTERNATIONAL CLASSIFICATION										
CLASS	SUBCLASS	CLAIMED					NON-CLAIMED					
514	20.5	A	6	1	K	38 / 13 (2006.01.01)						

CROSS REFERENCE(S)					
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)				

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	27	
/MARCELA M CORDERO GARCIA/ Primary Examiner.Art Unit 1676	12/14/2015	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14222478	ACHEAMPONG ET AL.
	Examiner	**Art Unit**
	MARCELA M CORDERO GARCIA	1676

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☒ T.D. ☐ R.1.47

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 27	
/MARCELA M CORDERO GARCIA/ Primary Examiner.Art Unit 1676 (Primary Examiner)	12/14/2015 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure none

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

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First Named Inventor	Andrew Acheampong
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Attorney Docket Number	17618-US-CN6CN1-AP

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Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published. ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.M.C.G./	T[5]
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	2	Allergan Dry Eye Product Portfolio Fact Sheet (http://www.allergan.com/assets/pdf/dry_eye_product_portfolio_fact_sheet.pdf), 4 Pages, 2015	☐
	3	Allergan, Inc. 2001 Annual Report, Downloaded from http://agn.client.shareholder.com/financials.cfm, last accessed January 1, 2015, 54 Pages	☐
	4	Allergan, Inc. 2002 Annual Report (http://agn.client.shareholder.com/financials.cfm), 52 Pages, 2015	☐
	5	Allergan, Inc. 2003 Annual Report, Downloaded from http://agn.client.shareholder.com/financials.cfm, last accessed January 1, 2015, 52 Pages	☐
	6	Allergan, Inc. 2004 Annual Report, Downloaded from http://agn.client.shareholder.com/financials.cfm, last accessed January 1, 2015, 16 Pages	☐
	7	Allergan, Inc. 2006 Annual Report, Downloaded from http://agn.client.shareholder.com/financials.cfm, last accessed January 1, 2015, 18 Pages	☐
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Attorney Docket Number	17618-US-CN6CN1-AP

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	12	Allergan, Inc. 2012 Annual Report, Downloaded from http://agn.client.shareholder.com/financials.cfm, last accessed January 1, 2015, 28 Pages	☐
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	59	USPTO Before the Patent Trial and Appeal Board, Apotex Corp., Apotex, Inc. Petitioner v. Allergan, Inc. Patent Owner, Case IPR2015-01278, Patent 8,633,162, pages 1 - 43, Dated September 18, 2015	☐
	60	USPTO Before the Patent Trial and Appeal Board, Apotex Corp., Apotex, Inc. Petitioner v. Allergan, Inc. Patent Owner, Case IPR2015-01282, Patent 8,629,111, pages 1 - 46, Dated September 17, 2015	☐
	61	USPTO Before the Patent Trial and Appeal Board, Apotex Corp., Apotex, Inc. Petitioner v. Allergan, Inc. Patent Owner, Case IPR2015-01283, Patent 8,685,930, pages 1 - 46, Dated September 17, 2015	☐
	62	USPTO Before the Patent Trial and Appeal Board, Apotex Corp., Apotex, Inc. Petitioner v. Allergan, Inc. Patent Owner, Case IPR2015-01284, Patent 8,648,048, pages 1 - 43, Dated September 22, 2015	☐
	63	USPTO Before the Patent Trial and Appeal Board, Apotex Corp., Apotex, Inc. Petitioner v. Allergan, Inc. Patent Owner, Case IPR2015-01286, Patent 8,642,556, pages 1 - 47, Dated September 18, 2015	☐
	64	In the United States District Court for the Eastern District of Texas Marshall Division, Allergan, Inc. (Plaintiff) v. Actavis, Inc., Watson Laboratories, Inc., and Actavis Pharma, Inc. (f/k/a Watson Pharma, Inc.) (defendants), C.A. No. 2:14-cv-638-JRG-Lead Case Consolidated with 2:14-cv-188-JRG, Actavis, Inc., Waston Laboratories, Inc., and Actavis Pharma, Inc.'s Invalidity Contentions Pursuant to Local Patent Rules 3-3 and 3-8, pages 1-74, dated October 15, 2014	☐
	65	Letter from Victor Ramsaywak of Apotex, Inc., Notice of Certification Under 21 USC Section 355(j)(2)(B)(ii) (Section 505(j)(2)(B(ii) of the Federal Food, Drug and Cosmetic Act(and 21 CFR Section 314.95 dated July 23, 2015, pages 1-116	☐

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Attorney Docket Number	17618-US-CN6CN1-AP

	66	Letter from Shashank Upadhye, Counsel for InnoPharma, Inc., of Amin Talati & Upadhye, Notification of Certification of Invalidity, Unenforceability and/or Non-infringement for U.S. Patent Nos. 5,474,979; 8,629,111; 8,633,162; 8,642,556; 8,648,048; and 8,685,930 Pursuant to Section 505(j)(2)(B)(iv) of the Federal Food, Drug, and Cosmetic Act, dated July 31, 2015, pages 1-58 ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.M.C.G./	☐
	67	Letter from J.C. Rozendaal of Kellogg, Huber, Hansen, Todd, Evans & Figel, PLLC, Notice of ANDA No. 203880 Concerning Cyclosporine Ophthalmic Emulsion, 0.05% with Paragraph IV Certification Concerning U.S. Patent Nos. 8,629,111; 8,633,162; 8,642,556; 8,648,048; and 8,685,930 dated July 22, 2015, pages 1-40	☐
	68	Letter from Joseph M. Reisman, Counsel for Mylan Pharmaceuticals Inc., of Knobbe Martens, Cyclosporine Emulsion 0.05%, Route of Administration: Ophthalmic, U.S. Patent Nos. 8,629,111; 8,633,162; 8,642,556; 8,648,048; and 8,685,930, Notice of Paragraph IV Certification, dated July 20, 2015, pages 1-226	☐
	69	Letter from Joseph Bonaccorsi, General Counsel, Akorn, Inc., Notification of Certification for U.S. Patent Nos. 8,629,111; 8,633,162; 8,642,556; 8,648,048; and 8,685,930 Pursuant to Section 505(j)(2)(B)(iv) of the Federal Food, Drug, and Cosmetic Act - 21 USC Section 355(j)(2)(B)(iv) Akorn ANDA 204561, dated July 10, 2015, pages 1-26	☐
	70	USPTO Before the Patent Trial and Appeal Board, Apotex, Inc. Petitioner v. Allergan, Inc. Patent Owner, Case IPR2015-01278, Patent 8,633,162, Pages 1-63, Dated June 4, 2015	☐
	71	USPTO Before the Patent Trial and Appeal Board, Apotex, Inc. Petitioner v. Allergan, Inc. Patent Owner, Case IPR2015-01282, Patent 8,629,111, Pages 1-63, Dated June 4, 2015	☐
	72	USPTO Before the Patent Trial and Appeal Board, Apotex, Inc. Petitioner v. Allergan, Inc. Patent Owner, Case IPR2015-01283, Patent 8,685,930, Pages 1-63, Dated June 4, 2015	☐
	73	USPTO Before the Patent Trial and Appeal Board, Apotex, Inc. Petitioner v. Allergan, Inc. Patent Owner, Case IPR2015-01284, Patent 8,648,048, Pages 1-63, Dated June 4, 2015	☐
	74	USPTO Before the Patent Trial and Appeal Board, Apotex, Inc. Petitioner v. Allergan, Inc. Patent Owner, Case IPR2015-01286, Patent 8,642,556, Pages 1-63, Dated June 4, 2015	☐

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature	/Marcela Cordero Garcia/	Date Considered	12/11/2015

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

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	14222478 Receipt date: 10/22/2015
Filing Date	2014-03-21
First Named Inventor	Andrew Acheampong
Art Unit	1676
Examiner Name	CORDERO GARCIA, MARCELA M
Attorney Docket Number	17618-US-CN6CN1-AP

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.C.G./

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	14222478	Receipt date: 10/22/2015
Filing Date	2014-03-21	
First Named Inventor	Andrew Acheampong	
Art Unit	1676	
Examiner Name	CORDERO GARCIA, MARCELA M	
Attorney Docket Number	17618-US-CN6CN1-AP	

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.M.C.G./

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☒ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☐ None

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Laura L. Wine/	Date (YYYY-MM-DD)	2015-10-22
Name/Print	Laura L. Wine	Registration Number	68,681

This collection of information is required by 37 CFR 1.97 and 1.98. 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 1 hour 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.**

Receipt date: 10/22/2015

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.M.C.G./

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

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PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

51957 7590 12/18/2015
ALLERGAN, INC.
2525 DUPONT DRIVE, T2-7H
IRVINE, CA 92612-1599

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

Laura L. Wine	(Depositor's name)
Laura L. Wine	(Signature)
December 18, 2015	(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/222,478	03/21/2014	Andrew Acheampong	17618CON6CON1 (AP)	9616

TITLE OF INVENTION: METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	03/18/2016

EXAMINER	ART UNIT	CLASS-SUBCLASS
CORDERO GARCIA, MARCELA M	1676	514-020500

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
- ☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 Laura L. Wine
2 Joel B. German
3 Debra D. Condino

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: Allergan, Inc.
(B) RESIDENCE: (CITY and STATE OR COUNTRY): Irvine, CA

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:
- ☒ Issue Fee
- ☐ Publication Fee (No small entity discount permitted)
- ☐ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
- ☐ A check is enclosed.
- ☐ Payment by credit card. Form PTO-2038 is attached.
- ☒ The director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number 010885 (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
- ☐ Applicant certifying micro entity status. See 37 CFR 1.29 — NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
- ☐ Applicant asserting small entity status. See 37 CFR 1.27 — NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
- ☐ Applicant changing to regular undiscounted fee status. — NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature /Laura L. Wine/ Date December 18, 2015
Typed or printed name Laura L. Wine Registration No. 68681

PTOL-85 Part B (10-13) Approved for use through 10/31/2013. OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF C CE

Docket No. 17618CON6CON1 (AP)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Acheampong, *et al.*	Examiner: Marcela M Cordero Garcia
Serial No.: 14/222,478	Group Art Unit: 1676
Filed: March 21, 2014	Confirmation No. 9616
For: METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS	Customer No.: 51957

COMMENTS ON EXAMINER'S STATEMENT OF REASONS FOR ALLOWANCE AND INTERVIEW SUMMARY

Mail Stop - Issue Fee
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

In response to the Statement of Reasons for Allowance in the Notice of Allowance mailed December 18, 2015, Applicant respectfully submits the following comments.

A Summary of Interviews begins on page 2 of this paper.

Comments on Statement of Reasons for Allowance begin on page 3 of this paper.

SUMMARY OF TELEPHONE INTERVIEWS

Attendees, Date and Type of Interviews

Telephone interviews were conducted on December 10 and 11 and attended by Examiner Marcela M Cordero Garcia and Laura L. Wine.

Identification of Claims Discussed

The Claims were discussed, focusing on Claims 37, 49, 53, and 57.

Principal Arguments and Other Matters

Laura L. Wine and Examiner Cordero Garcia discussed the rejection under 35 U.S.C. § 112, first paragraph in the June 10, 2015 Non-Final Office Action. The Applicants argued that the Claims of the present application contained proper written description support.

Results of Interviews

It was agreed that the Applicants' arguments were persuasive to overcome the rejections of record in the June 10, 2015 Non-Final Office Action.

COMMENTS ON STATEMENTS OF REASONS FOR ALLOWANCE

Applicants respectfully submit the following comments on the Examiner's Statement of Reasons for Allowance.

To the extent that there is any implication in such Statement that the patentability of the claims rests on the recitation of a single feature or the combination of particular features, Applicants respectfully disagree, since patentability rests on each claim taken as a whole. For example, Applicants submit that there are additional features from the claims that are not set forth in the cited art. Further, the Examiner's Statement refers to certain features of the claims. To the extent that the Examiner's Statement omits claim elements, groups claims together, or identifies purportedly distinguishing features of a claim or a group of claims, Applicants respectfully disagree with the Examiner's Statement. Rather, Applicants submit that the claims are allowable, because each claim, taken as a whole, recites a unique combination of features that is not anticipated or rendered obvious by the prior art.

Applicants also hereby traverse and respectfully reserve the right to traverse the characterizations of what any particular reference shows or teaches, or what any combination of references shows or teaches, or the appropriateness of combining references, and reserve the right to continue to do so in the future. In addition, Applicants respectfully traverse any characterizations of which references are deemed to be the closest prior art. Further, by making certain amendments to the claims, Applicants are not conceding that previously pending claims are not patentable. Rather, the amendments are being made to facilitate expeditious prosecution of this application. Applicants reserve the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the application's disclosure. Moreover, any arguments in support of patentability and based on a portion of a claim should not be taken as founding patentability solely on the portion in question; rather, it is

the combination of features or acts recited in a claim taken as a whole which distinguishes it over the identified references.

Applicants attach herewith payment of the issue fee and requests that the application proceed to issuance. Should the Examiner have any concerns, the Examiner is invited to contact the undersigned at the telephone number below.

Respectfully submitted,

/Laura L. Wine/

Date: December 18, 2015

Laura L. Wine
Attorney of Record
Registration Number 68,681

Please direct all inquiries and correspondence to:
Laura L. Wine, Esq.
Allergan, Inc.
2525 Dupont Drive, T2-7H
Irvine, California 92612
Tel: (714) 246-6996 Fax: (714) 246-4249

Electronic Patent Application Fee Transmittal

Application Number:	14222478
Filing Date:	21-Mar-2014
Title of Invention:	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS
First Named Inventor/Applicant Name:	Andrew Acheampong
Filer:	Laura Lee Wine/Maria Stein
Attorney Docket Number:	17618CON6CON1 (AP)

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

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:				
Utility Appl Issue Fee	1501	1	960	960

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**960**

Electronic Acknowledgement Receipt

EFS ID:	24411956
Application Number:	14222478
International Application Number:	
Confirmation Number:	9616
Title of Invention:	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS
First Named Inventor/Applicant Name:	Andrew Acheampong
Customer Number:	51957
Filer:	Laura Lee Wine/Maria Stein
Filer Authorized By:	Laura Lee Wine
Attorney Docket Number:	17618CON6CON1 (AP)
Receipt Date:	18-DEC-2015
Filing Date:	21-MAR-2014
Time Stamp:	14:58:25
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$960
RAM confirmation Number	1432
Deposit Account	010885
Authorized User	WINE, LAURA L.

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Issue Fee Payment (PTO-85B)	17618CON6CON1_PTOL85.pdf	114712 1a8ae8c8cdf1dc4c1ec78dee094011ca6a5366fa	no	1
Warnings:					
Information:					
2	Applicant summary of interview with examiner	17618CON6CON1_INTERVIEW_SUMMARY_AND_RESPONSE_TO_ALLOWANCE.pdf	109453 0176adcfd771cd341daca744d7129c5923dad44f	no	4
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	30866 3029a192d6d44c93ed8962d17662e0725157001a	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	255031		

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.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Acheampong, *et al.*	Examiner: Marcela M Cordero Garcia
Serial No.: 14/222,478	Group Art Unit: 1676
Filed: March 21, 2014	Confirmation No. 9616
For: METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS	Customer No.: 51957

COMMUNICATION UNDER MPEP 502.3

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

Dear Sir:

Recognizing that Internet communications are not secure, I hereby authorize the USPTO to communicate with me concerning any subject matter of this application by electronic mail. I understand that a copy of these communications will be made of record in the application file.

Respectfully submitted,

/Laura L. Wine/

Date: December 14, 2015

Laura L. Wine
Attorney of Record
Registration Number 68,681

Please direct all inquiries and correspondence to:
Laura L. Wine, Esq.
Allergan, Inc.
2525 Dupont Drive, T2-7H
Irvine, California 92612
Tel: (714) 246-6996 Fax: (714) 246-4249

Electronic Acknowledgement Receipt

EFS ID:	24351915
Application Number:	14222478
International Application Number:	
Confirmation Number:	9616
Title of Invention:	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS
First Named Inventor/Applicant Name:	Andrew Acheampong
Customer Number:	51957
Filer:	Laura Lee Wine/Lauren Barberena
Filer Authorized By:	Laura Lee Wine
Attorney Docket Number:	17618CON6CON1 (AP)
Receipt Date:	14-DEC-2015
Filing Date:	21-MAR-2014
Time Stamp:	15:06:29
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	Miscellaneous Incoming Letter	17618CON6CON1_COMM_UNDER_MPEP_5023.pdf	95433 e8815c4fd1e2825c278034994 0b2a4fd8401aa3a	no	1

Warnings:	
Information:	

Total Files Size (in bytes):	95433

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.

Docket No. 17618CON6CON1 (AP)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Acheampong, *et al.*	Examiner: Marcela M Cordero Garcia
Serial No.: 14/222,478	Group Art Unit: 1676
Filed: March 21, 2014	Confirmation No. 9616
For: METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS	Customer No.: 51957

SUPPLEMENTAL AMENDMENT

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

Dear Sir:

These papers are filed as a supplement to the 10/22/15 Response to the Non-Final Office Action filed mailed June 10, 2015.

The Commissioner is authorized to charge any fee which may be required in connection with this Amendment to deposit account No. 01-0885.

SUMMARY OF INTERVIEW

Attendees, Date and Type of Interview

A telephonic interview was conducted on December 14, 2015 and was attended by Examiner Cordero Garcia and Laura Wine.

Identification of Claims Discussed

The Claims were discussed.

References Discussed

U.S. Patent No. 9,101,574 ("the '574 patent").

Principal Arguments and Other Matters

Claim 1 of the '574 patent was discussed as grounds for a potential obviousness-type double patenting rejection. The Applicants disagreed that a double patenting rejection was proper, because the pending Claims of the present application are patentably distinct over Claim 1 of the '574 patent.

Results of Interview

It was agreed that the Applicants' representative would file a supplemental amendment, presenting arguments discussed during the interview.

REMARKS

This Reply is a supplement to the 10/22/15 Response to the Non-Final Office Action filed sent 6/10/15 The Applicants respectfully submit that the claims are in condition for allowance.

Obviousness-Type Double Patenting

The Examiner has brought Claim 1 of U.S. Patent No. 9,101,574 ("the '574 patent") to the Applicants' attention as a potential grounds for rejection of the pending Claims for obviousness-type double patenting. The Applicants disagree with the proposed grounds of rejection.

The Applicants submit that an obviousness-type double patenting rejection over Claim 1 of the '574 patent would be improper. 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 claims. MPEP § 804. The Applicants submit that the pending Claims of the current application are patentably distinct from Claim 1 of the '574, because the Claims of the present application recite several non-obvious elements not recited in Claim 1 of the '574 patent.

As a non-limiting example, each pending independent claim (i.e., Claims 37, 49, 53, and 57) recites therapeutic methods including topical administration of a topical ophthalmic emulsion, where the emulsion comprises cyclosporin A in an amount of about 0.05% by weight and castor oil in an amount of about 1.25% by weight. The non-obviousness of this selection of the specific percentages of cyclosporin A and castor oil within the topical ophthalmic emulsion has been established throughout the prosecution of related cases (*See*, *e.g.*, Reasons for Allowance, pages 2-6 of the Notice of Allowance mailed on 1/28/14 for parent U.S. Patent Application No. 13/961,828), and has been

acknowledged by the Examiner in the present case (see 6/10/15 Non-Final Office Action, paragraph 13).

Claim 1 of the '574 patent does not recite these specific amounts of cyclosporin A and castor oil, and instead recites: "An ophthalmically acceptable emulsion comprising from about 0.001% to 0.4% cyclosporin A, castor oil, Polysorbate 80, Pemulen, and a cellulose derivative selected from the group consisting of hydroxypropylmethyl cellulose and carboxymethyl cellulose." Nothing in this claim would lead one of skill in the art to modify Claim 1 of the '574 patent to arrive at the currently claimed methods, and the non-obviousness of the selection of the specific amounts of cyclosporin A and castor oil has already been established. Thus, because the pending Claims in the present application are patentably distinct from Claim 1 of the '574 patent, an obviousness-type double patenting rejection would be improper and thus should not be made.

There are several other patentably distinct features of the currently pending Claims, and the Applicants reserve the right to argue these additional features at a later date, if necessary.

CONCLUSION

The Applicants believe all claims now pending in the present application are in condition for allowance.

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.

If the Examiner believes a telephone conference would expedite prosecution of this application, please contact the undersigned at (714) 246-6996.

Respectfully submitted,

/Laura L. Wine/

Date: December 14, 2015

Laura L. Wine
Attorney of Record
Registration Number 68,681

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2525 Dupont Drive, T2-7H
Irvine, California 92612
Tel: (714) 246-6996 Fax: (714) 246-4249

Electronic Acknowledgement Receipt

EFS ID:	24354408
Application Number:	14222478
International Application Number:	
Confirmation Number:	9616
Title of Invention:	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS
First Named Inventor/Applicant Name:	Andrew Acheampong
Customer Number:	51957
Filer:	Laura Lee Wine/Maria Stein
Filer Authorized By:	Laura Lee Wine
Attorney Docket Number:	17618CON6CON1 (AP)
Receipt Date:	14-DEC-2015
Filing Date:	21-MAR-2014
Time Stamp:	16:23:35
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		17618C6C1_Supplemental_Response.pdf	116116 e625aef0b10f5d9cf1a9041cc8491beccc539191	yes	5

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Supplemental Response or Supplemental Amendment	1	1
	Applicant Arguments/Remarks Made in an Amendment	2	5
Warnings:			
Information:			
	Total Files Size (in bytes):	116116	

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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
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Electronic Acknowledgement Receipt

EFS ID:	23869531
Application Number:	14222478
International Application Number:	
Confirmation Number:	9616
Title of Invention:	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS
First Named Inventor/Applicant Name:	Andrew Acheampong
Customer Number:	51957
Filer:	Laura Lee Wine/Ken Dinh
Filer Authorized By:	Laura Lee Wine
Attorney Docket Number:	17618CON6CON1 (AP)
Receipt Date:	22-OCT-2015
Filing Date:	21-MAR-2014
Time Stamp:	21:50:19
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	Non Patent Literature	65-Apotex_Para_IV.pdf	10222550 2216ec48d12acdfb882ce087ce35fe95d6b72c64	no	116

Warnings:	
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2	Non Patent Literature	66-2015-08-03_ParaIV_Ltr_Inno Pharma.pdf	7755028 821cd9b7d467d1764ca4351d3d843b6963c677b8	no	98
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Information:					
3	Non Patent Literature	67-2015-07-23_ParaIV_Ltr_Teva_RESTASIS.pdf	3331902 37c7fce52b8af9dfcb6aad200fda2d86c4e4938f	no	40
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Information:					
4	Non Patent Literature	68-2015-07-21_ParaIV_Ltr_Mylan_RESTASIS.pdf	11764636 bc9b70c403c142b0f108edd182db6e4c892b5f54	no	226
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5	Non Patent Literature	69-Akorn-Para-IV.pdf	6728857 11f0e1ae4d4cf5098dda70fac11fa81ff8238111	no	26
Warnings:					
Information:					
6	Non Patent Literature	70-IPR2015-01278-Petition-for-Inter-Partes-Review.pdf	8731940 47bd495e5e19eff8d2eddab11a213f5c8fd90ad9	no	63
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Information:					
7	Non Patent Literature	71-IPR2015-01282-Petition-for-Inter-Partes-Review.pdf	258252 5615296987403526e24a08f2003371a55aa24703	no	63
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Information:					
8	Non Patent Literature	72-IPR2015-01283-Petition-for-Inter-Partes-Review.pdf	235680 2275320de355a4343841b6945dc781cc1c62d174	no	63
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9	Non Patent Literature	73-IPR2015-0128-Petition-for-Inter-Partes-Review.pdf	175795 866e8f81e46a3243c0e05cf645c69a275017f4a0	no	63
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11	Non Patent Literature	8-2005AnnualReport.pdf	3116041 069deaba3a472848bf122ee4b8c6d8fe0b0684cb	no	35
Warnings:					
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12	Non Patent Literature	9-2009AnnualReport.pdf	2212691 28549e26209dcbd5e2f23d51a78e077b35d1d8a2	no	18
Warnings:					
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13	Non Patent Literature	25-Xia2015.pdf	1315020 caaf25594ac474c9d5a3bc1f98e894ad1ef234f6	no	17
Warnings:					
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14	Non Patent Literature	12-2012AnnualReport.pdf	2295053 73c75e077fc203e2891364bd6ca51169e8064b6c	no	28
Warnings:					
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Warnings:					
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Information:					
			Total Files Size (in bytes):	59951432	

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New International Application Filed with the USPTO as a Receiving Office

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Docket No. 17618CON6CON1 (AP)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Acheampong, *et al.*	Examiner: Marcela M Cordero Garcia
Serial No.: 14/222,478	Group Art Unit: 1676
Filed: March 21, 2014	Confirmation No. 9616
For: METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS	Customer No.: 51957

RESPONSE TO OFFICE ACTION DATED JUNE 10, 2015

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

Dear Sir:

These papers are filed in reply to the Office Action mailed June 10, 2015.

The Commissioner is authorized to charge any fee which may be required in connection with this Amendment to deposit account No. 01-0885.

A Summary of Interview begins on page 2 of this paper.

Remarks begin on page 3 of this paper.

SUMMARY OF INTERVIEW

Attendees, Date and Type of Interview

A Telephonic interview was conducted on August 14, 2015 and was attended by Examiner Cordero Garcia and Laura Wine.

Identification of Claims Discussed

The Claims were discussed.

Principal Arguments and Other Matters

The rejection under 35 U.S.C. § 112, first paragraph was discussed. The Applicants' representative argued that proper written description support for the Claims was present in the specification as originally filed. The Applicants pointed to further examples of support for the Claims in the specification, including, but not limited to, page 3, line 29 – page 4, line 19.

Results of Interview

It was agreed that the Applicants' representative would file a response to the Office Action, presenting arguments discussed during the interview.

REMARKS

This Reply responds to the Office Action sent June 10, 2015, in which the Office Action rejected Claims 37-63. The Applicants respectfully submit that the claims are in condition for allowance.

Claim Rejections

35 U.S.C. § 112, first paragraph

Claims 37-63 were rejected under 35 U.S.C § 112, first paragraph as failing to comply with the written description requirement. As will be explained in further detail below, the Applicants submit that the Claims are properly supported by the specification as originally filed, and that it is clear that the inventors had possession of the invention claimed at the time of filing of the application.

The Claims Comply with the Written Description Requirement

Written Description Requirement

According to the MPEP, an objective standard for determining compliance with the written description requirement, which is "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989). The test for sufficiency of support in a parent application is whether the disclosure of the application relied upon "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." *Ralston Purina Co.v.Far-Mar-Co., Inc.,* 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985) (quoting *In re Kaslow*, 707 F.2d 1366, 1375, 217 USPQ 1089, 1096 (Fed. Cir. 1983)). *MPEP§ 2163.02.*

The Applicants submit that the specification as filed reasonably conveys that the inventors were in possession of the claimed subject matter, and that the description clearly allows persons of ordinary skill in the art to recognize that they invented what is claimed. The specification adequately describes the claimed invention.

Looking at the specification, it is clear that the inventors had invented a method of treating dry eye disease using formulations disclosed, as well as methods incorporating administration of the cyclosporin formulations at a frequency of twice a day:

> 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.**

Page 9, line 25 – page 10, line 7 of the specification of the present application as originally filed (emphasis added).

Another benefit recognized by the inventors was the efficacy of the methods of administering the cyclosporin formulations compared to formulations compared to formulations containing 0.1% cyclosporin:

> 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.

Page 3, line 29 – page 4, line 19 of the specification of the present application as originally filed (emphasis added).

This benefit, as well as other benefits compared to a formulation comprising about 0.1 % cyclosporin by weight and about 1.25% castor oil by weight are further described later in the specification under Example 1, which compared the efficacy of Composition I and Composition II, two formulations administered to human patients in a Phase 3, double-masked, randomized, parallel group study for the treatment of dry eye disease.

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	0.1	0.05
Castor Oil	1.25	1.25
Polysorbate 80	1.00	1.00
Pemulen®	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.

Page 26, lines 22-27 of the specification of the present application as originally filed (emphasis added).

> 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.

Page 27, lines 10 – 17 of the specification of the present application as originally filed (emphasis added).

The Applicants submit that, based on at least the disclosures above, one of skill would reasonably conclude and recognize that the inventors of the patent had possession of what is claimed in the pending Claims. The specification demonstrates that the inventors possessed their invention – the Claims recite a method of treating dry eye disease by administering a formulation at the frequency of twice a day, wherein the method provides overall efficacy substantially equal to administration of a second formulation comprising cyclosporin in an amount of about 0.1% by weight and castor oil in an amount of about 1.25% by weight at a frequency of twice a day – and the specification discloses such a method.

The Standards for Compliance with the Written Description Requirement Stated in the Office Action are Improper

The Office Action states that the Claims lack written description support because the claims lack ipsis verbis support in the specification as originally filed. See 6.10.2015 Non-Final Office Action at paragraph 8. However, the Applicants submit that the Office Action's proposed requirement for explicit, ipsis verbis, support is not the standard under the law, the CFR, or the MPEP. Several Federal Circuit decisions have confirmed that "ipsis verbis disclosure is not necessary to satisfy the written description requirement of section 112. Instead the disclosure need only reasonably convey to persons skilled in the

art that the inventor had possession of the subject matter in question." *See Fujikawa v. Wattanasin*, 93 F.3d 1559, 1570, 39 USPQ 2d 1895, 1904 (Fed. Cir. 1996).[1]

As described above, it is clear from reviewing the specification that the Applicants were in possession of the subject matter claimed, and thus satisfy the written description requirement.

Thus, the Applicants respectfully request that the claim rejections under 35 U.S.C § 112, first paragraph as failing to comply with the written description requirement be withdrawn.

CONCLUSION

The Applicants believe all claims now pending in the present application are in condition for allowance.

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.

If the Examiner believes a telephone conference would expedite prosecution of this application, please contact the undersigned at (714) 246-6996.

Respectfully submitted,

/Laura L. Wine/

Date: October 22, 2015

Laura L. Wine
Attorney of Record
Registration Number 68,681

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Laura L. Wine, Esq.
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2525 Dupont Drive, T2-7H
Irvine, California 92612
Tel: (714) 246-6996 Fax: (714) 246-4249

[1] *See also In re* Alton, 76 F3d 1168, 1175, 37 USPQ2d 1578, 1584 (Fed. Cir. 1996) ("If a person of ordinary skill in the art would have understood the inventor to have been in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate written description requirement is met.").

Electronic Patent Application Fee Transmittal

Application Number:	14222478
Filing Date:	21-Mar-2014
Title of Invention:	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS
First Named Inventor/Applicant Name:	Andrew Acheampong
Filer:	Laura Lee Wine
Attorney Docket Number:	17618CON6CON1 (AP)

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

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($)
Extension - 2 months with $0 paid	1252	1	600	600
Miscellaneous:				
			Total in USD ($)	**600**

Electronic Acknowledgement Receipt

EFS ID:	23869604
Application Number:	14222478
International Application Number:	
Confirmation Number:	9616
Title of Invention:	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS
First Named Inventor/Applicant Name:	Andrew Acheampong
Customer Number:	51957
Filer:	Laura Lee Wine
Filer Authorized By:	
Attorney Docket Number:	17618CON6CON1 (AP)
Receipt Date:	22-OCT-2015
Filing Date:	21-MAR-2014
Time Stamp:	22:07:38
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$600
RAM confirmation Number	6696
Deposit Account	010885
Authorized User	WINE, LAURA L.

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		17618CON6CON1_Response_to_NFOA_dated_06_10_15.pdf	550991 c15c8e295df453eee9886a7504f201029207fb42	yes	7

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment/Req. Reconsideration-After Non-Final Reject	1	1
	Applicant summary of interview with examiner	2	2
	Applicant Arguments/Remarks Made in an Amendment	3	7

Warnings:

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Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14222478
	Filing Date	2014-03-21
	First Named Inventor	Andrew Acheampong
	Art Unit	1676
	Examiner Name	CORDERO GARCIA, MARCELA M
	Attorney Docket Number	17618-US-CN6CN1-AP

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	5578586		1996-11-26	Glonek et al	
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	14222478
Filing Date	2014-03-21
First Named Inventor	Andrew Acheampong
Art Unit	1676
Examiner Name	CORDERO GARCIA, MARCELA M
Attorney Docket Number	17618-US-CN6CN1-AP

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	ALBIETZ, JULIE, Dry Eye: An Update on Clinical Diagnosis, Management and Promising New Treatments, Clin & Exp. Optometry, 2001, 4-18, 84	☐
	2	Allergan Dry Eye Product Portfolio Fact Sheet (http://www.allergan.com/assets/pdf/dry_eye_product_portfolio_fact_sheet.pdf), 4 Pages, 2015	☐
	3	Allergan, Inc. 2001 Annual Report, Downloaded from http://agn.client.shareholder.com/financials.cfm, last accessed January 1, 2015, 54 Pages	☐
	4	Allergan, Inc. 2002 Annual Report (http://agn.client.shareholder.com/financials.cfm), 52 Pages, 2015	☐
	5	Allergan, Inc. 2003 Annual Report, Downloaded from http://agn.client.shareholder.com/financials.cfm, last accessed January 1, 2015, 52 Pages	☐
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	8	Allergan, Inc. 2005 Annual Report, Downloaded from http://agn.client.shareholder.com/financials.cfm, last accessed January 1, 2015, 35 Pages	☐
	9	Allergan, Inc. 2009 Annual Report, Downloaded from http://agn.client.shareholder.com/financials.cfm, last accessed January 1, 2015, 18 Pages	☐
	10	Allergan, Inc. 2010 Annual Report, Downloaded from http://agn.client.shareholder.com/financials.cfm, last accessed January 1, 2015, 206 Pages	☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14222478
	Filing Date	2014-03-21
	First Named Inventor	Andrew Acheampong
	Art Unit	1676
	Examiner Name	CORDERO GARCIA, MARCELA M
	Attorney Docket Number	17618-US-CN6CN1-AP

	11	Allergan, Inc. 2011 Annual Report, Downloaded from http://agn.client.shareholder.com/financials.cfm, last accessed January 1, 2015, 174 Pages	☐
	12	Allergan, Inc. 2012 Annual Report, Downloaded from http://agn.client.shareholder.com/financials.cfm, last accessed January 1, 2015, 28 Pages	☐
	13	Allergan, Inc. 2013 Annual Report, Downloaded from http://agn.client.shareholder.com/financials.cfm, last accessed January 1, 2015, 28 Pages	☐
	14	American Academy of Ophthalmology Cornea/External Disease Panel. Preferred Practice Pattern Guidelines. Dry Eye Syndrome. San Francisco, CA: American Academy of Ophthalmology, 2013, 44 Pages	☐
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	First Named Inventor	Andrew Acheampong
	Art Unit	1676
	Examiner Name	CORDERO GARCIA, MARCELA M
	Attorney Docket Number	17618-US-CN6CN1-AP

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	65	Letter from Victor Ramsaywak of Apotex, Inc., Notice of Certification Under 21 USC Section 355(j)(2)(B)(ii) (Section 505(j)(2)(B(ii) of the Federal Food, Drug and Cosmetic Act(and 21 CFR Section 314.95 dated July 23, 2015, pages 1-116	☐

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	66	Letter from Shashank Upadhye, Counsel for InnoPharma, Inc., of Amin Talati & Upadhye, Notification of Certification of Invalidity, Unenforceability and/or Non-infringement for U.S. Patent Nos. 5,474,979; 8,629,111; 8,633,162; 8,642,556; 8,648,048; and 8,685,930 Pursuant to Section 505(j)(2)(B)(iv) of the Federal Food, Drug, and Cosmetic Act, dated July 31, 2015, pages 1-98	☐
	67	Letter from J.C. Rozendaal of Kellogg, Huber, Hansen, Todd, Evans & Figel, PLLC, Notice of ANDA No. 203880 Concerning Cyclosporine Ophthalmic Emulsion, 0.05% with Paragraph IV Certification Concerning U.S. Patent Nos. 8,629,111; 8,633,162; 8,642,556; 8,648,048; and 8,685,930 dated July 22, 2015, pages 1-40	☐
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	69	Letter from Joseph Bonaccorsi, General Counsel, Akorn, Inc., Notification of Certification for U.S. Patent Nos. 8,629,111; 8,633,162; 8,642,556; 8,648,048; and 8,685,930 Pursuant to Section 505(j)(2)(B)(iv) of the Federal Food, Drug, and Cosmetic Act - 21 USC Section 355(j)(2)(B)(iv) Akorn ANDA 204561, dated July 10, 2015, pages 1-26	☐
	70	USPTO Before the Patent Trial and Appeal Board, Apotex, Inc. Petitioner v. Allergan, Inc. Patent Owner, Case IPR2015-01278, Patent 8,633,162, Pages 1-63, Dated June 4, 2015	☐
	71	USPTO Before the Patent Trial and Appeal Board, Apotex, Inc. Petitioner v. Allergan, Inc. Patent Owner, Case IPR2015-01282, Patent 8,629,111, Pages 1-63, Dated June 4, 2015	☐
	72	USPTO Before the Patent Trial and Appeal Board, Apotex, Inc. Petitioner v. Allergan, Inc. Patent Owner, Case IPR2015-01283, Patent 8,685,930, Pages 1-63, Dated June 4, 2015	☐
	73	USPTO Before the Patent Trial and Appeal Board, Apotex, Inc. Petitioner v. Allergan, Inc. Patent Owner, Case IPR2015-01284, Patent 8,648,048, Pages 1-63, Dated June 4, 2015	☐
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Attorney Docket Number	17618-US-CN6CN1-AP

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Attorney Docket Number	17618-US-CN6CN1-AP

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Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

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☒ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

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SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Laura L. Wine/	Date (YYYY-MM-DD)	2015-10-22
Name/Print	Laura L. Wine	Registration Number	68,681

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Application Number:	14222478
Filing Date:	21-Mar-2014
Title of Invention:	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS
First Named Inventor/Applicant Name:	Andrew Acheampong
Filer:	Laura Lee Wine/Ken Dinh
Attorney Docket Number:	17618CON6CON1 (AP)

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
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Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
		Total in USD ($)		**180**

Electronic Acknowledgement Receipt

EFS ID:	23869444
Application Number:	14222478
International Application Number:	
Confirmation Number:	9616
Title of Invention:	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS
First Named Inventor/Applicant Name:	Andrew Acheampong
Customer Number:	51957
Filer:	Laura Lee Wine/Ken Dinh
Filer Authorized By:	Laura Lee Wine
Attorney Docket Number:	17618CON6CON1 (AP)
Receipt Date:	22-OCT-2015
Filing Date:	21-MAR-2014
Time Stamp:	21:48:06
Application Type:	Utility under 35 USC 111(a)

Payment information:

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Payment Type	Deposit Account
Payment was successfully received in RAM	$180
RAM confirmation Number	6642
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Information:					
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22	Non Patent Literature	26-Boghigian2015.pdf	67933 3eb7c665d9963c4196732d48971d60e2ac0f8c8f	no	11
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Information:					
23	Non Patent Literature	27-DePaiva_2008.pdf	82792 4dd317bda060d2e3a5fab7d173fd19f673ac86f3	no	7
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Information:					
24	Non Patent Literature	28-Declaration_of_Christopher_Ta.pdf	898978 9e1393cfaefb26b69e2ea0186a662d73e8d00249	no	57
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Information:					
25	Non Patent Literature	29-Declaration_of_Erning_Xia.pdf	570041 bebbf4b177c6267d4da99f81059013e375e1e194	no	197
Warnings:					

Information:					
26	Non Patent Literature	30-Declaration_of_Harry_Boghigian.pdf	224119 26ed7ad7ccad4ce900b34731180ae4301b76b8d4	no	37
Warnings:					
Information:					
27	Non Patent Literature	31-DrugsFDA-FDA_Approved_Drug_Products-Lacrisert.pdf	98132 6145010b412ba090a1adb5a2c38bc57fed2a9fb7	no	2
Warnings:					
Information:					
28	Non Patent Literature	32-DrugsFDA_Restasis_NDA_Number.pdf	101335 23b87c74ebc2c9824417bbc6149ba031f564678a	no	2
Warnings:					
Information:					
29	Non Patent Literature	33-SYSTANE_ULTRA.pdf	106040 823fbe353fc5d79cec671d1f6f5fec155aa8f569	no	2
Warnings:					
Information:					
30	Non Patent Literature	34-Freeman-1975.pdf	824096 6a0aef77358c1a0236a2459414356893ac1d1f43	no	8
Warnings:					
Information:					
31	Non Patent Literature	35-Gilbard_1999.pdf	1655617 f6f2caf10750806b760b2c156165f3b416fb0b50	no	7
Warnings:					
Information:					
32	Non Patent Literature	36-Goto_2002.pdf	131711 f118c0ed202e33ce6c6c4e8641fe033dfa1a3635	no	6
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Information:					
33	Non Patent Literature	37-Inatomi_1996.pdf	4043479 90c60e29866ca1cf9c9582e388d7185d3adb1f79	no	9
Warnings:					
Information:					
34	Non Patent Literature	38-Kunert-2000.pdf	1887798 974d5e8ea565c925d6defa8f1383185ed95d040a	no	10
Warnings:					

Information:					
35	Non Patent Literature	39-Lacrisert_Approved_Label.pdf	342990 1049556890ec281e28e0475c24d9e48f737cdb5b	no	7
Warnings:					
Information:					
36	Non Patent Literature	40-SYSTANE_Gel_Drops.pdf	98965 7389705040af0e40b894e60462a1b935eca30c93	no	2
Warnings:					
Information:					
37	Non Patent Literature	41-Lemp_1995.pdf	1419730 39bb26b9613ef12397b9063618d2a61b5eca9317	no	12
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Information:					
38	Non Patent Literature	42-Liu_2012.pdf	304884 6b4ba660cc8a3dc8b34ed40431bfb1a749c79368	no	20
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Information:					
39	Non Patent Literature	43-Maissa_2010.pdf	284313 2e7733b3e6ccac79cad7e4a46f9889bd809db929	no	7
Warnings:					
Information:					
40	Non Patent Literature	44-Mann_2007.pdf	198950 78d259ce8a334eb16f13bfb7b56ba4741623e10a	no	11
Warnings:					
Information:					
41	Non Patent Literature	45-Murphy_2000.pdf	79641 cddaac123030af8c12d48986f8a9cde5cf68666f	no	6
Warnings:					
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42	Non Patent Literature	46-Napper_2003.pdf	546635 1745a8af25371d2fc3faef0c68bca3c5f1d73e80	no	2
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43	Non Patent Literature	47-Federal_Register_1988.pdf	9149292 308bcd9f4144f17d323dfaf70571e8bbcb6e5cd9	no	18
Warnings:					

Information:					
44	Non Patent Literature	48-Orange_Book_Patent_and_Data.pdf	68334 c0b3938f56bcd0d7a34dae786500428534f7f561	no	1
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45	Non Patent Literature	49-personalcarecouncil_website.pdf	99997 fbb3fe369b01086a8ced448f6aa89083597bd8bc	no	3
Warnings:					
Information:					
46	Non Patent Literature	50-Pflugfelder_2000.pdf	112022 0dfb43502893ccc8b086cb4788d0493eebad9c9e	no	6
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Information:					
47	Non Patent Literature	51-Restasis_label.pdf	88958 14ba58133ee6f63ad4358d64560397b7b84ba8ce	no	6
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48	Non Patent Literature	52-Rowe_EL_1965.pdf	1095627 ae274ce76151760bb46d272a1badfbf4027c61d2	no	6
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49	Non Patent Literature	53-Solomon_2000.pdf	257458 46b710c7928f70bd8bddc3b8cd1909b7c3430ff5	no	14
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Information:					
50	Non Patent Literature	54-SYSTANE_BALANCE.pdf	104274 4c5a896d13ea984a5bb40eae5329fcf10f9ab76c	no	2
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51	Non Patent Literature	55-SYSTANE_Lubricant_Eye_Gel.pdf	101250 1d32d73825a29d45f088ab33185ac7f85dbc0d70	no	2
Warnings:					
Information:					
52	Non Patent Literature	56-Taban_2006.pdf	3615485 b002171ab25af0ec194606a31a2106fc54fbacd0	no	8
Warnings:					

Information:					
53	Non Patent Literature	57-Turner_2000.pdf	571723 8e39345486c360b4292fb7fc2d3975499074bc98	no	7
Warnings:					
Information:					
54	Non Patent Literature	58-Yeh_2003.pdf	252635 3edd0311574249121e7bcd955e56d97b7597ec37	no	6
Warnings:					
Information:					
55	Non Patent Literature	59-IPR2014-01278-Patent-Owner-Preliminary-Response.pdf	151071 c6615c65e163c80c18123179ea4c97b50e227dff	no	43
Warnings:					
Information:					
56	Non Patent Literature	60-IPR2015-01282-Patent-Owner-Preliminary-Response.pdf	144350 49f0f2b408cbeee37f76e3fab0a5b71bf3ac0999	no	46
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57	Non Patent Literature	61-IPR2015-01283-Patent-Owner-Preliminary-Response.pdf	145110 500f7a0ca7147172185bdff761ba1bac22e74684	no	46
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Information:					
58	Non Patent Literature	62-IPR2015-01284-Patent-Owner-Preliminary-Response.pdf	151362 695bd029ed182b10921aa46b32456d4c33496f18	no	43
Warnings:					
Information:					
59	Non Patent Literature	63-IPR2015-01286-Patent-Owner-Preliminary-Response.pdf	160103 88315e8d187dce82952194bc105d05187717a9bb	no	47
Warnings:					
Information:					
60	Non Patent Literature	64-Defs_Invalidity_Contentions_2014-10-15.pdf	287871 401c1ab15244eb7209fee29c2b5c38cfc0ddc92e	no	74
Warnings:					
Information:					
61	Fee Worksheet (SB06)	fee-info.pdf	30785 31f8eef446de50351b0e0b1be9895084f40e0dbd	no	2
Warnings:					

Information:	
Total Files Size (in bytes):	56579441

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.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/222,478	03/21/2014	Andrew Acheampong	17618CON6CON1 (AP)	9616

51957 7590 08/20/2015

ALLERGAN, INC.
2525 DUPONT DRIVE, T2-7H
IRVINE, CA 92612-1599

EXAMINER
CORDERO GARCIA, MARCELA M

ART UNIT	PAPER NUMBER
1676	

NOTIFICATION DATE	DELIVERY MODE
08/20/2015	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
pair_allergan@firsttofile.com

Applicant-Initiated Interview Summary	Application No.	Applicant(s)	
	14/222,478	ACHEAMPONG ET AL.	
	Examiner	Art Unit	
	MARCELA M. CORDERO GARCIA	1676	

All participants (applicant, applicant's representative, PTO personnel):

(1) *MARCELA M. CORDERO GARCIA*. (3)_____.

(2) *LAURA L. WINE*. (4)_____.

Date of Interview: *8/14/2015*.

Type: ☒ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☒ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☒112 ☐102 ☐103 ☐Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: *37-63*.

Identification of prior art discussed: *Sall et al. (Ophthalmology, 2000)*.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

Applican'ts representative discussed the support for the claims, mentioning pages 3-4. Examiner indicated that pointing this section in the response to the new matter rejection of record would be helpful. Additional, inclusion of Example 1 which has the components of the compositions within the claimed methods was suggested by Examiner. No agreement was reached. Applicant's representative plans to follow up with a written response.

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/MARCELA M CORDERO GARCIA/ Primary Examiner, Art Unit 1676	

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews
Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:
1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

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ALLERGAN, INC.
2525 DUPONT DRIVE, T2-7H
IRVINE CA 92612-1599

Doc Code: TRACK1.GRANT

Decision Granting Request for Prioritized Examination (Track I or After RCE)	Application No.: 14/222,478

1. THE REQUEST FILED May 26, 2015 IS **GRANTED.**

The above-identified application has met the requirements for prioritized examination

A. ☐ for an original nonprovisional application (Track I).
B. ☒ for an application undergoing continued examination (RCE).

2. **The above-identified application will undergo prioritized examination.** The application will be accorded special status throughout its entire course of prosecution until one of the following occurs:

A. filing a **petition for extension of time** to extend the time period for filing a reply;
B. filing an **amendment to amend the application to contain more than four independent claims, more than thirty total claims**, or a multiple dependent claim;
C. filing a **request for continued examination**;
D. filing a notice of appeal;
E. filing a request for suspension of action;
F. mailing of a notice of allowance;
G. mailing of a final Office action;
H. completion of examination as defined in 37 CFR 41.102; or
I. abandonment of the application.

Telephone inquiries with regard to this decision should be directed to **Michelle R. Eason** at (571) 272-4231. In his/her absence, calls may be directed to Brian W. Brown at (571) 272-5338.

/Michelle R. Eason/
(*Signature*)

Paralegal Specialist, Office of Petitions
(Title)

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/222,478	03/21/2014	Andrew Acheampong	17618CON6CON1 (AP)	9616

51957 7590 06/10/2015

ALLERGAN, INC.
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EXAMINER
CORDERO GARCIA, MARCELA M

ART UNIT	PAPER NUMBER
1676	

NOTIFICATION DATE	DELIVERY MODE
06/10/2015	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
pair_allergan@firsttofile.com

Office Action Summary	Application No. 14/222,478	Applicant(s) ACHEAMPONG ET AL.	
	Examiner MARCELA M. CORDERO GARCIA	Art Unit 1676	AIA (First Inventor to File) Status No

-- 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* MONTHS 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 *5/26/2015*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ 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*

5)☒ Claim(s) *37-63* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *37-63* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ 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).

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).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

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) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

1. The present application is being examined under the pre-AIA first to invent provisions.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. 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 finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/26/2015 has been entered.

Any rejection from the previous office action, which is not restated here, is withdrawn.

Election/Restrictions

3. Upon reconsideration, the election restriction requirement mailed on 5/9/2014 is herein vacated.

Status of the claims

4. Claims 37-63 are pending. Claims 37-63 are presented for examination on the merits.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112(a):

> (a) IN GENERAL.—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 or joint inventor of carrying out the invention.

The following is a quotation of the first paragraph of pre-AIA 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.

6. Claims 37-63 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. Claims 37, 49 and 57 comprise the limitations Claim 37: "(…) wherein the method provides overall efficacy substantially equal to administration of a second topical ophthalmic emulsion to a human eye in need thereof at a frequency of twice a day, the second emulsion comprising cyclosporine A in an amount of about 0.1% by weight and castor oil in an amount of about 1.25% by weight (..)"

Claim 49 "(…) wherein the method is therapeutically effective in treating dry eye disease and wherein the method achieves at least as much therapeutic efficacy as administration of a second topical ophthalmic emulsion to a human eye in need thereof at a frequency of twice a day, the second emulsion comprising cyclosporin A in an amount of about 0.1% by weight and castor oil in an amount of about 1.25% by weight (...)"

Claim 57 "(…) wherein the method demonstrates a reduction in adverse events in the human compared to administration of a second topical ophthalmic emulsion to a human eye in need thereof at a frequency of twice a day, the second topical ophthalmic emulsion comprising cyclosporine A in an amount of about 0.1% by weight and castor oil in an amount of about 1.25% by weight (…)"

New Matter

7. The claims have been amended (cf. amendment 3/21/2014) to include new claims. Applicants state that the amendments add no new matter, and point out at least at page 4, line 25- page 5, line 14, page 14, line 28 -page 15, line 1, page 26, lines 5-19, and page 27, lines 4-31 of the application specification filed herewith as support for the amendments.

Lack of Ipsis verbis support

8. With respect to the limitations above, such embodiments does not appear to be expressly disclosed nor described in the Example 1.

Lack of Inherent support

9. "While there is no in *haec verba* requirement, newly added claim limitations must be supported in the specification through express, implicit, or inherent disclosure." See MPEP 2163. Example 1 of the instant disclosure, which encompasses the claimed concentrations is silent with regards to the frequency of administration.

All other claims that depend directly or indirectly from rejected claims and are, therefore, also rejected under USC 112, first paragraph for the reasons set forth above.

Applicants' arguments

10. The Applicants do not agree with the rejection, and respectfully submit that the Claims comply with the written description requirement for the reasons previously submitted to the Office. For example, support for the aforementioned limitation can be found, at least, in the paragraph at page 9, line 25 - page 10, line 7 of the specification as originally filed:

> 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.**

Specification filed March 21, 2014 at page 9, line 25 - page 10, line 7 (Emphasis Added).

Moreover, the Applicants further respectfully submit that the Claims comply with the written description requirement, at least, because the "at a frequency of twice a day" limitation is supported in the specification as required by MPEP § 2163. The Applicants submit that the written description clearly shows that the descriptive matter (the "twice a day" limitation) is present in the specification. Example 1 of the present application describes the testing of the 0.05% CsA and 0.1% CsA formulations (see present Application specification as filed, page 26, lines 1-21):

EXAMPLE 1

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

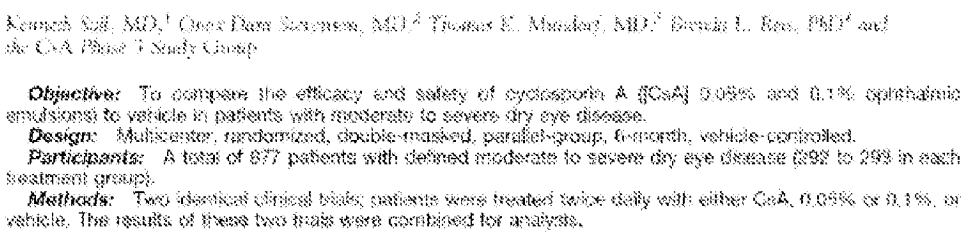
	Composition I	Composition II
	wt%	wt%
Cyclosporin	0.1	0.05
Castor Oil	1.25	1.25
Polysorbate 80	1.00	1.00
Purite®	0.05	0.05
Glycerine	2.20	2.20
Sodium hydroxide	qs	qs
Purified Water	qs	qs
pH	7.2-7.6	7.2-7.6
Weight Ratio of Cyclosporin A to Castor Oil	0.08	0.04

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

The Applicants note that those formulations were disclosed to a person of skill in the art for the first time in the present application family, including US Patent Application No. 10/927,857 and Provisional US Patent Application No. 60/503,137. A person of skill in the art would not have known those formulations prior to the filing of the instant patent application family.

Upon learning the formulations of the compositions used in the Phase 3, double-masked, randomized, parallel group studies described in the application, a person of skill would have understood that the application was describing the Phase 3, double-masked, randomized, parallel group study described earlier in the specification:

In addition, cyclosporin A compositions used in treating ophthalmic conditions is the subject of a number of publications. (...) "Two multicenter, randomized studies of the efficacy and safety of cyclosporine ophthalmic emulsion in moderate to severe dry eve disease. CsA Phase 3 Study Group," Sall et al., Ophthalmology, 2000 Apr, 107(4):631-9. See Present Application Specification as filed, page 1, line 21 - page 2, line 15. The abstract of Sall describes that the patients in the Phase 3 study received either a 0.05% CsA Formulation or 0.1% CsA Formulation at a frequency of twice a day (Sall, ABSTRACT):



Kenneth Sall, MD,[1] Owen Dean Stevenson, MD,[2] Thomas E. Mundorf, MD,[3] Brenda L. Reis, PhD[4] and the CsA Phase 3 Study Group

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.

The Sall paper does not disclose the compositions of the formulations, and a person of skill in the art would not have known these formulations. Hence, the "twice a day" limitation is present in the present application and a person of skill's knowledge of the 0.05% CsA Phase 3 trial as disclosed in the Sall paper would lead them to understand that both the 0.05% CsA and 0.1% CsA formulations were dosed at a

frequency of twice a day. Thus, the Applicants submit that the "twice a day" limitation is properly supported and the claims satisfy the written description requirement.

Response to arguments

11. Applicant's arguments have been carefully considered but not deemed persuasive for the reasons of record and for the following reasons: According to MPEP 609.01 and 37 C.F.R. 1.57:

"Essential material" may be incorporated by reference, but only by way of an incorporation by reference to a U.S. patent or U.S. patent application publication, which patent or patent application publication does not itself incorporate such essential material by reference. "Essential material" is material that is necessary to:

(1) Provide a written description of the claimed 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 set forth the best mode contemplated by the inventor of carrying out the invention as required by 35 U.S.C. 112(a);

(2) Describe the claimed invention in terms that particularly point out and distinctly claim the invention as required by 35 U.S.C. 112(b); or

(3) Describe the structure, material, or acts that correspond to a claimed means or step for performing a specified function as required by 35 U.S.C. 112(f).

In the instant case, Applicant's representative is incorporating essential subject matter (i.e., the instantly claimed wherein clauses as listed above in pages 3-4) by relying on a NPL reference (Sall, 2000) which was not expressly incorporated by reference, nor is it a U.S. Patent or a U.S. Patent Application as required by 37 CFR 1.57. Thus it is deemed that Applicants did not have possession of the invention as claimed. For these reasons, the new matter rejection of record is maintained.

Conclusion

13. No claim is currently allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. An obviousness rejection over Sall et al. (Ophthalmology, 2000, cited in the IDS dated 3/28/2014) in view of Ding et al. (US 5,474,979, cited in the IDS dated 3/28/2014) is not being made for the reasons summarized by Examiner in the Declarations under 37 CFR 1.132 and Reasons for Allowance, pages 2-6 of the Notice of Allowance mailed out on 1/28/2014 for 13/961,828, of which the instant application is a continuation.

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, Karlheinz R. Skowronek can be reached on (571)-272-9047. 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/
Primary Examiner, Art Unit 1676

MMCG 06/2015

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14222478	ACHEAMPONG ET AL.
	Examiner	Art Unit
	MARCELA M CORDERO GARCIA	1676

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner
none	none	6/16/2014	MMCG

SEARCH NOTES		
Search Notes	Date	Examiner
EAST search (attached)	6/14/2014	MMCG
STN search (attached)	6/16/2014	MMCG
also ran PALM Inventor search	6/16/2014	MMCG
EAST updated (attached)	11/6/2014	MMCG
also updated PALM Inventor search	11/6/2014	MMCG
EAST search (attached)	6/4/2015	MMCG
also ran PALM Inventor search	6/4/2015	MMCG

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner
EAST updated	attached	11/6/2014	MMCG

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	1137	polysorbate same acrylate same alkyl same acrylate	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/06/04 16:17
L2	90	polysorbate near3 acrylate same alkyl same acrylate	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/06/04 16:17
L3	37	polysorbate near3 acrylate near3 alkyl same acrylate	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/06/04 16:17
L4	9	polysorbate near3 acrylate near3 alkyl same acrylate and cyclosporin	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/06/04 16:18
L5	132	"polysorbate 80" and acrylate near3 alkyl same acrylate and cyclosporin	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/06/04 16:18
L6	7	"polysorbate 80" and acrylate near3 c10-30 Near3 alkyl same acrylate and cyclosporin	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/06/04 16:18
L7	185	"5474979"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/06/04 16:27

EAST Search History (Interference)

< This search history is empty>

6/4/2015 6:08:06 PM

Doc code: RCEX
Doc description: Request for Continued Examination (RCE)

PTO/SB/30EFS (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
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 contains a valid OMB control number.

REQUEST FOR CONTINUED EXAMINATION(RCE)TRANSMITTAL
(Submitted Only via EFS-Web)

Application Number	14222478	Filing Date	2014-03-21	Docket Number (if applicable)	17618-CON6CON1 (AP)	Art Unit	1676
First Named Inventor	Andrew Acheampong			Examiner Name	Codero Garcia, Marcela M.		

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. The Instruction Sheet for this form is located at WWW.USPTO.GOV

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).

☐ 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.

- ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
- ☐ Other _____

☒ Enclosed

- ☒ Amendment/Reply
- ☐ Information Disclosure Statement (IDS)
- ☐ Affidavit(s)/ Declaration(s)
- ☐ Other _____

MISCELLANEOUS

☐ 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)

☐ Other _____

FEES

☒ **The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.**
The Director is hereby authorized to charge any underpayment of fees, or credit any overpayments, to Deposit Account No 010885

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

☒ Patent Practitioner Signature

☐ Applicant Signature

PTO/SB/30EFS (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Signature of Registered U.S. Patent Practitioner			
Signature	/Laura L. Wine/	Date (YYYY-MM-DD)	2015-05-26
Name	Laura L. Wine	Registration Number	68681

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.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Doc Code: TRACK1.REQ
Document Description: TrackOne Request

PTO/AIA/424 (04-14)

CERTIFICATION AND REQUEST FOR PRIORITIZED EXAMINATION UNDER 37 CFR 1.102(e) (Page 1 of 1)

First Named Inventor:	Andrew Acheampong	Nonprovisional Application Number (if known):	14222478
Title of Invention:	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS		

APPLICANT HEREBY CERTIFIES THE FOLLOWING AND REQUESTS PRIORITIZED EXAMINATION FOR THE ABOVE-IDENTIFIED APPLICATION.

1. The processing fee set forth in 37 CFR 1.17(i)(1) and the prioritized examination fee set forth in 37 CFR 1.17(c) have been filed with the request. The publication fee requirement is met because that fee, set forth in 37 CFR 1.18(d), is currently $0. The basic filing fee, search fee, and examination fee are filed with the request or have been already been paid. I understand that any required excess claims fees or application size fee must be paid for the application.

2. I understand that the application may not contain, or be amended to contain, more than four independent claims, more than thirty total claims, or any multiple dependent claims, and that any request for an extension of time will cause an outstanding Track I request to be dismissed.

3. The applicable box is checked below:

I. ☐ Original Application (Track One) - Prioritized Examination under § 1.102(e)(1)

i. (a) The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a). This certification and request is being filed with the utility application via EFS-Web.

---OR---

(b) The application is an original nonprovisional plant application filed under 35 U.S.C. 111(a). This certification and request is being filed with the plant application in paper.

ii. An executed inventor's oath or declaration under 37 CFR 1.63 or 37 CFR 1.64 for each inventor, **or** the application data sheet meeting the conditions specified in 37 CFR 1.53(f)(3)(i) is filed with the application.

II. ☑ Request for Continued Examination - Prioritized Examination under § 1.102(e)(2)

i. A request for continued examination has been filed with, or prior to, this form.
ii. If the application is a utility application, this certification and request is being filed via EFS-Web.
iii. The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a), or is a national stage entry under 35 U.S.C. 371.
iv. This certification and request is being filed prior to the mailing of a first Office action responsive to the request for continued examination.
v. No prior request for continued examination has been granted prioritized examination status under 37 CFR 1.102(e)(2).

Signature /Laura L. Wine/	Date May 26, 2015
Name (Print/Typed) Laura L. Wine	Practitioner Registration Number 68681

Note: *This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. Submit multiple forms if more than one signature is required.**

☑ *Total of 1 forms are submitted.

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Docket No. 17618CON6CON1 (AP)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Acheampong, *et al.*	Examiner: Marcela M Cordero Garcia
Serial No.: 14/222,478	Group Art Unit: 1676
Filed: March 21, 2014	Confirmation No. 9616
For: METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS	Customer No.: 51957

RESPONSE TO FINAL OFFICE ACTION DATED NOVEMBER 24, 2014

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

Dear Sir:

These papers are filed in reply to the final Office Action mailed November 24, 2014.

The Commissioner is authorized to charge any fee which may be required in connection with this Amendment to deposit account No. 01-0885.

SUMMARY OF INTERVIEW

Attendees, Date and Type of Interview

Telephonic interviews were conducted on November 12 and 17, 2014 and were attended by Examiner Cordero Garcia and Laura Wine.

Identification of Claims Discussed

The Claims were discussed, focusing on Claims 37, 49, and 57.

Principal Arguments and Other Matters

The rejection under 35 U.S.C. § 112, first paragraph was discussed. No substantive agreement was reached.

Results of Interview

It was understood that a final office action would be issued.

REMARKS

This Reply responds to the Final Office Action sent November 24, 2014, in which the Office Action rejected Claims 37-63. The Applicants respectfully submit that the claims are in condition for allowance.

Claim Rejections

35 U.S.C. § 112, first paragraph

Claims 37-63 were rejected under 35 U.S.C § 112, first paragraph as failing to comply with the written description requirement with regards to the limitation in Claims 37, 49, and 57 of "at a frequency of twice a day" within the following wherein clauses:

"(…) wherein the method provides overall efficacy substantially equal to administration of a second topical ophthalmic emulsion to a human eye in need thereof at a frequency of twice a day, the second emulsion comprising cyclosporin A in an amount of about 0.1% by weight and castor oil in an amount of about 1.25% by weight (..)"
Claim 37

"(…) wherein the method is therapeutically effective in treating dry eye disease and wherein the method achieves at least as much therapeutic efficacy as administration of a second topical ophthalmic emulsion to a human eye in need thereof at a frequency of twice a day, the second emulsion comprising cyclosporin A in an amount of about 0.1% by weight and castor oil in an amount of about 1.25% by weight(…)"
Claim 49

"(…) wherein the method demonstrates a reduction in adverse events in the human, compared to administration of a second topical ophthalmic emulsion to a human eye in need thereof at a frequency of twice a day, the second topical ophthalmic emulsion

comprising cyclosporin A in an amount of about 0.1% by weight and castor oil in an amount of about 1.25% by weight(…)"

Claim 57

The Applicants do not agree with the rejection, and respectfully submit that the Claims comply with the written description requirement for the reasons previously submitted to the Office. For example, support for the aforementioned limitation can be found, at least, in the paragraph at page 9, line 25 – page 10, line 7 of the specification as originally filed.

Moreover, the Applicants further respectfully submit that the Claims comply with the written description requirement, at least, because the "at a frequency of twice a day" limitation is supported in the specification as required by MPEP § 2163.

The Applicants submit that the written description clearly shows that the descriptive matter (the "twice a day" limitation) is present in the specification. Example 1 of the present application describes the testing of the 0.05% CsA and 0.1% CsA formulations:

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	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.

Present Application Specification as filed, page 26, lines 1-21.

The Applicants note that those formulations were disclosed to a person of skill in the art for the first time in the present application family, including US Patent Application No. 10/927,857 and Provisional US Patent Application No. 60/503,137. A person of skill in the art would not have known those formulations prior to the filing of the instant patent application family.

Upon learning the formulations of the compositions used in the Phase 3, double-masked, randomized, parallel group studies described in the application, a person of skill would have understood that the application was describing the Phase 3, double-masked, randomized, parallel group study described earlier in the specification:

> In addition, cyclosporin A compositions used in treating ophthalmic conditions is the subject of a number of publications. (…) "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*.

See Present Application Specification as filed, page 1, line 21 – page 2, line 15.

The abstract of Sall describes that the patients in the Phase 3 study received either a 0.05% CsA Formulation or 0.1% CsA Formulation at a frequency of twice a day:

Kenneth Sall, MD,[1] Onex Dara Stevenson, MD,[2] Thomas K. Mundorf, MD,[3] Brenda L. Reis, PhD[4] and the CsA Phase 3 Study Group

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.

Sall, ABSTRACT. The Sall paper does not disclose the compositions of the formulations, and a person of skill in the art would not have known those formulations.

Hence, the "twice a day" limitation is present in the present application and a person of skill's knowledge of the 0.05% CsA Phase 3 trial as disclosed in the Sall paper would lead them to understand that both the 0.05% CsA and 0.1% CsA formulations were dosed at a frequency of twice a day. Thus, the Applicants submit that the "twice a

day" limitation is properly supported and the Claims satisfy the written description requirement.

In view of the above, the Applicants respectfully submit that the disclosure of the present application reasonably shows that the Applicants were in possession of what is now claimed at the time of filing, and request that the rejection of Claims 37-63 under 35 U.S.C. § 112, first paragraph be withdrawn.

Conclusion

The Applicants believe all claims now pending in the present application are in condition for allowance.

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.

If the Examiner believes a telephone conference would expedite prosecution of this application, please contact the undersigned at (714) 246-6996.

Respectfully submitted,

/Laura L. Wine/

Date: May 26, 2015

Laura L. Wine
Attorney of Record
Registration Number 68,681

Please direct all inquiries and correspondence to:
Laura L. Wine, Esq.
Allergan, Inc.
2525 Dupont Drive, T2-7H
Irvine, California 92612
Tel: (714) 246-6996 Fax: (714) 246-4249

Electronic Patent Application Fee Transmittal

Application Number:	14222478
Filing Date:	21-Mar-2014
Title of Invention:	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS
First Named Inventor/Applicant Name:	Andrew Acheampong
Filer:	Laura Lee Wine/Maria Stein
Attorney Docket Number:	17618CON6CON1 (AP)

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Request for Prioritized Examination	1817	1	4000	4000
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Extension - 3 months with $0 paid	1253	1	1400	1400
Miscellaneous:				
Request for Continued Examination	1801	1	1200	1200
		Total in USD ($)		**6600**

Electronic Acknowledgement Receipt

EFS ID:	22449941
Application Number:	14222478
International Application Number:	
Confirmation Number:	9616
Title of Invention:	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS
First Named Inventor/Applicant Name:	Andrew Acheampong
Customer Number:	51957
Filer:	Laura Lee Wine/Maria Stein
Filer Authorized By:	Laura Lee Wine
Attorney Docket Number:	17618CON6CON1 (AP)
Receipt Date:	26-MAY-2015
Filing Date:	21-MAR-2014
Time Stamp:	18:30:43
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$6600
RAM confirmation Number	9350
Deposit Account	010885
Authorized User	WINE, LAURA L.

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

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)	17618CON6CON1_RCE.PDF	697619 4f1401512339bb0638516ba40f5304f757c0e19d	no	3
Warnings:					
Information:					
2		17618CON6CON1_Response_05-26-2015.pdf	730195 a241f4316df503c303469bd0388201f6eedd5ea7	yes	8

Multipart Description/PDF files in .zip description

Document Description	Start	End
TrackOne Request	1	2
Response After Final Action	3	3
Applicant summary of interview with examiner	4	4
Applicant Arguments/Remarks Made in an Amendment	5	8

Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	34286 128098f4342a56017c699f6d1495d0796a7e2e2a	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	1462100		

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.

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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www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/222,478	03/21/2014	Andrew Acheampong	17618CON6CON1 (AP)	9616

51957 7590 11/24/2014

ALLERGAN, INC.
2525 DUPONT DRIVE, T2-7H
IRVINE, CA 92612-1599

EXAMINER
CORDERO GARCIA, MARCELA M

ART UNIT	PAPER NUMBER
1676	

NOTIFICATION DATE	DELIVERY MODE
11/24/2014	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
pair_allergan@firsttofile.com

Examiner-Initiated Interview Summary	Application No.	Applicant(s)	
	14/222,478	ACHEAMPONG ET AL.	
	Examiner	Art Unit	
	MARCELA M. CORDERO GARCIA	1676	

All participants (applicant, applicant's representative, PTO personnel):

(1) *MARCELA M. CORDERO GARCIA*. (3)_____.

(2) *LAURA WINE*. (4)_____.

Date of Interview: *12 November 2014*.

Type: ☒ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☒ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☒112 ☐102 ☐103 ☐Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: *37,49,53 and 57*.

Identification of prior art discussed: *N/A*.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

Discussed the limitation"twice a day" within the claim limitation "wherein the method provides overall efficacy substantially equal to administration of a second topical ophthalmic emulsion to a human eye in need thereof at a frequency of twice a day, the second emulsion comprising cyclosporin A in an amount of about 0.1% by weight of castor oil in an amount of about 1.25 % by weight". Applicants' arguments were not persuasive with respect to the rejection of record because the unexpected results described in the disclosure (e.g., Example 1) are not limited to twice a day administration (see attached Office Action). Applicant's representative requested a written office action in a telephonic conversation on 11/17/2014.

Applicant recordation instructions: It is not necessary for applicant to provide a separate record of the substance of interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☒ Attachment

/MARCELA M CORDERO GARCIA/ Primary Examiner, Art Unit 1676	

Office Action Summary	Application No. 14/222,478	Applicant(s) ACHEAMPONG ET AL.	
	Examiner MARCELA M. CORDERO GARCIA	Art Unit 1676	AIA (First Inventor to File) Status No

-- 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* MONTHS 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 *9/25/2014*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ 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*

5)☒ Claim(s) *37-63* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *37-63* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ 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).

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).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

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) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date *7/8/2014*.

3) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *20141106* .

4) ☐ Other: _____.

1. The present application is being examined under the pre-AIA first to invent provisions.

DETAILED ACTION

2. This Office Action is in response to the reply received on 9/25/2014.

Any rejection from the previous office action, which is not restated here, is withdrawn.

Election/Restrictions

3. Upon reconsideration, the election restriction requirement mailed on 5/9/2014 is herein vacated.

Status of the claims

4. Claims 37-63 are pending. Claims 37-63 are presented for examination on the merits.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112(a):

> (a) IN GENERAL.—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 or joint inventor of carrying out the invention.

The following is a quotation of the first paragraph of pre-AIA 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.

6. Claims 37-63 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. Claims 37, 49 and 57 comprise the limitation "at a frequency of twice a day", specifically in the wherein clause defining the unexpected results, i.e., "wherein the method provides overall efficacy substantially equal to administration of a second topical ophthalmic emulsion to a human eye in need thereof at a frequency of twice a day, the second emulsion comprising cyclosporin A in an amount of about 0.1% by weight of castor oil in an amount of about 1.25 % by weight".

New Matter

7. The claims have been amended (cf. amendment 3/21/2014) to include new claims. Applicants state that the amendments add no new matter, and point out at least at page 4, line 25- page 5, line 14, page 14, line 28 -page 15, line 1, page 26, lines 5-19, and page 27, lines 4-31 of the application specification filed herewith as support for the amendments.

Lack of Ipsis verbis support

8. With respect to the limitation “at a frequency of twice a day” in the wherein clause “wherein the method provides overall efficacy substantially equal to administration of a second topical ophthalmic emulsion to a human eye in need thereof at a frequency of twice a day, the second emulsion comprising cyclosporin A in an amount of about 0.1%

by weight of castor oil in an amount of about 1.25 % by weight", such embodiment does not appear to be expressly disclosed nor described in the Example 1. Furthermore, the limitation "at a frequency of twice a day" does not appear to be expressly disclosed with respect to the unexpected results described in claims 37, 49, 53 and 57 (as described in the respective wherein clauses). Note that in all the independent claims an unexpected result is described that depends on the "twice a day" administration. However, the disclosure and the examples do not require this "twice a day" limitation for the unexpected results as claimed.

Lack of Inherent support

9. "While there is no in *haec verba* requirement, newly added claim limitations must be supported in the specification through express, implicit, or inherent disclosure." See MPEP 2163. Example 1 of the instant disclosure, which encompasses the claimed concentrations is silent with regards to the frequency of administration.

All other claims that depend directly or indirectly from rejected claims and are, therefore, also rejected under USC 112, first paragraph for the reasons set forth above.

Applicants' arguments

10. The Applicants submit that the currently pending Claims contain sufficient written description support for the "at a frequency of twice a day" limitation within the specification of the present application as originally filed. For example, support for this limitation can be found, at least, in the paragraph at page 9, line 25 - page 10, line 7 of the specification as originally filed, which reads:

> 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.**

Specification filed March 21, 2014 at page 9, line 25 - page 10, line 7 (Emphasis Added).

In view of the above, the Applicants respectfully submit that the disclosure of the present application reasonably shows that the Applicants were in possession of what is now claimed at the time of filing, and request that the rejection of Claims 37-63 under 35 U.S.C. § 112, first paragraph be withdrawn.

Response to arguments

11. Applicants' arguments have been carefully considered and deemed persuasive for the generic method, i.e., lines 1-5 of claim 37, but not deemed persuasive for the unexpected results set forth in the wherein clause of claim 37 for the following reasons: With respect to the limitation “at a frequency of twice a day” in the wherein clause “wherein the method provides overall efficacy substantially equal to administration of a second topical ophthalmic emulsion to a human eye in need thereof at a frequency of twice a day, the second emulsion comprising cyclosporin A in an amount of about 0.1% by weight of castor oil in an amount of about 1.25 % by weight”, such embodiment does not appear to be expressly disclosed nor described in the Example 1. Furthermore, the limitation “at a frequency of twice a day” does not appear to be expressly disclosed with respect to the unexpected results described in independent claims 49, 53 and 57 (as described in the respective wherein clauses) for analog reasons as those set forth in claim 37. Note that in all the independent claims an unexpected result is described that requires "twice a day" administration. However, the disclosure and the examples do not require this "twice a day” limitation for the unexpected results as claimed.

"While there is no in *haec verba* requirement, newly added claim limitations must be supported in the specification through express, implicit, or inherent disclosure." See MPEP 2163. Example 1 of the instant disclosure, which encompasses the claimed concentration range for the claimed unexpected results is silent with regards to the frequency of administration.

Thus it is deemed that Applicants did not have possession of the invention as claimed, and therefore the new matter rejection is maintained.

Terminal disclaimers

12. Terminal disclaimers for US 8,685,930; 8,648,048; 8,642,556; 8,633,162 and 8,629,111 have been received and approved, thus obviating the ODP rejections of record.

Conclusion

13. No claim is currently 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, Karlheinz R. Skowronek can be reached on (571)-272-9047. 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/
Primary Examiner, Art Unit 1676

MMCG 11/2014

Examiner-Initiated Interview Summary	Application No.	Applicant(s)	
	14/222,478	ACHEAMPONG ET AL.	
	Examiner	Art Unit	
	MARCELA M. CORDERO GARCIA	1676	

All participants (applicant, applicant's representative, PTO personnel):

(1) *MARCELA M. CORDERO GARCIA*. (3)_____.

(2) *LAURA WINE*. (4)_____.

Date of Interview: *12 November 2014*.

Type: ☒ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☒ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☒112 ☐102 ☐103 ☐Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: *37,49,53 and 57*.

Identification of prior art discussed: *N/A*.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

Discussed the limitation"twice a day" within the claim limitation "wherein the method provides overall efficacy substantially equal to administration of a second topical ophthalmic emulsion to a human eye in need thereof at a frequency of twice a day, the second emulsion comprising cyclosporin A in an amount of about 0.1% by weight of castor oil in an amount of about 1.25 % by weight". Applicants' arguments were not persuasive with respect to the rejection of record because the unexpected results described in the disclosure (e.g., Example 1) are not limited to twice a day administration (see attached Office Action). Applicant's representative requested a written office action in a telephonic conversation on 11/17/2014.

Applicant recordation instructions: It is not necessary for applicant to provide a separate record of the substance of interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☒ Attachment

/MARCELA M CORDERO GARCIA/ Primary Examiner, Art Unit 1676	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	14222478
Filing Date	2014-03-21
First Named Inventor	Andrew Acheampong
Art Unit	1676
Examiner Name	Cordero Garcia, Marcela M.
Attorney Docket Number	17618 CON6CON1 (AP)

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.M.C.G./

U.S.PATENTS

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	4347238		1982-08-31	Hollingsbee	

If you wish to add additional U.S. Patent citation information please click the Add button.

U.S.PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

If you wish to add additional U.S. Published Application citation information please click the Add button.

FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	2222770	GB	A	1990-03-21	Sandoz Ltd		☐
	2	198901772	WO	A1	1989-03-09	University of Georgia Research Foundation, Inc.		☐
	3	199318752	WO	A1	1993-09-30	Pharmos Corp.		☐

Receipt date: 07/08/2014	Application Number	14222478	14222478 - GAU: 1676
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99**)	Filing Date	2014-03-21	
	First Named Inventor	Andrew Acheampong	
	Art Unit	1676	
	Examiner Name	Cordero Garcia, Marcela M.	
	Attorney Docket Number	17618 CON6CON1 (AP)	

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.M.C.G./

	4	0558906	JP	A	1993-03-09	Sankyo Co.		☐

If you wish to add additional Foreign Patent Document citation information please click the Add button

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1		☐

If you wish to add additional non-patent literature document citation information please click the Add button

EXAMINER SIGNATURE

Examiner Signature	/Marcela Cordero Garcia/	Date Considered	10/10/2014

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

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

Receipt date: 07/08/2014	Application Number	14222478 14222478 - GAU: 1676
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99**)	Filing Date	2014-03-21
	First Named Inventor	Andrew Acheampong
	Art Unit	1676
	Examiner Name	Cordero Garcia, Marcela M.
	Attorney Docket Number	17618 CON6CON1 (AP)

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☒ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☐ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Laura L. Wine/	Date (YYYY-MM-DD)	2014-07-08
Name/Print	Laura L. Wine	Registration Number	68681

This collection of information is required by 37 CFR 1.97 and 1.98. 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 1 hour 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.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	421	cyclosporin same castor	US-PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2014/11/06 15:36
L2	47	cyclosporin same castor and "1.5" near10 "0.5"	US-PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2014/11/06 15:36
L3	31	cyclosporin same castor and "1.25" near10 "0.05"	US-PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2014/11/06 15:36

EAST Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L4	9	cyclosporin same castor and "1.25" near10 "0.05"	USPAT; UPAD	ADJ	ON	2014/11/06 16:00

11/6/2014 4:00:56 PM
C:\Users\mgarcia\Documents\EAST\Workspaces\12347683.wsp

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14222478	ACHEAMPONG ET AL.
	Examiner	Art Unit
	MARCELA M CORDERO GARCIA	1676

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner
none	none	6/16/2014	MMCG

SEARCH NOTES		
Search Notes	Date	Examiner
EAST search (attached)	6/14/2014	MMCG
STN search (attached)	6/16/2014	MMCG
also ran PALM Inventor search	6/16/2014	MMCG
EAST updated (attached)	11/6/2014	MMCG
also updated PALM Inventor search	11/6/2014	MMCG

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner
EAST updated	attached	11/6/2014	MMCG

Doc Code: DIST.E.FILE **Document Description: Electronic Terminal Disclaimer - Filed**	PTO/SB/26 U.S. Patent and Trademark Office Department of Commerce

Electronic Petition Request	**TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A "PRIOR" PATENT**
Application Number	14222478
Filing Date	21-Mar-2014
First Named Inventor	Andrew Acheampong
Attorney Docket Number	17618CON6CON1 (AP)
Title of Invention	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS

☒ Filing of terminal disclaimer does not obviate requirement for response under 37 CFR 1.111 to outstanding Office Action

☒ This electronic Terminal Disclaimer is not being used for a Joint Research Agreement.

Owner	Percent Interest
Allergan, Inc.	100%

The owner(s) with percent interest listed above in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of prior patent number(s)

8685930

8648048

8642556

8633162

8629111

as the term of said prior patent is presently shortened by any terminal disclaimer. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the prior patent are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of the term of any patent granted on the instant application that would extend to the expiration date of the full statutory term of the prior patent, "as the term of said prior patent is presently shortened by any terminal disclaimer," in the event that said prior patent later:
- expires for failure to pay a maintenance fee;
- is held unenforceable;
- is found invalid by a court of competent jurisdiction;
- is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321;
- has all claims canceled by a reexamination certificate;
- is reissued; or
- is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

(●) Terminal disclaimer fee under 37 CFR 1.20(d) is included with Electronic Terminal Disclaimer request.

( ) I certify, in accordance with 37 CFR 1.4(d)(4), that the terminal disclaimer fee under 37 CFR 1.20(d) required for this terminal disclaimer has already been paid in the above-identified application.

Applicant claims the following fee status:

( ) Small Entity

( ) Micro Entity

(●) Regular Undiscounted

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.

THIS PORTION MUST BE COMPLETED BY THE SIGNATORY OR SIGNATORIES

I certify, in accordance with 37 CFR 1.4(d)(4) that I am:

(●) An attorney or agent registered to practice before the Patent and Trademark Office who is of record in this application

Registration Number 68681

( ) A sole inventor

( ) A joint inventor; I certify that I am authorized to sign this submission on behalf of all of the inventors as evidenced by the power of attorney in the application

( ) A joint inventor; all of whom are signing this request

Signature	/Laura L. Wine/
Name	Laura L. Wine

*Statement under 37 CFR 3.73(b) is required if terminal disclaimer is signed by the assignee (owner).
Form PTO/SB/96 may be used for making this certification. See MPEP § 324.

Electronic Patent Application Fee Transmittal

Application Number:	14222478
Filing Date:	21-Mar-2014
Title of Invention:	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS
First Named Inventor/Applicant Name:	Andrew Acheampong
Filer:	Laura Lee Wine/Maria Stein
Attorney Docket Number:	17618CON6CON1 (AP)

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Statutory or Terminal Disclaimer	1814	1	160	160
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($)
Miscellaneous:				
			Total in USD ($)	**160**

Doc Code: DISQ.E.FILE
Document Description: Electronic Terminal Disclaimer – Approved

Application No.: 14222478

Filing Date: 21-Mar-2014

Applicant/Patent under Reexamination: Acheampong et al.

Electronic Terminal Disclaimer filed on September 25, 2014

☒ APPROVED

This patent is subject to a terminal disclaimer

☐ DISAPPROVED

Approved/Disapproved by: Electronic Terminal Disclaimer automatically approved by EFS-Web

U.S. Patent and Trademark Office

Electronic Acknowledgement Receipt

EFS ID:	20246997
Application Number:	14222478
International Application Number:	
Confirmation Number:	9616
Title of Invention:	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS
First Named Inventor/Applicant Name:	Andrew Acheampong
Customer Number:	51957
Filer:	Laura Lee Wine/Maria Stein
Filer Authorized By:	Laura Lee Wine
Attorney Docket Number:	17618CON6CON1 (AP)
Receipt Date:	25-SEP-2014
Filing Date:	21-MAR-2014
Time Stamp:	16:22:40
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$160
RAM confirmation Number	2933
Deposit Account	010885
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Electronic Terminal Disclaimer-Filed	eTerminal-Disclaimer.pdf	35317 0120546a576347d21f62d6fb53c00068455 27467	no	3
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30289 6b6345ed2c8b85fd47cf1c0d708505fff7797 f99	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	65606		

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.

Docket No. 17618CON6CON1 (AP)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Acheampong, *et al.*	Examiner: Marcela M Cordero Garcia
Serial No.: 14/222,478	Group Art Unit: 1676
Filed: March 21, 2014	Confirmation No. 9616
For: METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS	Customer No.: 51957

RESPONSE TO NON-FINAL OFFICE ACTION DATED JUNE 25, 2014

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

Dear Sir:

These papers are filed in reply to the non-final Office Action mailed June 25, 2014.

The Commissioner is authorized to charge any fee which may be required in connection with this Amendment to deposit account No. 01-0885.

Remarks begin on page 2 of this paper.

REMARKS

This Reply responds to the Office Action sent June 25, 2014, in which the Office Action rejected Claims 37-63. The Applicants respectfully submit that the claims are in condition for allowance.

Claim Rejections

35 U.S.C. § 112, first paragraph

Claims 37-63 were rejected under 35 U.S.C § 112, first paragraph as failing to comply with the written description requirement with regards to the limitation in Claims 37, 49, and 57 of "at a frequency of twice a day".

The Applicants submit that the currently pending Claims contain sufficient written description support for the "at a frequency of twice a day" limitation within the specification of the present application as originally filed. For example, support for this limitation can be found, at least, in the paragraph at page 9, line 25 – page 10, line 7 of the specification as originally filed, which reads:

> 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**.

Specification filed March 21, 2014 at page 9, line 25 – page 10, line 7 (Emphasis Added).

In view of the above, the Applicants respectfully submit that the disclosure of the present application reasonably shows that the Applicants were in possession of what is now claimed at the time of filing, and request that the rejection of Claims 37-63 under 35 U.S.C. § 112, first paragraph be withdrawn.

Obviousness-Type Double Patenting Rejection

Claims 37-63 were rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-27 of U.S. Patent No. 8,629,111. Claims 37-63 were also rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-24 of U.S. Patent No. 8,633,162. Claims 37-63 were also rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-20 of U.S. Patent No. 8,642,556. Claims 37-63 were also rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-23 of U.S. Patent No. 8,648,048. Claims 37-63 were also rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-36 of U.S. Patent No. 8,685,930.

While the Applicants do not agree with the non-statutory obviousness-type double patenting rejections recited above, in order to expedite prosecution, terminal disclaimers were filed on September 24, 2014 . Thus, the Applicants submit that the obviousness-type double patenting rejections have been rendered moot and request that the obviousness-type double patenting rejections be withdrawn.

Conclusion

In view of the foregoing, the Applicants believe all claims now pending in the present application are in condition for allowance.

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.

If the Examiner believes a telephone conference would expedite prosecution of this application, please contact the undersigned at (714) 246-6996.

Respectfully submitted,

/Laura L. Wine/

Date: September 25, 2014

Laura L. Wine
Attorney of Record
Registration Number 68,681

Please direct all inquiries and correspondence to:
Laura L. Wine, Esq.
Allergan, Inc.
2525 Dupont Drive, T2-7H
Irvine, California 92612
Tel: (714) 246-6996 Fax: (714) 246-4249

Electronic Acknowledgement Receipt

EFS ID:	20247409
Application Number:	14222478
International Application Number:	
Confirmation Number:	9616
Title of Invention:	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS
First Named Inventor/Applicant Name:	Andrew Acheampong
Customer Number:	51957
Filer:	Laura Lee Wine/Maria Stein
Filer Authorized By:	Laura Lee Wine
Attorney Docket Number:	17618CON6CON1 (AP)
Receipt Date:	25-SEP-2014
Filing Date:	21-MAR-2014
Time Stamp:	16:38:41
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		17618CON6CON1_Response_092514.pdf	117409 c2e9138ffcfcd9ed846e7072cb02de837abcc098	yes	4

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment/Req. Reconsideration-After Non-Final Reject	1	1
	Applicant Arguments/Remarks Made in an Amendment	2	4
Warnings:			
Information:			
	Total Files Size (in bytes):	117409	

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.

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 NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
14/222,478	03/21/2014	Andrew Acheampong	17618CON6CON1 (AP)

CONFIRMATION NO. 9616

51957
ALLERGAN, INC.
2525 DUPONT DRIVE, T2-7H
IRVINE, CA 92612-1599

PUBLICATION NOTICE

OC000000069795556

Title:METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS

Publication No.US-2014-0206626-A1
Publication Date:07/24/2014

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Office of Public Records. The Office of Public Records can be reached by telephone at (703) 308-9726 or (800) 972-6382, by facsimile at (703) 305-8759, by mail addressed to the United States Patent and Trademark Office, Office of Public Records, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently http://pair.uspto.gov/. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

Office of Data Managment, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	14222478
Filing Date	2014-03-21
First Named Inventor	Andrew Acheampong
Art Unit	1676
Examiner Name	Cordero Garcia, Marcela M.
Attorney Docket Number	17618 CON6CON1 (AP)

U.S.PATENTS

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	4347238		1982-08-31	Hollingsbee	

If you wish to add additional U.S. Patent citation information please click the Add button.

U.S.PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

If you wish to add additional U.S. Published Application citation information please click the Add button.

FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	2222770	GB	A	1990-03-21	Sandoz Ltd		☐
	2	198901772	WO	A1	1989-03-09	University of Georgia Research Foundation, Inc.		☐
	3	199318752	WO	A1	1993-09-30	Pharmos Corp.		☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99**)		
	Application Number	14222478
	Filing Date	2014-03-21
	First Named Inventor	Andrew Acheampong
	Art Unit	1676
	Examiner Name	Cordero Garcia, Marcela M.
	Attorney Docket Number	17618 CON6CON1 (AP)

	4	0558906	JP	A	1993-03-09	Sankyo Co.		☐

If you wish to add additional Foreign Patent Document citation information please click the Add button

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1		☐

If you wish to add additional non-patent literature document citation information please click the Add button

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

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

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(**Not for submission under 37 CFR 1.99**)

Application Number	14222478
Filing Date	2014-03-21
First Named Inventor	Andrew Acheampong
Art Unit	1676
Examiner Name	Cordero Garcia, Marcela M.
Attorney Docket Number	17618 CON6CON1 (AP)

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 4 : A61K 9/00, 9/08, 37/02

A1

(11) International Publication Number: **WO 89/ 01772**

(43) International Publication Date: 9 March 1989 (09.03.89)

(21) International Application Number: PCT/US88/03039

(22) International Filing Date: 31 August 1988 (31.08.88)

(31) Priority Application Numbers: 092,466
117,218
187,823

(32) Priority Dates: 3 September 1987 (03.09.87)
4 November 1987 (04.11.87)
29 April 1988 (29.04.88)

(33) Priority Country: US

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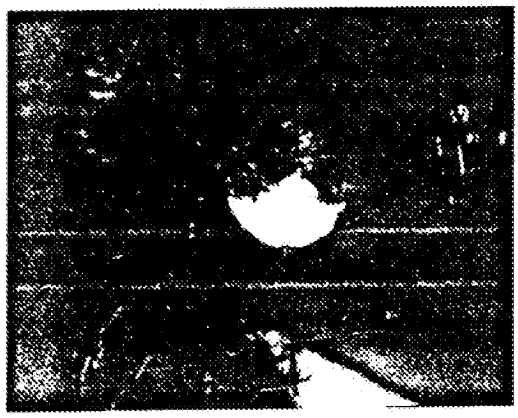
(81) Designated States: AT (European patent), AU, BE (European patent), CH (European patent), DE (European patent), DK, FR (European patent), GB (European patent), IT (European patent), JP, KR, LU (European patent), NL (European patent), SE (European patent).

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

(54) Title: OCULAR CYCLOSPORIN COMPOSITION



(57) Abstract

A method for enhancing or restoring lacrimal function by the topical administration of a cyclosporin in a pharmaceutically acceptable excipient. Lacrimal function is enhanced or restored in patients suffering from abnormalities of the tear film including an absolute or partial deficiency in aqueous tear production, called keratoconjunctivitis sicca or KCS, regardless of etiology, including autoimmune dysfunction of the lacrimal glands. The treatment is also useful in the enhancement or restoration of normal tear production, and normal healing of the surface of the eye. The preferred composition for topical administration to the eye consists of cyclosporin dissolved in corn oil. The composition may further include antioxidants, lubricants, antibiotics, antifungals, antivirals, pilocarpine, vasoconstrictors, surfactants, wetting agents, anti-inflammatory agents (i.e. corticosteroids), preservatives, mucolytic agents (i.e. bromhexine, acetylcysteine), as well as other compounds. The most preferred composition is 2% cyclosporin, 1 mole % alpha tocopherol and 0.005% methyl paraben in corn oil.

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OCULAR CYCLOSPORIN COMPOSITION

The present invention relates to a method and composition for increasing tear production by the topical administration of cyclosporin to the patient's eyes.

BACKGROUND OF THE INVENTION

The exposed part of a normal eye is covered by a continuous thin tear film which is important for the well-being of the corneal and conjunctival epithelium and provides the cornea with an optically high quality surface. In addition, the aqueous part of the tear film acts as a lubricant to the eyelids during blinking of the lids. Certain enzymes contained in the tear fluid, for example immunoglobulin A, lysozyme and beta lysin, also have bacteriostatic properties.

The lacrimal apparatus consists of the secretory system (the source), the distribution system and the excretory system (the sink). In the secretory system, the bulk of the tear film, the aqueous tears, are supplied by the main and accessory lacrimal glands. The continuous production and drainage of aqueous tears is important in maintaining the corneal and conjunctival epithelium in a moist state, in providing nutrients for epithelial respiration, in supplying bacteriostatic agents and in cleaning the ocular surface by the flushing action of tear movement.

Abnormalities of the tear film include an absolute or partial deficiency in aqueous tear production, called keratoconjunctivitis sicca or KCS. In relatively mild cases, the main symptom of KCS is a foreign body sensation or a mild "scratchiness". This can develop into a constant, intense burning or

irritative sensation which can be debilitating to the patient. More severe forms lead to the development of filamentary keratitis, a painful condition characterized by the appearance of numerous strands or filaments attached to the corneal surface. Recent evidence suggests that these filaments represent breaks in the continuity of the normal corneal epithelial cells. The shear created by lid motion pulls these filaments, causing pain. Management of this stage of KCS is very difficult.

A frequent complication of KCS is secondary infection. Several breakdowns in the eye's normal defense mechanism seem to occur, presumably attributable to a decrease in the concentration of antibacterial lysozyme in the aqueous tears of a patient suffering from KCS.

Although KCS can develop in the absence of any other overt systemic abnormality, there is a frequent association of KCS with systemic disease. KCS can occur as part of a larger systemic involvement known as Sjogren's syndrome which is characterized by dry eyes, dry mouth, and arthritis.

Histologically in KCS (as part of Sjogren's syndrome or in isolation), the initial changes seen in the lacrimal gland are those of focal lymphocytic and plasma cell infiltrates associated with degeneration of glandular tissue. These changes resemble those seen in autoimmune disease in other tissue, giving rise to the speculation that KCS has an autoimmune basis.

Sjogren's syndrome is recognized as an exocrine glad dysfunction. Characteristically, the lacrimal glands show a mononuclear-cell infiltration that

ultimately leads to destruction of the glandular structure.

Conventional treatment of KCS is symptomatic. Normally, aqueous-deficient dry eye states are treated by supplementation of the tears with artificial tear substitutes. However, relief is limited by the retention time of the administered artificial tear solution in the eye. Typically, the effect of an artificial tear solution administered to the eye dissipates rapidly, within about thirty to forty-five minutes. The effect of such products, while soothing initially, does not last long enough. The patient is inconvenienced by the necessity of repeated administration of the artificial tear solution in the eye as needed to supplement the normal tears. Moreover, such treatment merely acts to alleviate the symptoms of the dry eye state and does not cure any underlying disorders or causes of the dry eye state.

The systemic use of corticosteroids has been advocated to treat these conditions. However, the merit of systemic corticosteroids in dry eye states has not been established. In most dry eye cases the hazards of long-term use of antiinflammatory agents would seem to outweigh their potential merit. It has also been suggested to administer orally a dilute solution of pilocarpine to stimulate the autonomic nervous system to effect increased aqueous tear production. This method of treatment has not met with universal favor because of the unpleasant side effects of ingested pilocarpine.

Surgical procedures have also been suggested in the management of dry eye states. Where there has been significant conjunctival destruction, mucous

membrane transplants have been advocated. It has also been suggested that parotid (saliva) duct transplantation can be useful in the management of dry eyes. However, since surgical alterations to combat dry eye conditions constitute such a drastic remedy and the benefit resulting from these alterations is questionable, these methods are usually used only as a last resort.

Cyclosporin is a metabolite isolated from the culture broths of the fungal species Tolypocladium inflatum Gams. A neutral, hydrophobic cyclic peptide composed of eleven amino acid resides, cyclosporin includes a previously unknown N-methylated amino acid composed of nine carbon atoms. Wenger, Synthesis of Cyclosporin and Analoques, pp. 14-25 in Cyclosporin A 1, Grune & Stratton, Inc. (New York 1983). A number of additional cyclosporins (B, C, D, E, and G) have been reported since the first cyclosporin was isolated (CsA). As described in U.S. Patent No. 4,117,118 issued September 26, 1978 to Harri et al., cyclosporin is readily soluble in most of the usual organic solvents and practically insoluble in petroleum ether and water. As distributed by Sandoz Ltd., Basel, Switzerland, under the tradename Sandimmune, cyclosporin for oral administration is dissolved in olive oil for further dilution with food and in polyoxyethylated castor oil and ethanol for intravenous injection.

Cyclosporin A was first proposed for use as an antifungal agent, but its immunosuppressive effects were found to be more marked than its antifungal potential. A potent immunosuppressive agent, cyclosporin is used to prolong survival of allogeneic

transplants involving skin, heart, kidney, pancreas, bone marrow, small intestine and lung. The exact mechanism of action is not known but experimental evidence suggests that the effectiveness of cyclosporin is due to specific and reversible inhibition of immunocompetent cells, primarily T-helper cells. Lymphokine production, gamma interferon production and release of interleukin-2 or T-cell growth factor are also inhibited by cyclosporin.

Cyclosporin's immunosuppressive properties have led to its use in immune system related diseases. For example, U.S. Patent No. 4,649,047 describes a method for the treatment of phacoanaphylactic endophthalmitis and uveitis in the anterior or posterior segment of an eye wherein cyclosporin is topically administered to the eye. In other ophthalmic applications, cyclosporin has been used topically only for the treatment of external (e.g., corneal) eye diseases.

BenEzra et al., Amer. J. Ophthalmol. 101: 278-282 (1986), describe the effect of 2% cyclosporin eyedrops on severe vernal keratoconjunctivitis. Severe vernal keratoconjunctivitis is a seasonal allergic disorder unrelated to tear deficiency.

Hunter et al., Clin. Exp. Immunol. 45: 173-177 (1981) describe the topical administration of cyclosporin in a rabbit model of corneal graft rejection with positive results.

Boisjoly et al., Arch. Ophthalmol. 102: 1804-1807 (1984), have reported that topical application of cyclosporin had a beneficial prophylactic effect towards the treatment of severe herpetic stromal keratitis.

Mosteller et al., Investigative Ophthalmol. Supp. 25, 3: 38 (1984), disclose treating corneal allograft rejection in rabbits by applying a single dose of a 10% Cyclosporin A ointment in the lower cul-de-sac of the eyelids.

Cyclosporin has also been used systemically in other ophthalmic applications, where the disease being treated is not limited to the eye surface. For example, Nussenblatt et al., Amer. J. Ophthalmol. 96: 275-282 (1983), have reported clinical improvement in some patients with noninfectious posterior uveitis following systemic treatment with cyclosporin.

Cyclosporin is primarily administered orally or by injection. Unfortunately, cyclosporin used systemically has been associated with a high incidence of renal toxicity (kidney failure), some cases of hepatotoxicity, increased incidence of lymphoid tumors and increased incidence of opportunistic infections. Cyclosporin is only slightly less toxic than other immunosuppressive agents such as cytoxan or aziothioprine. The systemic side effects of cyclosporin are so severe and so common that they limit its use to life-threatening or in some cases severe sight-threatening disease. Finally, systemic application of cyclosporin is limited by its prohibitive cost.

As described in U.S. Patent No. 4,649,047 issued March 10, 1987 to Kaswan, topical administration of cyclosporin is useful in the treatment of a variety of immune mediated disorders of the eye, including uveitis and phacoanaphylactic endophthalmitis. This is also the preferred mode of administration to avoid

the undesirable side effects and cost of systemic administration.

To date, there has been no suggestion to treat a glandular dysfunction, a lacrimal gland dysfunction or an aqueous-deficient dry eye state with a cyclosporin, either topically or systemically.

Although cyclosporin has been topically administered in a variety of vehicles including arachis oil, a commercially available ointment base, and castor oil, the conventional carrier is olive oil. Unfortunately, topical administration of cyclosporin in olive oil to the eye of either humans or dogs is frequently accompanied by a burning sensation, pain, and redness. In some cases, other side effects have been observed including lid edema and periocular alopecia (hair loss around the eye). Similar problems have occurred with topical ophthalmic use of cyclosporin in the other vehicles. Studies have now demonstrated that these unpleasant side effects are due to the carrier, not to the cyclosporin. Unfortunately, cyclosporin is of very limited solubility and the number of acceptable carriers for ophthalmic use is limited.

It is therefore an object of this invention to provide a method of increasing tear production for a normal or tear-deficient eye, regardless of cause.

It is another object of this invention to provide a cyclosporin-based treatment of lacrimal gland dysfunction without the accompanying adverse physiological responses and economic difficulties associated with systemic cyclosporin treatments.

It is another object of the present invention to provide a composition containing an effective

concentration of cyclosporin for topical ophthalmic use which does not cause burning, redness or irritation.

It is a still further object of the present invention to provide a composition for topical ophthalmic use which is stable upon storage.

It is still another object of the present invention to provide a composition for topical ophthalmic use which promotes normal healing of the epithelial surface of the eye.

SUMMARY OF THE INVENTION

The present invention is directed to a method of treating a dry eye state in a patient by administering a cyclosporin topically to the patient's eye. The treatment is useful regardless of the cause of the dry eye, and includes treatment of autoimmune dysfunction of the lacrimal glands. The treatment is also useful in the enhancement or restoration of normal tear production, and normal healing of the surface of the eye.

The preferred composition for topical administration to the eye consists of cyclosporin dissolved in corn oil. The composition may further include antioxidants, lubricants, antibiotics, antifungals, antivirals, pilocarpine, vasoconstrictors, surfactants, wetting agents, anti-inflammatory agents (i.e. corticosteroids), preservatives, mucolytic agents (i.e. bromhexine, acetylcysteine), as well as other compounds.

The most preferred composition is 2%

cyclosporin, 1 mole % alpha tocopherol and 0.005% methyl paraben in corn oil.

Brief Description of the Drawings

Figure 1 is a graph demonstrating the effect of topical cyclosporin on lacrimination (STT mm/min) over time (days) in twelve normal male beagle dogs; following three days of baseline measurement with no treatment, six dogs were treated with 2% cyclosporin in olive oil applied topically two times daily, and six dogs were treated with placebo (olive oil) applied topically two times daily. The STT were determined twice daily in the cyclosporin treated dogs (■ ---- ▨) and in the olive oil treated dogs (▲ ---▲). Following 7 days all dogs were crossed over into the opposite treatment groups for an additional three days.

Figure 2 is a comparison of the appearance of the eye of a dog suffering from keratoconjunctivitis sicca before (Figure 2A) and after (Figure 2B) treatment for four weeks with 2% cyclosporin.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a method of treating tear-deficient dry eyes due to autoimmune disease or of unknown etiology which includes the step of administering a cyclosporin topically to the patient's eye. The invention includes a corn oil based cyclosporin composition which provides greatly enhanced benefits when applied topically to the eye over previous cyclosporin compositions.

Despite the apparent similarities in chemical structure, studies demonstrate the significant differences in comfort and incidence of side effects between cyclosporin in previously described carriers such as olive oil and cyclosporin in corn oil, both with and without preservative and antioxidant. These studies also establish that topically applied cyclosporin can be used to promote or effect normal healing and prevent or reverse scar formation on the ocular surface.

In accordance with the present invention, the cyclosporin may be used in any efficacious concentration, e.g., 0.01 to saturation (e.g., up to 50 weight percent of a cyclosporin) in a pharmaceutically acceptable excipient. Concentrations of 1.1 to 20 weight percent of a cyclosporin are preferred. Although the preferred vehicle is corn oil, as described below, other pharmaceutically acceptable excipients are, for example, animal oil, vegetable oil, appropriate organic or aqueous solvents, artificial tear solutions in which the cyclosporin is soluble, and natural or synthetic polymers or appropriate membranes.

Examples of these pharmaceutically acceptable excipients are olive oil, arachis oil, castor oil, mineral oil, petroleum jelly, dimethyl sulfoxide, chremophor, Miglyol 182 (commercially available from Dynamit Nobel Kay-Fries Chemical Company, Mont Vale, New Jersey), alcohol (e.g., ethanol, n-propyl alcohol or iso-propyl alcohol), liposomes or liposome-like products, silicone fluids and mixtures thereof.

Examples of artificial tear excipients which can be advantageously used in the practice of this

invention are isotonic sodium chloride, cellulose ethers such as hydroxypropylmethylcellulose and hydroxyethylcellulose, polyvinyl alcohol and other commercially available artificial tear solutions. An example of a useful polymeric excipient is polyoxyethylated castor oil. Examples of pharmaceutically acceptable membranes which can advantageously be used in the practice of this invention are: microdone, an artificial lipid membrane, polyvinylalcohol, or methylcellulose.

Cyclosporins which are useful in the practice of the present invention include both natural or synthetic cyclosporins. Cyclosporin A is preferred in the practice of the present invention. Other forms of cyclosporins (e.g., analogs and isomers such as Cyclosporins B, C, D, E, and H) may also be used. Mixtures of different cyclosporins may be used.

In the preferred method of treating a specific antigen mediated immune response in a patient having more than one involved site of the immune mediated response, the cyclosporin is applied locally to each involved site. For example, where only one eye appears to suffer from immune mediated KCS, both eyes should be treated. Surprisingly, unless each involved site is treated with cyclosporin, no appreciable benefit is obtained from cyclosporin treatment at any one of the sites, i.e., if only the affected eye is treated, little benefit of the cyclosporin is obtained. This suggests that locally administered cyclosporin interferes with and blocks the afferent immune recognition of the specific antigen which triggers the immune mediated response. Unless each of the sites wherein the specific antigen occurs is

treated with the cyclosporin, T-cell antigen signaling occurs continuously in the untreated site causing local lymphokine production that triggers a cascading systemic immune response that adversely affects both the treated and untreated sites.

In other words, local administration of cyclosporin acts to inhibit the continuous afferent immune response, for example within an eye, when antigens placed in the eye are associated with intraocular MHC antigen bearing accessory cells and are presented to T-cells. However, if an untreated eye or a distal skin graft is used to initiate antigen recognition, an afferent immune response begins at the site distal to the treatment site, T-cells are activated, lymphokines produced, and the systemic immune response proceeds to an efferent immune response affecting both eyes.

Thus, in any experiment in which an intrasubject control eye is used, local therapy in one eye will have diminished effect unless it is given in such quantity as to produce systemic immuno-suppression. Moreover, when treating an immune mediated response which exists to a much greater degree at one site of a patient, such as in or near one eye of the patient, than at another site of the patient, such as in the other eye of the patient, so as to be apparent at only the one site, the cyclosporin is advantageously administered locally in a therapeutically effective amount to each of the sites. An immune mediated response which appears to exist in only one eye of a patient is advantageously treated by administering a therapeutically effective amount of a cyclosporin

locally to both eyes of the patient to achieve maximal benefit.

If administered locally to each of the sites of the patient affected by the immune mediated response, cyclosporin can be used advantageously to treat a variety of immune mediated disorders. Ocular diseases which are successfully treated in animal models by local administration of cyclosporin to each site of the patient effected by the immune mediated response include immune-mediated melting ulcers in cats and dogs, chronic neovascularization and proliferative keratitis in cats and dogs, stromal keratitis subsequent to ulcerative Herpes keratitis in cats, pigmentary keratitis in dogs and KCS in dogs.

Numerous advantages accrue with the practice of the present invention. The method of the present invention is useful in that it can locally prevent activation of a pre-systemic response. Topical administration of a cyclosporin into a patient's tear deficient eye increases tear production in the eye. Thus, such treatment further serves to correct corneal and conjunctival disorders exacerbated by tear deficiency and KCS, such as corneal scarring, corneal ulceration, inflammation of the cornea or conjunctiva, filamentary keratitis, mucopurulent discharge and vascularization of the cornea. Furthermore, cyclosporin directly decreases the immune response of granulation and neovascularization in the cornea.

Further objects of this invention, together with additional features contributing thereto and advantages accruing therefrom, will be apparent from the following examples of the invention.

Example 1: Effectiveness and distribution of topical cyclosporin.

Topical administration to a patient's eye has surprisingly been found to be an excellent method for providing a cyclosporin to the lacrimal glands of the patient to treat KCS. Additionally, since by its very nature topical administration does not require cyclosporin dispersion throughout the patient's system as is the case with systemic administration, the present invention provides a means for directing cyclosporin to the desired location without the accompanying high risk of adverse responses and high cost associated with systemic treatments.

Cyclosporin concentration has been determined for various eye compartments and tissues surrounding the eye after bilateral topical administration of cyclosporin to the eyes of three rabbits. The cyclosporin was administered in each of the rabbits' eyes in drops (approximately 17 microliters) of 2% radiolabelled cyclosporin in an olive oil solution applied every 15 minutes for 6 applications, followed by a period of two hours to allow for absorption. The rabbits were then euthanized and the eyes and surrounding tissue enucleated and frozen. The eyes and surrounding tissue were dissected into their component parts. These were then digested in collagenase and the resulting solutions analyzed by liquid scintillation counting for cyclosporin content. The following average cyclosporin concentrations were measured:

Accessory lacrimal gland: 2850 ng of cyclosporin/gram of tissue;

Periorbital fat: 800 ng/gram;

Cornea: 4700 ng/gram;

Iris: 1200 ng/gram;

Retina: 50 ng/gram;

Aqueous humor: 30 ng/gram;

Vitreous humor: 30 ng/gram;

Anterior sclera: 3150 ng/gram; and

Posterior sclera: 1550 ng/gram.

Example 2: Comparison of treatment of dry eye with anti-inflammatory steroid and cyclosporin.

A one year old standard female Poodle with conjunctivitis exhibited mild aqueous tear deficiency in both eyes. The dog had a Schirmer tear test value of 15 mm/minute in the right eye and 10 mm/minute in the left eye.

The Schirmer tear test is a test of aqueous tear production. The test depends upon observing the extent of wetting of a strip of filter paper placed over the lower lid of an eye for a specified time. Standardized strips are commercially available. The strip is folded at a notched marking and is then placed over the edge of the lateral one-third of the eyelid. The strip is usually left in place for a period of time while the patient looks straight ahead in dim light.

The degree of wetting of the paper is measured in mm from the notch. For human patients, a normal end point is 5 mm of wetting at five minutes. For canine patients, the normal tear production is 14 to 20 mm of wetting at one minute.

The dog was originally treated with dexamethasone by topical administration in both eyes four times daily. Although initially somewhat effective, treatment was subsequently discontinued and the same dog at approximately six years old still exhibited conjunctivitis in both eyes and had a Schirmer tear test value of 3 mm/minute in both eyes. Topical dexamethasone was then applied to both eyes twice daily for nine weeks without benefit.

The dog was then treated by topical application of 2% cyclosporin in an olive oil solution in both eyes once daily without any other medications. After ten days, the dog showed markedly increased tear production and had a Schirmer tear test value of 22 mm/minute in the right eye and 8 mm/minute in the left eye.

The treatment by topical application of 2% cyclosporin in an olive oil solution in both eyes once daily was continued for an additional three weeks. At this time, the dog exhibited plentiful aqueous tear production and the treatment was stopped for one week. After the one week, the dog had a Schirmer tear test value of 10 mm/minute in the right eye and 9 mm/minute in the left eye.

At this time, the treatment by topical application of 2% cyclosporin in an olive oil solution in both eyes once daily was reinstituted and continued for six days. After the six days, the dog had a Schirmer tear test value of 22 mm/minute in the right eye and 16 mm/minute in the left eye.

In this case, a dog with chronic tear deficiency in which prior use of corticosteroids failed to improve tear secretion showed a surprising increase in

tear production with cyclosporin treatment. The increased tear production continued only while cyclosporin therapy continued. When the treatment was stopped for a week, the eyes again became tear deficient. However, tear production increased to normal levels after the treatment was restarted.

Example 3: Treatment of dry eye and enhancement of corneal healing with topical cyclosporin treatment.

An eight year old male Lhasa Apso had a four year old cat scratch in his left eye and an active 4 mm stromal ulcer in his right eye. An ocular examination of the dog showed conjunctivitis in both eyes with mucopurulent discharge, diffuse irregular corneal surfaces, pigment formation and neovascularization in the cornea of the left eye. The Schirmer tear test values were 12 mm/minute in the right eye and 3 mm/minute in the left eye.

The dog was treated with topical administration to both eyes of 2% cyclosporin in an olive oil solution once daily, neosporin twice daily and ophthalmic petrolatum. After five days, the Schirmer tear test values were 22 mm/minute in the right eye and 23 mm/minute in the left eye. In addition, the ulcer in the right eye was healed to 2 mm and the left eye was assessed to have decreased vascularization.

In this case, cyclosporin increased tear production significantly in a short period of time. Moreover, cyclosporin, unlike corticosteroids, did not retard corneal healing nor activate corneal collagenase. Accordingly, cyclosporin can be used in eyes having active corneal ulcers.

Example 4: Comparison of treatment of dry eye with pilocarpine alone and in combination with cyclosporin.

A six year old male English Bulldog with a long history of KCS had Schirmer tear test values of 2 mm/minute in the right eye and 3 mm/minute in the left eye.

The right eye was neovascularized over the entire cornea. No intraocular detail could be visualized through the opaque cornea. The cornea was grossly thick and irregular in surface. The left eye had neovascularization over about half of the cornea, mostly axially.

The dog was treated with three drops of 2% pilocarpine by mouth. After two hours, the Schirmer tear test values were 0 mm/minute in the right eye and 10 mm/minute in the left eye.

The dog was then treated with 2% cyclosporin in an olive oil solution administered topically to both eyes once daily and three drops of 2% pilocarpine administered by mouth twice daily. After twelve days, the Schirmer tear test values were 10 mm/minute in the right eye and 15 mm/minute in the left eye.

In this case, while pilocarpine alone increased tear production in the left eye from a Schirmer tear test value of 3 mm/minute to 10 mm/minute, pilocarpine did not increase tear production in the right eye. Use of cyclosporin with pilocarpine increased tear production to a Schirmer tear test value of 15 mm/minute in the left eye and from 0 mm/minute to 10 mm/minute in the right eye. The use of cyclosporin markedly increased tear production over the use of pilocarpine alone.

Example 5: Correction of dry eye and restoration of normal vision by topical treatment with cyclosporin.

A seven year old Miniature Poodle had a history of severe KCS of six to seven months duration. Treatment with artificial tears six times daily did not affect the apparent blindness.

The dog showed marked mucopurulent discharge in both eyes. The Schirmer tear test values were 0 mm/minute in both eyes. The dog's corneas were thickened and neovascularized with an irregular surface. No intraocular detail could be visualized through the opaque corneas.

The dog was treated with one drop of 2% pilocarpine by mouth two times daily and ophthalmic petrolatum four times daily. After two weeks, the Schirmer tear test values were still 0 mm/minute in both eyes. The corneal vascularity and scarring remained dense and the anterior chambers of the dog's eye were not visualizable.

The dog was then treated with 2% cyclosporin in an olive oil solution administered topically in both eyes once daily and two drops pilocarpine administered by mouth twice daily.

After two weeks, the Schirmer tear test values were 8 mm/minute in the right eye and 6 mm/minute in the left eye. Although corneal vascularization and scarring remained, the iris and lens could be evaluated, there was no mucoid discharge in either eye as previously and the KCS was assessed as medically improved.

After similar treatment for another two months, the Schirmer tear test values were 11 mm/minute in the

right eye and 17 mm/minute in the left eye. The dog's eyes had minimal corneal vascularization and minimal scarring.

In this case, although the dog was treated initially with pilocarpine, pilocarpine alone is not known to cause such a drastic improvement in tear production. After treatment with cyclosporin, the dog improved from no tear flow in either eye to normal tear production in both eyes. The dog improved from blinding corneal inflammation to very mild corneal pigmentation in both eyes. Treatment with cyclosporin markedly increased tear production and allowed the dog to return to normal vision.

Example 6: Stimulation of tearing in normal dogs.

Studies were conducted on the effect of applying topical 2% cyclosporin in olive oil to the eyes of normal dogs. The results are shown in Figure 1 comparing the effect of topical cyclosporin on lacrimination in six normal male beagle dogs, before and after several days of olive oil therapy alone. In both studies, no treatment was given on days 1 to 3 to establish a baseline. On days 4-10, as graphed by the triangles, one drop of olive oil was administered twice daily (BID) to each eye. On days 11-13, one drop of 2% cyclosporin in olive oil was administered twice daily. A significant increase in tearing was observed. On days 4-10, as graphed by the squares, one drop of 2% cyclosporin in olive oil was administered twice daily. On days 11-13, one drop of olive oil was applied to each eye twice daily. The significant increase in tearing observed over days 4-10 persisted through days 11-13 in the absence of cyclosporin treatment.

The data conclusively demonstrate that topically applied cyclosporin increases glandular function, i.e., lacrimination, in normal eyes.

Since cyclosporin has very low solubility in most solutions which can be administered to the eye, the cyclosporin in the majority of studies on the efficacy of topical administration of cyclosporin has been suspended in olive oil. Unfortunately, controlled studies comparing olive oil alone and in combination with cyclosporin demonstrate that the vehicle, the olive oil, produces redness and burning. In animals, pain is evidenced by the animal holding its eyes shut. In approximately 5 to 10% of approximately 1000 months of treatment (based on number of bottles of 2% cyclosporin dispensed for veterinary use where one bottle is sufficient for treatment of an animal twice daily for about one month), other side effects were observed, including lid edema, corneal surface irregularities, and periocular alopecia.

The present invention includes the surprising discovery that corn oil can be substituted for olive oil as the vehicle for topical administration of cyclosporin to the eye to avoid the undesirable side effects due to the use of the olive oil. Over 3000 bottles of 2% cyclosporin have now been dispensed for treatment of animals twice daily without any apparent side effects for periods of time up to four months.

Additives to the corn oil which enhance stability of the cyclosporin solution include antioxidants such as alpha tocopherol and preservatives such as methyl paraben. Other antioxidants are known to those skilled in the art.

There are some indications that alpha tocopherol (Vitamin E) may also have beneficial effects on the eye since oxidative radicals increase inflammatory damage. Preliminary clinical observations on the protective action of oral administration of vitamins A and E on the corneal epithelium were recently published by Gerhardinger, et al., in Acta Vitaminol. Enzymol. 7(Supp),71-74 (1985). Other compounds which may be added to the cyclosporin solution include emollients, viscosity modifying agents, antioxidants, preservatives, antibiotics, antifungals, antivirals, lubricants, surfactants, vasoconstrictors, DMSO, parasympathomimetics, cholinergics, neurotransmitters, lacrimogenic agents, substance P agonists, substance P antagonists, mucolytics, prostaglandin antagonists, lipogenase inhibitors, cyclooxygenase inhibitors, antiinflammatories, oxygen scavengers, hydrating agents, and epitheliotropic agents. Specific examples, in addition to alpha tocopherol and methyl paraben, include vitamin A, retinoic acid, pilocarpine, hyaluronic acid, polyvinyl alcohol, methylcellulose, eledoisin, physalaemin, bromhexine, mucosolvan, acetylcysteine, indomethacin, and corticosteroids.

The most preferred formulation at this time for topical ophthalmic use consists of 2% cyclosporin, 1 mole % alpha tocopherol and 0.005% methyl paraben. However, cyclosporin solutions can be prepared of between approximately 0.01% by weight and saturation, approximately 20% by weight. Unless otherwise specified, all percentages of compounds herein are by weight.

Although the usual means of administration of the compound is by administration of cyclosporin drops to the surface of the eye, delayed or prolonged release of the cyclosporin at a selected site can also be achieved by encapsulating the cyclosporin-oil mixture within a polymeric implant, liposomes, or microcapsules. Methods for making polymeric implants for ocular use are taught by U.S. Patent No. 3,960,150 to Hussain et al. Both non-degradable and biodegradable polymers can be used, including polyethylene, polystyrene, polypropylene, polyanhydrides, polyorthoester, polylactic acid, and polyglycolic acid. Methods for encapsulating materials within liposomes are taught by PCT/US85/00220 publication WO 85/03640 29 August 1985 by the Liposome Company. Methods for encapsulation of biological material within microcapsules for implantation are taught by U.S. Patent No. 4,352,883 to Lim. Other suitable methods and materials are known to those skilled in the art.

The following non-limiting examples demonstrate the efficacy and advantages of topical cyclosporin in corn oil for treatment of immune disorders, enhancement or restoration of tear production, and enhancement or effecting of normal healing of the surface of the eye.

Example 6: Stimulation of tearing in normal dogs.

Studies were conducted on the effect of applying topical 2% cyclosporin in olive oil to the eyes of normal dogs. The results are shown in Figure 1 comparing the effect of topical cyclosporin on lacrimination in six normal male beagle dogs, before and after several days of olive oil therapy alone. In

both studies, no treatment was given on days 1 to 3 to establish a baseline. On days 4-10, as graphed by the triangles, one drop of olive oil was administered twice daily (BID) to each eye. On days 11-13, one drop of 2% cyclosporin in olive oil was administered twice daily. A significant increase in tearing was observed. On days 4-10, as graphed by the squares, one drop of 2% cyclosporin in olive oil was administered twice daily. On days 11-13, one drop of olive oil was applied to each eye twice daily. The significant increase in tearing observed over days 4-10 persisted through days 11-13 in the absence of cyclosporin treatment.

The data conclusively demonstrate that topically applied cyclosporin increases glandular function, i.e., lacrimination, in normal eyes.

Example 7: Topically applied cyclosporin: Lacrimomimetic effects and reduction of corneal scars in dogs with KCS.

Twenty five cases (22 bilateral, 2 unilateral cases) of spontaneous KCS were treated with a solution of 2% cyclosporin (CsA) in olive oil, 1 gtt QD - BID, OU, and evaluated for changes in tear production as determined by Schirmer tear test (STT) and for changes in the surface of the globe.

The effects of cyclosporin were twofold: cyclosporin increased tear production in 84% of idiopathic cases of canine KCS and cyclosporin caused marked regression of corneal pathology including superficial granulation tissue, neovascularization and pigmentation, without retarding healing of corneal ulcers. Case histories are summarized in Table 1.

The diagnosis of KCS preceded CsA use by 0-60 months, with an average of 1.1 yr. Prior treatment included artificial tears in 16/25 dogs, oral or topical pilocarpine in 11/25 dogs, oral or topical corticosteroids in 11/25 dogs, topical antibiotics in 9/25 dogs, or no prior treatment in 5/25 dogs.

Contrary to expectation, the longevity of KCS did not correlate inversely with response to therapy. The average STT before administration of cyclosporin was 2.54 mm/min right eye and 2.46 mm/min left eye. During the period in which cyclosporin eyedrops were administered, the mean STT value was 11.38 mm/min right eye and 11.50 mm/min left eye. The average increase in STT was 8.84 mm/min right eye ($t = 7.5$ Student's T -test for related measures, $p<0.0005$), and 9.04 mm/min left eye ($t = 6.7$, $p<0.0005$). 38 eyes were initially diagnosed as having severe KCS (STT 0-4 mm/min). Following treatment, STT values increased by greater than 5 mm/min in 84% of severely affected eyes. Dogs were noted to have increased STT beginning 3 to 56 days after onset of cyclosporin therapy. Of the six eyes (6/38, 16%) determined to be nonresponsive, five were evaluated for only a short period (7 to 35 days). Because STT value in responsive eyes increased with increased frequency and duration of treatment (see Table I, cases 21 and 22), the 84% success rate may be an underestimate.

In six dogs whose STT values increased in response to cyclosporin, treatment was discontinued and the STT values regressed. When cyclosporin was reinstituted, the STT increased back to maximal levels in six hours in one case, and in 1-7 days in the other four cases. In two dogs receiving cyclosporin on

alternate days, the STT values decreased on nontreatment days. Even with sporadic interruptions in administration of cyclosporin treatment, no dog has lost responsiveness to cyclosporin. Many of the cyclosporin responsive dogs previously had been unresponsive to corticosteroids administered topically, subconjunctivally, and parenterally.

In dogs with superficial corneal granulation tissue, continuous use of cyclosporin resulted in a progressive decrease in the abnormal thickness and opacity of the cornea. Even in dogs that did not have an increase in tear secretion, alleviation of the corneal disease was generally marked. Most dogs with dense blinding pigmentation and superficial granulation had marked clearing of the corneas after several months of treatment. Three dogs had corneal ulcers at the onset of treatment with cyclosporin; each healed within 48 hours of onset of treatment. Dogs maintained for prolonged periods (8-12 months) relapsed into KCS within 2-3 days of withdrawal of cyclosporin.

TABLE 1. Previous ocular therapy, and Schirmer tear test (STT) values before and while using, cyclosporin eyedrops in 25 cases of canine keratoconjunctivitis sicca.

Case #, Breed, Sex, Age +/-Keratitis (response to CsA)	Treatment Interval/ Frequency	STT Values Before CsA OD/OS	STT Values With CsA OO/OS
1. Standard Poodle, F,7 yr no keratitis	6 wk/QD	3/3	22/16
2. Cocker Spaniel, F 7 yr, Pigmentary keratitis (marked improvement)	5 mo/BID	0/0	10/13
3. Min. Schnauzer, F/S, 11 yr, Pigmentary keratitis (Marked improvement)	5 wk/QD	2/0	8/1
4. Eng. Bulldog, M, 7yr, Chronic keratitis, visual deficits (Resolved)	7 wk/BID	2/3	13/20
5. Samoyed, F/S, 14 yr, mild keratitis (Resolved)	1 mo/BID	2/11	18/17
6. Shih-tzu, M, 10 yr Pigmentary keratitis, visual deficits (Marked improvement)	13 wk/QD	4/10	13/14
7. Min. Poodle, M, 7 yr, blind dt corneal scarring (Resolved completely)	16 wk/BID	0/0	11/17
8. Mixed breed, F/S, 5 yrs diffuse fluorescein uptake (No staining)	8 mo/BID	0/0	19/17
9. W H W Terrier, F/S 5 yr, Pigmentary keratitis/blind (Improved visual)	4 wks/QD	0/0	13/0
10. Shih tzu M 4 yr, Chronic keratitis OD (Much improved)	26 wk/QD	15/1	15/6

Table 1 continued (page 2)

11. Poodle x, F, 6 yr, Mild superficial keratitis (Improved)	22 wk/QD	0/0	12/18
12. Shih tzu, F, 3 yr, Pigmentary keratitis (Marked Improvement)	17 wk/QD	0/0	3/10
13. Dachshund F, 10 yr, Minimal superficial keratitis (Resolved)	15 wk/BID	5/0	10/2
14. Scottish Terrier, M, 12 yr, Pigmentary keratitis (50% resolution)	9 wk/QD	6/8	12/18
15. Lhasa Apso M/C, 10 yr Pigmentary keratitis (50% resolution)	8 wk/QD	13/1	18/19
16. Lhasa Apso M, 9 yr, Pigmentary keratitis (Slight Improvement)	5 wk/QD	8/16	19/22
17. Min. Schnauzer, M, 11 yr Pigmentary keratitis/ blind (Slight improvement)	9 wk/BID	0/4	5/10
18. Min. Poodle F, 7 yr Marked keratitis (Marked improvement)	5 wk/QD	0/0	2/1
19. Cocker Spaniel, F, yr 1.5 yr, no keratitis	5 wk/QD	7/5	15/10
20. Boston terrier, F/S, 7 yr, no keratitis	6 wk/QD	4/4	14/19
21. Dachshund, M, 3 yr, Mild superficial keratitis (Nearly resolved)	4 wk/BID	1/5	3/17

Table 1 continued (page 3)

22. Peke/Pomeranian X, F/S 5 yr,Pigmentary keratitis 100% (50% improved)	12 wk/BID	0/0	20/18
23. Min. Poodle, M, 9 mo. Chronic keratitis (Marked improvement)	4 wk/QD	4/4	13/13
24. Toy Poodle, F/S, 15 yr Chronic keratitis, visual loss (Marked improvement)	7 wk/BID	3/0	16/0
25. Peke/Pomeranian, F/S, 6 yr, Pigmentary keratitis, blind (Marked improvement/ visual)	11 wk/BID	0/0	8/8

Abbreviations: F (female), M (male), C (castrated), S (spayed), CsA (2% cyclosporin), QD (once daily), BID (twice daily)

Corneal lesions and changes in the corneal lesions were bilateral unless otherwise indicated.

Example 8: Stimulation of tearing in humans suffering from Sjogren's syndrome.

Sjogren's syndrome is characterized by chronic infiltration of the exocrine glands, principally the lacrimal and salivary glands, by mononuclear leukocytes. The process causes the progressive destruction of the glandular tissue and is characterized by the development of keratoconjunctivitis sicca (KCS), or "dry eye". Neither topical nor parenteral treatment using steroids has been completely effective in decreasing irritation of the corneal surface nor in preventing corneal ulcer formation. In fact, topical or parenteral corticosteroids do not enhance lacrimation and can retard healing of corneal ulcers and are therefore considered to be contraindicated by many ophthalmologists.

A human patient with primary Sjogren's syndrome (dry eye with dry mouth) was treated with topical 2% cyclosporin in corn oil. The patient had been treated for years with conventional therapy, artificial tears Q 15 mins. For the past several months his STT were 2-3 mm/5min/eye. (In humans the STT is measured for 5 minutes, unlike the dog where it is measured for only 1 min. However, the expected normal values are the same, i.e., normal is 14 mm, values under 5 mm are indicative of a severe case of dry eye).

Following 9 days of twice daily therapy of both eyes, his STT was 20 and 23 mm/5 min/eye, a significant increase over the pretreatment values. Prior to treatment, the corneas had stained diffusely in both eyes with fluorescein dye, an indication of corneal ulcers. After 9 days of therapy, one eye had

no staining and one eye only stained over 1/3 of the surface.

Three women with severe chronic secondary Sjogren's syndrome were treated for 1 week with BID 2% cyclosporin in corn oil containing 1 mole% alpha tocopherol and 0.005%methyl paraben. All three had abnormal corneas. The first had a nonhealing corneal ulcer which penetrated the full thickness of the surface epithelium covering the cornea. This ulcer healed within two days of onset of therapy. The second had a "contact lens cornea", an indentation at the circumference of the cornea which gives it the appearance of an eye wearing a contact lens, when no lens is present, which is analogous to a scar. The indentation showed evidence of filling in within 7 days of therapy. The third had corneal lesions which also showed improvement within one week. All had increases in the STT.

The results conclusively demonstrate the effectiveness of topically administered cyclosporin in alleviating the symptoms of KCS, promoting normal healing and actually reducing scar tissue on the surface of the eye.

Example 9: Promotion of normal healing of the eye surface without restoration of normal tearing in a dog.

An 11-year old spayed Miniature Schnauzer had been determined to have KCS 8 months before admission. Analysis of a specimen obtained by conjunctival scraping at that time revealed distemper virus. The dog had been treated with 2% pilocarpine, (1 gtt PO q 12 h) which initially caused an increase in the STT to 8 mm/min bilaterally but later lost efficacy, as

the STT decreased to 0 mm/min bilaterally. Treatment had been dexamethasone ointment Q 12 h bilaterally, artificial tears approximately 6 times daily, and petrolatum ointment at bedtime. On admission, ophthalmic observation showed the STT to be 2 mm/min right eye, 0 mm/min left eye, with mucoid conjunctivitis bilaterally, dorsal corneal pigmentation of approximately 40-50% of the corneal surface, and superficial neovascularization extending approximately 6 mm into the dorsal half of the cornea bilaterally (Fig. 2B). The corneal surfaces were modeled irregularly but translucent, and there were no apparent visual deficits. Complete blood count and serum thyroxin were normal and the only abnormality detected on serum profile was an elevated serum alkaline phosphatase (667 mg/dl).

Cyclosporin (2% 1 gtt QD, bilaterally) was prescribed, with artificial tears to be administered as needed. In 4 weeks, the STT had increased to 8 mm/min in the right eye but was still 0-1 mm/min in the left eye. The conjunctivitis had improved, but was still evident in the left eye. However, there was marked improvement of the corneal surface bilaterally (Fig. 2B).

A parotid duct transposition was performed at this time and the lacrimal gland of each third eyelid biopsied. Microscopically both glands were similar, with diffuse often intense periductal and interstitial infiltration of plasma cells and lymphocytes, and fibrosis of the acini and tubules. Focal areas of normal acinar tissue were seen in each gland, and some areas contained dilated tubules lined with flattened epithelium. The results in the preceding examples

establish that topically applied cyclosporin can be used to resolve corneal ulcers even in the absence of restoration of tearing. As dramatically shown by Figure 2A and 2B, the eye surface becomes clearer, smoother, and vision is improved.

Example 10: Comparison of olive oil and corn oil vehicles for cyclosporin for topical ophthalmic use.

Among the animals treated with cyclosporin in olive oil, within four days of beginning treatment, four dogs and one cat had ocular irritation reactions including: hyperemia of the bulbar conjunctiva, corneal surface irregularities with apparent corneal edema, and blepharospasms indicative of ocular pain.

In each case therapy was withdrawn and these symptoms resolved. Therapy with cyclosporin in corn oil was begun in three of the dogs following resolution of the ocular irritation reactions. All three dogs tolerated the corn oil/cyclosporin mixture well.

In the fourth dog, cyclosporin in olive oil was used less frequently than the BID prescription because the owner thought the drug irritated the eyes, but kept using it on an infrequent basis. Following two to three weeks of use, bilateral periocular alopecia occurred and the lids were intensely hyperemic. The cyclosporin in olive oil was discontinued for several weeks. Cyclosporin in corn oil was begun BID bilaterally. The lesions of chronic corneal vascularization and superficial keratitis resolved markedly, the STT increased, and there was no recurrence or irritation or alopecia.

Olive oil and corn oil were also compared in normal, human eyes. The olive oil produced a burning sensation lasting 15 to 60 minutes. The corn oil produced a milder sensation lasting only 1 to 2 minutes.

No side effects have been noted in the any of the 3000 bottles of 2% cyclosporin in corn oil dispensed for animal use, in comparison with the 5 to 10% incidence of side effects in 1000 bottles of 2% cyclosporin in olive oil dispensed for animal use. The substantial difference in tolerance of the two oils is surprising since the chemical nature of olive oil and corn oil is very similar. Tests of the levels of free fatty acids and pH do not indicate any significant differences which could account for the decreased tolerance for olive oil. Substitution of purified olive oil, Sigma Chemical Co., St. Louis, MO, or first press olive oil, for the Berio brand olive oil, obtained from the grocery store, which was used initially, does not eliminate the irritation.

Modifications and variations of the present invention, an improved cyclosporin composition for topical ophthalmic use, will be obvious to those skilled in the art from the foregoing detailed description of the invention. Such modifications and variations are intended to come within the scope of the appended claims.

CLAIMS:

1. A method of enhancing or restoring lacrimal gland function comprising topically administering a cyclosporin.

2. The method of claim 1 for increasing tear production in a tear-deficient eye comprising topically administering a therapeutically effective amount of a cyclosporin to the eye.

3. The method of claim 1 wherein said cyclosporin is administered as a solution, suspension or ointment comprising between approximately 0.01 to 50 weight percent of cyclosporin in a pharmaceutically acceptable excipient.

4. The method of claim 3 wherein said cyclosporin is administered in an amount of 0.1 to 20 weight percent.

5. The method of claim 3 wherein the pharmaceutically acceptable excipient comprises corn oil, olive oil, arachis oil, castor oil, polyoxyethylated castor oil, mineral oil, petroleum jelly, dimethyl sulfoxide, an alcohol, liposome, silicone fluid or a mixture thereof.

6. The method of claim 1 wherein said cyclosporin is Cyclosporin A.

7. The method of claim 1 for increasing tear production in an eye of a patient suffering from an autoimmune dysfunction of the lacrimal glands comprising administering a therapeutically effective amount of a cyclosporin topically to the patient's eye.

8. The method of claim 1 for treating keratoconjunctivitis sicca in a patient comprising the step of administering a therapeutically effective amount of a cyclosporin topically to both of the patient's eyes.

9. The method of claim 1 for treating a disorder caused by excessive immune activity in a lacrimal gland of a patient comprising the step of topically administering to both of the patient's eyes an amount of a cyclosporin sufficient to reduce the immune activity.

10. The method of claim 1 for treating a disorder exacerbated by kerato-conjunctivitis sicca in a patient comprising administering to the patient's eye a therapeutically effective amount of a cyclosporin to promote corneal healing.

11. A topical ophthalmic composition comprising

cyclosporin in a corn oil base.

12. The composition of claim 11 wherein the concentration of cyclosporin is between about 0.01% and saturation.

13. The composition of claim 11 further comprising a compound selected from the group consisting of emollients, viscosity modifying agents, antioxidants, preservatives, antibiotics, antifungals, antivirals, lubricants, surfactants, vasoconstrictors, DMSO, parasympathomimetics, cholinergics, neurotransmitters, lacrimogenic agents, substance P agonists, substance P antagonists, mucolytics, prostaglandin antagonists, lipogenase inhibitors, cyclooxygenase inhibitors, antiinflammatories, oxygen scavengers, hydrating agents, and epitheliotropic agents.

14. The composition of claim 13 wherein the compound is selected from the group consisting of vitamin A, vitamin E, retinoic acid, pilocarpine, hyaluronic acid, polyvinyl alcohol, methylcellulose, methyl paraben, eledoisin, physalaemin, bromhexine, mucosolvan, acetylcysteine, indomethacin, and corticosteroids.

15. The composition of claim 11 comprising 2% cyclosporin in corn oil.

16. The composition of claim 15 further comprising a compound selected from the group consisting of alpha tocopherol and methyl paraben.

17. The composition of claim 11 wherein said composition is encapsulated.

18. The composition of claim 17 wherein said composition is encapsulated within a polymeric matrix.

19. The composition of claim 18 wherein said composition is encapsulated within a polymeric matrix formed of a polymer selected from the group consisting of polyethylene, polystyrene, polypropylene, polyanhydrides, polyorthoester, polylactic acid, and polyglycolic acid.

20. The composition of claim 17 wherein said composition is encapsulated within liposomes.

21. The composition of claim 17 wherein said composition is microencapsulated.

22. The composition of claim 11 wherein said cyclosporin is in a concentration which promotes normal wound healing.

23. The composition of claim 23 wherein said cyclosporin is in a concentration which stimulates or restores lacrimal gland activity.

24. The composition of claim 11 wherein said cyclosporin is in a concentration which suppresses an immune disorder.

FIG.I
Topical Cyclosporine 2%: Effects on Lacrimation

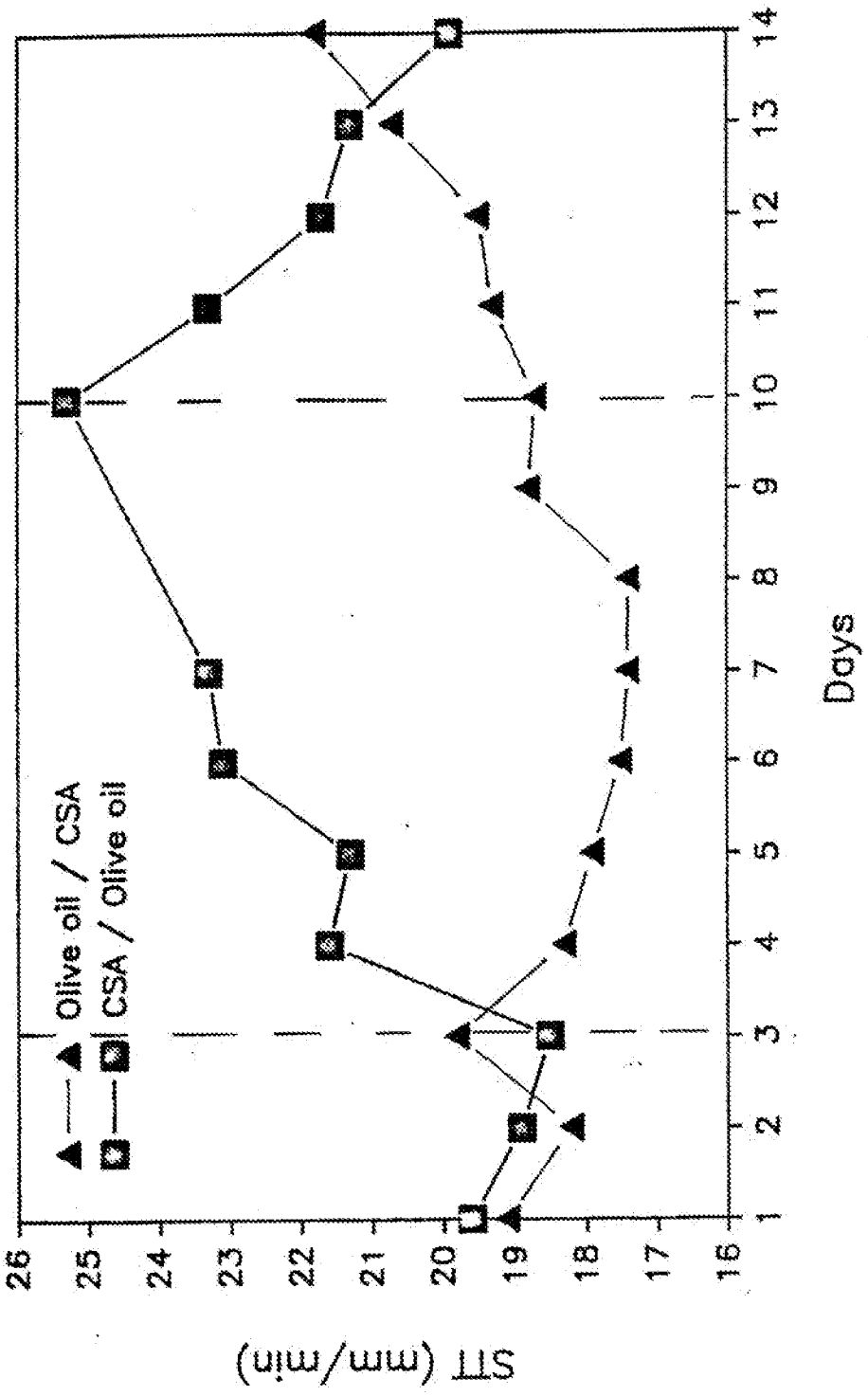


FIG. 2A

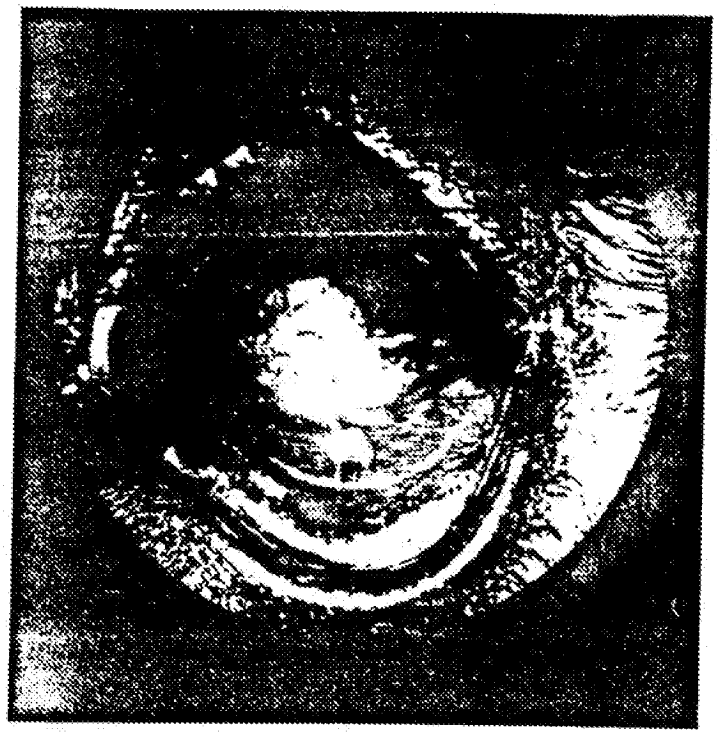
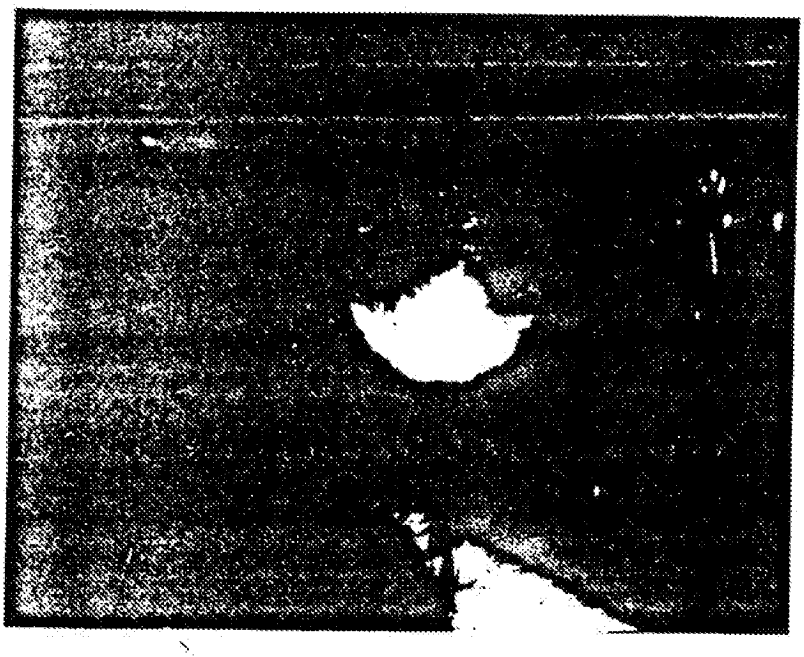


FIG. 2B



INTERNATIONAL SEARCH REPORT

International Application No PCT/US88/03039

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [5]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[4]: A 61 K 9/00; A 61 K 9/08; A 61 K 37/02

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[4]	A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
Y	US, A, 4 649 047 (R KASWAN) 10 March 1987 see claims 5-11, column 3 and 6 --	11,12,15,24
Y	Dialog Information Services, File 351: WPI 81-88, 51 accession no 4331684 (WPI accession no. 86-335072), H. Mizushima: "Eyedrops composed of lipid microspheres contg. remedies for eye troubles", & JP, A, 61249918, published 7 November 1986 --	11,15,17,20, 21
Y	US, A, 3 608 073 (R E PHARES JR) 21 September 1971 see claim 1, example 4 --	11,15
Y	KLIN MBL AUGENHEILK., Vol. 187, 1985, F. Hoffman et al.: "Lokale Behandlung des Hornhauttransplantates beim Menschen mit Cyclosporin A", pages 92-96, see page 95 --	11,12,14,15, 22,24

* Special categories of cited documents: [14]

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

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

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

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

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

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

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

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

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
28th November 1988	28 DEC 1988
International Searching Authority: EUROPEAN PATENT OFFICE	Signature of Authorized Officer: P.C.G. VAN DER PUTTEN

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category*	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
Y	US, A, 4 388 307 (T CAVANAK) 14 June 1984 see column 5, claims 9 and 15 --	11,12,24
Y	WO, A, 85/03640 (THE LIPOSOME COMPANY, INC) 29 August 1985 see page 14, line 32, claims 49 and 76 --	11,17,21
Y	US, A, 4 115 544 (J W SHELL) 19 September 1978 see claims --	11,13,14, 17-19,21
Y	EP, A, 0 224 352 (IMPERIAL CHEMICAL INDUSTRIES PLC) 3 June 1987 see claims 4, 6 and 8 --	11,13,14, 24
Y	DE, A, 3 526 545 (SANDOZ-PATENT-GMBH) 13 February 1986 see pages 4-5 ---	11,22-24

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. [X] Claim numbers 1-10 because they relate to subject matter not required to be searched by this Authority, namely:

Methods for treatment of the human or animal body by therapy (Rule 39.1.iv)

2. [ ] Claim numbers ..... because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claim numbers ..... because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

PCT/US88/03039
SA 24168

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 02/11/88
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A- 4649047	10-03-87	None	
US-A- 3608073	11-05-71	None	
US-A- 4388307	14-06-83	BE-A- 874628	05-09-79
		GB-A- 2015339	12-09-79
		NL-A- 7901703	11-09-79
		FR-A- 2419072	05-10-79
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		JP-A-54132223	15-10-79
		CA-A- 1139667	18-01-83
		CH-A- 636013	13-05-83
		AU-A- 528714	12-05-83
		SE-A- 7901683	08-09-79
		AT-A- 375828	10-09-84
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		US-A- 4708861	24-11-87
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EP-A- 0224352	03-06-87	JP-A-62142110	25-06-87
DE-A- 3526545	13-02-86	EP-A- 0170623	05-02-86
		JP-A-61043120	01-03-86

EPO FORM P0479

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : A61K 9/127, A61F 13/02 — A1

(11) International Publication Number: **WO 93/18752**

(43) International Publication Date: 30 September 1993 (30.09.93)

(21) International Application Number: PCT/US93/02800

(22) International Filing Date: 25 March 1993 (25.03.93)

(30) Priority data:

101387	26 March 1992 (26.03.92)	IL
Not furnished	23 March 1993 (23.03.93)	US

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(81) Designated States: AU, BB, BG, BR, CA, CZ, FI, HU, JP, KR, KZ, LK, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SK, UA, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: TOPICAL AND TRANSDERMAL DELIVERY SYSTEM UTILIZING SUBMICRON OIL SPHERES

(57) Abstract

The present invention relates to a delivery system which includes a bioactive drug or cosmetic substance presented in the form of submicron oil spheres alone, or drugs or cosmetic substances in a combination with the oil spheres in an aqueous suspension or emulsion. Optionally, a skin penetration enhancer may be included in such formulations. Such preparations achieve improved bioavailability and exert larger pharmacological effects than an equivalent dose of the drug or cosmetic formulated in conventional creams, lotions or oleaginous bases.

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TOPICAL AND TRANSDERMAL DELIVERY SYSTEM UTILIZING SUBMICRON OIL SPHERES

FIELD OF THE INVENTION

The present invention relates to the field of drug delivery and, particularly, to the administration of various pharmaceutical or cosmetic agents to a patient through the skin or mucous membranes by the application of innovative, non-irritating topical compositions of these agents in the form of submicron oil spheres.

BACKGROUND OF THE PRESENT INVENTION

The delivery of drugs to the skin and systemically via the skin is hampered by the natural barrier of the stratum corneum. Creams and lotions are classical vehicles for delivering drugs and cosmetics to the skin. These preparations are semi-solid, bi-phasic preparations where oil spheres are dispersed in water. The droplet size of these spheres has not been a concern in conventional pharmaceutically marketed semi-solid creams and lotions. Most commercially marketed medical creams include oil spheres having a size of 5 to 50 microns. For example, VOLTAREN EMULGEL has a droplet size above five microns, as confirmed both microscopically and with photon correlation spectroscopy (Coulter N4MD).

Moreover, the scientific literature does not address the droplet size of the internal oily phase of topically applied emulsions. On the few occasions that refer to topical cream or lotion dosage forms, the indicated droplet size is in the range of a few to tens of microns. For example, U.S. Patent 4,529,601 relates to an eutectic mixture of lidocaine and tetracaine which allegedly produces a good local anesthetic effect that may not be achieved otherwise.

EP 00 63 870 claims good anti-inflammatory activity and high safety of an anti-inflammatory substance in

combination with MCT oil and carboxy vinyl polymer. Again, droplet size is not emphasized.

EP 04 33 132 discloses the topical cosmetic application of vesicles for incorporation of essential oils. It is also possible, according to that patent application, that small droplets of various sizes of the essential oils may be formed.

The cases cited above exemplify numerous patents concerning topical uses of classical macroemulsions, in which the oily droplets are generally well above one micron in diameter. There is also a vast body of prior art utilizing liposome preparations for enhanced dermal penetration of pharmaceuticals (Egbaria & Weiner, Adv. Drug Delivery Rev. 5, 287 (1990)). However, there are inherent problems in formulating stable liposomes, since these structures are lipid bilayers enveloping an aqueous phase. Another type of drug carrier, distinct from both classical emulsions and liposomes are the microemulsions which are usually thermodynamically stable, transparent and have particles consistently below 200 nm (Rosano, H.L., Carallo, J.L. and Lyons, G.B. Microemulsion Systems, Vol. 24, Chap. 16, H.L. Rosano and M. Clause eds. Marcel Dekker, Inc., N.Y. (1987), pp. 271). However, microemulsions contain a large proportion of surfactant to lipid and therefore are inappropriate for dermal applications due to anticipated problems of irritancy.

EP 05 06 197 discloses an aqueous suspension of nanoparticles of at least one lipid and an emulsifier, wherein the nanoparticles have a size of between 50 and 1000 nm. The lipids used therein, however, are either a solid lipid or a mixture of solid lipids.

In the field of topical and transdermal medication and delivery of drugs, much effort has been invested in providing chemical enhancers of drug penetration, such as DMSO and azones. Many of these substances cause irritation and are not desirable due to their toxicity. There remains a need, therefore, for a method and vehicle

which will enable or facilitate efficient transport of poorly soluble drugs through the skin for topical or transdermal use, when provided as an aqueous dispersion of same.

SUMMARY OF THE INVENTION

This invention relates to a composition for topical application of pharmaceuticals or cosmetics comprising submicron size droplets of a drug with oily excipients either alone or dispersed in an aqueous medium. The droplet size is below one micron, and preferably in the range of about 0.05 to 0.5 microns. A semi-solid state is advantageous for the practical application of the dosage form on the skin when used as a cream.

Specifically, the submicron size droplets include about 0.5 to 30% of a first component comprising an oily liquid, about 0.1 to 10% of a second component of an emulsifier and about 0.05 to 5% of a non-ionic surfactant. These droplets are suspended in an aqueous component which forms the continuous phase of an emulsion. The composition provides enhanced topical and/or transdermal systemic effects compared to similar compositions which have larger size droplets. A mean droplet size in the range of between about 0.1 and 0.3 μm is preferred.

The first component is typically present in an amount of about 5 to 20%, and includes oily liquids such as a medium chain triglyceride oil having a chain length of about 8 to 12 carbons, a vegetable oil, a mineral oil, an oil of animal source, a synthetic derivative thereof, or mixtures thereof. To form a viscous composition, the oily liquid may be present in an amount of about 20 to 30%. Alternatively, one or more adjuvants such as gelling agents or thickening agents may be included to increase the viscosity of the composition and form a cream.

The emulsifier may be a phospholipid compound or a mixture of phospholipids, such as lecithin, phosphatidylcholine, phosphatidylethanolamine or mixtures

thereof, in an amount of about 0.2 to 5%. The surfactant may be a non-ionic alkylene oxide condensate of an organic compound which contains one or more hydroxyl groups, such as an ethoxylated alcohol or ester compound, in an amount of about 0.2 to 5%.

The first component may comprise an active ingredient in any one of a number of forms. For simplicity, the active ingredient may be in the form of an essentially water-insoluble oily liquid, such that other oily liquids are either not needed or can be mixed therewith. Instead, the active ingredient can be present as a solid, essentially water-insoluble or slightly water-soluble substance which is partially or fully dissolved or dispersed in one of the oily liquids mentioned above. For such mixtures or dispersions, the active ingredient may be present in an amount of 0.05 to 2.5%.

The active ingredient may be one or more of the following: a steroid, non-steroidal anti-inflammatory drug, antibiotic, tranquilizer, sedative, anti-histaminic, antifungal, antibacterial, antiviral, disinfectant, antipsoriasis agent or a local anesthetic. Specifically, the active ingredient is clotrimazole, bifonazole, tetracycline, miconazole, triamcinolone, amphotericin B, gentamicin, hydrocortisone, iodoxuridine, diphenhydramine, minoxidil, lidocaine, tetracaine and clindamycin.

The composition may also include a dispersion enhancer in an amount sufficient to promote the homogeneity of the composition, or a viscosity enhancing agent in an amount sufficient to impart a semi-solid form to the composition. A preferred viscosity enhancing agent is a physiologically acceptable high molecular weight compound. In addition, a skin penetration enhancer may be added in an amount sufficient to enhance the penetration of the composition through skin after the composition is topically applied thereto.

The invention also relates to a method for obtaining enhanced topical and/or transdermal systemic effects which

comprises formulating one of the compositions described above and topically applying the composition to the skin of a subject, wherein the composition provides enhanced topical and/or transdermal systemic effects compared to the same compositions which have larger size droplets. In this method, the active ingredient may be a barbiturate, benzodiazepine, ketotifen, phenytoin, phenothiazines, cyclosporin, diphenoxylate, diclofenac, dexamethasone, prostaglandin, nifedipine, nitroglycerine, atropine, verapamil, fentanyl, lipophilic peptide or miconazole.

When the method is used to treat a skin condition, the active ingredient may be Vitamin A, Vitamin E, a retinoid, a carotene or benzoyl peroxide, and is applied to alleviate, reduce or prevent dermatological conditions and diseases, including atopic dermatitis, psoriasis, acne and other types of skin inflammations or viral, fungal or bacterial skin infections.

The invention also relates to a method for reducing local irritation produced by pharmaceuticals which induce local inflammatory reactions by topically applying one of the compositions described above. Depending upon the selection of the active ingredient, the method may be used for achieving local anesthesia or analgesia, or for providing general analgesia.

Also, an article, such as an occlusive dressing or adhesive patch, can be used to administer active ingredients such as a steroid, nicotine, nitroglycerine or the like.

BRIEF DESCRIPTION OF THE DRAWINGS

In the following detailed description, reference will be made to the annexed drawings, in which:

Fig. 1 is a graphical illustration of the effects of edema over time during treatment with various diclofenac creams;

Fig. 2 is a graphical illustration of the relative difference over time during treatment with various diclofenac creams; and

Fig. 3 is a graphical illustration of the effects of edema over time during treatment with various naproxen creams.

DETAILED DESCRIPTION OF THE INVENTION

According to the present invention, pharmaceutical and cosmetic compositions are provided in the form of submicron droplets of water-insoluble liquid drugs or cosmetically active substances alone, or drugs or cosmetically active substances with oily excipients and/or solvents in an aqueous medium. These compositions promote percutaneous penetration on topical application and local or transdermal effects. Advantageously, a chemical entity which acts as a skin penetration enhancer may be added to the above for enhancing activity. Thus, the overall pharmacological effect, while using such a chemical enhancer in conjunction with such submicron oil spheres, will be greater than either one of them alone.

In contrast to the prior art, the present invention relates to oily spheres having an average diameter in the submicron range, which are both physically and chemically distinct from the known art of liposome-type lipid vesicles and from the known art of microemulsions in which surfactants or synthetic emulsifiers comprise a large proportion of the composition. In terms of chemical composition, the particles are somewhat similar to classical emulsions, but due to the finely divided particulate nature of the current invention, a significantly enhanced dermal penetration is achieved. We have thus termed these droplets as submicron emulsion oil spheres.

Insoluble drugs or cosmetically active substances may be dispersed in an aqueous medium as solid or liquid particles to form a suspension. One aspect of this

invention relates to drugs or cosmetically active substances that are liquid at room temperature and may be dispersed as liquid, water-insoluble droplets with the desired droplet size range. Otherwise, for drugs or cosmetics which are solid at room temperature and in the shape of powder or crystals, mixtures with an oil are a preliminary required step in order to obtain oily droplets in aqueous suspension.

An emulsion is a dispersion of oil in water ("o/w"), and can be defined as either a macroemulsion or a microemulsion. A macroemulsion is a cloudy turbid composition having an oil-droplet size of 0.5 to 100 μm and is generally thermodynamically unstable. In comparison, a microemulsion is a translucent to transparent composition having a droplet size of 0.005 to 0.5 μm, is thermodynamically stable and is generally self emulsifying. See, e.g., Friberg et al. (1987) Microemulsions Structure and Dynamics, CRC Press Inc., Boca Raton, FL, pp. 154. Also, the proportion of surfactants to oil required to generate microemulsions is generally much higher than in macroemulsions.

The term "submicron" is used herein to mean a size of about 0.05 to 0.5 μm, and preferably about 0.1 to 0.3 μm. Thus, submicron droplets of these sizes would be smaller than those of a classical macroemulsion, which has droplet sizes of above about 0.5 μm, but generally larger than those of a classical microemulsion, which, for practical purposes, has droplet sizes of less than about 0.1 μm.

These submicron droplets can easily be sterilized by filtration, for example, in 0.45 μm and/or 0.22 μm filters, are more stable in long-term storage and can better withstand sterilization in an autoclave.

An oil-in-water emulsion is a dispersion of droplets or colloidal particles in an aqueous medium, with the colloid particles having an oily core surrounded by an interfacial film of the emulsifiers and surface acting

agents or surfactants. For clarity in understanding the present invention, the following terms will be used:

"aqueous phase" - to denote the aqueous solution in which the droplets or colloid particles are dispersed;

"oily phase" - to denote the oily cores of the droplets or colloidal particles; and

"amphiphilic phase" - to denote the interfacial films of emulsifier and surfactant surrounding the oily phase of the droplets or colloidal particles.

In this invention, the oil may be a vegetable oil, a mineral oil, a medium chain triglyceride (MCT) oil, i.e., a triglyceride oil in which the carbohydrate chain has 8-12 carbons, or a combination of two or three of such oils. Although MCT oil can be considered as a component of vegetable oil, it is separately identified herein because of its particular utility as a preferred oil for use in the present droplets. In addition, MCT oil is available commercially. Examples of such MCT oils include TCR (trade name of Societe Industrielle des Oleagineaux, France for a mixture of triglycerides wherein about 95% of the fatty acid chains have 8 or 10 carbons) and MIGLYOL 810 or 812 (trade name of Dynamit Nobel, Sweden for a mixed triester of glycerine and of caprylic and capric acids). Examples of vegetable oils include soybean oil, cotton seed oil, olive oil, sesame oil and castor oil. The mineral oils may be natural hydrocarbons or their synthetic analogs. Oily fatty acids, such as oleic acid and linoleic acid, fatty alcohols, such as oleyl alcohol, and fatty esters, such as sorbitan monooleate and sucrose mono- di- or tri-palmitate, can be used as the oil component, although these are not as preferred as the other oils mentioned above. The excipient oil may also be of animal source or any acceptable synthetic substitute therefore.

The amphiphilic phase comprises the emulsifiers and surfactants. Preferred emulsifiers include a phospholipid compound or a mixture of phospholipids. Suitable

components include lecithin; MONTANOL-68, EPICURON 120 (Lucas Meyer, Germany) which is a mixture of about 70% of phosphatidylcholine, 12% phosphatidylethanolamine and about 15% other phospholipids; OVOTHIN 160 (Lucas Meyer, Germany) which is a mixture comprising about 60% phosphatidylcholine, 18% phosphatidylethanolamine and 12% other phospholipids; a purified phospholipid mixture; LIPOID E-75 or LIPOID E-80 (Lipoid, Germany) which is a phospholipid mixture comprising about 80% phosphatidylcholine, 8% phosphatidylethanolamine, 3.6% non-polar lipids and about 2% sphingomyelin. Purified egg yolk phospholipids, soybean oil phospholipids or other purified phospholipid mixtures are useful as this component. This listing is representative and not limiting, as other phospholipid materials which are known to those skilled in the art can be used.

The surfactant chosen should preferably be non-ionic to minimize irritation, and one skilled in the art can conduct tests to routinely select specific surfactants for this purpose. Generally, the surfactant is a non-ionic alkylene oxide condensate of an organic compound which contains one or more hydroxyl groups. For example, ethoxylated and/or propoxylated alcohol or ester compounds or mixtures thereof are commonly available and are well known to those skilled in the art. Suitable surfactants include, but are not limited to, TYLOXAPOL; POLOXAMER 4070; POLOXAMER 188; POLYOXYL 40 Stearate; EMULFOR EL-620, POLYSORBATE 80, and POLYSORBATE 20, as well as various compounds sold under the trade name TWEEN (ICI American Inc., Wilmington, Delaware, U.S.A.), PLURONIC F-68 (trade name of BASF, Ludwigshafen, Germany for a copolymer of polyoxyethylene and polyoxypropylene). At this time, PLURONIC F-68 and the POLOXAMER 188 are preferred. The TYLOXAPOL and TWEEN surfactants are also preferred because they are FDA approved for human use.

The aqueous component will be the continuous phase of the emulsion and may be water, saline or any other

suitable aqueous solution which can yield an isotonic and pH controlled preparation.

In addition, the compositions of the invention may also comprise conventional additives such as preservatives and antioxidants. Typical preservatives include Thimerosal, chlorbutanol, and methyl, ethyl, propyl or butyl parabens. The preferred oil phase antioxidant is α-tocopherol or α-tocopherol succinate. The aqueous phase may also include an antioxidant or a chelating agent of a polyamine carboxylic acid such as ethylene diamine tetraacetic acid ("EDTA"), or a pharmaceutically acceptable salt thereof.

The drug, cosmetic, or active ingredient, alone or with the oily excipients, are mixed with a sufficient amount of surfactants and/or dispersing and suspending agents to allow dispersibility within the desired size range in aqueous medium. The surfactant(s) may be any pharmaceutically acceptable one(s) that enable(s) adequate dispersibility and stability of the droplets in aqueous medium, in a form of stable submicron size-range droplets. The drug, with or without oily excipients, is vigorously mixed with an aqueous solution that may contain surfactants, to result in submicron droplets of the drug and excipients. If needed, a high shear mixer and a high pressure homogenizer are employed to achieve the desired droplet size. Sonication is an alternative method to achieve the desired submicron droplet size.

Highly efficient delivery of the submicron droplets to the skin is obtained with a dosage form which is semi-solid. To produce a semi-solid composition, many methods may be applied; addition of gelling agents, such as carbopols and adjusting to a pH, organic thickening agents such as polyvinyl pyrrolidone (PVP) or a hydroxypropyl methyl cellulose (HPMC) polymer, or cetostearyl alcohol and other waxes that may rigidify, solidify or increase the viscosity of the aqueous dispersion to the desired consistency level. Inorganic thickening agents such as

fumed silica (AEROSIL or CABOSIL), alumina, clay or other similar colloidal particles can be used to increase the viscosity of the formulation. It is also possible to use oil concentrations on the higher end of the disclosed range to achieve higher viscosity compositions. However, use of greater than 30% oil causes difficulty in achieving the desired droplet size.

Chemical skin penetration enhancers may be incorporated into the formulation to enhance penetration of the active ingredient through the skin. In this regard, DMSO, decyl methyl sulfoxide, N-dodecyl pyrrolidone, decanol, dodecanol, an organic acid such as oleic acid, or the like can be used. Overall pharmacological effects achieved with the combination of chemical enhancers and submicron droplets are greater than for either component used by itself.

This invention provides submicron spheres (or droplets) that are an insoluble assembly of unique entities dispersed in an aqueous phase with the aid of appropriate surfactants or emulsifying agents. The emulsifying agent and surfactant form a protective layer around the droplets thus enabling efficient dispersion and suspension of the oily phase in water. This layer is a monolayer, polar by virtue of the surfactants. The present droplets are neither vesicles nor liposomes since no bilayers resembling the bilayer forming the living cell wall is formed. Micelles may be formed and be present, but may account for only a very small fraction of the surfactants and insoluble matter of the formula and in negligible quantities, usually less than about 1% of the total mass of insoluble matter and surfactants or dispersing agents.

Experiments carried out and measurements by means of photon correlation spectroscopy (Coulter N4MD) and laser diffraction (Coulter LS130) indicated that the droplet size in the compositions of the invention is in the size range of about 0.02 to about 0.5 microns. Preferably, the

size range is mainly in the 0.1 to 0.3 micron (i.e., 100 to 300 nm) range.

Depending on the inherent activity of the active ingredient its quantity has to be adjusted for each specific drug.

Compositions according to the invention for topical application to obtain a topical or systemic effect, contain, for example as active ingredient: steroids or non-steroidal anti-inflammatory drugs, antibiotics, antifungals, antivirals, antihistamines, antineoplastics or local anesthetics. Specific examples would include substances such as clotrimazole, bifonazole, tetracycline, miconazole, triamcinolone, amphotericin gentamicin, hydrocortisone, iodoxuridine, diphenhydramine, minoxidil, lidocaine, tetracaine and clindamycin.

For systemic effects, the following categories of drugs are suitable: hypnotics, sedatives, anxiolytics, antidepressants, anticonvulsants, anti-inflammatory drugs, anti-fungals, prostanoids, prostanoid agonists, prostanoid antagonists, analgesics, hormones and vitamins. Specific examples would include lipophilic peptides, barbiturates, benzodiazepines, phenothiazines, cyclosporin, diphenoxylate, physotigmine, tacrine, diclofenac, dexamethasone, prostaglandins, nifedipine, nitroglycerine, atropine, verapamil, fentanyl, lipophilic peptides, ketotifen, phenytoin, miconazole and ketoconazole.

For cosmetic effects, the active ingredient might be for example Vitamin A, Vitamin E, a polyunsaturated fatty acid such as eicosapentanoic acid, retinoids, carotenes and benzoyl peroxide.

Instead of a viscous composition, the droplets of the invention can be topically and transdermally applied by an article which includes the droplets, an active ingredient and a support for retaining the composition thereon. The support would include an adhesive for securing the article to the skin of a subject. A wide variety of active ingredients, including steroids such as estradiol,

nicotine or nitroglycerine, can be administered by this article, which would generally be in the form of an occlusive dressing or an adhesive patch.

In the following description, concentrations will be indicated by % which denotes the concentration by weight of the component per 100 units volume of entire composition. All indicated concentrations should be understood as standing each by itself, and not cumulative. It should be appreciated by the artisan, however, that there is some dependency between the concentrations of the components, e.g., higher concentrations of the oil will generally require higher concentrations of the emulsifier and surfactant.

The emulsion used in the compositions of the present invention may comprise about 0.5 to 30% oil, about 0.1 to 10% emulsifier and about 0.05 to 5% surfactants. Generally, increasing the concentration of the non-aqueous phase, i.e., the combined concentration of the oily and the amphiphilic phase, increases viscosity of the composition. In order to obtain a viscous composition, the concentration of the oil could be increased to about 20 to 30%. As noted above, another way to increase the viscosity is to add a pharmaceutically acceptable gelling or thickening agent, such as Carbopol or the like. These viscous compositions are useful as creams or ointments.

Preferred concentrations of the components are as follows: about 5 to 20% oil; about 0.2 to 5% of the emulsifier, with about 0.2 to 1% being particularly preferred; and about 0.2 to 5% for the surfactant, with about 0.2 to 1% being particularly preferred. For a viscous composition, about 0.2 to 15% of the gelling or thickening agent can be included.

The drug or cosmetic agent (the active ingredient) is present in an amount of about 0.05 to 5% by weight of the composition, preferably about 0.1 to 2.5%. Depending upon whether the active ingredient is hydrophilic or hydrophobic, it will be physically present in the oily

phase or the aqueous component. Also, the pH of these compositions should be in a range which is suitable for the stability of the active ingredient, but silghtly acidic or as close to neutral as possible for compatibility with the skin.

The invention is illustrated with reference to the above-mentioned examples, which are to be construed in a strictly non-limitative manner.

EXAMPLES

The enhanced topical and transdermal effects of drugs administered in emulsions comprised of submicron size droplets in comparison to standard cream formulations and commercial preparations was established in several test systems. Antiinflammatory agents were tested utilizing the carrageenan induced paw edema in guinea pigs. Tranquilizers were assessed in guinea pigs utilizing behavioral tests indicative of sedation. Local anesthetics were tested in healthy human volunteers on the basis of loss of local sensation following application of various preparations.

The following summarizes the systems used and results obtained with the formulations tested. The following cases are to be construed as examples in a strictly non-limitative manner.

EXAMPLE 1: A diazepam submicron cream preparation was made as follows: 0.5 g of diazepam are mixed with 9 g of medium chain triglyceride (MCT) oil and 1 g of lecithin until an homogeneous oily phase is achieved. The oily phase is then dispersed into 90 ml of an aqueous phase which includes 2 g of PLURONIC F-68 and 0.1 g of a mixture of methyl and propyl parabens by initial mixing with a magnetic stirrer followed by a high shear mixer (Polytron K3000) for 5 minutes at 20,000 RPM to form an emulsion. Further treatment of the emulsion is conducted in a high pressure homogenizer (APV - Gaulin) at 800 bar for 6

minutes (about 10 cycles) at 45-55°C. Thereafter, the emulsion was cooled to room temperature and the mean droplet size was measured size to be 120 nanometers having a very narrow distribution with practically no droplets above one micron (less than 0.5%) being detected. CARBOPOL is added to a final concentration of 0.3%. Finally, the pH is elevated with sodium hydroxide to 7 and a semi-solid submicron droplet preparation is achieved.

EXAMPLE 2: Example 1 was repeated using 6 g MCT oil and 3 g oleic acid. The mean droplet size was found to be 150 nanometers.

EXAMPLE 3: (Comparative) A formulation was made in the same manner as Example 2 but without the procedure to reduce the droplet size. The final droplet size was between 5 and 50 microns.

EXAMPLE 4: (Comparative) A conventional diazepam cream was prepared as follows: diazepam 0.5 g, MCT oil 9 g, emulsifying wax 9 g, hot water 81 ml. A classical technique was used whereby the wax was melted, the oil and drug were added, and then the hot water was added with vigorous stirring. The mean droplet size of the cream was between 5 and 50 microns.

EXAMPLE 5: The systemic tranquilizing effect of topically applied diazepam creams of the first four examples were investigated and compared to the systemic administration of diazepam, as follows.

Materials and Methods

Guinea pigs, males and females, having a body weight of about 250 g were shaved 24 hours before application of the creams. The following formulations were applied: (a) diazepam 0.5% - small drops (Example 1); (b) diazepam 0.5% - small drops with oleic acid (Example 2);

(c) diazepam 0.5% - large drops with oleic acid (Example 3); (d) diazepam 0.5% in a conventional cream of large droplet size (Example 4). Five grams of each preparation was applied on the shaved area, i.e., about 20 cm_2 of each guinea pig.

Commercially available parenteral preparations were also used as controls, as follows: (e) diazepam 5 mg/ml (vials of 2 ml), 10 mg/kg administered intramuscularly, and (f) the same preparation administered subcutaneously (10 mg/kg).

Clinical appearance, following application or injection, was checked and recorded. The onset and termination times of the effects were recorded.

Three basic behavioral tests, indicating level of sedation, were used

(a) Righting reflex: animals are positioned on their back and the time that is required to return to normal position was recorded. Three levels of sedation are scored: low (score 1) - animal returns immediately to normal position; moderate (score 2) - up to 30 seconds are needed to return to normal position; severe-deep (score 3) - more than 30 seconds are needed to regain normal position.

(b) Step test: animals are positioned on a 5 cm high step, with the forelegs on the step. The time interval for changing this position was measured for each animal. The same course of time that was used for scoring of righting reflex was used here.

(c) Animals were positioned on their hind legs, their forelegs put on the top of their cage (20 cm high). The time interval for changing this position was measured for each animal. The same scoring methodology as above was used here.

(d) A total aggregate score for each animal was calculated to show the state of sedation for this study.

The results are shown in Table 1. It was found that topically applied diazepam is very effective when delivered in submicron droplets. A systemic-like effect

may be achieved with this preparation, but the same dose in large droplet formulation was not effective. Also, the inclusion of oleic acid in the formulation reduces the time for onset of activity and duration.

Table 1: Efficacy of Different Topical and Systemic Diazepam Formulations in Guinea Pigs.

Treatment	No. of Animals	Score	Time of Activity (min)
Diazepam, i.m., 10 mg/kg	4	39.0	15-120
Diazepam, s.c., 10 mg/kg	4	52.8	15-120
Diazepam 0.5% cream (5 g) submicron drops	5	47.5	45-240
Diazepam 0.5% cream (5 g) submicron drops with oleic acid	6	43.7	30-120
Diazepam 0.5% cream (5 g) large drops with oleic acid	5	3.0	--
Classical diazepam 0.5% cream (5 g)	5	--	--

EXAMPLE 6: Example 1 was repeated using TWEEN-80 instead of PLURONIC F-68. The mean droplet size was 170 nanometers and an enhanced tranquilizing effect substantially equivalent to that of Example 1 was detected.

EXAMPLE 7: Example 1 was repeated using EMULFOR EL-620 instead of PLURONIC F-68. The mean droplet size was found to be 100 nanometers and the activity was comparable to that of Example 1.

EXAMPLE 8: Example 1 was again repeated except that the formulation contained 20 g MCT oil. The mean droplet size was found to be 210 nanometers, but the activity was significantly increased in comparison to Comparative Example 4 and was as good as that of Example 1.

EXAMPLE 9: Example 1 was repeated except that 20 g MCT oil and 1 g diazepam were used. The mean droplet size was 250 nanometers and the preparation exhibited increased activity compared to that of Comparative Example 4 which was at least as good as that of Example 1.

EXAMPLE 10: Example 1 was again repeated but 1 g oleic acid was included. The mean droplet size was 100 nanometers and the composition was found to be as active as that of Example 1.

EXAMPLE 11: Example 1 was repeated using TWEEN-65 instead of lecithin. The mean droplet size was found to be 250 nanometers and the formulation was much more active (a score of 35) than that of Example 4.

EXAMPLE 12: Example 1 was repeated using MONTANOL-68 instead of lecithin. The mean droplet size was found to be 300 nanometers and the formulation was much more active (a score of 30) than that of Example 4.

EXAMPLE 13: Example 1 was repeated using soybean oil instead of MCT oil. The mean droplet size was found to be 180 nanometers and the formulation was as active as that of Example 1 (a score of 45).

EXAMPLE 14: Example 1 was repeated with the addition of α-tocopherol as an antioxidant. The mean droplet size was found to be 100 nanometers and the formulation was as active as that of Example 1. This formulation was also found to be suitable for administering oxidation sensitive drugs such as nifedipine.

EXAMPLES 15-16: Example 1 was again repeated but 2 g of AEROSIL silica and hydroxypropyl cellulose, respectively, were included instead of CARBOPOL, and the pH was adjusted to 5.5. The mean droplet size for each example was found

to be 180 nanometers and the compositions were found to be as active as that of Example 1.

EXAMPLE 17: An indomethacin submicron cream preparation was made a follows: indomethacin 0.5 g, MCT oil 17 g, lecithin 0.8 g, EMULFOR EL-620 1.6 g, CARBOPOL 1.7 g and water 78 ml. The procedure of Example 1 was followed to obtain a mean droplet size of 130 nanometers.

EXAMPLE 18: (Comparative) A conventional, large droplet size indomethacin cream was prepared as follows: indomethacin 0.5 g, MCT oil 15 g, emulsifying wax 9 g, water 75 ml. The composition was prepared as in Example 2. The mean droplet size was found to be between 5-50 μm.

EXAMPLE 19: The topical anti-inflammatory effect of topically-applied indomethacin creams of Examples 17-18 were investigated and compared for their anti-inflammatory effect versus systemic administration.

Animals and Materials

(a) Guinea pigs (250 g).

(b) Indomethacin 0.5% in submicron cream (Example 17).

(c) Indomethacin 0.5% in conventional cream (Example 18).

(d) Indomethacin 0.5% in solution.

Study Procedure

(a) All animals received an injection of 0.1 ml carrageenan 0.1% into the hind paw. Measurements were taken from the area of injection and followed for up to 5 hours.

(b) The above creams were administered at carrageenan administration site and the solution of indomethacin was administered intramuscularly 15 minutes prior to carrageenan administration.

(c) The circumference of the paw was again measured and the change in size was compared for the different treatments. The volume changes were measured by a plethysmometer (Ugo, Basel).

The results presented in Table 2 demonstrate that a local application of indomethacin in submicron droplet cream was the most effective in reducing the edema caused by the carrageenan injection, and was more effective than large droplets of indomethacin cream or the same dose administered intramuscularly.

Table 2: Performance of Different Indomethacin Formulations in Paw Edema Model in Guinea Pigs

Treatment	No. of Animals	Average change of circumference, percent — Hours after carrageenan injection				
		1	2	3	4	5
Control (Carrageenan)	4	17	32	61	80	83
Indomethacin 0.5%, in cream small droplets	4	0	7.3	24	32	36
Indomethacin in cream, Large droplets	4	16	55	67	47	39
Indomethacin 10 mg/kg i.m. in solution	4	19	22	25	36	33

EXAMPLE 20: A lidocaine submicron cream preparation was made as follows: lidocaine 4 g, MCT oil 6.5 mg, lecithin 0.8 g, EMULFOR EL-620 1.5 g, water 78 ml and CARBOPOL 1.7 g. Again, the procedures were the same as in Examples 1 and 17. The mean droplet size was found to be 160 nm.

EXAMPLE 21: (Comparative) A conventional, large droplet size lidocaine cream was prepared as per Example 3 except with lidocaine 4 g, MCT oil 5.5 g, emulsifying wax 8 g, petroleum 14 g, water 69 ml. The mean droplet size was greater than 50 microns.

EXAMPLE 22: A small droplet size eutectic local anesthetic was prepared as follows. 2.2 g lidocaine,

2.2 g tetracaine, 2 g PLURONIC F-68, 89 g water, and carbopol 4.5 g. The preparation procedure was as per Example 1, the pH was adjusted to 7.5 and the mean droplet size was found to be 250 nanometers.

EXAMPLE 23: (Comparative) A conventional, large droplet size eutectic local anesthetic was prepared as follows. The same formulation as in Example 22 was prepared but without the procedure to reduce the droplet size. The final droplet size was found to be between 20-100 μm.

EXAMPLE 24: The local anesthetic effect of topically applied lidocaine creams of Examples 20-23 were investigated and compared. Each preparation was applied to the forearm of 4 male human volunteers and the degree of local anesthesia with time was monitored. A gentle touch was made with a sharp needle and the sensitivity of an adjacent (untreated) area was compared to the application site to estimate the effectiveness of the tested preparation. The experiment was blind for the volunteers. The sensitivity at the site of application was given a score of intensity of 1 to 4 and an average dosage form performance was calculated. The results are shown in Table 3.

Table 3: Average Score (Effectiveness) of Small vs. Large Droplet Size Lidocaine Creams

Droplets	Small	Large
Example #	19	20
Drug Conc., %	4	4
Droplet size, um	0.25	10-50
Delay, hours	0.5	1
Duration, hours	4.5	3
Effectiveness (Average Score)	28	17

These data show that lidocaine alone in oleaginous base or in regular cream of emulsifying wax (i.e., one having a droplet size of greater than 50 microns), was not effective as local anesthetic. However, the small droplet size preparation of lidocaine provided local anesthesia and performed better than larger droplet size which was very poor. Moreover, the small droplet size eutectic mixture performed better than the same formulation but with large droplet size, as shown in Table 4.

Table 4: Average Score (Effectiveness) of Small vs. Large Droplet Size Eutectic Local Anesthetic Mixture Creams

Droplets	Small	Large
Example #	21	22
Drug Conc., %	4.4	4.4
Droplet size, μm	0.295	20-100
Delay, hours	0.3	0.5
Duration, hours	6	4.5
Effectiveness (Average Score)	58	40

EXAMPLE 25: A diclofenac submicron cream was prepared as follows: Oil phase - diclofenac diethylammonium 12.2 g, MCT oil 170 g, LIPOID E-80 30 g, α-tocopherol succinate 0.4 g; Aqueous phase - EDTA disodium salt 1 g, EMULFOR EL-620 25 g, glycerol 17.5 g, preservatives (methyl and propyl parabens) 0.5 g, reverse osmosis purified water to 1000 g.

The composition was prepared as follows. The emulsion was prepared by combining the oil and aqueous phases together with a magnetic stirrer for 5 minutes, followed by a high-speed, high-shear mixer (Polytron K3000) for 5 minutes at 3000 RPM. The emulsion which was obtained was treated by a high pressure homogenizer (APV-Gaulin) at 800 bar (6 minutes, about 10 cycles) at

45-55 °C. After homogenization, the emulsion was allowed to cool to room temperature, the particle size distribution was determined and the emulsion was then filtered through a 0.45 micron pore size filter (Unimodal) size after 8 cycles/800 bar is 120 ± 30 nm, with the dust before filtration being in the range of 2-4%.

The cream formulation was prepared as follows: To 1000 g of the emulsion, 50 g of 10% CARBOPOL 940, which was pre-swollen in purified water, was added and mixed thoroughly with the Polytron K3000 device at 5-10,000 RPM for 2-3 minutes. Pure triethanolamine was added dropwise with mixing to adjust the pH to 6-6.5. A final mixing with the Polytron K3000 device at the same conditions produces a cream which contains 1.16% Diclofenac DEA (which is equal to a 1% solution of sodium diclofenac). After pH, viscosity and drug content testing, the cream is packed into aluminum tubes.

EXAMPLE 26: A topical edema treatment by diclofenac in different droplet size formulations was evaluated. A formulation containing submicron droplets of diclofenac (Example 25) was compared to standard preparation using the carrageenan paw edema model (guinea pigs). Carrageenan (0-1 ml of 0.1% solution) was injected into hind paw (at time=o). Start size of edema at time zero was taken as 100% level. Surface of edema was treated immediately after carrageenan injection by test preparations:

a) 1.16% diclofenac diethylammonia (equivalent to 1.0% Diclofenac sodium) in submicron emulsion (90-150 nm droplets) (Example 25).

b) VOLTAREN EMULGEL (Ciba-Geigy) - as a reference composition with known activity. c) 1.16% diclofenac diethylammonia in large droplets (5-10 μm).

Changes in volume were made using a plethysmometer (Ugo, Basel), and the results are shown in Fig. 1.

EXAMPLE 27: A piroxicam small droplet cream was prepared from the following components: piroxicam 0.25 g, MCT oil 9.5 g, lecithin 0.5 g, Tween-80 0.5 g, water 38.4 g, carbopol 0.2 g, triethylamine 0.2 g. The composition was prepared as in Example 1. The mean droplet size was found to be 127 nm.

EXAMPLE 28: (Comparative) A conventional piroxicam (large droplet) cream was prepared as follows: piroxicam 0.178 g, MCT oil 5 g, cetosteryl alcohol 2.7 g, sodium dodecylsulfate 0.3 g, water 27 g. After melting together the cetostearyl alcohol with sodium dodecylsulfate, the MCT oil was added. Piroxicam was mixed with ready hot oil phase, and then 27 ml of boiling water was added and mixed thoroughly. After cooling to room temperature, the cream was obtained.

EXAMPLE 29: A topical edema treatment by piroxicam in different emulsion formulations was studied. The submicron droplets of piroxicam (Example 27) was compared to standard cream (Example 28) using the carrageenan paw edema model (guinea pigs) of Example 26. As shown in Fig. 3, piroxicam in the cream of Example 27 demonstrates relatively low antiinflammatory activity, while the formulation of Example 26 was found to be much more effective.

EXAMPLE 30: A topical naproxen submicron cream was prepared from the following components: naproxen 1g; Miglyol 810 17g; LIPOID E-80 3g; α-tocopherol succinate 0.04g; EMULFOR EL-620 2.5g; glycerol 1.75g; EDTA disodium dihydrate 0.1g; CARBOPOL 940 0.5g; triethanolamine 0.5g; and pure water to 100g. The naproxen, MIGLYOL 810, LIPOID E-80 and α-tocopherol succinate were mixed together at 45°C until completely dissolved to form an oil phase. The EMULFOR, glycerol and EDTA were dissolved in water and mixed thoroughly with the oil phase in a high shear mixer

(Polytron K3000) for 5 minutes at about 20,000 RPM to form an emulsion. Further treatment of the emulsion is conducted in a high pressure homogenizer (APV - Gaulin) at 800 bar for 8 cycles to a droplet size of about 100-150 nm. After filtration through a 0.45 micron filter, CARBOPOL in the form of a preswollen gel (10% in water) was added and mixed in the Polytron device for 2 minutes at 5000 RPM. The triethanolamine was added to a final pH of 5.5-6.5 and the formulation was mixed in the Polytron device until a homogeneous cream was obtained.

EXAMPLE 31: A topical edema treatment by naproxen in different formulations was studied. A submicron droplet cream of naproxen (Example 30) was compared to a standard cream using the carrageenan paw edema model (guinea pigs) of Examples 26 and 29 for the following formulations:

a) Naproxen in a submicron emulsion (100-150 nm droplets as per Example 30) applied topically.

b) Naproxen in a conventional cream (droplets larger than 20 microns) applied topically.

The results are illustrated in Fig. 3

THE CLAIMS

What is claimed is:

1. A composition for topical application of pharmaceuticals or cosmetics comprising submicron size droplets comprising about 0.5 to 30% of a first component of an oily liquid, about 0.1 to 10% of a second component of an emulsifier and about 0.05 to 5% of a non-ionic surfactant, said droplets having a mean droplet size in the range of 0.05 to 0.5 μm, wherein said composition provides an enhanced topical and/or transdermal systemic effect compared to the same compositions which have larger size droplets.

2. The composition of claim 1 wherein the mean droplet size is between about 0.1 and 0.3 μm.

3. The composition of claim 1 wherein the first component comprises a medium chain triglyceride oil having a chain length of about 8 to 12 carbons, a vegetable oil, a mineral oil, an oil of animal source, a synthetic derivative thereof, or mixtures thereof.

4. The composition of claim 3 wherein the first component is present in an amount of about 20 to 30% to form a viscous composition.

5. The composition of claim 1 wherein the emulsifier is a phospholipid compound or a mixture of phospholipids.

6. The composition of claim 5 wherein the phospholipid is lecithin, phosphatidylcholine, phosphatidylethanolamine or mixtures thereof.

7. The composition of claim 5 wherein the emulsifier is present in an amount of about 0.2 to 5%.

8. The composition of claim 1 wherein the surfactant is a non-ionic alkylene oxide condensate of an organic compound which contains one or more hydroxyl groups.

9. The composition of claim 8 wherein the surfactant is an ethoxylated alcohol or ester compound.

10. The composition of claim 9 wherein the non-ionic surfactant is present in an amount of about 0.2 to 5%.

11. The composition of claim 1 which further comprises an active ingredient in an amount of 0.5 to 5%.

12. The composition of claim 1 wherein the first component comprises an active ingredient in the form of an essentially water-insoluble oily liquid.

13. The composition of claim 12 wherein the active ingredient is present with another oily liquid.

14. The composition of claim 1 wherein the first component comprises an active ingredient in the form of a solid, essentially water-insoluble or slightly water-soluble substance which is at last partially dissolved or dispersed in the oily liquid.

15. The composition of claim 1, further comprising an aqueous component which forms the continuous phase of an oil-in-water emulsion, with the droplets forming the oil phase of the emulsion.

16. The composition of claim 1, further comprising a dispersion enhancer in an amount sufficient to promote the homogeneity of the composition.

17. The composition of claim 1 further comprising a viscosity enhancing agent in an amount sufficient to impart a semi-solid form to the composition.

18. The composition of claim 17, wherein the viscosity enhancing agent is a physiologically acceptable organic or inorganic thickening agent

19. The composition of claim 18, wherein the viscosity enhacing agent is an organic thickening agent comprising a high molecular weight organic compound or an inorganic thichening agent comprising colloidal particles.

20. The composition of claim 1 further comprising a skin penetration enhancer in an amount sufficient to enhance the penetration of the composition through skin after the composition is topically applied thereto.

21. The composition of claim 20, wherein the skin penetration enhancer is DMSO, decyl methyl sulfoxide,

N-dodecyl pyrrolidone, decanol, dodecanol or an organic acid.

22. The composition of claim 11, wherein the active ingredient is at least one lipophilic peptide.

23. The composition of claim 11, wherein the active ingredient is at least one steroid, non-steroidal anti-inflammatory drug, antibiotic, tranquilizer, sedative, anti-histaminic, antifungal, antibacterial, antiviral, disinfectant, antipsoriasis, immunosuppressant, vasodilator or vasoconstrictor agent or a local anesthetic.

24. The composition of claim 23 where the active ingredient is clotrimazole, bifonazole, tetracycline, miconazole, triamcinolone, amphotericin B, gentamicin, hydrocortisone, iodoxuridine, diphenhydramine, minoxidil, lidocaine, tetracaine and clindamycin.

25. A method for enhanced topical and/or transdermal, systemic effects which comprises formulating the composition of claim 11 and topically applying the composition to the skin of a subject, wherein the composition provides enhanced topical and/or transdermal, systemic effects compared to the same compositions which have larger size droplets.

26. The method of claim 25, which further comprises selecting the active ingredient to be a lipophilic peptide, a prostanoid, a prostanoid agonist, a prostanoid antagonist, a polyunsaturated fatty acid or an anti-fungal agent prior to formulating the composition.

27. The method of claim 25, which further comprises selecting the active ingredient to be a barbiturate, benzodiazepine, ketotifen, phenytoin, phenothiazines, cyclosporin, physotigmine, tacrine, diphenoxylate, diclofenac, dexamethasone, prostaglandin, nifedipine, nitroglycerine, atropine, verapamil, fentanyl, miconazole or ketoconazole prior to formulating the composition.

28. The method of claim 25, which further comprises selecting the active ingredient to be Vitamin A, Vitamin

E, eicosapentanoic acid, a retinoid, a carotene or benzoyl peroxide.

29. A method for treating the skin of a subject which comprises formulating the composition of claim 11 and topically applying the composition to the skin of a subject, wherein the composition provides enhanced topical and/or transdermal systemic effects compared to the same compositions which have larger size droplets to alleviate, reduce or prevent dermatological conditions and diseases, including atopic dermatitis, psoriasis, acne and other types of skin inflammations or viral, fungal or bacterial skin infections.

30. A method for reducing local irritation produced by pharmaceuticals which induce local inflammatory reactions which comprises formulating the composition of claim 11 and topically applying the composition to the skin of a subject, wherein the composition provides enhanced topical and/or transdermal systemic effects compared to the same compositions which have larger size droplets.

31. A method for achieving local anesthesia or analgesia, or for providing general analgesia which comprises formulating the composition of claim 11 and topically applying the composition to a subject.

32. An article for topically and transdermally applying an active ingredient which comprises the composition of claim 11 and a support for retaining the composition thereon, said support including an adhesive for securing the article to the skin of a subject.

33. The article of claim 32 wherein the active ingredient is a steroid, nicotine or nitroglycerine.

34. The article of claim 32 in the form of an occlusive dressing or an adhesive patch.

DICLOFENAC ANTIINFLAMMATORY ACTIVITY IN VOLTAREN EMULGEL AND SME CREAM (Carrageenan paw edema model)

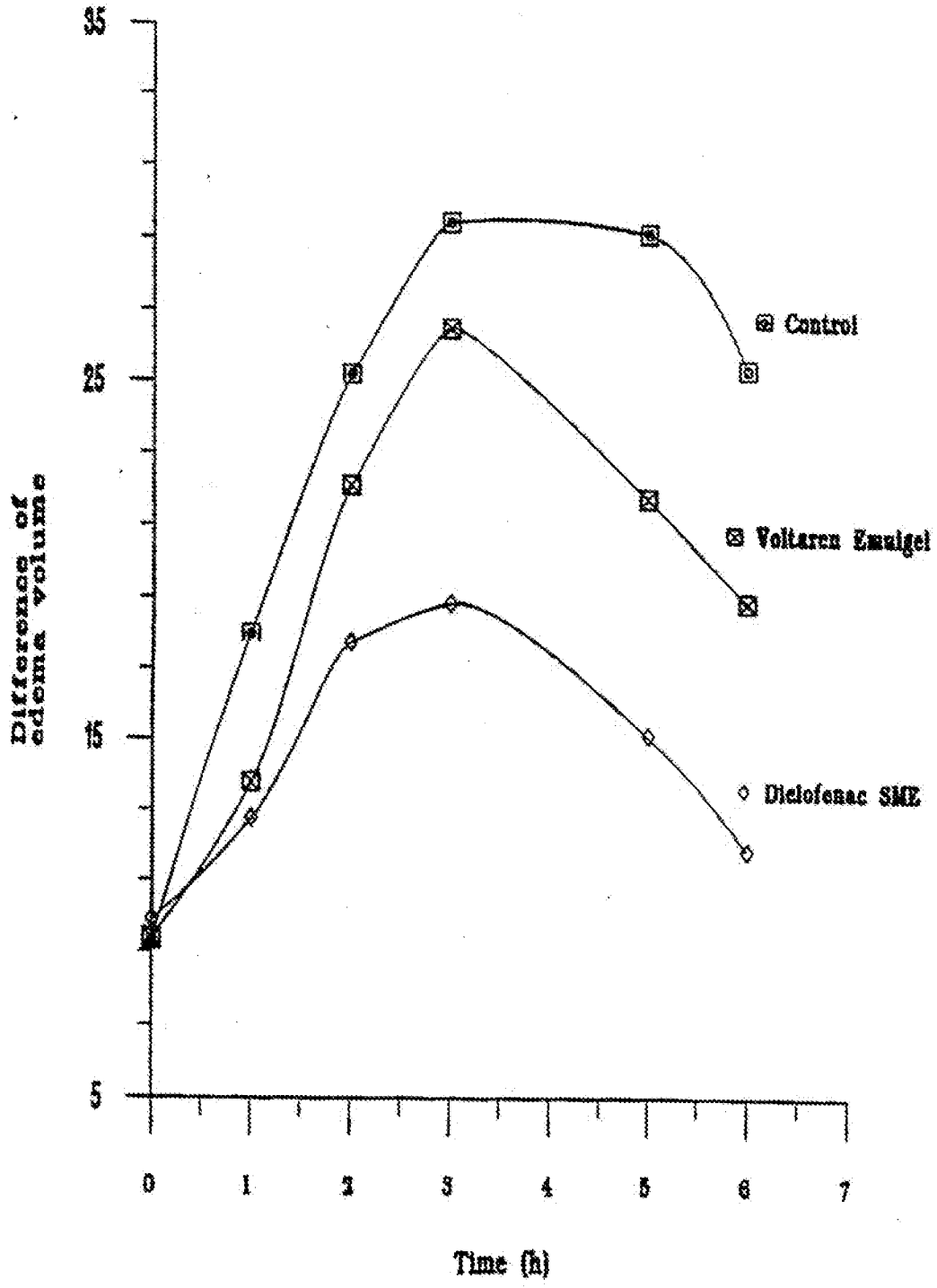


FIG. 1

PIROXICAM ANTIINFLAMMATORY ACTIVITY IN REGULAR CREAM AND SME CREAM (Carrageenan paw edema model)

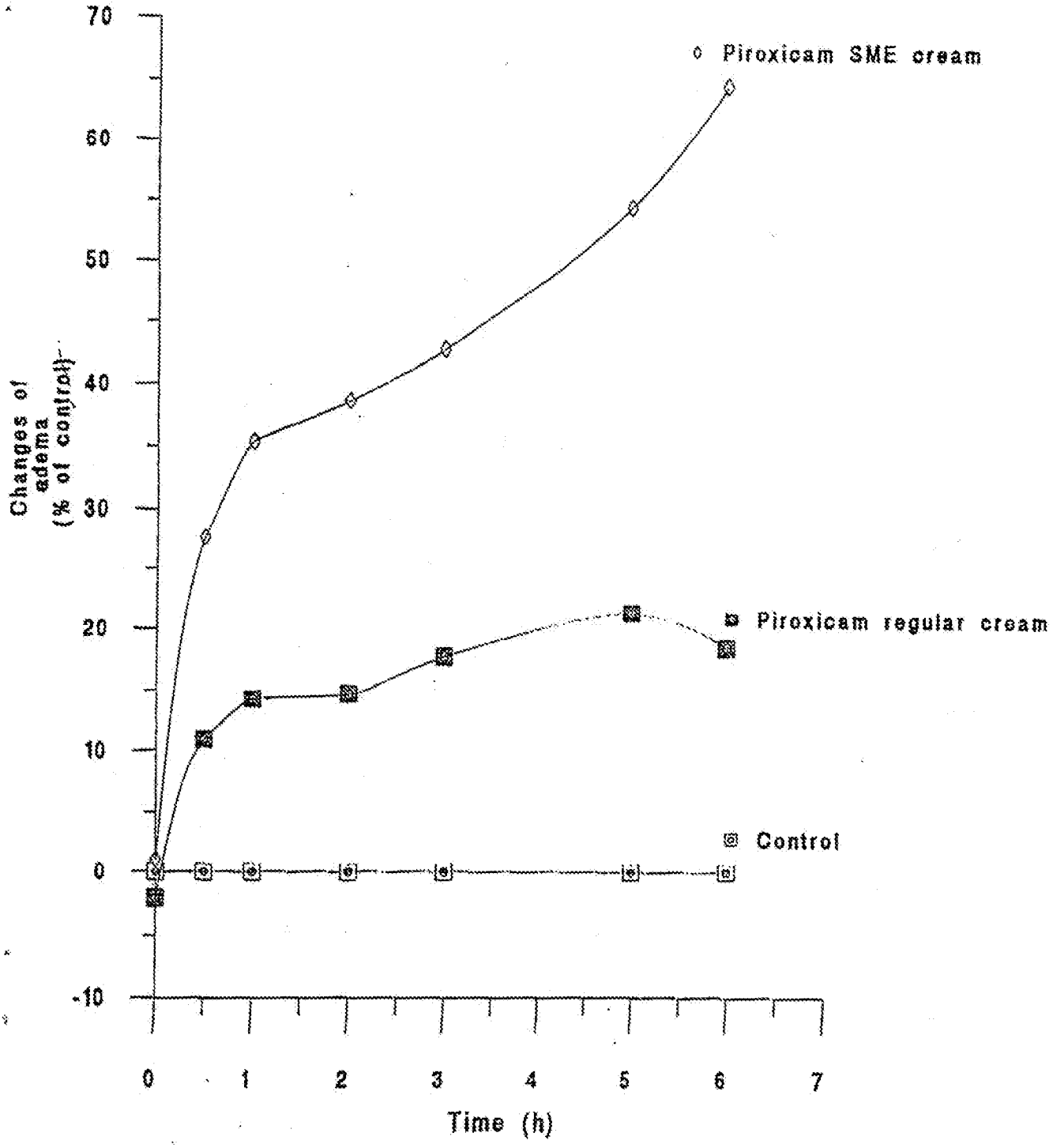
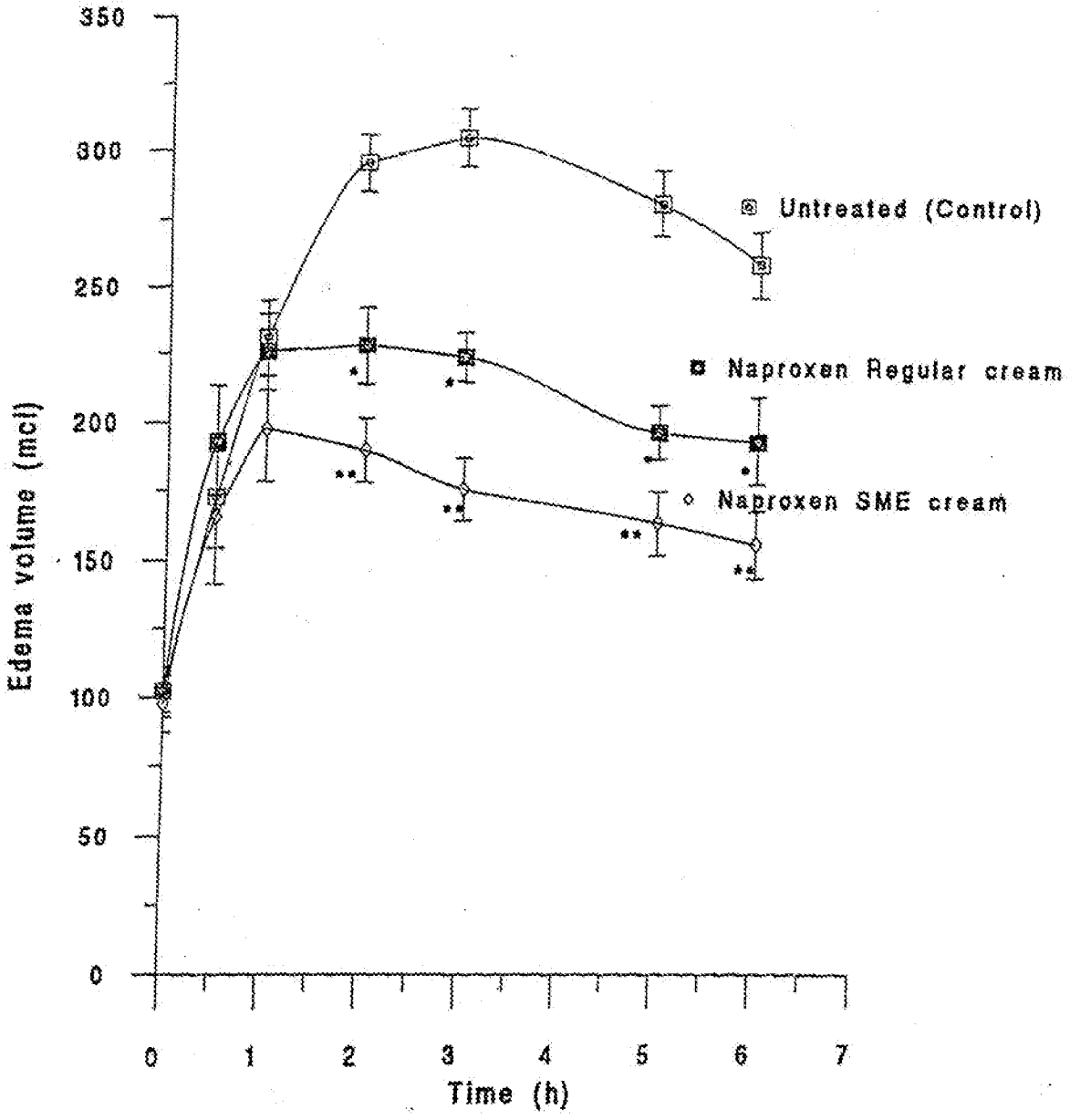


FIG. 2

NAPROXEN ANTIINFLAMMATORY ACTIVITY A COMPARISON OF REGULAR CREAM AND PHARMOS SME CREAM (1%)
Carrageenan paw edema model, edema volume-+S.D.
N=8 Rats



* Naproxen regular cream is different from Untreated (P<0.01)

** Naproxen SME cream is different from Untreated(P<0.01) and Naproxen regular cream(P<0.05)

FIG. 3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/02800

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61K 9/127; A61F 13/02
US CL :424/450
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/450, 447, 448; 514/859, 861, 863, 864, 886, 887, 938, 941, 943

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS: Microemulsions; Transdermal; Topical

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	US, A, 4,647,586 (MIZUSHIMA) 03 MARCH 1987; See column 3, line 61 through column 6, line 49.	1-7,10-13, 20-23,8-9, 14-15,24
Y	US, A, 4,963,367 (ECANOW) 16 OCTOBER 1990 See the Abstract, column 7, line 25 through column 14, line 54; column 15, lines 58-68.	16-19,25-32
Y	US, A, 4,613,330 (MICHELSON) 23 SEPTEMBER 1986. See column 5, line 6 through column 6, line 4.	29-34

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 JUNE 1993	29 JUL 1993
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. NOT APPLICABLE	Authorized officer G. S. KISHORE Telephone No. (703) 308-2351

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

【発行国】

日本国特許庁（ＪＰ）

【公報種別】 (19)日本国特許庁（ＪＰ） (12) **公開特許公報（Ａ）** (11)特許出願公開番号

特開平5－58906

(43)公開日 平成5年(1993)3月9日

公開特許公報（Ａ）

(51)Int.Cl.[5]	識別記号	庁内整理番号	ＦＩ	技術表示箇所
Ａ６１Ｋ 37/02		8314－4C		
9/08	Ｖ	7329－4C		
9/14	Ｅ	7329－4C		
47/14	Ｇ	7329－4C		
47/34	Ｇ	7329－4C		

【公開番号】 特開平５－５８９０６

審査請求 未請求 請求項の数 2（全 4 頁） 最終頁に続く

【公開日】 (21)出願番号 特願平3－226990

(22)出願日 平成３年(1991)９月６日

平成５年（１９９３）３月９日

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【発明の名称】

シクロスポリン点眼製剤

(54)【発明の名称】 シクロスポリン点眼製剤

【国際特許分類第５版】

(57)【要約】

【構成】

A61K 37/02 1）シクロスポリンと２）ポリソルベート、ポリオキシエチレン硬化ヒマシ油およびポリオキシエチレン脂肪酸
9/08 エステルから選ばれた一種または二種以上の界面活性剤からなる点眼用水溶液製剤、および
9/14 1）シクロスポリンと２）ポリソルベート、ポリオキシエチレン硬化ヒマシ油およびポリオキシエチレン脂肪酸
47/14 エステルから選ばれた一種または二種以上の界面活性剤からなる水溶液を凍結乾燥した点眼用製剤。
47/34 【効果】本発明のシクロスポリン水溶液製剤および凍結乾燥製剤は、点眼用として優れた効果を示す。
47/44 G 7329-4C

【審査請求】未請求

【請求項の数】２

【全頁数】４

【出願番号】

【特許請求の範囲】
【請求項１】
１）シクロスポリンと２）ポリソルベート、ポリオキシエチレン硬化ヒマシ油およびポリオキシエチレン脂肪酸エステルから選ばれた一種または二種以上の界面活性剤からなる点眼用水溶液製剤。
【請求項２】
１）シクロスポリンと２）ポリソルベート、ポリオキシエチレン硬化ヒマシ油およびポリオキシエチレン脂肪酸エステルから選ばれた一種または二種以上の界面活性剤からなる水溶液を凍結乾燥した点眼用製剤。
【発明の詳細な説明】
【０００１】
【産業上の利用分野】本発明は安全且つ使用時刺激を与えないシクロスポリン（Cyclosporin ）を含有する点眼製剤に関する。
【０００２】
【従来の技術】シクロスポリンは現在までA乃至Ｉまでの 9 種類が知られている。これらはいずれも分子量が約 1200 の、11 個のアミノ酸からなる環状ペプチドであり、（以下、本発明でいう「シクロスポリン」には、これらの各ペプチドおよびこれらの各ペプチドの混合物を含む。）医療上有用な免疫抑制、抗真菌、抗炎症作用等を有する（メルクインデックス、2748、396 頁、10 版： Helv.Chim.Acta 、60巻、1568-1578 頁（1977 年）： Helv.Chim.Acta 、65 巻、1655-1677 頁（1982 年）等）。
【０００３】そして現在、シクロスポリン製剤（シクロスポリンＡを主成分とする）は市販されており、免疫抑制剤として経口投与剤および注射剤の形態で使用されている（商品名「サンディミュン」；「最近の新薬」139-144 頁、38 集、1987年版）。しかし、シクロスポリンの水に対する溶解度が 20 ～30 μg ／ml と極めて低いため、上記注射剤はエタノールを含む界面活性剤溶液、経口投与剤は油性溶液製剤として調製されている。
【０００４】そして最近特に眼科領域で、免疫抑制剤として有用であることが、金井ら（第93 回日本眼科学会総会講演抄録、239 頁、「シクロスポリン点眼液の角膜移植後免疫抑制効果について」日本眼科学会雑誌、第93 巻臨時増刊号、平成元年 4月 5 日発行）により確認されるに至った。
【０００５】シクロスポリン点眼製剤としては、例えばシクロスポリンをα－サイクロデキストリンを用いる方法（特開昭 64 －85921 号）、中級脂肪酸モノおよび／またはジグリセリドを用いる方法（特開平 2－49733 号）、植物油または鉱物油を用いる方法（特公表平 3－503159号）などが知られている。
【０００６】
【発明が解決しようとする課題】本発明者らは、刺激や視野の曇りが発生しないシクロスポリン点眼製剤を見出し、本発明を完成した。
【０００７】
【課題を解決するための手段】本発明は、
（Ｉ） １）シクロスポリンと２）ポリソルベート、ポリオキシエチレン硬化ヒマシ油およびポリオキシエチレン脂肪酸エステルから選ばれた一種または二種以上の界面活性剤からなる点眼用水溶液製剤、および（ＩＩ）１）シクロスポリンと２）ポリソルベート、ポリオキシエチレン硬化ヒマシ油およびポリオキシエチレン脂肪酸エステルから選ばれた一種または二種以上の界面活性剤からなる水溶液を凍結乾燥した点眼用製剤、からなる。
【０００８】即ち、以下の条件
（１） シクロスポリンを界面活性剤のみで可溶化する目的で界面活性剤への溶解性、（２）可溶化したシクロスポリン液に緩衝剤、浸透圧調整剤、防腐剤、等を加えた場合の経時後の外観変化、（３）可溶化後、点眼濃度まで水で希釈した場合のウサギ点眼による目刺激試験、を満足する界面活性剤について、種々検討した結果、ポリソルベート、ポリオキシエチレン硬化ヒマシ油、ポリオキシエチレン脂肪酸エステル、が意外にも他の界面活性剤に比べて優れた効果を示した。
【０００９】本発明において使用されるポリソルベートとしては、例えば ポリソルベート20 、 40 、 80 などを挙げることができる。好適にはポリソルベート 80 である。
【００１０】本発明において使用されるポリオキシエチレン硬化ヒマシ油としては、例えばポリオキシエチレン硬化ヒマシ油 40 、60、80、100 などを挙げることができる。好適にはポリオキシエチレン硬化ヒマシ油 60 である。
【００１１】本発明において使用されるポリオキシエチレン脂肪酸エステルとしては、例えばポリオキシエチレン脂肪酸モノステアレート（40）、モノラウレート（10）、モノオレエート（10）などを挙げることができる。好適にはポリオキシエチレン脂肪酸モノステアレート（40）である。
【００１２】本発明のシクロスポリンと界面活性剤との使用割合（重量比）は好ましくは 1：5 ないし 1：200 であり、更に好ましくは 1：20 ないし 1：100 である。
【００１３】本発明の水に対するシクロスポリンの濃度は、好ましくは 0.1～2.0 mg／ml、更に好ましくは 0.2～1.5 mg／mlである本発明の凍結乾燥した点眼用製剤は、可溶化した溶液に必要に応じて賦形剤として多価アルコール、例えば、グルコース、フラクトース、マルトース、スクロース、ソルビトール、キシリトール、マンニトールなどの糖類の一種または二種以上の混合物；ポリエチレングリコール 500 からポリエチレングリコール 30000；などを添加する。シクロスポリンと多価アルコール類との使用割合（重量比）は好ましくは 1：5 な

いし 1：200 であり、更に好ましくは 1：20 ないし 1：100 である。

【００１４】本発明において、これらの基本形に浸透圧調整剤として塩化ナトリウム，塩化カリウムのような無機塩類またはグルコース，マンニトール，ソルビトールのような糖類；防黴剤として塩化ベンザルコニウム，クロロブタノールなど；その他に緩衝剤としてクエン酸ナトリウム、リン酸ナトリウム等を加えて製剤上の改善を図ることは当業界の技術水準内のことであり、本発明に包含されるものである。

【００１５】本発明の点眼用水溶液製剤は、シクロスポリンを上記界面活性剤に溶解し、次いで水を加えて点眼濃度まで希釈することによって製造できる。このようにして得られた水溶液製剤は、必要に応じて緩衝剤を用いてｐＨを約 6.0 に調整後，無菌的な条件下で点眼容器に分別し使用に供しうる。

【００１６】また、本発明の凍結乾燥した点眼用製剤は、上記の可溶化した溶液に必要に応じて多価アルコールを添加し溶解する。次いで、バイアルに分注し、凍結乾燥機中で－40 ℃に凍結後、10 ℃の棚温で約 48時間真空乾燥することによって製造できる。このようにして得られた凍結乾燥剤は、使用時に防黴剤、浸透圧調整剤を添加した溶液で溶解し、点眼容器に移し使用に供しうる。

【００１７】

【実施例】以下に実施例、試験例を挙げるが、これらは本発明の説明のためのものであって、これによって本発明が限定されるものではない。

【００１８】なお、実施例、試験例で用いられるシクロスポリンはスイス国 Sandoz Ltd.から供給されたものであり、市販されている「サンディミュン」（商品名）の主剤と同じである。

【００１９】実施例　１．シクロスポリン 0.5ｇ をポリオキシエチレン硬化ヒマシ油（60） 20ｇに加温しつつ溶解した。溶解確認後、注射用水を徐々に添加しシクロスポリン・活性剤を可溶化した。さらに浸透圧調整剤として塩化ナトリウム 8ｇ 、防黴剤を適量添加後、全量を 1000 ml とした。メンブランフィルターにて無菌的に沪過し、点眼容器に分注後、使用に供した。

【００２０】実施例　２．シクロスポリン 0.5 ｇを 20 gのポリソルベート 80 に溶解した。注射用水1000 ｍl を徐々に添加し、シクロスポリン均一水溶液を得た。次いで賦形剤としてグルコース 20ｇを添加溶解、通常の方法で凍結乾燥を行なった。使用時には無菌注用水にて溶解し、使用に供した。

【００２１】実施例　３．シクロスポリン 0.5ｇ を 20 gのポリソルベート８０中に溶解した。防黴剤を添加し非水の状態で保存した。使用時に浸透圧調整剤として塩化ナトリウム 9gを溶解した注射用水 1000 ml で使用濃度まで溶解希釈し点眼に供した。

【００２２】実施例　４．シクロスポリン 0.5ｇ をポリオキシエチレン脂肪酸モノステアレート（40）20ｇに溶解後、注射用水 100 ml を添加し均一溶液を得た。別に、マルトース10ｇを注射用水 100 ml で溶解し，シクロスポリン均一溶液に加え、注射用水にて全量 1000 ml とした。これをバイアルに分注後、凍結乾燥機中で －40℃に凍結した。さらに凍結乾燥を 10℃の棚温で 48 時間、30 ℃で 10 時間行ないシクロスポリン凍結乾燥製剤を得た。使用時には無菌注用水にて溶解し、使用に供した。

【００２３】実施例　５．シクロスポリン 1.0ｇ をポリオキシエチレン硬化ヒマシ油（６０）20ｇ に加温しつつ溶解した。これに注射用水 900 ml を徐々に添加し均一溶液を得た。40ｇのポリエチレングリコール 4000 を均一溶液に添加溶解し、注射用水にて全量を 1000 ml とした。これをバイアルに分注後、凍結乾燥機中で －50 ℃に凍結した。さらに、凍結乾燥を 0 ℃の棚温で 48 時間、30 ℃の棚温で行ないシクロスポリン凍結乾燥製剤を得た。使用時に防黴剤として塩化ベンザルコニウム、浸透圧調整剤として塩化カリウムを溶解した液にて溶解後、点眼容器に移し使用に供した。

【００２４】試験例　１．各種界面活性剤に対するシクロスポリンの溶解性、経時安定性および目刺激性を常法に従って調べた。結果を表に示す。

【００２５】

【表】

界面活性剤	シクロスポリンの溶解性	経時安定性	目刺激性
ポリソルベート 80	○	○	○
ＰＯＥ硬化ヒマシ油 (60)	○	○	○
ＰＯＥ脂肪酸モノステアレート (40)	○	○	○
ＰＯＥ脂肪酸エーテル (25)	○	○	△
プルロニックＦ68（商品名）	○	×	—
精製卵黄レシチン	×	×	—
庶糖脂肪酸ラウリルエステル	×	×	—
ポリグリセリンラウリルエステル	○	×	—

POE＝ポリオキシエチレン

【００２６】

【実施例の効果】シクロスポリン水溶液製剤はシクロスポリンを、選択した界面活性剤のみで溶解後、注射用水を可溶化の要領で徐々に添加し、使用濃度まで 25 ～500 倍に希釈すると澄明な水溶液として得られた。希釈した液は室温にて 6　カ月以上保存したが、析出や沈澱等は発生せず十分に点眼用に供するに可能な事がわかった。シクロスポリン凍結乾燥製剤は、水溶液の状態に比べ経時安定性に優れ、シクロスポリンの含量低下がほとんどない事を確認した。再溶解性は多価アルコール類を添加した場合、再溶解時の溶解性や外観が特によく凍結乾燥前の溶液状態となんら差は認められなかった。

【００２７】

【発明の効果】本発明のシクロスポリン水溶液製剤および凍結乾燥製剤は、点眼用として優れた効果を示す。

フロントページの続き

(51)Int.Cl.[5]	識別記号	庁内整理番号	ＦＩ	技術表示箇所
Ａ６１Ｋ　47/44		Ｇ　7329－4Ｃ		

(12) UK Patent Application (19) GB (11) 2 222 770 (13) A

(43) Date of A publication 21.03.1990

(21) Application No 8920597.5

(22) Date of filing 12.09.1989

(30) Priority data
(31) 8821754 (32) 16.09.1988 (33) GB
8902903 09.02.1989
8902900 09.02.1989

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(51) INT CL*
A61K 9/10 37/02

(52) UK CL (Edition J)
A5B BKA BLB B170 B180 B190 B21Y B216 B26Y B30Y B303 B31Y B317 B34Y B340 B343 B35Y B351 B40Y B403 B822
U1S S2411

(56) Documents cited
None

(58) Field of search
UK CL (Edition J) A5B BKA BKS
INT CL* A61K
Online databases : WPI

(54) Cyclosporin emulsion compositions

(57) Pharmaceutical compositions comprising a cyclosporin, e.g. Ciclosporin or [Nva]^2–Ciclosporin, in "microemulsion pre-concentrate" and microemulsion form. The compositions typically comprise (1.1) a C_{1-5} alkyl or tetrahydrofurfuryl di– or partial-ether of a low molecular weight mono– or poly-oxy-alkane diol, as hydrophilic component. Compositions are also provided comprising a cyclosporin and (1.1) and, suitably, also a saccharide monoester, e.g. raffinose or saccharose monolaurate. Dosage forms include topical formulations and, in particular, oral dosage forms.

GB 2 222 770 A

At least one drawing originally filed was informal and the print reproduced here is taken from a later filed formal copy.

FIG. 1

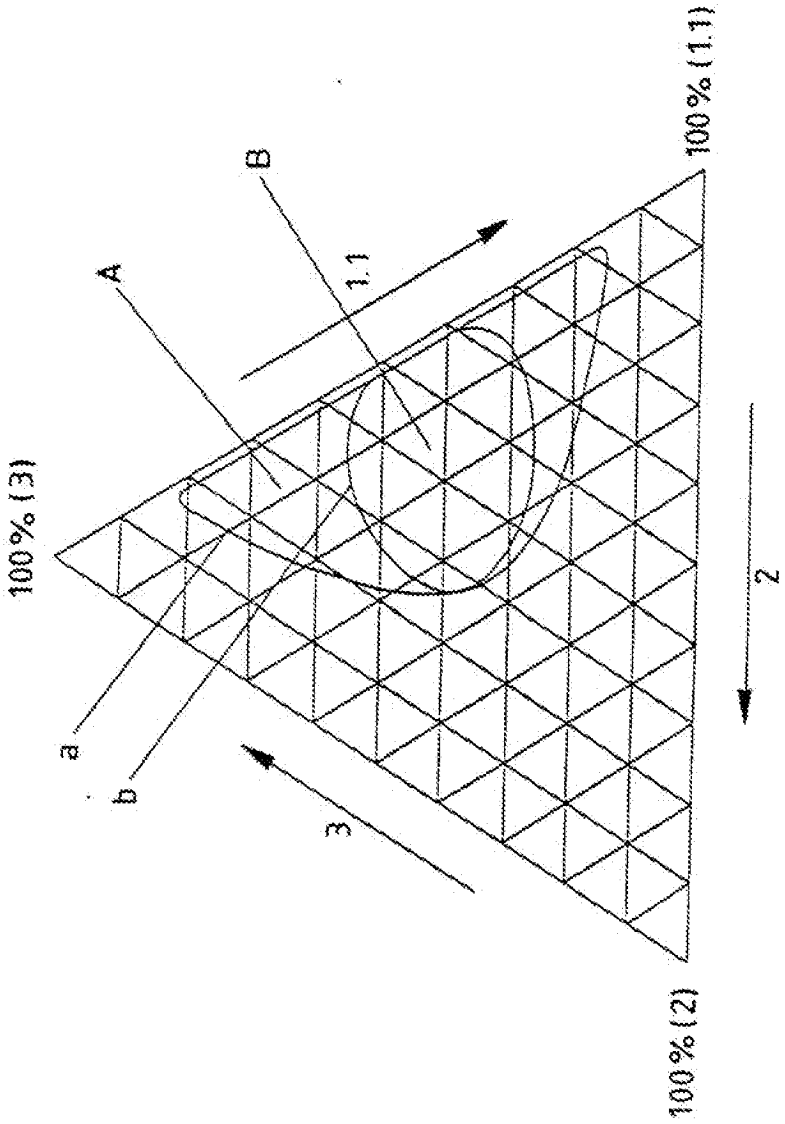

FIG. 2

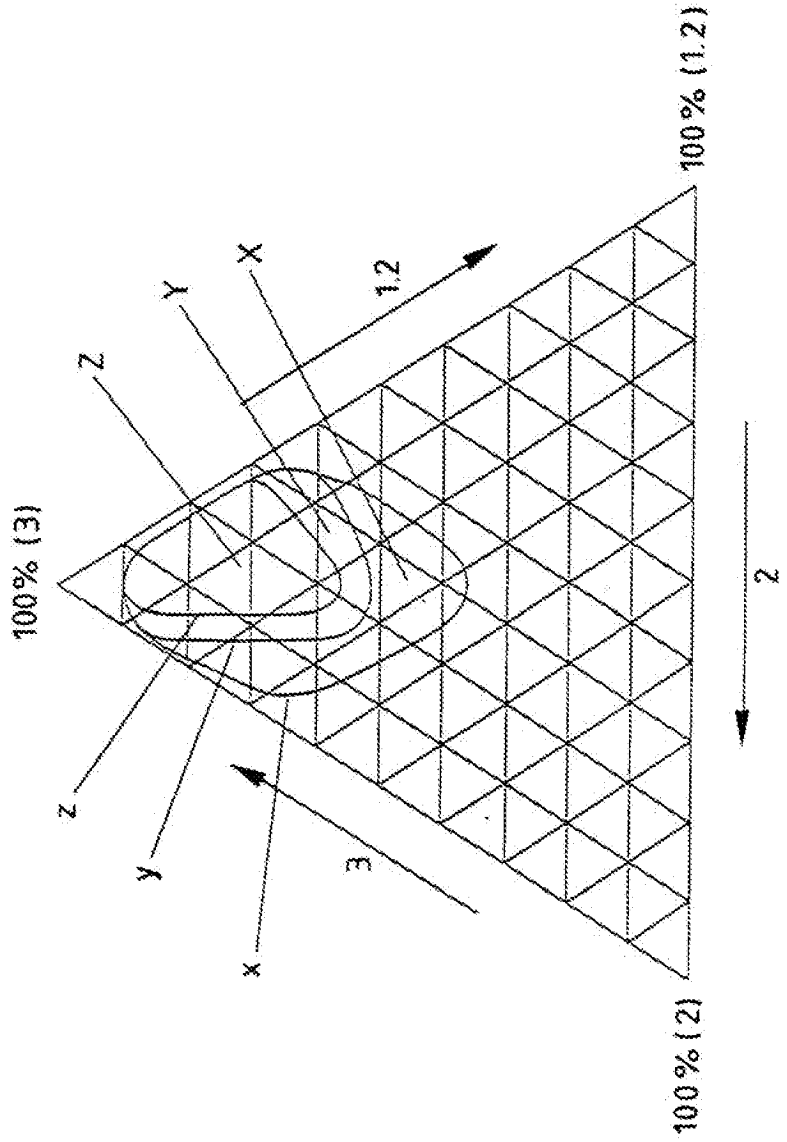

FIG. 3

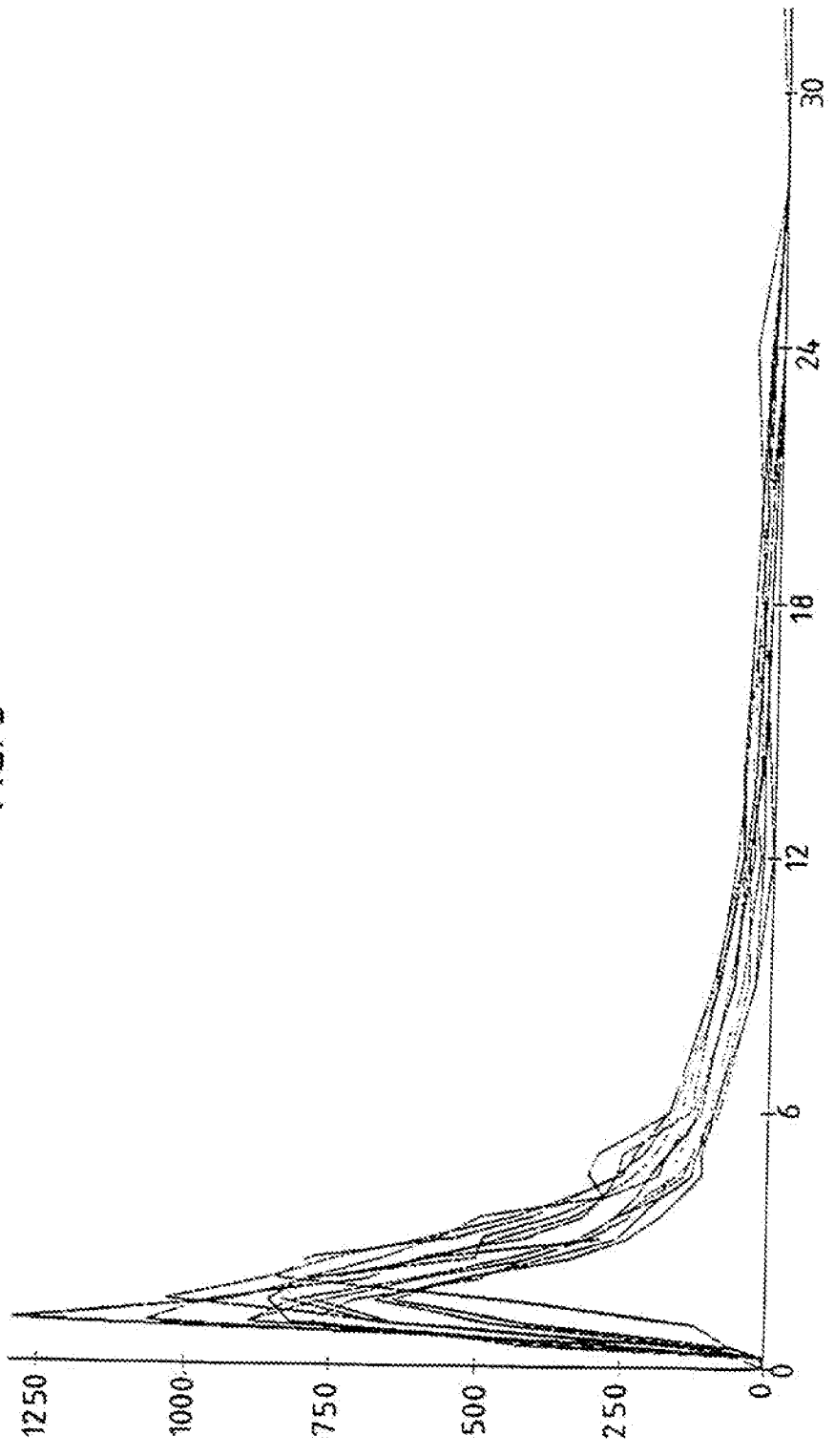

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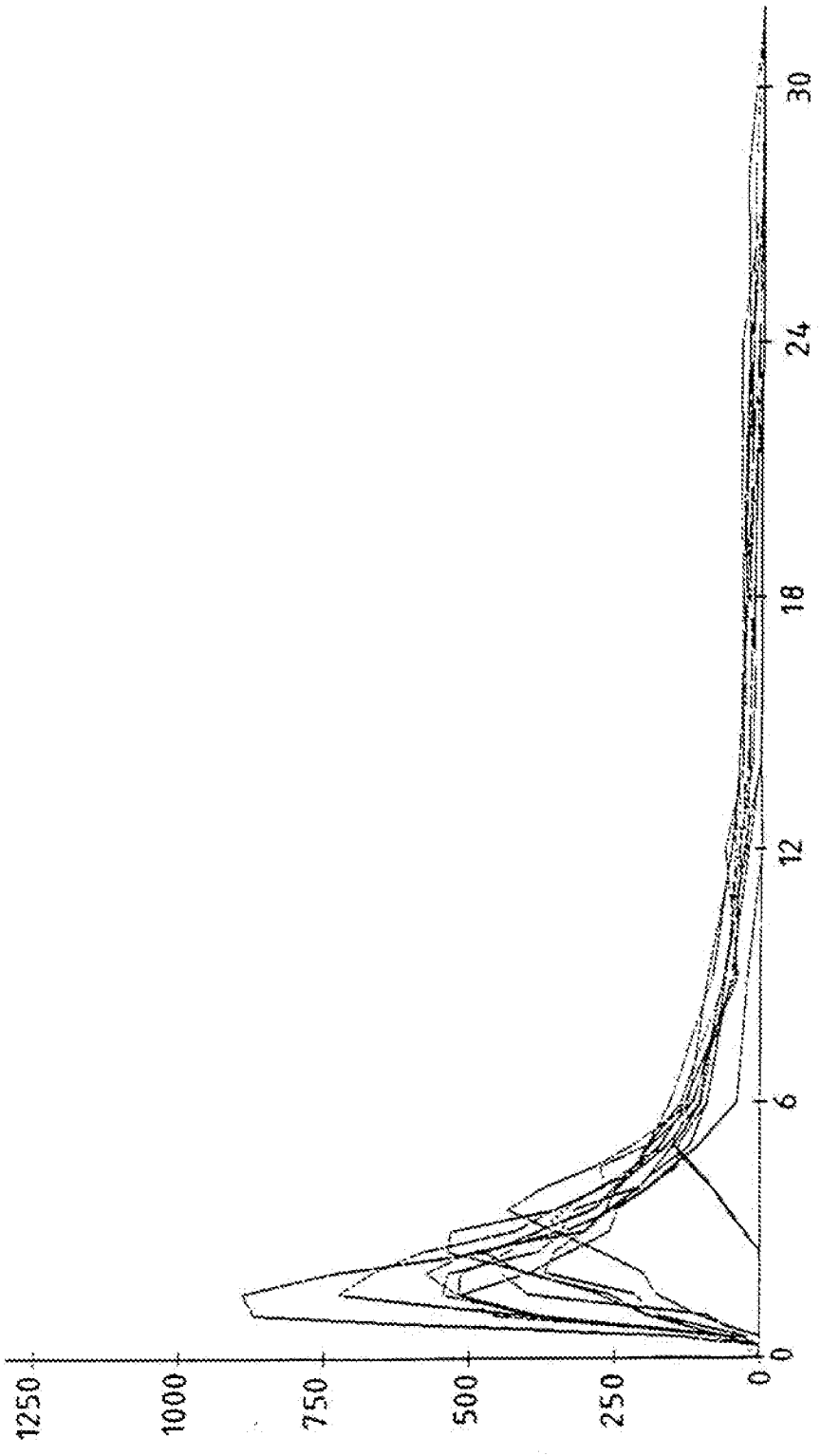
FIG. 4



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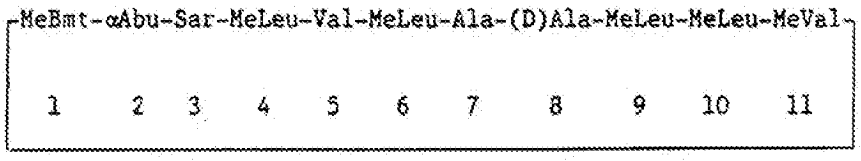
PHARMACEUTICAL COMPOSITIONS COMPRISING CYCLOSPORINS

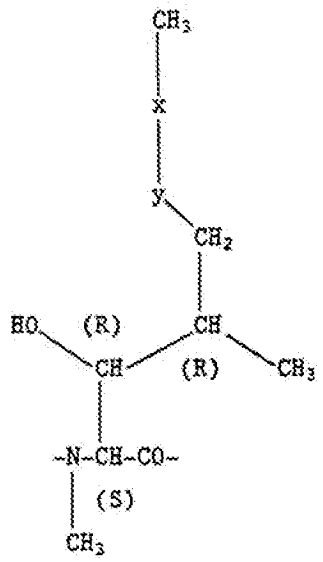
The present invention relates to novel galenic formulations comprising a cyclosporin as active ingredient.

The cyclosporins comprise a class of structurally distinctive, cyclic, poly-N-methylated endecapeptides, commonly possessing pharmacological, in particular immunosuppressive, anti-inflammatory and/or anti-parasitic activity. The first of the cyclosporins to be isolated was the naturally occurring fungal metabolite Ciclosporin or Cyclosporine, also known as cyclosporin A and commercially available under the Registered Trade Mark SANDIMMUN® or SANDIMMUNE®. Ciclosporin is the cyclosporin of formula A.



(A)

wherein -MeBmt- represents the N-methyl-(4R)-4-but-2E-en-1-yl-4-methyl-(L)threonyl residue of formula B



(B)

in which -x-y- is -CH=CH- (trans).

As the parent of the class Ciclosporin has so far received the most attention. The primary area of clinical investigation for Ciclosporin has been as an immunosuppressive agent, in particular in relation to its application to recipients of organ transplants, e.g. heart, lung, combined heart-lung, liver, kidney, pancreatic, bone-marrow, skin and corneal transplants and, in particular, allogenic organ transplants. In this field Ciclosporin has achieved a remarkable success and reputation.

At the same time, applicability of Ciclosporin to various autoimmune diseases and to inflammatory conditions, in particular inflammatory conditions with an aetiology including an autoimmune component such as arthritis (for example rheumatoid arthritis, arthritis chronica progrediente and arthritis deformans) and rheumatic diseases, has been intensive and reports and results in vitro, in animal models and in clinical trials are wide-spread in the literature. Specific

auto-immune diseases for which Ciclosporin therapy has been proposed or applied include, autoimmune hematological disorder (including e.g. hemolytic anaemia, aplastic anaemia, pure red cell anaemia and idiopathic thrombocytopaenia), systemic lupus erythematosus, polychondritis, sclerodoma, Wegener granulamatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, psoriasis, Steven-Johnson syndrome, idiopathic sprue, autoimmune inflammatory bowel disease (including e.g. ulcerative colitis and Crohn's disease) endocrine opthalmopathy, Graves disease, sarcoidosis, multiple sclerosis, primary billiary cirrhosis, juvenile diabetes (diabetes mellitus type I), uveitis (anterior and posterior), keratoconjunctivitis sicca and vernal keratoconjunctivitis, interstitial lung fibrosis, psoriatic arthritis and glomerulonephritis (with and without nephrotic syndrome, e.g. including idiopathic nephrotic syndrome or minimal change nephropathy).

Further areas of investigation have been potential applicability as an anti-parasitic, in particular anti-protozoal agent, with possible uses suggested including treatment of malaria, coccidiomycosis and schistosomiasis and, yet more recently, use as an agent for reversing or abrogating anti-neoplastic agent resistance in tumours and the like.

Since the original discovery of ciclosporin, a wide variety of naturally occurring cyclosporins have been isolated and identified and many further non-natural cyclosporins have been prepared by total- or semi-synthetic means or by the application of modified culture techniques. The class comprised by the cyclosporins is thus now substantial and includes, for example, the naturally occurring cyclosporins A through Z [c.f. Traber et al. 1, Helv. Chim. Acta. 60, 1247-1255 (1977); Traber et al. 2, Helv. Chim. Acta. 65 no. 162, 1655-1667 (1982); Kobel et al., Europ. J. Applied Microbiology and Biotechnology 14, 273-240 (1982); and von Wartburg et al., Progress in Allergy, 38, 28-45 (1986)], as well as various non-natural cyclosporin derivatives and artificial or synthetic cyclosporins including the so called

dihydro-cyclosporins [in which the moiety -x-y- of the -MeBmt- residue (Formula B above) is saturated to give -x-y- = $-CH_2-CH_2-$; derivatised cyclosporins (e.g. in which a further substituent is introduced at the α-carbon atom of the sarcosyl residue at the 3-position of the cyclosporin molecule); cyclosporins in which the -MeBmt- residue is present in isomeric form (e.g. in which the configuration across positions 6' and 7' of the -MeBmt- residue is cis rather than trans); and cyclosporins wherein variant amino acids are incorporated at specific positions within the peptide sequence, employing e.g. the total synthetic method for the production of cyclosporins developed by R. Wenger - see e.g. Traber 1, Traber 2 and Kobel loc. cit.; U.S. Patents Nos. 4 108 985, 4 210 581 and 4 220 641; European Patent Publication Nos. 0 034 567 and 0 056 782; International Patent Publication No. WO 86/02080; Wenger 1, Transp. Proc. 15, Suppl. 1:2230 (1983); Wenger 2, Angew. Chem. Int. Ed., 24, 77 (1985); and Wenger 3, Progress in the Chemistry of Organic Natural Products 50, 123 (1986).

The class comprised by the cyclosporins is thus now very large indeed and includes, for example, $[Thr]^2$-, $[Val]^2$-, $[Nva]^2$- and $[Nva]^2$-$[Nva]^5$-Ciclosporin (also known as cyclosporins C,D, G and H respectively), $[3\text{-}O\text{-acyl-MeBmt}]^1$-Ciclosporin (also known as cyclosporin A acetate), $[Dihydro\text{-}MeBmt]^1$-$[Val]^2$-Ciclosporin (also known as dihydro-cyclosporin D), $[(D)Fluoromethyl\text{-}Sar]^3$-Ciclosporin, $[(D)Ser]^8$-Ciclosporin, $[MeIle]^{11}$-Ciclosporin, $[(D)MeVal]^{11}$-Ciclosporin (also known as cyclosporin H), $[MeAla]^6$-Ciclosporin, $[(D)Pro]^3$-Ciclosporin and so on.

[In accordance with now conventional nomenclature for cyclosporins, these are defined by reference to the structure of Ciclosporin (i.e. Cyclosporin A). This is done by first indicating the amino acid residues present which differ from those present in Ciclosporin (e.g. "$[(D)Pro]^3$" to indicate that the cyclosporin in question has a -(D)Pro- rather than -Sar- residue at the 3-position) and then applying the term "Ciclosporin" to characterise remaining residues

which are identical to those present in Ciclosporin. Individual residues are numbered starting with the residue -MeBmt- or -dihydroMeBmt- in position 1.]

Very many of these further cyclosporins exhibit comparable pharmaceutical utility to Ciclosporin or more specific utility, for example activity particularly in reversing tumor resistance to cytostatic therapy, and proposals for their application as therapeutic agents abound in the literature.

Despite the very major contribution which Ciclosporin has made, in particular to the areas of organ transplant and the therapy of autoimmune diseases, difficulties encountered in providing more effective and convenient means of administration as well as the reported occurrence of undesirable side reactions, in particular nephrotoxic reaction, have been obvious serious impediments to its wider use or application. The cyclosporins are characteristically highly hydrophobic. Proposed liquid formulations, e.g. for oral administration of cyclosporins, have hitherto been based primarily on the use of ethanol and oils or similar excipients as carrier media. Thus the commercially available Ciclosporin drink-solution employs ethanol and olive oil as carrier medium in conjunction with labrafil as a surfactant - see e.g. US patent no. 4,388,307. Use of the drink-solution and similar compositions as proposed in the art is however accompanied by a variety of difficulties.

First, the necessity to use oils or oil based carriers may lend the preparations an unpleasant taste or otherwise reduce palatability, in particular for the purposes of long-term therapy. These effects can be masked by presentation in gelatin capsule form. However, in order to maintain the cyclosporin in solution, the ethanol content has to be kept high. Evaporation of the ethanol, e.g. from capsules or from other forms, e.g. when opened, results in the development of a cyclosporin precipitate. Where such compositions are presented in e.g.

soft gelatin encapsulated form, this particular difficulty necessitates packaging of the encapsulated product in an air-tight compartment, for example an air-tight blister or aluminium-foil blister-package. This in turn renders the product both bulky and more expensive to produce. The storage characteristics of formulations as aforesaid are far from ideal.

Bioavailability levels achieved using existing oral cyclosporin dosage systems are also low and exhibit wide variation between individuals, individual patient types and even for single individuals at different times during the course of therapy. Thus reports in the literature indicate that currently available therapy employing the commercially available Ciclosporin drink solution provides an average absolute bioavailability of ca. 30% only, with marked variation between individual groups, e.g. between liver (relatively low bioavailability) and bone-marrow (relatively high bioavailability) transplant recipients. Reported variation in bioavailability between subjects has varied from anything between one or a few percent for some patients to as much as 90% or more for others. And as already noted, marked change in bioavailability for individuals with time is frequently observed.

To achieve effective immunosuppressive therapy, cyclosporin blood or blood serum levels have to be maintained within in a specified range. The required range can in turn vary, depending on the particular condition being treated, e.g. whether therapy is to prevent transplant rejection or for the control of an autoimmune disease, and on whether or not alternative immunosuppressive therapy is employed concomitantly with cyclosporin therapy. Because of the wide variations in bioavailability levels achieved with conventional dosage forms, daily dosages needed to achieve required blood serum levels will also vary considerably from individual to individual and even for a single individual. For this reason it is necessary to monitor blood/blood-serum levels of patients receiving cyclosporin therapy at regular and frequent intervals. Monitoring of blood/blood-serum

levels, which is generally performed by RIA or equivalent immunoassay technique, e.g. employing monoclonal antibody based technology, has to be carried out on a regular basis. This is inevitably time consuming and inconvenient and adds substantially to the overall cost of therapy.

Beyond all these very evident practical difficulties lies the occurrence of undesirable side reactions already alluded to, observed employing available oral dosage forms.

Several proposals to meet these various problems have been suggested in the art, including both solid and liquid oral dosage forms. An overriding difficulty which has however remained is the inherent insolubility of the cyclosporins, e.g. Ciclosporin, in aqueous media and hence provision of a dosage from which can contain cyclosporins in sufficiently high concentration to permit convenient use and yet meet the required criteria in terms of bioavailability, e.g. enabling effective resorption from the stomach or gut lumen and achievement of consistent and appropriately high blood/blood-serum levels.

The particular difficulties encountered in relation to oral dosaging with cyclosporins have inevitably led to restrictions in the use of cyclosporin therapy for the treatment of relatively less severe or endangering disease conditions. A particular area of difficulty in this respect has been the adoption of cyclosporin therapy in the treatment of autoimmune diseases and other conditions affecting the skin, for example for the treatment of atopic dermatitis and psoriasis and, as also widely proposed in the art, for hair growth stimulation, e.g. in the treatment of alopecia due to ageing or disease.

Thus while oral Ciclosporin therapy has shown that the drug is of considerable potential benefit to patients suffering e.g. from psoriasis, the risk of side-reaction following oral therapy has prevented common use. Various proposals have been made in the art for

application of cyclosporins, e.g. Ciclosporin, in topical form and a number of topical delivery systems have been described. Attempts at topical application have however failed to provide any demonstrably effective therapy. A means of topical application providing effective dermal delivery and useful, e.g. for the treatment of psoriasis, would effectively make cyclosporin therapy available to, what is, a major patient population at need.

By the present invention there are provided novel cyclosporin galenic formulations in the form of a micro-emulsion pre-concentrate and/or based on the use of particular solvent media as hereinafter defined, which meet or substantially reduce difficulties in cyclosporin, e.g Ciclosporin, therapy hitherto encountered in the art. In particular it has been found that the compositions of the invention permit the preparation of solid, semi-solid and liquid compositions containing a cyclosporin in sufficiently high concentration to permit, e.g. convenient oral administration, while at the same time achieving improved efficacy, e.g. in terms of bioavailability characteristics.

More particularly it has been found that compositons in accordance with the present invention enable effective cyclosporin dosaging with concomitant enhancement of resorption/bioavailability levels, as well as reduced variability in resorption/bioavailability levels achieved both for individual patients receiving cyclosporin therapy as well as between individuals. By application of the teachings of the present invention cyclosporin dosage forms are obtainable providing reduced variablility in achieved cyclosporin blood/blood serum levels between dosages for individual patients as well as between individuals/ individual patient groups. The invention thus enables reduction of cyclosporin dosage levels required to achieve effective therapy. In addition it permits closer standardisation as well as optimisation of on-going daily dosage requirements for individual subjects receiving cyclosporin therapy as well as for groups of patients undergoing equivalent therapy.

By closer standardisation of individual patient dosaging rate and blood/blood-serum level response, as well as dosaging and response parameters for patient groups, monitoring requirements may be reduced, thus substantially reducing the cost of therapy.

By reduction of required cyclosporin dosaging/standardisation of achieved bio-availability characteristics, the present invention also offers a means permitting reduction in the occurrence of undesirable side-effects, in particular nephrotoxic reaction, in patients undergoing cyclosporin therapy.

In addition, the present invention enables the preparation of compositions which are non-alkanol based, e.g. which may be free or substantially free of ethanol. Such compositions avoid stability and related processing difficulties as hereinbefore discussed, inherent to known alkanolic compositions. The invention thus provides inter al. compositions which are better adapted, e.g. for presentation in capsule, e.g. hard or soft gelatin capsule form and/or which eliminate or substantially reduce packaging difficulties, for example as hereinbefore discussed, e.g. for soft gelatin encapsulated forms.

In relation to topical application, the present invention further enables the preparation of novel galenical formulations comprising a cyclosporin, e.g. Ciclosporin, as active ingredient and permitting improved treatment for autoimmune diseases affecting the skin, in particular, of dermatological disease involving morbid proliferation and/or keratinisation of the epidermis, especially of psoriasis and atopic dermatosis. Topically applicable compositions in accordance with the invention are also of use in the treatment of alopecia, e.g. for use in the promotion of hair growth.

In a first aspect, the present invention specifically provides pharmaceutical compositions comprising a cyclosporin as active ingredient, which compositions are in the form of a "microemulsion

pre-concentrate".

By the term "microemulsion pre-concentrate" as used herein is meant a system capable on contacting with, e.g. addition to, water of providing a microemulsion. The term microemulsion as used herein is used in its conventionally accepted sense as a non-opaque or substantially non-opaque colloidal dispersion comprising water and organic components including hydrophobic (lipophilic) organic components. Microemulsions are identifiable as possessing one or more of the following characteristics. They are formed spontaneously or substantially spontaneously when their components are brought into contact, that is without substantial energy supply, e.g. in the absence of heating or the use of high shear equipment or other substantial agitation. They exhibit thermodynamic stability. They are monophasic. They are substantially non-opaque, i.e. are transparent or opalescent when viewed by optical microscopic means. In their undisturbed state they are optically isotropic, though an anisotropic structure may be observable using e.g. x-ray technique.

Microemulsions comprise a dispersed or particulate (droplet) phase, the particles of which are of a size less than 2,000 Å, hence their optical transparency. The particles of a microemulsion may be spherical, though other structures are feasible, e.g. liquid crystals with lamellar, hexagonal or isotropic symmetries. Generally, micro-emulsions comprise droplets or particles having a maximum dimension (e.g. diameter) of less than 1,500 Å, e.g. typically from 100 to 1,000 Å.

[For further discussion of the characteristics of microemulsions see, e.g. Rosof, Progress in Surface and Membrane Science, 12, 405 et seq. Academic Press (1975); Friberg, Dispersion Science and Technology, 6 (3), 317 et seq. (1985); and Müller et al. Pharm. Ind., 50 (3), 370 et seq. (1988)].

From the foregoing it will be understood that the "microemulsion pre-concentrates" of the invention are galenic systems comprising a cyclosporin as active ingredient capable of forming a microemulsion, spontaneously or substantially spontaneously on contact with water alone.

Pharmaceutical "microemulsion pre-concentrate" compositions comprising cyclosporins as active ingredient are novel. Accordingly in one aspect the present invention provides:

A) A pharmaceutical composition comprising a cyclosporin as active ingredient, which composition is a "microemulsion pre-concentrate".

(The term "pharmaceutical composition" as used herein and in the accompanying claims is to be understood as defining compositions of which the individual components or ingredients are themselves pharmaceutically acceptable, e.g. where oral administration is foreseen, acceptable for oral use and, where topical administration is foreseen, topically acceptable.)

In addition to the cyclosporin active ingredient, the "microemulsion pre-concentrate" compositions of the invention will appropriately comprise:

1) a hydrophilic phase;
2) a lipophilic phase; and
3) a surfactant.

The cyclosporin is carried in the lipophilic phase. Suitably both the hydrophilic and lipophilic phases will serve as carrier medium.

"Microemulsion pre-concentrates" of the invention are of a type providing o/w (oil-in-water) microemulsions. As will be appreciated

however, compositions in accordance with (A) may contain minor quantities of water or otherwise exhibit fine structural features characteristic of microemulsions, e.g. of o/w or w/o (water-in-oil) type. The term "microemulsion pre-concentrate" as used herein is accordingly to be understood as embracing such possibilities.

Microemulsions obtained on contacting the "microemulsion pre-concentrate" compositions of the invention with water or other aqueous medium exhibit thermodynamic stability, that is they will remain stable at ambient temperatures, e.g. without clouding or regular emulsion size droplet formation or precipitation, over prolonged periods of time. [It will of course be understood that, to obtain a microemulsion, adequate water will be required. While the upper limit of dilution is not critical, a dilution of 1:1, e.g. 1:5 "p.p.w. ("microemulsion pre-concentrate": H_2O) or more will generally be appropriate.] Preferably, on contacting with water, the "microemulsion pre-concentrate" compositions of the invention are capable of providing microemulsions which remain stable at ambient temperatures, e.g. as evidenced by absence of any optically observable clouding or precipitation, over periods of at least 2 hours, more preferably at least 4 hours, most preferably at least 12 to 24 hours. Microemulsions obtainable from "microemulsion pre-concentrates" of the invention, e.g. at dilutions as indicated above, will preferably have an average particle size of less than about 1,500Å, more preferably of less than about 1,000 or 1,100Å, e.g. down to about 150 or 200Å.

Especially preferred in accordance with the present invention are compositions as defined under (A) in which the hydrophilic phase comprises:

1.1. A pharmaceutically acceptable C_{1-5}alkyl or tetrahydrofurfuryl di- or partial-ether of a low molecular weight mono- or poly-oxy-alkanediol; or

1.2. 1,2-propyleneglycol.

Suitable components (1.1.) are, e.g. di- or partial-, especially partial-, -ethers of mono- or poly-, especially mono- or di-, -oxy-alkanediols comprising from 2 to 12, especially 4 carbon atoms. Preferably the mono- or poly-oxy-alkanediol moiety is straight-chained. Especially suitable for use in accordance with the invention are di- or partial-ethers of formula I

$$R_1 - [O-(CH_2)_2]_x-OR_2 \qquad (I)$$

wherein R_1 is C_{1-5} alkyl or tetrahydrofurfuryl,

R_2 is hydrogen, C_{1-5}alkyl or tetrahydrofurfuryl, and

x is an integer of from 1 to 6, especially from 1 to 4, most especially about 2.

Particularly preferred for use in accordance with the invention are partial ethers as defined above, e.g. products of formula I, wherein R_2 is hydrogen.

C_{1-5}alkyl moieties in the above defined ethers may be branched or straight chain, e.g. including methyl, ethyl, n-propyl, i-propyl, n-butyl and t-butyl groups.

Such ethers are known products and commercially available or may be produced analogously to the known products. Especially preferred products of formula I for use in relation to the present invention are those known and commercially available under the trade names Transcutol and Glycofurol.

Transcutol is the compound diethyleneglycol monoethyl ether of formula I, wherein $R_1 = C_2H_5$, $R_2 = H$ and $x = 2$.

Glycofurol, also known as tetrahydrofurfuryl alcohol polyethylene

glycol ether or α-(tetrahydrofuranyl)-ω-hydroxypoly(oxy-1,2-ethanediyl) has the formula I wherein R_1 =  , R_2 = H and x has an average value of from 1 to 2. It has an average molecular weight of ca. 190; a b.p. of from ca. 80-100°C (at 40N/m²), a density of ca. 1.070 - 1.090 g/cm³ (at 20°C); a hydroxy value of ca. 300-400; a refractive index of ca. 1.4545 (sodium D line, 589mm) (at 40°C); and a viscosity of ca. 8-18 mN s/m² (at 20°). [c.f. "Handbook of Pharmaceutical Excipients, published by American Pharmaceutical Association/ The Pharmaceutical Society of Great Briatin (1986), p. 127 and Fiedler, "Lexikon der Hilfstoffe", 3rd edition (1989), p. 577.]

The precise properties of Glycofurol vary according to relative purity. Thus lower quality grades contain significant amounts of tetrahydrofurfuryl alcohol and other impurities. For the purposes of the present invention Glycofurol 75, designating a product meeting the above physical data and for which the fraction having the formula I above in which x = 1-2 amounts to a minimum of 95%, is preferred.

Use of components defined under (1.1.) and (1.2.) above has in particular been found to provide compositions in accordance with (A) in which the hydrophilic phase is especially well suited as cyclosporin carrier medium, e.g. in which the hydrophilic phase enables cyclosporin-loading of the composition, adequate for convenient therapeutic dosaging, e.g. for oral administration.

Compositions in accordance with (A) comprising components as defined under (1.1.) and/or (1.2.) as hydrophilic phase may of course additionally include one or more further ingredients as hydrophilic phase component. Preferably however any additional components will comprise materials in which the cyclosporin active ingredient is sufficiently soluble, such that the efficacy of the hydrophilic phase as cyclosporin carrier medium is not materially impaired. Examples of possible additional hydrophilic phase components are lower (e.g. C_{1-5})

alkanols, in particular ethanol.

While, however, use of alkanols, e.g. ethanol, as hydrophilic phase component is contemplated by the present invention, for reasons hereinbefore discussed, this will be generally less preferred. Preferably, compositions as defined under (A) will be non-alkanol-based, i.e. will not comprise an alkanol as a predominant hydrophilic phase component. Suitably the hydrophilic phase comprises less than 50%, more preferably less than 25%, most preferably less than 10% by weight alkanolic components. Most suitably, the hydrophilic phase will be free or substantially free of alkanolic components, i.e. comprise less than 5%, preferably less than 2%, e.g. from 0 to 1% alkanolic components. By "alkanol" is meant, in particular, C_{1-5}alkanols, especially ethanol.

In an especially preferred embodiment the hydrophilic phase of compositions defined under (A) will consist or consist essentially of components as defined under (1.1.) or (1.2.) above, in particular Transcutol, Glycofurol and/or 1,2-propylene glycol. Most suitably they will consist or consist essentially of either components (1.1.) or component (1.2.).

Compositions in accordance with (A) comprising a component (1.1), especially Glycofurol, are of particular interest in that they are well adapted for presentation in soft gelatin encapsulated form. Such compositions have, in accordance with the invention, also been found to exhibit surprisingly advantageous stability, e.g. as evidenced in long-term stability tests at normal and elevated temperatures. Such compositions are thus particularly well suited to meet difficulties commonly encountered in transport and storage of drug products, including long term storage at the user end, e.g. in hospitals, clinics and like facilities.

Compositions defined under (A) additionally comprise a lipophilic phase (2).

Suitable components for use as lipophilic phase include any pharmaceutically acceptable solvent which is non-miscible with the selected hydrophilic phase, e.g. as defined under (1.1.) or (1.2.). Such solvents will appropriately be devoid or substantially devoid of surfactant function. Especially suitable components for use as lipophilic phase components (2) are, e.g.:

Fatty acid triglycerides, preferably medium chain fatty acid triglycerides. Especially suitable are neutral oils, e.g. neutral plant oils, in particular fractionated coconut oils such as known and commercially available under the trade name Miglyol (c.f. Fiedler, loc. cit. pp. 808-809), including the products:

Miglyol 810: a fractionated coconut oil comprising caprylic-capric acid triglycerides and having a molecular weight : ca. 520. Fatty acid composition = C_6 max. 2%, C_8 ca. 65-75%, C_{10} ca. 25-35%, C_{12} max. 2%; acid no. = ca. 0.1; saponification no. = ca. 340-360; iodine no. = max. 1;

Miglyol 812: a fractionated coconut oil comprising caprylic-capric acid triglycerides and having a molecular weight = ca. 520. Fatty acid composition = C_6 max. ca. 3%, C_8 ca. 50-65%, C_{10} ca. 30-45%, C_{12} max. 5%; acid no. = ca. 0.1; saponification no. = ca. 330-345; iodine no. = max. 1;

Miglyol 818: a caprylic-capric-linoleic acid triglyceride having a molecular weight = ca. 510. Fatty acid composition = C_6 max. 3, C_8 ca. 45-60, C_{10} ca. 25-40, C_{12} ca. 2-5, $C_{18:2}$ ca. 4-6; acid no. = max. 0.2; saponification no. = ca. 315-335, iodine no. = max. 10; and

Captex 355([1]) a caprylic-capric acid triglyceride. Fatty acid content

= caproic ca. 2%, caprylic ca. 55%, capric ca. 42%. Acid no. = max. 0.1; saponification no. = ca. 325-340; iodine no. = max. 0.5.

Also suitable are caprylic-capric acid triglycerides such as known and commercially available under the trade name Myritol (c.f. Fiedler loc. cit., p. 834) including the product Myritol 813 which has an acid no. = max. 1, a saponification no. = ca. 340-350 and an iodine no. = ca. 0.5.

Further suitable products of this class are Capmul MCT(1), Captex 300(1) and Captex 800(1), Neobee M5(2) and Mazol 1400(3).

[(1) = Capital City Products, PO.Box 569, Columbus, OH, USA. (2) = Stepan, PVO Dept., 100 West Hunter Ave., Maywood, NJ 07607, USA. (3) = Mazer Chemicals, 3938 Porett Drive, Gurnee, IL, USA).]

Especially preferred as lipophilic phase component is the product Miglyol 812.

Compositions in accordance with the invention defined under (A) further comprise a pharmaceutically acceptable surfactant (3). The surfactant component may comprise (3.1.) hydrophilic or (3.2.) lipophilic surfactants, or mixtures thereof. Especially preferred are non-ionic hydrophilic and non-ionic lipophilic surfactants. Examples of suitable hydrophilic surfactants for use as surfactant components are e.g.:

3.1.1. Reaction products of natural or hydrogenated vegetable oils and ethylene glycol, i.e. polyoxyethylene glycolated natural or hydrogenated vegetable oils, for example polyoxyethylene glycolated natural or hydrogenated castor oils. Such products may be obtained in known manner, e.g. by reaction of a natural or hydrogenated castor oil or fractions thereof with ethylene oxide, e.g. in a molar ratio of from about 1:35 to about 1:60,

with optional removal of free polyethyleneglycol components from the product, e.g. in accordance with the methods disclosed in German Auslegeschriften 1,182,388 and 1,518,819. Especially suitable are the various tensides available under the trade name Cremophor. Particularly suitable are the products Cremophor RH 40 having a saponification no. ca. 50-60, an acid no. = <1, an iodine no. = <1, a water content (Fischer) = <2%, an n_D^{60} = ca. 1,453 - 1,457 and an HLB = ca. 14 - 16; Cremophor RH 60 having a saponification no. = ca. 40 - 50, an acid No. = <1, an iodine no. = <1, a water content (Fischer) = ca. 4.5-5.5%, an n_D^{25} = ca. 1.453 - 1,457 and an HLB = ca. 15 - 17; and Cremophor EL having a molecular weight (by steam osmometry) = ca. 1630, a saponification no. = ca. 65-70, an acid no. = ca. 2, an iodine no. = ca. 28 - 32 and an n_D^{25} = ca. 1.471 (c.f. Fiedler loc. cit. pp. 326-327). Also suitable for use in this category are the various tensides available under the trade name Nikkol, e.g. Nikkol HCO-60. The said product Nikkol HCO-60 is a reaction product of hydrogenated castor oil and ethylene oxide exhibiting the following characteristics: Acid no. = ca. 0.3; Saponification no. = ca. 47.4; Hydroxy value = ca. 42.5; pH (5%) = ca. 4.6; Color APHA = ca. 40; m.p. = ca. 36.0°C; Freezing point = ca. 32.4°C; H_2O content (%, KF) = ca. 0.03;

3.1.2. Polyoxyethylene-sorbitan-fatty acid esters e.g. mono- and trilauryl, palmityl, stearyl and oleyl esters e.g. of the type known and commercially available under the trade name Tween (c.f. Fiedler, loc. cit. pp. 1300-1304) including the products Tween

20 [polyoxyethylene(20)sorbitanmonolaurate],
40 [polyoxyethylene(20)sorbitanmonopalmitate],
60 [polyoxyethylene(20)sorbitanmonostearate],
80 [polyoxyethylene(20)sorbitanmonooleate],
65 [polyoxyethylene(20)sorbitantristearate],

85 [polyoxyethylene(20)sorbitantrioleate],
21 [polyoxyethylene(4)sorbitanmonolaurate],
61 [polyoxyethylene(4)sorbitanmonostearate], and
81 [polyoxyethylene(5)sorbitanmonooleate].

Especially preferred products of this class for use in the compositions of the invention are the above products Tween 40 and Tween 80;

3.1.3. Polyoxyethylene fatty acid esters, for example polyoxyethylene stearic acid esters of the type known and commercially available under the trade name Myrj (c.f. Fiedler, loc. cit., p. 834) as well as polyoxyethylene fatty acid esters known and commercially available under the trade name Cetiol HE. (c.f. Fiedler, loc. cit., p. 284); an especially preferred product of this class for use in the compositions of the invention is the product Myrj 52 having a D^{25} = ca. 1.1., m.p. = ca. 40-44°C, an HLB = ca. 16.9., an acid no. = ca. 0-1 and a saponification no. = ca. 25-35;

3.1.4. Polyoxyethylene-polyoxypropylene co-polymers, e.g. of the type known and commercially available under the trade names Pluronic and Emkalyx (c.f. Fiedler, loc. cit., pp. 956-958). An especially preferred product of this class for use in the compositions of the invention is the product Pluronic F68;

3.1.5. Polyoxyethylene-polyoxypropylene block co-polymers, e.g. of the type known and commercially available under the trade name Poloxamer (c.f. Fiedler, loc. cit., pp. 959). An especially suitable product of this class for use in the compositions of the invention is the product Poloxamer 188;

3.1.6. Dioctylsuccinate, dioctylsodiumsulfosuccinate, di-[2-ethylhexyl]-succinate or sodium lauryl sulfate;

3.1.7. Phospholipids, in particular lecithins (c.f. Fiedler, loc. cit., pp. 731-733). Lecithins suitable for use in the compositions of the invention include, in particular, soya bean lecithins;

3.1.8. Propylene glycol mono- and di-fatty acid esters such as propylene glycol dicaprylate, propylene glycol dilaurate, propylene glycol hydroxystearate, propylene glycol isostearate, propylene glycol laurate, propylene glycol ricinoleate, propylene glycol stearate and so forth (c.f. Fiedler, loc. cit., pp. 1013 et seq.). Especially preferred is propylene glycol caprylic-capric acid diester as known and commercially available under the trade name Miglyol 840 (c.f. Fiedler, loc. cit., p. 809). Miglyol 840 has a fatty acid content = C_6 max. ca. 3%, C_8 ca. 65-80%, C_{10} ca. 15-30%, C_{12} max. 3%. Acid no. = max. 0.1, iodine no. = ca. 320-340, iodine no. = max. 1; and

3.1.9. Bile salts, e.g. alkali metal salts, for example sodium taurocholate.

Examples of suitable lipophilic surfactants for use as surfactant component are, e.g.:

3.2.1. Trans-esterification products of natural vegetable oil triglycerides and polyalkylene polyols. Such trans-esterification products are known from the art and may be obtained e.g. in accordance with the general procedures

described in US Patent No. 3,288,824. They include transesterification products of various natural (e.g. non-hydrogenated) vegetable oils for example, maize oil, kernel oil, almond oil, ground nut oil, olive oil and palm oil and mixtures thereof with polyethylene glycols, in particular polyethylene glycols having an average molecular weight of from 200 to 800. Preferred are products obtained by trans-esterification of 2 molar parts of a natural vegetable oil triglyceride with one molar part of polyethylene glycol (e.g. having an average molecular weight of from 200 to 800). Various forms of trans-esterification product of the class defined are known and commercially available under the trade name Labrafil [see Fiedler, loc. cit., 707]. Especially useful as components of the compositions of the invention are the products: Labrafil M 1944 CS, a trans-esterification product of kernel oil and polyethylene glycol having an acid no. = ca. 2, a saponification no. ca. 145 - 175 and an iodine no. = ca. 60 - 90; and Labrafil M 2130 CS, a trans-esterification product of a C_{12}- to C_{18}- glyceride and polyethylene glycol having a melting point = ca. 35 - 40°C., an acid no. = <2, a saponification no. = ca. 185 - 200 and an iodine no. = <3;

3.2.2. Mono-, di- and mono/di-glycerides, especially esterification products of caprylic or capric acid with glycerol. Preferred products of this class are e.g. those comprising or consisting mainly or essentially of caprylic/capric acid mono- and di-glycerides such as are commercially available under the trade name Imwitor (c.f. loc. cit., pp. 645). A particularly suitable product of this class for use in the compositions of the invention is the product Imwitor 742, which is the esterification product of a mixture of ca. 60 p.p.w. caprylic acid and ca. 40 p.p.w. capric acid with glycerol. Imwitor 742 is typically a yellowish crystalline mass, liquid at ca. 26°C;

acid no. = max. 2; iodine no. = max. 1; saponification no. = ca. 235 - 275; % monoglycerides = ca. 40-50%; free glycerol = max. 2%; m.p. = ca. 24 - 26°C; unsaponifiables = 0.3% max.; peroxide no. = max. 1;

3.2.3. Sorbitan fatty acid esters e.g. of the type known and commercially available under the trade name Span, for example including sorbitan-monolauryl, -monopalmityl, -monostearyl, -tristearyl, -monooleyl and -trioleyl esters - (c.f. Fiedler, loc. cit., pp. 1139-1140);

3.2.4. Pentaerythritol fatty acid esters and polyalkylene glycol ethers, for example pentaerythrite- -dioleate, -distearate, -monolaurate, -polyglycol ether and -monostearate as well as pentaerythrite-fatty acid esters (c.f. Fiedler, loc. cit. pp. 923-924);

3.2.5. Monoglycerides, e.g. glycerol monooleate, glycerol monopalmitate and glycerol monostearate, for example as known and commercially available under the trade names Myvatex, Myvaplex and Myverol (c.f. Fiedler, loc. cit., pp. 836), and acetylated, e.g. mono-and di-acetylated monoglycerides, for example as known and commercially available under the trade name Myvacet (c.f. Fiedler, loc. cit., pp. 835);

3.2.6. Glycerol triacetate or (1,2,3)-triacetin (c.f. Fiedler, loc. cit., pp. 952); and

3.2.7. Sterols and derivatives thereof, for example cholesterols and derivatives thereof, in particular phytosterols, e.g. products comprising sitosterol, campesterol or stigmasterol, and ethylene oxide adducts thereof, for example soya sterols and derivatives thereof, such as known under the trade name Generol (c.f. Fiedler loc. cit., p.p. 554 and 555) in particular the products Generol 122, 122 E5, 122 E10, and 122 E25.

Compositions as defined under (A) above include systems comprising either a single surfactant or mixture of surfactants, e.g. comprising a first surfactant and one or more co-surfactants. Surfactant and co-surfactant combinations may be selected, e.g. from any of the surfactant types indicated under (3.1.1.) to (3.2.7.) above.

When the hydrophilic phase comprises a di- or partial-ether as defined under (1.1) above, in particular Transcutol or Glycofurol, use of a single surfactant will generally be sufficient, though co-surfactants may be added if desired, e.g. to further improve stability characteristics. When 1,2-propylene glycol is employed as sole or principle hydrophilic phase component, the use of at least two surfactants, i.e. a surfactant and co-surfactant, will generally be required. Compositions as defined under (A) comprising 1,2-propylene glycol as hydrophilic phase thus suitably comprise both a surfactant and a co-surfactant.

Surfactants as defined under (3.1.1.), (3.1.3.), (3.1.7), (3.2.2.) and (3.2.5.) above are of particular interest for use in compositions as defined under (A). Especially suitable surfactant/co-surfactant combinations are hydrophilic/lipophilic surfactant combinations, e.g. combinations of surfactants in accordance with (3.1.1.) with surfactants in accordance with (3.2.5.).

When the surfactant comprises an effective solvent for the cyclosporin active ingredient, as in the case e.g. of surfactants or mixtures of

surfactants under (3.1.1.) to (3.2.7.) above, it may be incorporated into compositions as defined under (A), not only as surfactant, but in excess as an additional carrier or co-solvent phase, i.e. as part of the hydrophilic or lipophilic phase.

Compositions in accordance with (A) above may also comprise:

4. A thickening agent.

Suitable thickening agents may be of those known and employed in the art, including, e.g. pharmaceutically acceptable polymeric materials and inorganic thickening agents, for example of the following types:

4.1. Polyacrylate and polyacrylate co-polymer resins, for example poly-acrylic acid and poly-acrylic acid/methacrylic acid resins, such as known and commercially available under the trade name Carbopol (c.f. Fiedler, loc. cit., pp. 254-256), in particular the products Carbopol 934, 940 and 941, and Eudragit (c.f. Fiedler, loc. cit., pp. 486-487), in particular the products Eudragit E, L, S, RL and RS and, most especially, the products Eudragit E, L and S;

4.2. Celluloses and cellulose derivatives including: alkyl celluloses, e.g. methyl-, ethyl- and propyl-celluloses; hydroxyalkyl-celluloses, e.g. hydroxypropyl-celluloses and hydroxypropylalkyl-celluloses such as hydroxypropyl-methyl-celluloses; acylated celluloses, e.g. cellulose-acetates, cellulose-acetatephthallates, cellulose-acetatesuccinates and hydroxypropylmethyl-cellulose phthallates; and salts thereof such as sodium-carboxymethyl--celluloses. Examples of such products suitable for use in accordance with the present invention are those known and

commercially available, e.g. under the trade names Klucel and Methocel (c.f. Fiedler, loc. cit., pp. 688 and 790), in particular the products Klucel LF, MF, GF and HF and Methocel K 100, K 15M, K 100M, E 5M, E 15, E 15M and E 100M;

4.3. Polyvinylpyrrolidones, including for example poly-N-vinylpyrrolidones and vinylpyrrolidone co-polymers such as vinylpyrrolidone-vinylacetate co-polymers. Examples of such compounds suitable for use in accordance with the present invention are those known and commercially available, e.g. under the trade name Kollidon (or, in the USA, Povidone) (c.f. Fiedler, loc. cit., pp. 694-696), in particular the products Kollidon 30 and 90;

4.4. Polyvinyl resins, e.g. including polyvinylacetates and alcohols, as well as other polymeric materials including gum traganth, gum arabicum, alginates, e.g. alginic acid, and salts thereof, e.g. sodium alginates;

4.5. Inorganic thickening agents such as atapulgite, bentonite and silicates including hydrophilic silicon dioxide products, e.g. alkylated (for example methylated) silica gels, in particular colloidal silicon dioxide products as known and commercially available under the trade name Aerosil [c.f. Handbook of Pharmaceutical Excipients, loc. cit., p.p. 253-256] in particular the products Aerosil 130, 200, 300, 380, 0, OX 50, TT 600, MOX 80, MOX 170, LK 84 and the methylated Aerosil R 972.

In the case of compositions in accordance with (A) which are intended for oral administration, such thickening agents may be included, e.g.

to provide a sustained release effect. However, where oral administration is intended, the use of thickening agents as aforesaid will generally not be required and is generally less preferred. Use of thickening agents is, on the other hand, indicated, e.g. where topical application is foreseen.

Compositions in accordance with (A) above may also include one or more further ingredients in particular diluents, anti-oxidants [e.g. ascorbyl palmitate, butyl hydroxy anisole (BHA), butyl hydroxy toluene (BHT) and tocopherols, e.g. α-tocopherol (vitamin E)], flavouring agents and so forth. Use of an anti-oxidant, in particular a tocopherol, is particularly advantageous.

While it is foreseen, especially where oral administration is contemplated, that compositions in accordance with the invention as defined under (A) should comprise end dosage forms for administration as such, the present invention also provides pharmaceutical compositions comprising a cyclosporin as active ingredient and which are themselves microemulsions. Thus where oral administration is practiced, microemulsions obtained, e.g. by diluting a "microemulsion pre-concentrate" as defined under (A) with water or other aqueous medium may be employed as formulations for drinking. Similarly, where topical application is foreseen, compositions comprising a hydrocolloid thickening agent, e.g. as set forth under (4.2.) or (4.4.) above will suitably also comprise water, thus providing an aqueous microemulsion in gel, paste, cream or like form. Such compositions are also new. Accordingly in a yet further aspect the present invention provides:

B) A pharmaceutical composition which is a microemulsion and comprises a cyclosporin as active ingredient.

Compositions as defined under (B) may comprise any of components (1) to (3) as hereinbefore described in relation to compositions as

defined under (A) and water. Compositions (B) are o/w microemulsions. Preferably they will exhibit stability characteristics as hereinbefore described in relation to microemulsions obtainable from compositions defined under (A).

In accordance with the present invention it has further been found that use of di- or partial-ethers as defined under (1.1.) as carrier media is quite generally advantageous for the preparation of pharmaceutical compositions comprising cyclosporins, not only in relation to the preparation of "microemulsion pre-concentrate" and microemulsion formulations as hereinbefore described. Thus use of such ethers as components of other oral and, in particular, topical delivery systems is surprisingly found of itself to meet difficulties hitherto encountered in the art as hereinbefore described. Such compositions are also new. Accordingly in a yet further embodiment the present invention also provides:

C) A pharmaceutical composition comprising a cyclosporin as active ingredient, together with a pharmaceutically acceptable C_{1-5}alkyl or tetrahydrofurfuryl di- or partial-ether of a low molecular weight mono- or poly-oxy-alkane diol.

Preferred ether components for use in compositions as defined under (C) above are as hereinbefore described in relation to (1.1.), the products Transcutol and Glycofurol being especially preferred. Compositions in accordance with (C) suitably contain one or more further ingredients, e.g. surfactants, co-solvents or thickening agents.

In particular, compositions as defined under (C) will suitably also comprise a pharmaceutically acceptable hydrophilic surfactant especially a non-ionic hydrophilic surfactant. Suitable hydrophilic surfactant components are any of those hereinbefore described under (3.1.1.) to (3.1.9.).

Compositions as defined under (C) also suitably comprise a pharmaceutically acceptable lipophilic surfactant either as a surfactant or as a co-solvent, or a pharmaceutically acceptable co-solvent. Suitable co-solvent/lipophilic surfactant components are any of those hereinbefore described under (2) and (3.2.1.) to (3.2.7.).

Compositions in accordance with (C) include forms other than as defined under (A) and (B), for example solutions, suspensions, dispersions regular emulsions and the like. In partiuclar compositions in accordance with (C) which additionally comprise a surfactant or both a surfactant and a co-solvent include, for example, emulsion pre-concentrates (i.e. compositions which, on contacting with water, provide regular emulsions - as opposed to microemulsions - of the o/w or w/o type), and regular emulsions of both hydrophilic/lipophilic and lipophilic/hydrophilic type. In the case of formulations, e.g. for drinking or for topical application, they will in particular also include aqueous emulsions of o/w or w/o type. In general emulsion pre-concentrates giving o/w emulsions and (ii) o/w emulsions as such will be preferred, in particular where oral administration is contemplated.

Compositions as defined under (C) may further comprise a pharmaceutically acceptable thickening agent, suitable thickening agents being any of those hereinbefore described under (4.1.) to (4.5.).

Compositions in accordance with (C) may also comprise further additives, e.g. preserving and flavouring agents etc... as hereinbefore described in relation to compositions (A). In particular they will preferably also include an anti-oxidant, e.g. any of the specific anti-oxidants hereinbefore described in relation to compositions (A).

Of particular interest in accordance with the present invention are:

D) Compositions as defined under (C) additionally comprising: (5) a fatty acid saccharide monoester.

Compositions as defined under (D) will generally comprise the cyclosporin in a carrier medium comprising components (1.1.), e.g. Glycofurol or Transcutol, and component (5). Commonly, the cyclosporin and component (5) will each be present in compositions in accordance with (D) in molecular dispersion or solution including, where appropriate, solid solution. Component (5) will generally act in compositions in accordance with (D) as solubilizor for the cyclosporin. Compositions in accordance with (D) have the particular advantage of meeting stability and related difficulties otherwise associated with components (5) resulting from their inherent strongly hygroscopic properties.

Preferred components (5) for use in compositions in accordance with (D) are water soluble fatty acid saccharide monoesters, e.g. fatty acid monoesters of saccharides having a solubility in water of at least 3.3% at ambient temperature, e.g. at ca. 20°C, i.e. which are soluble in water at ambient temperature in an amount of at least 1g monoester per 30 ml water.

The fatty acid moiety of components (5) may comprise saturated or unsaturated fatty acids or mixtures thereof. Particularly suitable components (5) are C_{6-18}-fatty acid saccharide monoesters, in particular water soluble C_{6-18}-fatty acid saccharide monoesters. Especially suitable components (5) are caproic (C_6), caprylic (C_8), capric (C_{10}), lauric (C_{12}), myristic (C_{14}), palmitic (C_{16}), oleic (C_{18}), ricinoleic (C_{18}) and 12-hydroxystearic (C_{18}) acid saccharide monoesters, especially lauric acid saccharide monoesters.

The saccharide moiety of component (5) may comprise any appropriate

sugar residue, e.g. mono-, di- or tri-saccharide residue. Suitably, the saccharide moiety will comprise a di- or tri-saccharide residue. Preferred components (5) comprise C_{6-14}-fatty acid di-saccharide monoesters and C_{8-18}-fatty acid tri-saccharide monoesters. Especially suitable saccharide moieties are saccharose and raffinose residues.

Particularly suitable components (5) are thus: saccharose monocaproate, saccharose monolaurate, saccharose monomyristate, saccharose monooleate, saccharose monoricinoleate, raffinose monocaproate, raffinose monolaurate, raffinose monomyristate, raffinose monopalmitate and raffinose monooleate. Most preferred components (5) are raffinose monolaurate and, especially, saccharose monolaurate.

Components (5) will suitably have a hydrophilic-lipophilic balance (HLB) of at least 10.

Components (5) suitably have an ester residue purity of at least 80%, more preferably at least 90%, most preferably at least 95%. Components (5) suitably have a melting point of from about 15° to about 60°C, more preferably from about 25° to about 50°C.

Compositions in accordance with (D) may also contain further ingredients, e.g. as hereinbefore described in relation to compositions (C).

In particular, they may include a component capable of modifying the release characteristics of the composition with respect to the cyclosporin, for example thickening agents, e.g. such as hereinbefore described under (4.1.) to (4.5.).

Compositions in accordance with (D) will in particular also suitably comprise one or more anti-oxidants, e.g. as hereinbefore specified in relation to compositions (A).

Compositions in accordance with (D) will also suitably comprise one or more stabilizors or buffering agents, in particular to prevent hydrolysis of component (5) during processing or on storage. Such stabilizors may include acid stabilizors such as citric acid, acetic acid, tartaric acid or fumaric acid as well as basic stabilizors such as potassium hydrogen phosphate.

Such stabilizors or buffer agents will appropriately be added in an amount sufficient to achieve or maintain a pH within the range of from about 3 to 8, more preferably about 5 to 6, compositions in accordance with (D) having a pH within the above indicated ranges being generally preferred.

Compositions in accordance with (D) will in particular also preferably comprise a polyoxyalkylene-free hydrophilic surfactant, such as set forth under (3.1.6.) or (3.1.7.) above.

Compositions in accordance with the present invention may be employed for administration in any appropriate manner, e.g. orally, e.g. in unit dosage form, for example in hard or soft gelatin encapsulated form, parenterally or topically e.g. for application to the skin, for example in the form of a cream, paste, lotion, gel, ointment, poultice, cataplasm, plaster, dermal patch or the like, or for ophthalmic application, for example in the form of an eye-drop, -lotion or -gel formulation. Readily flowable forms, for example solutions and microemulsions, may also be employed e.g. for intralesional injection for the treatment of psoriasis, or may be administered rectally, e.g. as an enema for the treatment of inflammatory bowel disease or Crohn's disease. Compositions in accordance with the invention are however primarily intended for oral or topical application, in particular application to the skin.

The relative proportion of ingredients in the compositions of the invention will, of course, vary considerably depending on the

particular type of composition concerned, e.g. whether it is a "microemulsion pre-concentrate", microemulsion, regular emulsion, solution and so forth. The relative proportions will also vary, depending on the particular function of ingredients in the composition, for example, in the case of a surfactant component of a "microemulsion pre-concentrate", on whether this is employed as a surfactant only or both a surfactant and a co-solvent. The relative proportions will also vary depending on the particular ingredients employed and the desired physical characteristics of the product composition, e.g. in the case of a composition for topical use, whether this is to be a free flowing liquid or a paste. Determination of workable proportions in any particular instance will generally be within the capability of the man skilled on the art. All indicated proportions and relative weight ranges described below are accordingly to be understood as being indicative of preferred or individually inventive teachings only and not as not limiting the invention in its broadest aspect.

The amount of cyclosporin in compositions of the invention will of course vary, e.g. depending on the intended route of administration and to what extent other components, in particular components (2) to (5) as hereinbefore described, are present. In general however the cyclosporin will be present in an amount within the range of from 0.05 especially about 0.1 to about 35% by weight based on the total weight of the composition.

Components (1) will suitably be present in the compositions of the invention in an amount of from about 0.5 to about 90% by weight based on the total weight of the composition. In the case of compositions in accordance with the invention comprising a component (1.1.) (e.g. Glycofurol or Transcutol), (1.1.) will generally be present in an amount of from about 1 to about 90% by weight, more commonly from about 5 or 10 to about 70% by weight based on the total weight of the composition. In the case of compositions in accordance with (A) or (B)

above comprising a component (1.2.), (1.2.) will generally be present in an amount of from about 2 to about 50% by weight based on the total weight of the composition. In the case of compositions in accordance with the invention comprising a component (2) or (3), these will each be generally present in an amount of from about 0.5 to about 90% by weight based on the total weight of the composition. In an especially preferred aspect the present invention relates to:

E) Compositions as defined under (A) or (C) above for oral administration, e.g. in a form suitable or convenient for oral administration.

For compositions as defined under (A) to (C) intended for non-topical administration and, in particular, for oral dosage forms (E):

a) The cyclosporin will generally be present in an amount of from about 1 or 2 to about 30%, suitably from about 4 to about 25% by weight based on the total weight of the composition. More suitably the cyclosporin will be present in an amount of from about 5 to about 25, especially to about 20%, e.g. from about 5 to 15% by weight based on the total weight of the composition;

b) Component (1.1) when present will generally be present in an amount of from about 15 to about 85, suitably from about 20 to about 80, more suitably from about 25 to about 70, e.g. from about 30 to about 50 or 60% by weight based on the total weight of the composition;

c) Cyclosporin and component (1.1.) when present will generally be present in a ratio of about 1:0.75 to 20, suitably about 1:1 to 15, more suitably about 1:1 to 5, e.g. about 1:1 or 1:1.5 to 4 p.p.w. [Cyclosporin: (1.1.)];

d) Component (1.2.) when present will generally be present in an amount of from about 3 to about 45, suitably about 5 to about 30% by weight based on the total weight of the composition;

e) Cyclosporin and component (1.2.) when present will generally be present in a ratio of about 1:0.1 to 20, suitably about 1:0.2 to 10 p.p.w.. More suitably they will be present in a ratio of about 1:0.3 to 6, e.g. about 1:0.5 to 3 p.p.w. [Cyclosporin: (1.1)].

f) Component (2) when present will generally be present in an amount up to about 45%, suitably up to about 40% by weight based on the total weight of the composition. More suitably component (2) will be present in an amount of from about 2 to about 45, yet more suitably from about 3 to about 35, most suitably from about 5 or 10 to about 30% by weight based on the total weight of the composition.

g) Components (2) and (1.1) when present will generally be present in a ratio of about 1:0.5 to 40, suitably about 1:0.5 to 20, more suitably about 1:0.75 to 10, e.g. about 1:0.75 to 4 p.p.w. [(2):(1)].

h) Components (2) and (1.2) when present will suitably be present in a ratio of about 1:0.075 to 22, suitably about 1:0.1 to 15, most suitably about 1:0.15 to 6 p.p.w., e.g. about 1:0.5 to 3 p.p.w. [(2):(1.2)].

i) Components (3) when present [including both components of type (3.1.) and (3.2.)], will generally be present in an amount of up to about 90, e.g. from about 20 to about 90% by weight based on the total weight of the composition. More suitably components (3) will be present in an amount of from about 20 or 25 to about 80 or 90% by weight based on the total weight of the composition, e.g. from about 25 to about 55% when a component (1.1) is employed or

from about 40 to 75% when a component (1.2) is employed.

j) Cyclosporin and component (3) [including both components of type (3.1.) and (3.2.)] when present will generally be present in a ratio of about 1:0.5 to 20, more suitably to 12 p.p.w.. Appropriately they will be present in a ratio of about 1:1 to 10 p.p.w., e.g. about 1:1 to 5 p.p.w. when a component (1.1) is present or about 1:3 to 8 p.p.w. when a component (1.2) is present. [Cyclosporin: (3)].

For compositions as defined under (A) and (B) ["microemulsion pre-concentrates" and microemulsions] the relative proportions of ingredients comprising (1) the hydrophilic phase, (2) the lipophilic phase and (3) the surfactant will vary with the concentration of cyclosporin present. They will also vary in relative proportion to each other.

Compositions according to (A) may thus be defined as comprising a cyclosporin together with (1) a hydrophilic phase [e.g. as defined under (1.1) or (1.2) above], (2) a lipophilic phase [e.g. as defined under (2.1) or (2.2) above] and a surfactant [e.g. as defined under (3.1) or (3.2) above], the relative proportions of cyclosporin: (1):(2):(3) being such that on contact with water, e.g. as hereinbefore indicated in relative proportions of 1:1 p.p.w. [cyclosporin+(1)+(2)+(3)):H_2O] or more, a microemulsion [e.g. of o/w type] is obtainable.

Similarly compositions according to (B) may be defined as comprising a cyclosporin together with components (1), (2) and (3) as aforesaid and water in relative proportions, e.g. as hereinbefore indicated, required to provide a microemulsion [e.g. of o/w type].

Compositions in accordance with (A) and (B) preferably comprise from about 2 to about 30, more preferably from about 5 to about 20, most

preferably from about 10 to about 15% by weight of cyclosporin based on the total weight of cyclosporin plus components (1) + (2) + (3).

When (1) of compositions (A) or (B) is as defined under (1.1) above, e.g. comprises Transcutol or Glycofurol, components (1.1), (2) and (3) will preferably be present in amounts of from about 15 to about 85%, more preferably from about 25 to about 65% of (1.1), from about 2 to about 40, more preferably from about 3 to about 35 most preferably from about 3 to about 30% of (2) and from about 15 to about 85, more preferably from about 25 to about 55 or 60% of (3), all %ages being by weight based on the total of (1.1) + (2) + (3). Use of Glycofurol is of particular interest.

When (1) of compositions (A) or (B) is 1,2-propylene glycol [(1.2) above], components (1.2.), (2) and (3) will suitably be present in amounts of from about 3 to about 35%, more preferably from about 3 to about 25% of (1.2), from about 2 to about 35%, more preferably from about 3 to about 30% of (2) and from about 45 to about 90%, more preferably from about 50 to about 90%, e.g. from about 55 to about 80% of (3), all %ages being by weight based on the total of (1.2) + (2) + (3). As previously indicated, when (1) is 1,2-propylene glycol component (3) will generally comprise both a surfactant and a co-surfactant. When a co-surfactant is employed, surfactant and co-surfactant will suitably be present in a ratio of up to about 50:1, preferably up to 20:1, more preferably up to 15:1, e.g. from 2 to 15:1 p.p.w. (surfactant: co-surfactant).

Fig. I attached, represents a three-way plot for relative concentrations of components (1.1) (e.g. Glycofurol), (2) (e.g. Miglyol 812), and (3) (e.g. Cremophore RH40) in compositions according to (A) and comprising ca. 10% cyclosporin (e.g. Ciclosporin) by weight. Relative concentration of component (1.1) increases from 0% along the left hand margin of the plot to 100% at the lower right corner, as indicated by the arrow "1.1". Concentration of component

(2) increases from 0% at the right hand margin of the plot to 100% at the lower left corner, as indicated by the arrow "2". Thus a composition comprising 50% of (1.1) and 50% of (2) only, is designated at the mid-point of the base-line of the plot. Relative concentration of component (3) increases from 0% at the base-line of the plot to 100% at the apex, as indicated by the arrow "3". Lines within the plot represent increments of 10%, from 0% at each margin to 100% at the apex opposite.

For compositions as defined under (A) and (B) the relative proportion of components (1.1), (2) and (3) will suitably lie within the area A defined by the line a of Fig. I. More suitably the relative proportion of components (1.1), (2) and (3) will lie within the area B defined by the line b of Fig. I, microemulsions based on these proportions being found to have greatest stability, e.g. of >24 hrs./an average particle size of less than 1,000Å. Compositions in accordance with the invention comprising the components (1.1), (2) and (3) in relative proportion as defined above with reference to Fig. I accordingly represent especially preferred embodiments.

Fig. II attached, represents a three-way plot for relative concentrations of components (1.2), (2) e.g. Miglyol 812 and (3) in compositions according to (A) and comprising ca. 10% cyclosporin (e.g. Ciclosporin) by weight. In this case (3) comprises an appropriate surfactant/co-surfactant mixture, e.g. in a ratio of 11:1 p.p.w., for example comprising 11 p.p.w. Cremophor RH40 and 1 p.p.w. Glycerinmonooleate. Relative amounts of components (1.2), (2) and (3) are indicated, as for Fig. I, by arrows "1.2", "2" and "3" respectively.

For compositions as defined under (A) and (B) the relative proportions of components (1.2), (2) and (3) will suitably lie within the area X defined by the line x of Fig. II. More suitably the relative proportion of components (1.2), (2) and (3) will lie within the area Y

defined by line y of Fig. II. Most suitably the relative proportion of components (1.2), (2) and (3) will lie within the area Z of Fig. I defined by line z, microemulsions based on proportions within the areas Y and Z having an average particle size of the order of 1,100Å and <200Å respectively and a stability, e.g. of >24 hrs..

Compositions in accordance with (E) above may additionally include a thickening agent, though, as previously indicated, this will generally be less preferred. Suitable thickening agents include any of those hereinbefore described under (4) above. The amount of thickening agent present may vary e.g. depending on the required consistency of the end product, e.g. whether it is to be in a thickened flowable form, for example for filling into a capsule or the like, or sufficiently resilient to be mouldable or formable, e.g. for use in the manufacture of tablets or the like. The amount will of course also depend on the nature of the thickening agent chosen. In general components (4), when present will be present in an amount of up to about 25% by weight based on the total weight of the composition, more suitably in an amount of up to about 15 or 20% by weight, e.g. in an amount of from 0.5 or 5 up to 15 or 20% by weight based on the total weight of the composition.

Compositions in accordance with (E) may also include further additives or ingredients, e.g. as hereinbefore described with reference to compositions (A) and (C). In particular they may comprise antioxidants, e.g. in an amount of up to about 0.5 or 1% by weight based on the total weight of the composition, and sweetening or flavouring agents, e.g. in an amount of up to about 2.5 or 5% by weight based on the total weight of the composition.

Compositions (E) in accordance with definition (A) have been found to exhibit especially advantageous properties when administered orally, e.g. in terms of both the consistancy and high level of bioavailability achieved. In particular, and in contrast with other

galenic systems, e.g. as known from the art, it has been found that such compositions are compatible with tenside materials, e.g bile salts, present in the gastro-intestinal tract. That is, they are fully dispersible in aqueous systems comprising such natural tensides and are thus capable of providing microemulsion systems in situ which are stable and do not exhibit precipitation or other disruption of fine particulate structure. Function of such systems on oral administration remains independent of and/or unimpaired by the relative presence or absence of bile salts at any particular time or for any given individual. Such compositions accordingly represent an especially preferred embodiment of the invention.

Compositions in accordance with (E) above will preferably be compounded in unit dosage form, e.g. by filling into orally administerable capsule shells, e.g. soft or hard gelatine capsule shells or by tabletting or other moulding process. Where compositions (E) are in unit dosage form, each unit dosage will suitably contain between about 5 or 10 and about 200mg cyclosporin, more suitably between about 15 or 25 and about 150mg, e.g. 25, 50 or 100mg cyclosporin. Thus unit dosage forms in accordance with the invention, suitable for administration 1x, 2x or 3x up to 5x daily (e.g. depending on the particular purpose of therapy, the phase of therapy etc...) will appropriately comprise e.g. about 50mg or about 100mg cyclosporin per unit dosage.

Compositions in accordance with (B) above for oral administration may be prepared, by addition of compositions as described in relation to (A) or (E) above to water or any other aqueous system, e.g. in relative proportions (composition:H_2O) as hereinbefore indicated, for example a sweetened or flavoured preparation for drinking. Such compositions may thus comprise any system as hereinabove defined or described in relation to compositions (A) or (E), plus sufficient water to form a microemulsion.

Compositions as defined under (D) above are, in particular, intended for oral administration, though use in form suitable, e.g. for topical, including dermal and topical ophthalmic, parenteral or rectal administration, as well as for intralesional injection, is also embraced.

In the case of compositions as defined under (D) the cyclosporin and required component (1.1) may be present in a ratio of about 1:0.5 to 200, preferably about 1:0.5 to 100, more preferably about 1:0.5 to 50 p.p.w.. Yet more suitably they will be present in a ratio of about 1:1 to 10, more preferably 1:1 to 5, most preferably about 1:1.5 to 2.5, e.g. about 1:1.6 or 1:2 p.p.w. [Cyclosporin: (1.1)]. Cyclosporin and required component (5) will suitably present in a ratio of about 1:3 to 200, preferably about 1:3 to 100, more preferably about 1:3 to 50 p.p.w.. Yet more suitably they will be present in a ratio of about 1:5 to 20, preferably about 1:5 to to 10, most preferably about 1:6.0 to 6.5, e.g. about 1:6.25 p.p.w. [Cyclosporin:(1.1)].

Suitably compositions in accordance with (D) will be made up in unit dosage form, whether for oral administration or otherwise.

The amount of cyclosporin present in such unit dosage forms will of course vary depending on e.g. the condition to be treated, the intended mode of administration and the effect desired. In general however, unit dosage forms in accordance with (D) will suitably comprise from about 2 to about 200mg cyclosporin, per unit dosage.

Suitable dosage forms for oral administration include e.g. liquids, granulates and the like. Preferred dosage forms are however unit dosage forms, for example tabletted or encapsulated forms, in particular hard or soft gelatin encapsulated forms.

Unit dosage forms for oral administration in accordance with (D) will suitably comprise from about 5 or 10 to about 200mg, more suitably

from about 15 or 20 to about 100mg, e.g. 25, 50 or 100mg cyclosporin per unit dosage.

Compositions (D) have the further advantage that they are able to provide the basis for compositions exhibiting modified release characteristics, for example delayed release of cyclosporin or release of cyclosporin over prolonged periods of time, e.g. following oral administration. Such compositions additionally comprise a component capable of modifying the release characteristics of the composition with respect to the cyclosporin. Such components include, for example, (4), a thickening agent, e.g. in accordance with any of (4.1) to (4.5) above.

When compositions (D) comprise a component (4), this is suitably present in an amount of from about 0.5 to 50%, more preferably from about 1 to 20%, most preferably from about 2 to 10% by weight based on the total weight of Cyclosporin plus (1.1) + (4) + (5).

As previously indicated, compositions in accordance with (D) will advantageously include one or more stabilizors or buffering agents or polyoxyalkylene-free surfactants. Such stabilizors and/or buffering agents will suitably be present in an amount of up to 5% by weight or, when citric or acetic acid are employed, up to 10% by weight based on the weight of cyclosporin plus (1.1) + (5). When a surfactant as aforesaid is present, this is suitably present in an amount of from about 5 to about 50, more preferably from about 10 to about 25% by weight based on the weight of component (5).

Compositions in accordance with (D) will also suitably comprise further additives in particular flavouring agents or, in particular, anti-oxidants. Suitable anti-oxidants and quantities employed are as hereinbefore described in relation to compositions (E).

Compositions in accordance with (D) will also preferably be free or

substantially free of lower alkanols, in particular ethanol, e.g. comprise less than 5%, more preferably less then 2%, e.g. from 0 to 1%, lower alkanolic components based on the total weight of the composition.

Compositions as defined under (A) to (C) are also of particular interest for topical administration. Accordingly in a yet further aspect the present invention provides:

F) Compositions as defined under any one of (A) to (C) above for topical, especially for dermal application, i.e. in a form suitable or convenient for topical application.

Where topical administration is contemplated, the cyclosporin will suitably be present in an amount of from about 0.05, more preferably from about 0.1, to about 15% by weight based on the total weight of the composition. More preferably the cyclosporin will be present in an amount of from about 0.1 to about 10% by weight.

In the case of compsitions (F) which are compositions in accordance with (A) or (B), the relative proportion of components (1), (2) and (3) will be as hereinbefore described for such compositions, e.g. with reference to Figs. I and II.

Compositions (F) in accordance with (C) the other hand may take any suitable form, e.g. comprise solutions, suspensions, dispersions and regular emulsions. Component (1.1) may suitably be present in such compositions in an amount of from about 1 to about 70%, preferably from about 5 to about 50%, more preferably from about 7 to about 25% by weight based on the total weight of the composition.

Compositions (F) will suitably comprise one or more carriers or diluents and/or other ingredients providing a carrier system, e.g. thickening agents, emulsifying agents, preserving agents, moisturising

agents, colourants and so forth.

Compositions (F) may be in any form suitable for topical application, e.g. application to the skin surface, for example flowable, e.g. liquid or semi-liquid form, in the form of a powder or in the form of a topically applicable spray. Examples of suitable flowable forms include e.g. gels, including oil-in-water and water-in-oil emulsions or microemulsions, creams, pastes amd ointments and the like as well as lotions, and tinctures, etc.. Such compositions also include, e.g. cataplasms and poultices as well as transdermal patch systems.

Selection of excipients for the preparation of such formulations will, of course, be determined by the type of formulation desired as well as the particular condition to be treated, the status of the condition, area to be treated, skin condition and effect desired. Thus chronic psoriatic plaques will more suitably be treated with hydrophobic, e.g. fat-based compositions, for example compositions in accordance with the invention comprising a petrolatum based ointment or cream as carrier medium. In contrast, compositions for use in the treatment of disease conditions involving acute phase inflammatory processes will more appropriately be treated with more hydrophilic compositions, e.g. compositions in accordance with the invention in the form of an oil-in-water emulsion or gel. Although, compositions (F) may comprise, e.g. lower alkanols, for example ethanol, for example as diluent or diluent component, use of these will preferably be avoided, e.g. where compromised skin is to be treated, as in the case of psoriasis. Preferred compositions (F) are thus free or substantially alkanol free, e.g. contain less than 5%, more preferably less than 2%, e.g. from about 0 to 1% by weight alkanolic components, in particular of ethanol.

Especially preferred compositions (F) are compositions in accordance with (A), (B) or (C) additionally comprising: (6) a (further) pharmaceutically acceptable diluent or carrier which is non-miscible

with component (1.1.). Compositions as aforesaid will preferably take the form of a water-free or substantially water-free emulsion, i.e. comprise less than 10%, preferably less than 5%, most preferably less than 1% water. Such emulsions include both emulsions comprising component (1.1.) in (6), and emulsions comprising (6) in (1.1.). Preferably they will comprise an emulsion of (1.1.) in (6).

Suitable components (6) include, for example:

6.1. Solid hydrocarbons, for example petroleum jellies, e.g. white petrolatum or Vaseline®, ceresin and solid paraffins, as well as waxes including animal, vegetable and synthetic waxes such as, for example, spermaceti, carnauba and bees wax;

6.2. Liquid hydrocarbons, e.g. liquid paraffins and fatty acid esters such as isopropylmyristate and cetyl palmitate;

6.3. Non-volatile silicones including silicone oils and pastes, and silicone-polyalkyleneoxide co-polylymers [c.f. Fiedler, loc.cit., pp. 1109 and 1110] for example such as known and commercially available under the trade name Piroethicon.

Components (6) will suitably be present in compositions (F) in an amount of up to about 80%, e.g. from about 5 to about 70%, preferably from about 25 to about 60% by weight based on the total weight of the composition.

By use of individual ingredients (6) or mixtures thereof, emulsions may be obtained in liquid or semi-solid form depending on, e.g., desired requirements for topical application.

Compositions (F) will suitably also comprise a surfactant. Suitable

surfactants include, in particular, lipophilic surfactants, including any of those listed under (3.2.1.) to (3.2.7.) above, especially surfactants having an HLB of ca. 5-7. Examples of surfactants of particular utility in relation to compositions (F) include for example, surfactants as described under (3.1.2.), and (3.2.3.) above as well as glycerol monstearate, propyleneglycol monostearate, diethyleneglycol monostearate and glycerol ricinoleate.

Surfactants as aforesaid will suitably be present in compositions (F) in an amount of up to about 60%, e.g. from about 2 to about 50%, preferably from about 10 to about 40% by weight based on the total weight of the composition.

Compositions (F) may further comprise one or more consistency promoting agents, for example microcrystalline waxes, vegetable oils such as olive oils, corn oils and kernel oils, and vegetable oil derivatives including hydrogenated vegetable oils and vegetable oil partial-glycerides, e.g. in an amount of from about 0.1 to about 10%, preferably from about 1 to about 5% weight based on the total weight of the composition.

Compositions (F) will also suitably comprise:

- an anti-oxidant, e.g. any of the antioxidants hereinbefore described in relation to compositions (A), for example in an amount of from about 0.01 to about 0.5% by weight based on the total weight of the composition;

- an anti-bacterial agent, e.g. benzyl alcohol, methyl- or propyl-paraben, benzalkonium chloride, benzoic acid, sorbic acid or chlorobutanol, for example in an amount of from about 0.05 to about 2% by weight based on the total weight of the composition;

- a stabilizor such as microcrystalline starch, sodium EDTA or magnesium sulfate, e.g. in an amount of from about 0.1 to about 10% by weight based on the total weight of the composition; and/or

- a skin penetration enhancer, for example a C_{12-24} mono- or poly-unsaturated fatty acid or alcohol (e.g. vaccenic, cis-vaccenic, linoleic, linolenic, elaidic oleic, petroselinic, erucic or nervonic acid or any of their corresponding alcohols, especially oleic acid or oleyl alcohol), or 1-dodecylazacycloheptan-2-one also known as Azone (c.f. Fiedler, loc. cit., p. 190), e.g. in an amount of from about 1 to about 20, suitably from about 3 to about 15% by weight based on the total weight of the composition.

In addition to the foregoing the present invention also provides a process for the production of a pharmaceutical composition as hereinbefore defined, e.g. as hereinbefore defined under anyone of (A) to (F) above, which process comprises bringing the individual components thereof into intimate admixture and, when required compounding the obtained composition in unit dosage form, for example filling said composition into gelatin, e.g. soft or hard gelatin, capsules.

In a more particular embodiment the invention provides a process for the preparation of a composition as defined under any one of (A) to (D) above, which process comprises bringing a cyclosporin, e.g. Ciclosporin, into inimite admixture with a component (1.1) as hereinbefore defined to obtain a composition as defined under (C) and, optionally, a component (5) as hereinbefore defined to obtain a composition as defined under (D), or with a component (1.2) as hereinbefore defined, whereby optionally when a component (1.1) is employed, or necessarily when a component (1.2) is employed, said aforesaid ingredients are further combined with a component (2) and a component (3) as hereinbefore defined, the relative proportions of

component (1.1) or (1.2), (2) and (3) being chosen such that a composition as defined under (A) is obtained and further, when required, contacting said obtained composition (A) with water, so as to obtain a composition as defined under (B) and when required, compounding an obtained composition (A), (C) or (D) in unit dosage form, e.g. soft or hard gelatin capsule form.

In a specific embodiment the present invention provides a process for producing a composition as defined under (A) above, which process comprises intimately admixing a cyclosporin, e.g Ciclosporin, with a component (1.1) or (1.2) as hereinbefore defined, and a component (2) and a component (3) as hereinbefore defined, the relative proportion of the components (1.1) or (1.2), (2) and (3) being selected relative to the quantity of cyclosporin employed such that a "microemulsion pre-concentrate", e.g. composition capable on addition to water, e.g. in a ratio of at least 1:1 p.p.w. (composition:H_2O) of providing a system comprising a dispersed or particle phase of which the individual particles have a size of less than 2,000 Å, preferably of from about 100 to about 1,000 Å is obtained.

The preferred cyclosporin in relation to the compositions of the invention is Ciclosporin. A further preferred cyclosporin to which the teachings of the present invention are applicable is [Nva]^2-Ciclosporin, also known as cyclosporin G.

The following examples are illustrative of compositions in accordance with the present invention. Examples 1,2,4,5 and 7 illustrate the preparation of compositions in oral unit dosage form, suitable for use, e.g. in the prevention of transplant rejection or for the treatment of autoimmune disease, e.g. any of the autoimmune diseases or conditions hereinbefore described, on administration of from 1 to 5 unit dosages/day. Examples 3 and 6 illustrate the preparation of compositions for topical application, suitable for treatment, e.g. of atopic or contact dermatitis, psoriasis or hair loss, on application

at the desired site of therapy, e.g. dermatitidic reaction or psoriatic lesion or to the scalp, at regular intervals, e.g. once, twice or three times per day.

The examples are described with particular reference to Ciclosporin. However, equivalent compositions may be obtained employing any other appropriate cyclosporin. In particular equivalent compositions may in all cases be obtained on replacement of Ciclosporin with [Nva]^2-Ciclosporin in the same amount as indicated for Ciclosporin.

EXAMPLE 1

Preparation of oral dosage forms: "microemulsion pre-concentrate" type:

1.1.	COMPONENT	QUANTITY (mg/capsule)
	Cyclosporin (e.g. Ciclosporin)	50.0
(1.1)	Glycofurol 75	180.0
(2.1)	Miglyol 812	90.0
(3.1.1)	Cremophor RH 40	180.0
	TOTAL	500.0

The cyclosporin is dissolved in (1.1) with stirring at room temperature and (2.1) and (3.1.1) are added to the obtained solution, again with stirring. The obtained mixture is filled into a size 1 hard gelatin capsule and sealed using Quali-Seal technique.

The following compositions may be prepared analogously for filling into size 1 or 2 hard gelatin capsules:

1.2.	COMPONENT	QUANTITY (mg/capsule)
	Cyclosporin (e.g. Ciclosporin)	50.0
(1.1)	Glycofurol 75	180.0
(2.1)	Miglyol 812	78.0
(3.1.1)	Cremophor RH 40	192.0
	TOTAL	500.0

1.3.	COMPONENT	QUANTITY (mg/capsule)
	Cyclosporin (e.g. Ciclosporin)	50.0
(1.1)	Glycofurol 75	200.0
(2.1)	Miglyol 812	60.0
(3.1.1)	Nikkol HCO-40	120.0
	Ethanol*	19.0
	Ascorbylpalmitate**	1.0
	TOTAL	450.0

*Co-solvent (hydrophilic phase)

**Antioxidant

1.4.	COMPONENT	QUANTITY (mg/capsule)
	Cyclosporin (e.g. Ciclosporin)	50.0
(1)	Glycofurol 75	100.0
(2.1)	Miglyol 812	75.0
(3.1.7)	Lecithin	75.0
	TOTAL	300.0

1.5.	COMPONENT	QUANTITY (mg/capsule)
	Cyclosporin (e.g. Ciclosporin)	100.0
(1.1)	Glycofurol 75	260.0
(1.2)	Propyleneglycol	50.0
(2.1)	Myritol 318	100.0
(3.1.1)	Cremophor RH 40	340.0
	BHA*	5.0
	TOTAL	855.0

*Anti-oxidant

1.6.

COMPONENT		QUANTITY (mg/capsule)
	Cyclosporin (e.g. Ciclosporin)	50.0
(1.2)	1,2-Propyleneglycol	68.0
(2.1)	Miglyol 812	68.0
(3.1.1)	Cremophor RH 40	250.0
(3.2.5)	Glycerol monooleate*	24.0
	TOTAL	460.0

1.7.

COMPONENT		QUANTITY (mg/capsule)
	Cyclosporin (e.g. Ciclosporin)	50.0
(1.2)	1,2-Propyleneglycol	68.0
(2.1)	Miglyol 812	24.0
(3.1.1)	Cremophor RH 40	250.0
(3.2.5)	Glycerol monooleate*	68.0
	TOTAL	460.0

1.8.

COMPONENT		QUANTITY (mg/capsule)
	Cyclosporin (e.g. Ciclosporin)	100 .0
(1.2)	1,2-Propyleneglycol	75.0
(2.1)	Miglyol 812	25.0
(3.1.1)	Cremophor RH 40	150.0
(3.2.5)	Glycerol monooleate*	150.0
	TOTAL	500.0

1.9.

COMPONENT		QUANTITY (mg/capsule)
	Cyclosporin (e.g. Ciclosporin)	50.0
(1.2)	1,2-Propyleneglycol	200.0
(2.1)	Miglyol 812	50.0
(3.1.1)	Cremophor RH 40	150.0
(3.2.7)	Generol 122 E16*	50.0
	TOTAL	500.0

1.10.	COMPONENT	QUANTITY (mg/capsule)
	Cyclosporin (e.g. Ciclosporin)	50.0
(1.2)	1,2-Propyleneglycol	75.0
(2.1)	Miglyol 812	75.0
(3.1.1)	Cremophor RH 40	250.0
(3.2.7)	Generol 122 E25*	50.0
	TOTAL	500.0

*Co-surfactant

Compositions 1.1, 1.2, 1.6 and 1.7 are especially preferred. Equivalent compositions to 1.1 to 1.5 can in all cases be prepared replacing the Glycofurol component with Transcutol in the same or equivalent amount.

Equivalent compositions to 1.1 to 1.5 may be prepared but replacing the 50mg amount of cyclosporin with 15, 20 or 100mg cyclosporin (e.g. Ciclosporin) the quantities of the remaining components for each composition remaining as indicated.

EXAMPLE 2

Preparation of oral dosage forms: thickened "microemulsion pre-concentrate" type:

2.1.	COMPONENT	QUANTITY (mg/capsule)
	Cyclosporin (e.g. Ciclosporin)	50.0
(1.1)	Glycofurol 75	180.0
(2.1)	Miglyol 812	90.0
(3.1.1)	Cremophor RH 40	180.0
(4.2)	Methocel K100	100.0
	TOTAL	600.0

Ciclosporin and (1.1) to (3.1.1) are combined as in example 1 and the obtained mixture mixed homogeneously with (4.2). The product is filled into size 2 hard gelatin capsules.

The following composition may be obtained analogously:

2.2.	COMPONENT	QUANTITY (mg/capsule)
	Cyclosporin (e.g. Ciclosporin	50.0
(1.1)	Glycofurol 75	180.0
(2.1)	Miglyol 812	90.0
(3.1.1)	Cremophor RH 40	180.0
(4.6)	Aerosil 200	9.0
(4.2)	Methocel K100	100.0
	TOTAL	609.0

2.3.	COMPONENT	QUANTITY (mg/capsule)
	Cyclosporin (e.g. Ciclosporin)	100.0
(1.1)	Glycofurol	210.0
(2.1)	Myritol 318	90.0
(3.1.1)	Nikkol HCO-60	170.0
(4.2)	Klucel EF	30.0
	TOTAL	600.0

Equivalent compositions to 2.1 to 2.3 can be prepared replacing the Glycofurol component with Transcutol in the same or equivalent amount.

EXAMPLE 3

Preparation of topically applicable form: "microemulsion pre-concentrate" type:

COMPONENT		% BY WEIGHT
	Cyclosporin (e.g. Ciclosporin)	0.1
(1.1)	Glycofurol	50.0
(2.1)	Miglyol 812	16.6
(3.1.1)	Cremophor RH 40	33.3

The above composition is prepared analogously to example 1. An equivalent composition is obtained on replacement of the Glycofurol component with Transcutol. The composition may be made the basis of a cream, gel or the like by combination with further additives, e.g. hydrocolloid thickening agents, paraffins etc... as hereinbefore described.

EXAMPLE 4

Preparation of oral dosage forms: regular emulsion pre-concentrate type:

4.1.	COMPONENT	QUANTITY (mg/capsule)
	Cyclosporin (e.g.Ciclosporin)	100.0
(1.1)	Transcutol	154.0
(3.1.1)	Cremophor RH 40	146.0
(3.2.1)	Labrafil M 1944 CS	50.0
	TOTAL	450.0

Cyclosporin is dissolved in (1.1) with stirring at room temperature and (3.1.1) and (3.2.1) added to the obtained solution, again with stirring. The obtained mixture is filled into size 1 hard gelatin capsules and sealed employing Quali-Seal technique.

The following compositions may be prepared analogously for filling into size 1 or 2 hard gelatin capsules as appropriate.

4.2.	COMPONENT	QUANTITY (mg/capsule)
	Cyclosporin (e.g. Ciclosporin)	50.0
(1.1)	Transcutol	80.0
(3.1.1)	Cremophor RH 40	75.0
(3.2.1)	Labrafil M 2130 CS	25.0
	TOTAL	230.0

4.3.	COMPONENT	QUANTITY (mg/capsule)
	Cyclosporin (e.g. Ciclosporin)	100.0
(1.1)	Glycofurol 75	150.0
(3.1.1)	Nikkol HCO-40	200.0
	TOTAL	450.0

4.4.	COMPONENT	QUANTITY (mg/capsule)
	Cyclosporin (e.g. Ciclosporin)	50.0
(1.1)	Transcutol	100.0
(3.1.1)	Cremophor RH 40	94.0
(3.2.1)	Labrafil M 1944	31.0
	TOTAL	275.0

Equivalent compositions may be prepared by replacing Transcutol in 4.1, 4.2 or 4.4 with the same or equivalent amount of Glycofurol, or the Glycofurol in 4.3 with the same or equivalent amount of Transcutol.

EXAMPLE 5

Preparation of oral dosage forms: thickened emulsion pre-concentrate type:

5.1.	COMPONENT		QUANTITY (mg/capsule)
		Cyclosporin (e.g. Ciclosporin)	50.0
	(1.1)	Transcutol	80.0
	(3.1.1)	Cremophor RH 40	75.0
	(3.2.1)	Labrafil M 1944 CS	25.0
	(4.1)	Eudragit E	50.0
		TOTAL	280.0

(3.1.1), (3.2.1) and (4.1) are combined with and dissolved in (1.1) with stirring and light warming. Cyclosporin is then added with light warming and further stirring and the product filled into size 2 hard-gelatin capsules and sealed.

The following compositions can be prepared analogously for filling into size 1 or 2 hard gelatin capsules as appropriate:

5.2.	COMPONENT		QUANTITY (mg/capsule)
		Cyclosporin (e.g. Ciclosporin)	100.0
	(1.1)	Transcutol	180.0
	(3.1.4)	Pluronic F68	140.0
	(3.1.6)	Sodium laurylsulphate	5.0
	(4.2)	Sodium carboxymethylcellulose	25.0
		TOTAL	350.0

5.3.	COMPONENT		QUANTITY (mg/capsule)
		Cyclosporin (e.g. Ciclosporin)	50.0
	(1.1)	Transcutol	163.0
	(3.1.1)	Cremophor RH 40	100.0
	(3.2.1)	Labrafil M 1944 CS	35.0
	(4.3)	Kollidon 30	72.0
		TOTAL	420.0

Equivalent compositions may be prepared by replacing the Transcutol

component with Glycofurol in the same or equivalent amount.

EXAMPLE 6

Preparation of topical dosage forms: emulsion type:

The following are prepared by intimate admixture of the indicated ingredients analogously to examples 2 and 5 above, to provide ointment preparations suitable for topical application:

6.1.	COMPONENT		% BY WEIGHT
		Cyclosporin (e.g. Ciclosporin)	0.1
	(1.1)	Transcutol	15.0
	(3.1.1)	Cremophor RH 40	5.0
	(3.2.1)	Labrafil M 213	15.0
	(3.2.5)	Glycerolmonostearate	10.0
	(6.2)	White petrolatum	54.9

6.2.	COMPONENT		% BY WEIGHT
		Cyclosporin (e.g. Ciclosporin)	0.1
	(1.2)	Glycofurol	15.0
	(3.2.5)	Glycerolmonostearate	8.0
	(6.1)	Mineral oil	39.0
	(6.1)	White petrolatum	37.9

EXAMPLE 7

Preparation of oral dosage forms: sugar ester type:

7.1.	INGREDIENT	AMOUNT (mg/capsule)
	Cyclosporin (e.g. Ciclosporin)	50.0
(1.1)	Glycofurol	100.0
(5)	Saccharose monolaurate L-1695*	312.5
	TOTAL	462.0

7.2.	INGREDIENT	AMOUNT (mg/capsule)
	Cyclosporin (e.g. Ciclosporin)	50.0
(1.1)	Transcutol	80.0
(5)	Saccharose monolaurate L-1695*	312.5
	TOTAL	442.5

7.3.	INGREDIENT	AMOUNT (mg/capsule)
	Cyclosporin (e.g. Ciclosporin)	50.0
(1.1)	Glycofurol	100.0
(5)	Saccharose monolaurate L-1695*	312.5
(4.2)	Klucel LF	50.0
	TOTAL	512.5

(* Product commercially available from Mitsubishi-Kasei Food Corp., Tokyo 104, Japan: HLB-value = at least 12.3: lauryl ester residue purity = at least 95%: M.P. = ca. 35°C: decomposition at ca. 235°C: surface tension of 0.1% by weight aqueous solution = ca. 72.0 dyn/cm at 25°C.)

The composition of example 7.1 is prepared by dissolving cyclosporin and (5) with stirring and warming over an oil bath at 100°C in component (1.1). The composition of examples 7.2 and 7.3 are prepared analogously.

The obtained compositions are filled, with warming, into hard gelatin capsules size 1 (compositions 7.1 and 7.2) or 0 (composition 7.3).

Utility of compositions in accordance with the invention may be shown in animal or clinical trials, for example performed as follows:

BIOAVAILABILITY STUDY FOR COMPOSITIONS IN ACCORDANCE WITH THE INVENTION IN THE DOG

a) Test compositions

COMPOSITION I	as per example	1.1
COMPOSITION II	"	1.2
COMPOSITION III	"	1.6
COMPOSITION IV	"	2.1
COMPOSITION V	"	2.2
COMPOSITION VI	"	4.4
COMPOSITION VII	"	5.3

b) Test method

Groups of 8 beagle dogs (male, ca. 11-13kg) are used. Animals receive no food within 18 hours of administration of test composition but are allowed free access to water until administration. Test compositions are administered by gavage, followed by 20ml NaCl 0.9% solution. The animals are allowed free access to food and water three hours after administration of test composition.

2ml blood samples (or 5ml for the blank) are taken from the vena saphena and collected in 5ml plastic tubes containing EDTA at

-15min. (blank), 30min., and 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 hours post administration. Blood samples are stored at -18°C pending assay.

Blood samples are analysed by RIA. Areas under the blood drug concentration versus time curves are calculated by the trapezoidal rule. Analysis of variance is performed with respect to AUC (area under curve), Cmax (maximum concentation) and Tmax (time of maximum).

c) Results

Calculated average AUC (in ng hr./ml^{-1}) and Cmax (in ng/ml^{-1}) values from typical trial runs are shown in the following table, together with calculated variation in response between test animals receiving the same composition (CV).

COMPOSITION	AUC (0-24h)	CV (%)	Cmax	CV%
I	2969	46.1	655	42.4
II	3315	35.9	606	29.0
III	3392	33.0	623	25.0
IV	4010	35.1	756	30.0
V	2769	27.8	469	21.7
VI	2375	40.3	518	29.2
VII	2329	23.1	470	36.1

As will be seen from the above table, compositions in accordance with the invention exhibit high bioavailability (AUC and Cmax.) coupled with relatively low variability in subject response both for AUC and Cmax.

Comparable advantageous results may be obtained employing other compositions in accordance with examples 1,2,4,5 and 7 herein, in particular the compositions of example 1.

The advantageous properties of the compositions of the invention on oral administration may also be demonstrated in clinical trials, e.g. performed as follows:

Trial subjects are adult volunteers, e.g. professionally educated males of from 30 to 55 years. Trial groups suitably comprise 12 subjects.

The following inclusion/exclusion criteria are applied:
Inclusion: Normal screening ECG; normal blood-pressure and heart rate; body weight = 50-95kg.
Exclusion: Clinically significant intercurrent medical condition which might interfere with drug absorption, distribution, metabolism, excretion or safety; symptoms of a significant clinical illness in the two-week pre-trial period; clinically relevant abnormal laboratory values or electrocardiogram; need for concomitant medication during the entire course of the study; administration of any drug known to have a well-defined potential toxicity to a major organ system within the previous 3 months; administration of any investigational drug within 6 weeks prior to entry into the trial; history of drug or alcohol abuse; loss of 500ml or more blood within the past 3 month period; adverse drug reaction or hypersensitivity; history of allergy requiring drug therapy; Hep.-B/HIV-positive.

Complete physical examination and ECG is performed pre- and post-trial. The following parameters are evaluated within 1-month periods pre- and post-trial:
Blood: - red blood cell count, haemoglobin, hematocrit, erythrocyte sedimentation, white blood cell count, smear, platelet count and fasting glucose;

Serum/plasma - total protein and electrophoresis, cholesterol, triglycerides, Na^+, K^+, Fe^{++}, Ca^{++}, Cl^- creatinine, urea, uric acid, SGOT, SGPT, -GT, alkaline phosphatase, total bilirubin, α-amylase; Urine - pH, microalbumin, glucose, erythrocytes, ketone bodies, sediment.
Creatinine clearance is also determined 1-month prior to trial entry.

Subjects each receive trial compositions in randomised sequence. Compositions are administered orally, once to a total dose of 150mg cyclosporin, e.g. Ciclosporin, and at least 14 days are allowed between each administration.

Administration is performed in the morning after an overnight fast of 10hrs. with only water allowed. Only caffein-free beverages are permitted within the 24hr. period following administration. Subjects are not allowed to smoke within the 12hr. period following administration. Subjects receive a standardised lunch 4 hrs. following administration.

Blood samples (2ml) are taken 1 hr. prior to administration and post-administration at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 9, 12, 14, 24, 28 and 32 hrs.. For determination of creatinine 2ml blood samples are taken immediately prior to administration and at 12, 24 and 48 hrs. post-administration. Samples for cyclosporin determination are collected in two EDTA coated polystyrene tubes (1ml each) at each time point and are deep frozen at -20°C after gentle agitation. Cyclosporin is assayed in whole blood using RIA with specific and/or non-specific MAB assay - detection limit in both cases = ca. 10ng/ml.

In one such trial COMPOSTION I above in accordance with the invention (hard gelatin encapsulated form) is compared with COMPOSITION X.

COMPOSITION X [COMPARATIVE (ART) COMPOSITION]

Unit dosage form (soft gelatin capsule) comprising

Ciclosporin	50mg
Labrafil	150mg
Ethanol	50mg
Maize oil	213mg
Total	463mg/dosage.

(* current Sandimmun oral, drink solution)

In a trial performed in this manner a bioavailability level of 149.0% (±48) is recorded for COMPOSITION I as compared with COMPOSITION X (for which bioavailability achieved is set as 100%). AUC values (0-32 hrs. ng.h/ml) and Cmax. values (ng/ml) established for COMPOSITION I are 2992 (±627) and 882 (±18) respectively as compared with 2137 (±606) and 515 (±180) for COMPOSITION X.

Figs. III and IV attached provide superimposed graphical representations from such a trial of whole blood Ciclosporin concentrations recorded for all 12 trial participants following single oral administrations of COMPOSITION I (Fig. III) and COMPOSITION X (Fig. IV), each in an amount providing a Ciclosporin dosage of 150mg, as determined by specific monoclonal RIA. Blood concentration (in ng/ml) is recorded vertically, and time (in hrs.) horizontally.

Comparison of Figs. III and IV clearly demonstrates the marked reduction in variability of inter-subject response with respect to bioavailability parameters recorded, on administration of COMPOSITION I as compared with COMPOSITION X. The determined coefficient of variation [(standard deviation/mean value) x 100] with respect to Cmax. for COMPOSITION X is 35% as compared with a value of only 20%

for COMPOSITION I.

Similar or equivalent results may be obtained following oral administration of other compositions in accordance with the invention, e.g. as herein described in the examples, in particular the compositions of example 1.

IN VIVO TESTING FOR TOPICAL FORMS

ALLERGIC CONTACT DERMATITIS TEST IN THE GUINEA PIG

Guinea pigs (Hartley, male, 400-500g) are sensitised by application of 50µl, 0.5% DNFB in acetone/olive oil (4:1) applied to marked areas on the shaven, left and right flank. This second challenge exposure induces an allergic inflammation, leading to reddening and cellular infiltration (thickening) of the skin. Test composition (e.g. in accordance with example 3,6.1 or 6.2 above) in an amount of from 200-250mg is applied with a spatula to the DNFB treated area of the right flank. The left flank is similarly treated with placebo as control. Application of test composition/placebo is effected 5x at intrvals of 20 mins., 8 hrs., 24 hrs., 32 hrs., and 48 hrs., after the challenge. Skin thickness at the site of application is determined before each application, and again 8 hrs. after the last application, by raising the skin into a fold and measuring the thickness of this. Degree of reddening or inflammation is also estimated visually on a scale of from 0 to 4. Efficacy of test preparation in preventing inflammatory response is determined by comparison with results recorded for placebo treated flanks.

In the above test method substantial reduction in skin thickening as compared with placebo are achieved following first application of test composition, e.g. in accordance with examples 3,6.1 or 6.2, continuing throught treatment until completion of the experiment.

The following results are recorded for the composition of example 3

TIME AFTER CHALLENGE (HRS)	8	24	32	48	56
% INHIBITION OF SKIN THICKNESS / US PLACEBO CONTROL	56	68	76	75	73

Claims

1. A pharmaceutical composition comprising a cyclosporin as active ingredient, which composition is a "microemulsion pre-concentrate".

2. A composition according to claim 1 comprising:
   1) a hydrophilic phase;
   2) a lipophilic phase, and
   3) a surfactant.

3. A composition according to claim 1 or 2 comprising:
   1.1) a pharmaceutically acceptable C_{1-5}alkyl or tetrahydrofurfuryl di- or partial-ether of a low molecular weight mono- or poly-oxy-alkanediol, or
   1.2) 1,2-propyleneglycol,
   as hydrophilic component.

4. A composition according to claim 3 comprising Transcutol or Glycofurol as hydrophilic component.

5. A composition according to claim 3 comprising 1,2-propyleneglycol as hydrophilic component.

6. A composition according to any one of claims 1 to 5 comprising a medium chain fatty acid triglyceride as lipophilic component.

7. A composition according to claim 6 comprising a caprylic-capric acid triglyceride as lipophilic component.

8. A composition according to any one of claims 1 to 7 comprising a polyoxyethylene glycolated natural or hydrogenated vegetable oil, a polyoxyethylene fatty acid ester, a phospholipid or a mono- or di-glyceride as surfactant.

9. A composition according to any one of claims 1 to 8 comprising 3a) a surfactant and 3b) a co-surfactant.

10. A composition according to any one of claims 1 to 9, capable on contacting with water of providing a microemulsion having an average particle size of <1,000A.

11. A pharmaceutical composition comprising a cyclosporin as active ingredient, which composition is a microemulsion.

12. A composition according to claim 11 comprising a composition as defined in any of claims 1 to 10 and water.

13. A pharmaceutical composition comprising a cyclosporin as active ingredient, together with (1.1) a pharmaceutically acceptable C_{1-5}alkyl or tetrahydrofurfuryl di- or partial-ether of a low molecular weight mono- or poly-oxy-alkanediol.

14. A composition according to claim 13, wherein (1.1) comprises Transcutol or Glycofurol.

15. A composition according to claim 13 or 14 additionally comprising:
2) a lipophilic co-solvent, or
3) a surfactant.

16. A composition according to claim 15, wherein (3) is a hydrophilic surfactant.

17. A composition according to claim 15 or 16, wherein (2) is a medium chain fatty acid triglyceride.

18. A composition according to any one of claims 13 to 17 additionally comprising:

5) a fatty acid saccharide monoester.

19. A composition according to claim 18, wherein (5) is raffinose or saccharose monolaurate.

20. A composition according to any one of claims 1 to 19 comprising from about 0.05 to about 35% by weight of cyclosporin based on the total weight of the composition.

21. A composition according to any one of claims 3, 4, 6 to 10 and 12 to 20, wherein (1.1) is present in an amount of from about 1 to about 90% by weight, based on the total weight of the composition.

22. A composition according to anyone of claims 3, 5 to 10 and 12, wherein (1.2) is present in an amount of from about 2 to about 50% by weight based on the total weight of the composition.

23. A composition according to any one of claims 2 to 10, 12 and 15 to 22, wherein (2) or (3) are each present in an amount of from about 0.5 to about 90% by weight based on the total weight of the composition.

24. A composition according to any one of claims 20 to 23 comprising from about 5 to about 25% by weight of cyclosporin.

25. A composition according to claim 24 comprising from about 5 to about 15% by weight of cyclosporin.

26. A composition according to any one of claims 21 and 23 to 25, wherein (1.1) is present in an amount of from about 20 to about 80% by weight.

27. A composition according to claim 26, wherein (1.1) is present in ana mount of from about 40 to about 70% by weight.

28. A composition according to any one of claims 22 to 25, wherein (1.2) is present in an amount of from about 3 to about 45% by weight.

29. A composition according to claim 28, wherein (1.2) is present in an amount of from about 5 to about 30% by weight.

30. A composition according to any one of claims 23 to 29, wherein (2) is present in an amount of from about 2 to about 45% by weight.

31. A composition according to claim 30, wherein (2) is present in an amount of from about 5 to about 25% by weight.

32. A composition according to any one of claims 23 to 31, wherein (3) is present in an amount of from about 20 to about 90% by weight.

33. A composition according to claim 32, wherein (3) is present in an amount of from about 25 to about 80% by weight.

34. A composition according to claim 33 comprising a component (1.1) and wherein (3) is present in an amount of from about 30 to about 50% by weight.

35. A composition according to claim 33 comprising a component (1.2) and wherein (3) is present in an amount of from about 40 to about 75% by weight.

36. A composition according to any one of claims 3, 4, 6 to 10 and 12, comprising from about 15 to about 85% of (1.1), from about 2

to about 40% of (2), and from about 15 to about 85% of (3), each by weight based on the total of (1.1)+(2)+(3).

37. A composition according to claim 36 comprising from about 25 to about 65% of (1.1), from about 3 to about 35% of (2), and from about 25 to about 60% of (3), each by weight based on the total of (1.1)+(2)+(3).

38. A composition according to any one of claims 3, 4, 6 to 10 and 12, wherein the relative proportion of components (1.1):(2):(3) lies within the area (A) defined by line (a) of accompanying Fig. I.

39. A composition according to claim 38, wherein the relative proportion lies within the area (B) defined by line (b) of Fig. I.

40. A composition according to any one of claims 3, 5 to 10 and 12, comprising from about 3 to about 35% of (1.2), from about 2 to about 35% of (2), and from about 45 to about 90% of (3), each by weight based on the total of (1.2)+(2)+(3).

41. A composition according to claim 40 comprising from about 3 to about 25% of (1.2), from about 3 to about 30% of (2), and from ab 55 to about 80% of (3), each by weight based on the total of (1.2)+(2)+(3).

42. A composition according to any one of claims 3, 5 to 10 and 12, wherein the relative proportion of components (1.2):(2):(3) lies within the area X defined by line x of accompanying Fig. II.

43. A composition according to claim 42, wherein the relative proportion lies within the area Y defined by line y of Fig. II.

44. A composition according to claim 43, wherein the relative proportion lies within the area Z defined by line z of Fig. II.

45. A composition according to any one of claims 40 to 44, wherein (3) comprises (3.1) a surfactant and (3.2) a co-surfactant.

46. A composition according to claim 45, wherein (3.1) and (3.2) are present in a ratio of about 1 to 50:1 p.p.w..

47. A composition according to claim 46, wherein the ratio is about 2 to 15:1 p.p.w..

48. A composition according to any one of claim 36 to 47, wherein the cyclosporin is present in an amount of from about 2 to about 30% by weight based on the total of [cyclosporin]+[(1.1) or (1.2)]+(2)+(3).

49. A composition according to claim 48, wherein the cyclosporin is present in an amount of from about 4 to about 25% by weight.

50. A composition according to claim 49, wherein the cyclosporin is present in an amount of from about 5 to about 20% by weight.

51. A composition according to claim 50, wherein the cyclosporin is present in an amount of from about 5 to about 15% by weight.

52. A composition according to any one of claims 18 to 21 and 23 to 25, wherein the cyclosporin and (1.1) are present in a ratio of about 1:0.5 to 200 p.p.w. [cyclosporin:(1.1)].

53. A composition according to claim 52, wherein the ratio is about 1:0.5 to 50 p.p.w..

54. A composition according to claim 53, wherein the ratio is about 1:1 to 10 p.p.w..

55. A composition according to claim 54, wherein the ratio is about 1:1 to 5 p.p.w..

56. A composition according to any one of claims 18 to 21, 23 to 25 and 52 to 55, wherein the cyclosporin and (5) are present in a ratio of about 1:3 to 200 p.p.w. [cyclosporin:(5)].

57. A composition according to claim 56, wherein the ratio is about 1:3 to 50 p.p.w..

58. A composition according to claim 57, wherein the ratio is about 1:5 to 10 p.p.w..

59. A composition according to any one of claims 1 to 12 and 36 to 51 which is non-alkanol-based.

60. A composition according to any one of claims 1 to 12 and 36 to 51 which is non-ethanol-based.

61. A composition according to any one of the preceding claims which is free or substantially free of ethanol.

62. A composition according to any one of the preceding claims in a form suitable or convenient for oral administration.

63. A composition according to any one of the preceding claims in unit dosage form.

64. A composition according to claim 63 in soft or hard gelatin encapsulated form.

65. A composition according to claim 63 or 64 comprising from about 5 to about 200mg cyclosporin/unit dosage.

66. A composition according to claim 65 comprising from about 15 to about 100mg cyclosporin/unit dosage.

67. A composition according to claim 66 comprising from about 20 to about 100mg cyclosporin/unit dosage.

68. A composition according to any one of claims 1 to 17 or 36 to 47 comprising from about 0.5 to about 50% by weight cyclosporin based on the total weight of the composition, in a form suitable or convenient for topical application.

69. A composition according to any one of claims 13 to 17 comprising from about 0.05 to about 50% by weight cyclosporin and from about 1 to about 70% by weight of (1.1) each based on the total weight of the composition, in a form suitable or convenient for topical application.

70. A composition according to claim 68 or 69 comprising from about 0.1 to about 10% by weight cyclosporin.

71. A composition according to claim 69 or 70 comprising from about 5 to about 50% by weight of (1.1).

72. A composition according to claim 71 comprising from about 7 to about 25% by weight of (1.1).

73. A composition according to any one of claims 68 to 72 comprising (6) a pharmaceutically acceptable solvent or carrier which is non-miscible with (1.1).

74. A composition according to claim 73, wherein (6) comprises a solid hydrocarbon, a wax, a liquid hydrocarbon, a fatty acid ester or a non-volatile silicone.

75. A composition according to claim 73 or 74, wherein (6) is present in an amount of up to about 80% by weight based on the total weight of the composition.

76. A composition according to claim 75, wherein (6) is present in an amount of from about 5 to about 70% by weight.

77. A composition according to claim 76, wherein (6) is present in an amount of from about 25 to about 60% by weight.

78. A composition according to any one of claims 68 to 77 comprising a surfactant.

79. A composition according to claim 78, wherein the surfactant has an HLB of ca. 5 to 7.

80. A composition according to claim 78 or 79, wherein the surfactant is present in an amount of up to about 60% by weight based on the total weight of the composition.

81. A composition according to claim 80, wherein (6) is present in an amount of from about 2 to about 40% by weight based on the total weight of the composition.

82. A composition according to claim 81, wherein the surfactant is present in an amount of from about 10 to about 40% by weight based on the total weight of the composition.

83. A composition according to any one of claims 68 to 82 additionally comprising a consistency promoting agent.

84. A composition according to claim 83, wherein the consistency promoting agent is a microcrystalline wax, a vegetable oil or a vegetable oil derivative.

85. A composition according to claim 83 or 84, wherein the consistency promoting agent is present in an amount of from about 0.1 to about 10% by weight based on the total weight of the composition.

86. A composition according to any one of claims 68 to 85 in flowable form, in the form of a powder, in the form of a topically applicable spray or in the form of a cataplasm, poultice or transdermal patch.

87. A composition according to claim 86 in the form of a gel, cream, paste, ointment or tincture.

88. A composition according to any of the preceding claims, wherein the cyclosporin is Ciclosporin.

89. A composition according to any of the proceding claims, wherein the cyclosporin is [Nva]^2-Ciclosporin.

90. A composition according to claim 1 or 2, substantially as hereinbefore described, in particular with reference to any one of examples 1.1 to 2.3.

91. A composition according to claim 13, substantially as hereinbefore described, in particular with reference to any one of examples 4.1 to 5.3.

92. A composition according to claim 68 or 69, substantially as hereinbefore described, in particular with reference to any one of examples 3 or 6.

93. A composition according to claim 18, substantially as hereinbefore described, in particular with reference to any one of examples 7.1 to 7.3.

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Electronic Patent Application Fee Transmittal

Application Number:	14222478
Filing Date:	21-Mar-2014
Title of Invention:	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS
First Named Inventor/Applicant Name:	Andrew Acheampong
Filer:	Laura Lee Wine/Maria Stein
Attorney Docket Number:	17618CON6CON1 (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($)
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
		Total in USD ($)		**180**

Electronic Acknowledgement Receipt

EFS ID:	19523368
Application Number:	14222478
International Application Number:	
Confirmation Number:	9616
Title of Invention:	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS
First Named Inventor/Applicant Name:	Andrew Acheampong
Customer Number:	51957
Filer:	Laura Lee Wine/Maria Stein
Filer Authorized By:	Laura Lee Wine
Attorney Docket Number:	17618CON6CON1 (AP)
Receipt Date:	08-JUL-2014
Filing Date:	21-MAR-2014
Time Stamp:	18:33:50
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$180
RAM confirmation Number	4809
Deposit Account	010885
Authorized User	

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Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		17618CON6CON1_IDS.pdf	19307634 c01c00293d3baaab4487be8b6a7ab893a871972c	yes	171

Multipart Description/PDF files in .zip description

Document Description	Start	End
Transmittal Letter	1	2
Information Disclosure Statement (IDS) Form (SB08)	3	6
Foreign Reference	7	52
Foreign Reference	53	87
Foreign Reference	88	91
Foreign Reference	92	171

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2	Fee Worksheet (SB06)	fee-info.pdf	30486 7c8a69f9dea2ab67e7c4e1fa42afd2ba666bb0a5	no	2

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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.

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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

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Docket No. 17618 CON6CON1 (AP)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the Patent Application of:

Andrew Acheampong, Andrew, et al.

Application No.: 14/222,478

Filing Date: March 21, 2014

Title: METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORING COMPONENTS

Examiner: Cordero Garcia, Marcela M.

Group Art Unit: 1676

Confirmation No.: 9616

INFORMATION DISCLOSURE STATEMENT UNDER 37 C.F.R. § 1.97 & § 1.98

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

Dear Sir:

Pursuant to 37 C.F.R. § 1.97 & § 1.98, Applicants submit for consideration in the above-identified application the documents listed on the attached Form PTO/SB/08a.

Pursuant to the USPTO notice dated July 11, 2003, waiving the requirements under 37 C.F.R. § 1.98 (a)(2)(i) to provide copies of U.S. Patents and U.S. Published Applications, copies of these documents if cited are not submitted herewith. However, copies of any foreign patent documents and non-patent literature documents that may be cited on the attached Form PTO/SB/08a are submitted herewith. The Examiner is requested to make these documents of record.

This Information Disclosure Statement is submitted:

[ ] With the application; accordingly, no fee or separate requirements are required.

[ ] Before the mailing of a first Office Action after the filing of a Request for Continued Examination under 37 C.F.R. § 1.114. However, if applicable, a certification under 37 C.F.R. § 1.97 (e)(1) is provided with the attached Form PTO/SB/08a.

[ ] Within three months of the application filing date or before mailing of a first Office Action on the merits; accordingly, no fee or separate requirements are required. However, if applicable, a certification under 37 C.F.R. § 1.97 (e)(1) is provided with the attached Form PTO/SB/08a.

[X] After receipt of a first Office Action on the merits but before mailing of a final Office Action or Notice of Allowance.

[X] A fee is required and submitted herewith.

[ ] A Certification under 37 C.F.R. § 1.97 (e) is provided with the attached Form PTO/SB/08a; accordingly; no fee is believed to be due.

[ ] After mailing of a final Office Action or Notice of Allowance, but before payment of the Issue Fee.

[ ] A fee is required and submitted herewith AND a Certification under 37 C.F.R. § 1.97 (e) is provided with the attached Form PTO/SB/08a.

Applicants would appreciate the Examiner initialing and returning the Form PTO/SB/08a indicating that the information has been considered and made of record herein.

If the Patent and Trademark Office determines that an extension and/or other relief (such as payment of a fee under 37 C.F.R. § 1.17 (p)) is required, Applicants petition for any required relief including extensions of time and authorize the Commissioner to charge the cost of such petition and/or other fees due in connection with the filing of this document to **Deposit Account No. 01-0885** referencing our docket number.

Respectfully submitted,

July 8, 2014 /Laura L. Wine/

Dated: By: Laura L. Wine, Reg. No. 68681

Allergan, Inc.
2525 Dupont Drive, T2-7H
Irvine, CA 9612
Telephone: (714) 246-6996
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/222,478	03/21/2014	Andrew Acheampong	17618CON6CON1 (AP)	9616

51957 7590 06/25/2014

ALLERGAN, INC.
2525 DUPONT DRIVE, T2-7H
IRVINE, CA 92612-1599

EXAMINER	
CORDERO GARCIA, MARCELA M	
ART UNIT	**PAPER NUMBER**
1676	

NOTIFICATION DATE	DELIVERY MODE
06/25/2014	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
pair_allergan@firsttofile.com

Office Action Summary	Application No. 14/222,478	Applicant(s) ACHEAMPONG ET AL.	
	Examiner MARCELA M. CORDERO GARCIA	Art Unit 1676	AIA (First Inventor to File) Status No

-- 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* MONTHS 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 *3/21/2014*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ 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*

5)☒ Claim(s) *37-63* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *37-63* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ 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).

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).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

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) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date *3/28/2014*.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

1. The present application is being examined under the pre-AIA first to invent provisions.

DETAILED ACTION

Election/Restrictions

2. Upon reconsideration, the election restriction requirement mailed on 5/9/2014 is herein vacated.

Status of the claims

3. Claims 37-63 are pending. Claims 37-63 are presented for examination on the merits.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112(a):

> (a) IN GENERAL.—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 or joint inventor of carrying out the invention.

The following is a quotation of the first paragraph of pre-AIA 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.

5. Claims 37-63 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. Claims 37, 49 and 57 comprise the limitation "at a frequency of twice a day"

New Matter

6. The claims have been amended (cf. amendment 3/21/2014) to include new claims. Applicants state that the amendments add no new matter, and point out at least at page 4, line 25- page 5, line 14, page 14, line 28 -page 15, line 1, page 26, lines 5-19, and page 27, lines 4-31 of the application specification filed herewith as support for the amendments.

Lack of Ipsis Verbis Support

7. With respect to the limitation “at a frequency of twice a day”, such embodiment does not appear to be expressly disclosed.

Lack of Inherent Support

8. “While there is no in haec verba requirement, newly added claim limitations must be supported in the specification through express, implicit, or inherent disclosure.” See MPEP 2163. Example 1 of the instant disclosure, which has the embodiments with the concentrations as claimed, however it is silent with regards to the frequency of administration.

All other claims that depend directly or indirectly from rejected claims and are, therefore, also rejected under USC 112, first paragraph for the reasons set forth above.

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 double patenting rejection is appropriate where the claims at issue 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 reference 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. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO internet Web site contains terminal disclaimer forms which may be used. Please visit http://www.uspto.gov/forms/. The filing date of the application will determine what form should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more

information about eTerminal Disclaimers, refer to

http://www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

10. Claims 37-63 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-27 of U.S. Patent No. 8,629,111 (cited in the IDS dated 3/28/2014). Although the claims at issue are not identical, they are not patentably distinct from each other because the claims in US '111 are drawn to a topical ophthalmic emulsion for treating an eye of a human comprising cyclosporin A in an amount of about 0.05% by weight, polysorbate 80, acrylate/C10-30 alkyl acrylate cross-polymer, water, and castor oil in an amount of about 1.25% by weight; wherein cyclosporin A is the only peptide present in the topical ophthalmic emulsion which encompasses and/or inherently discloses the instantly claimed method. Furthermore, the instantly claimed functional effects of the composition/method would necessarily be the same as all the structural/manipulative limitations of the instant claims are taught by the claims in '111.

Thus, the invention as a whole is prima facie obvious over the references, especially in the absence of evidence to the contrary.

11. Claims 37-63 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-24 of U.S. Patent No. 8,633,162 (cited in the IDS dated 3/28/2014). Although the claims at issue are not identical, they are not patentably distinct from each other because the claims in US ‘162 are drawn to a method of treating dry eye disease, the method comprising topically administering to the eye of a human in need thereof an emulsion at a frequency of twice a day, wherein the emulsion

comprises cyclosporin A in an amount of about 0.05% by weight, polysorbate 80, acrylate/C10-30 alkyl acrylate cross-polymer, water, and castor oil in an amount of about 1.25% by weight; and wherein the topical ophthalmic emulsion is effective in treating dry eye disease which encompasses and/or inherently discloses the instantly claimed method. Furthermore, the instantly claimed functional effects of the composition/method would necessarily be the same as all the structural/manipulative limitations of the instant claims are taught by the claims in '162. With regards to the claimed frequency of administration, it is noted that "[g]enerally, 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."" (MPEP 2144.05). Thus one of ordinary skill in the art would have been able to adjust the dosage as to find an effective dosage and timing of administration.

Thus, the invention as a whole is prima facie obvious over the references, especially in the absence of evidence to the contrary.

12. Claims 37-63 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-20 of U.S. Patent No. 8,642,556 (cited in the IDS dated 3/28/2014). Although the claims at issue are not identical, they are not patentably distinct from each other because the claims in US '556 are drawn to a first topical ophthalmic emulsion for treating an eye of a human, wherein the first topical ophthalmic

emulsion comprises cyclosporin A in an amount of about 0.05% by weight, polysorbate 80, acrylate/C10-30 alkyl acrylate cross-polymer, water, and castor oil in an amount of about 1.25% by weight; and wherein the first topical ophthalmic emulsion is therapeutically effective in treating dry eye disease; and wherein the first topical ophthalmic emulsion provides overall efficacy substantially equal to a second topical ophthalmic emulsion comprising cyclosporin A in an amount of about 0.1% by weight and castor oil in an amount of about 1.25% by weight which encompasses and/or inherently discloses the instantly claimed method. Furthermore, the instantly claimed functional effects of the composition/method would necessarily be the same as all the structural/manipulative limitations of the instant claims are taught by the claims in '556. With regards to the claimed frequency of administration, it is noted that "[g]enerally, 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."" (MPEP 2144.05). Thus one of ordinary skill in the art would have been able to adjust the dosage as to find an effective dosage and timing of administration.

Thus, the invention as a whole is prima facie obvious over the references, especially in the absence of evidence to the contrary.

13. Claims 37-63 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-23 of U.S. Patent No. 8,648,048 (cited in the IDS

dated 3/28/2014). Although the claims at issue are not identical, they are not patentably distinct from each other because the claims in US '048 are drawn to a method of increasing tear production in the eye of a human, the method comprising topically administering to the eye of the human in need thereof an emulsion at a frequency of twice a day, wherein the emulsion comprises cyclosporin A in an amount of about 0.05% by weight, polysorbate 80, acrylate/C10-30 alkyl acrylate cross-polymer, water, and castor oil in an amount of about 1.25% by weight; and wherein the topical ophthalmic emulsion is effective in increasing tear production which encompasses and/or inherently discloses the instantly claimed method. Furthermore, the instantly claimed functional effects of the composition/method would necessarily be the same as all the structural/manipulative limitations of the instant claims are taught by the claims in '048.

Thus, the invention as a whole is prima facie obvious over the references, especially in the absence of evidence to the contrary.

14. Claims 37-63 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-36 of U.S. Patent No. 8,685,930. Although the claims at issue are not identical, they are not patentably distinct from each other because the claims in US '930 are drawn to an topical ophthalmic emulsion for treating an eye of a human having keratoconjunctivitis sicca, wherein the topical ophthalmic emulsion comprises cyclosporin A in an amount of about 0.05% by weight, polysorbate 80, acrylate/C10-30 alkyl acrylate cross-polymer, water, and castor oil in an amount of about 1.25% by weight; and wherein the topical ophthalmic emulsion is therapeutically

effective in treating keratoconjunctivitis sicca, which encompasses and/or inherently discloses the instantly claimed method. Furthermore, the instantly claimed functional effects of the composition/method would necessarily be the same as all the structural/manipulative limitations of the instant claims are taught by the claims in '930. With regards to the claimed frequency of administration, it is noted that "[g]enerally, 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."" (MPEP 2144.05). Thus one of ordinary skill in the art would have been able to adjust the dosage as to find an effective dosage and timing of administration.

Thus, the invention as a whole is prima facie obvious over the references, especially in the absence of evidence to the contrary.

Conclusion

15. No claim is currently allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

16. 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, Karlheinz R. Skowronek can be reached on (571)-272-9047. 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/
Primary Examiner, Art Unit 1676

MMCG 06/2014

Notice of References Cited	Application/Control No. 14/222,478	Applicant(s)/Patent Under Reexamination ACHEAMPONG ET AL.	
	Examiner MARCELA M. CORDERO	Art Unit 1676	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-8,685,930	04-2014	Acheampong et al.	514/20.5
	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)
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*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
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BIB DATA SHEET

CONFIRMATION NO. 9616

SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
14/222,478	03/21/2014 RULE	514	1676	17618CON6CON1 (AP)

APPLICANTS

Allergan, Inc., Irvine, CA, Assignee (with 37 CFR 1.172 Interest);

INVENTORS

Andrew Acheampong, Irvine, CA;
Diane D. Tang-Liu, Las Vegas, CA;
James N. Chang, Newport Beach, CA;
David F. Power, San Clemente, CA;

**** CONTINUING DATA ***************************

This application is a CON of 13/961,828 08/07/2013 PAT 8685930
which is a CON of 11/897,177 08/28/2007 PAT 8618064
and is a CON of 10/927,857 08/27/2004 ABN
which claims benefit of 60/503,137 09/15/2003

**** FOREIGN APPLICATIONS ***************************

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ****

04/15/2014

Foreign Priority claimed	35 USC 119(a-d) conditions met	Verified and Acknowledged	Met after Allowance	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
☐ Yes ☑ No	☐ Yes ☑ No	/MARCELA M CORDERO GARCIA/ Examiner's Signature	☐ Initials	CA	0	27	4

ADDRESS

ALLERGAN, INC.
2525 DUPONT DRIVE, T2-7H
IRVINE, CA 92612-1599
UNITED STATES

TITLE

METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS

FILING FEE RECEIVED	FEES: Authority has been given in Paper	
2580	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
	14222478	ACHEAMPONG ET AL.
	Examiner	Art Unit
	MARCELA M CORDERO GARCIA	1676

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner
none	none	6/16/2014	MMCG

SEARCH NOTES		
Search Notes	Date	Examiner
EAST search (attached)	6/14/2014	MMCG
STN search (attached)	6/16/2014	MMCG
also ran PALM Inventor search	6/16/2014	MMCG

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

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                  New on STN
 NEWS  5  JAN 09  Chinese Dissertations Added to CAplus
 NEWS  6  JAN 27  STN on the Web Now Compatible with Microsoft Windows 8.1 and
                  current Versions of Internet Explorer and Google Chrome
 NEWS  7  JAN 27  Annual MEDLINE Reload on STN Introduces New Searching
                  Capabilities and the Updated 2014 MeSH Thesaurus
 NEWS  8  FEB 03  DWPI: Latest Manual Code Revision goes live
 NEWS  9  FEB 03  DWPI: New coverage of Singapore PCT-transfers and grants
 NEWS 10  FEB 24  INFULL and DEFULL databases Now Available via STN Viewer
 NEWS 11  MAR 28  New STN Platform Enhancements Available, Increase Efficiency
                  of Search Workflow.
 NEWS 12  APR 25  New Format Adopted for Taiwanese Granted Patent Numbers
                  in CAS Databases and INPADOC.
 NEWS 13  MAY 2   New STN Global Value Pricing Empowers You to Maximize the
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 NEWS 14  MAY 9   STN AnaVist, Version 2.1, Improves Operating System
                  Compatibility and Performance
 NEWS 15  MAY 19  Availability of Digital Object Identifiers (DOIs) Enhanced in
                  STN Databases
 NEWS 16  MAY 20  New Cluster NPS available for all Databases with the Numeric
                  Property Search feature
 NEWS 17  MAY 29  CAS REGISTRY BLAST Upgrade Improves Search Capabilities and
                  Results Ranking
 NEWS 18  JUN 10  Additional Experimental Spectra Now Available in CAS REGISTRY
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 NEWS 19  JUN 10  MEDLINE on STN Now Updated Daily
 NEWS 20  JUN 10  New Emtree Release Includes Changes in Cell Line Terminology

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=> cyclosporin (10a) (twice or two) (10a) (castor oil) (10a) (emulsion)
L1           0 CYCLOSPORIN (10A) (TWICE OR TWO) (10A) (CASTOR OIL) (10A) (EMULS
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ION)

=> cyclosporin (10a) (castor oil) (10a) (emulsion)
L2 14 CYCLOSPORIN (10A) (CASTOR OIL) (10A) (EMULSION)

=> d ibib abs total

L2 ANSWER 1 OF 14 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2012:1840673 CAPLUS
DOCUMENT NUMBER: 158:87295
TITLE: Non-irritating eyedrop nano-emulsion composition comprising cyclosporin utilized as active ingredient, and method for manufacturing it
INVENTOR(S): Hwang, Seong Ju; Cha, Gwang Ho; Kang, Han; Sun, Bo Gyeong
PATENT ASSIGNEE(S): Huons Co., Ltd., S. Korea; Yonsei University, Industry-Academic Cooperation Foundation
SOURCE: Repub. Korea, 16pp.
CODEN: KRXXFC
DOCUMENT TYPE: Patent
LANGUAGE: Korean
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
KR 1211902	B1	20121213	KR 2012-45708	20120430
WO 2013165074	A1	20131107	WO 2013-KR509	20130122

W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM

PRIORITY APPLN. INFO.: KR 2012-45708 A 20120430

AB The present invention relates to a non-irritating eyedrop nano-emulsion composition comprising cyclosporin utilized as an active ingredient, and a method for manufacturing the same. The composition comprises cyclosporine (0.01-1 weight%) as the active ingredient i.e. cyclosporine A; polyethoxylated castor oil or polyethoxylated hydrogenated castor oil (0.5-9.79 weight%); and phosphate buffer (90-99.29 weight%). The manufacturing method involves following step: (i) mixing and stirring the cyclosporine, polyethoxylated castor oil or polyethoxylated hydrogenated castor oil and water without utilizing a sep. emulsifier or high speed single machine to manufacture the non-irritating eyedrop nano-emulsion composition The composition has nano-emulsion with average particle size of less than or equal to 50nm. The composition further comprises a thickener (0.1-5 weight%) that is selected from hyaluronic acid or its salts, chitosan, hydroxypropyl methylcellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, polyvinylpyrrolidone, CM-cellulose, carbomer, glycerin and poly(ethylene oxide); and ethanol (0.1-3 weight%). According to the present invention, the eyedrop nano-emulsion composition has excellent non-irritating property and excellent phys. and chemical stabilities for long

term storage.

L2 ANSWER 2 OF 14 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2012:974032 CAPLUS
DOCUMENT NUMBER: 157:209519
TITLE: Cyclosporin-containing ophthalmic emulsion gel and its preparation method
INVENTOR(S): Mao, Yufeng
PATENT ASSIGNEE(S): Wuxi Xinrentang Pharmaceutical Technology Co., Ltd., Peop. Rep. China
SOURCE: Faming Zhuanli Shenqing, 12pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 102525887	A	20120704	CN 2012-10011033	20120116
PRIORITY APPLN. INFO.:			CN 2012-10011033	20120116

AB The ophthalmic emulsion gel is composed of hydrophilic polymer(polyalkenyl alc. or non-ionic surfactant emulsifier) 0.01-10, higher fatty acid glyceride(one or more of olive oil, peanut oil, castor oil, mineral oil, etc.) 0.01-10, hydrophobic drug cyclosporin A 0.001-10, gel matrix(one or more of hydroxypropyl Me cellulose, hydroxypropyl Et cellulose, Me cellulose, etc.) 0.02-10, pH regulator(one or more of NaOH, sodium bicarbonate, HCl, etc.) 0-10, osmotic pressure regulator(glucose, glycerol, 0.7-0.9% NaCl solution, mannitol or sorbitol) 0-10, and purified water 10-12 weight parts. The preparation method comprises mixing higher fatty acid glyceride with hydrophobic drug cyclosporin, dissolving, regulating pH to 3-9, obtaining oil phase; dissolving hydrophilic polymer in 1-2 parts of water for injection to obtain water phase; adding oil phase into water phase, mixing to obtain emulsion; adding 9-10 parts of water for injection into beaker, sprinkling gel matrix on the surface of water for injection, standing and swelling; mixing emulsion with gel, stirring, regulating pH with pH regulator to 3-9, adding osmotic pressure regulator till the osmotic pressure of mixed solution is 200-350 Osmol/kg, subpackaging, and sterilizing at 115-125 and 0.05-0.15 MPa for 15-25 min. The ophthalmic emulsion gel directly acts on infected part, and can throughly and effectively play its role.

L2 ANSWER 3 OF 14 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2011:1544834 CAPLUS
DOCUMENT NUMBER: 155:694448
TITLE: Cyclosporin emulsions
INVENTOR(S): Morgan, Aileen; Gore, Anuradha V.; Attar, Mayssa; Pujara, Chetan
PATENT ASSIGNEE(S): Allergan, Inc., USA
SOURCE: PCT Int. Appl., 23pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2011150102	A1	20111201	WO 2011-US37964	20110525
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP,				

KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA,
MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE,
PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV,
SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR,
HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS,
SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML,
MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL,
SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

US 20110294744	A1	20111201	US 2011-13115764	20110525
EP 2575854	A1	20130410	EP 2011-726545	20110525

R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR,
HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO,
RS, SE, SI, SK, SM, TR

PRIORITY APPLN. INFO.: US 2010-61347851 P 20100525
WO 2011-US37964 W 20110525

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB Disclosed herein is a composition comprising cyclosporin A at a concentration between about 0.001% (w/v) and about 1.0% (w/v), a plant oil at a concentration between about 0.01% (w/v) and about 10% (w/v), and macrogol 15 hydroxystearate at a concentration between about 0.01% (w/v) and about 10% (w/v).

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 4 OF 14 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2007:1175883 CAPLUS
DOCUMENT NUMBER: 147:455518
TITLE: Liquid crystal emulsion-type pharmaceutical compositions containing cyclosporin
INVENTOR(S): Akamatsu, Akira; Fujii, Masahiro; Sakaguchi, Tomonori; Horisawa, Eijiro
PATENT ASSIGNEE(S): Maruho Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 12pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2007269795	A	20071018	JP 2007-60987	20070309
JP 5026824	B2	20120919		
CA 2697756	A1	20090319	CA 2007-2697756	20070910
WO 2009034604	A1	20090319	WO 2007-JP67564	20070910

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA,
CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI,
GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG,
KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME,
MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL,
PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN,
TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE,
IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, BF,
BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW,
GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ,
BY, KG, KZ, MD, RU, TJ, TM

EP 2193798	A1	20100609	EP 2007-806996	20070910

R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE,
IS, IT, LI, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR,
AL, BA, HR, MK, RS

US 20100190695 A1 20100729 US 2010-676929 20100308
PRIORITY APPLN. INFO.: JP 2006-66545 A 20060310
WO 2007-JP67564 W 20070910
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
AB The invention provides a liquid crystal emulsion-type pharmaceutical composition
characterized by containing cyclosporin and a nonionic surfactant, wherein the composition provides improved transdermal absorption property. For example, a liquid crystal emulsion-type composition containing cyclosporin A 0.1, squalane 1.4,
behenic acid 0.2, cetostearyl alc. 0.9, glycerin monostearate 0.6, polyoxyethylene polyoxypropylene cetyl ether 0.6, 1,3-butylene glycol 9, L-arginine 0.1, pH adjuster q.s., and water balance to 100 % was formulated.

L2 ANSWER 5 OF 14 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2007:63260 CAPLUS
DOCUMENT NUMBER: 146:149038
TITLE: Opthalmic emulsion comprising cyclosporin
INVENTOR(S): Chang, James N.; Olejnik, Orest; Firestone, Bruce A.
PATENT ASSIGNEE(S): Allergan, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 24pp., Cont.-in-part of U.S. Ser. No. 181,409.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20070015694	A1	20070118	US 2005-255821	20051019
US 7288520	B2	20071030		
US 20070015690	A1	20070118	US 2005-181178	20050713
US 7297679	B2	20071120		
US 20070015710	A1	20070118	US 2005-181187	20050713
US 7276476	B2	20071002		
US 20070015691	A1	20070118	US 2005-181409	20050713
US 20070015692	A1	20070118	US 2005-181428	20050713
US 7202209	B2	20070410		
US 20070015693	A1	20070118	US 2005-181509	20050713
US 20070149447	A1	20070628	US 2007-679934	20070228
US 8536134	B2	20130917		
US 20080009436	A1	20080110	US 2007-857223	20070918
US 8211855	B2	20120703		
US 20080070834	A1	20080320	US 2007-940652	20071115
US 8575108	B2	20131105		
US 20120270805	A1	20121025	US 2012-13536479	20120628
US 8563518	B2	20131022		
US 20140011753	A1	20140109	US 2013-14027006	20130913
US 20140045772	A1	20140213	US 2013-14059025	20131021
US 20140057855	A1	20140227	US 2013-14071427	20131104

PRIORITY APPLN. INFO.:

US 2005-181178	A2	20050713
US 2005-181187	A2	20050713
US 2005-181409	A2	20050713
US 2005-181428	A2	20050713
US 2005-181509	A2	20050713
US 2005-255821	A3	20051019
US 2007-679934	A1	20070228
US 2007-857223	A1	20070918
US 2007-940652	A1	20071115
US 2012-13536479	A1	20120628

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB A composition is disclosed herein comprising from about 0.001% to about 0.4% cyclosporin A, castor oil, and a surfactant selected from the group consisting of alc. ethoxylated, alcs., alkyl glycosides, alkyl polyglycosides, alkylphenol ethoxylates, amine oxides, block polymers, carboxylated alc. or alkylphenol ethoxylates, carboxylic adds/fatty acids, cellulose derivs., ethoxylated alcs., ethoxylated alkylphenols, ethoxylated aryl phenols, ethoxylated fatty acids, ethoxylated fatty acids, ethoxylated fatty esters and oils, fatty alcs., fatty esters, glycol esters, lanolin-based derivs., lecithin and lecithin derivs., lignin and lignin derivs., Me esters, monoglycerides and derivs., phospholipids, polyacrylic acids, polyethylene glycols, polyethylene oxide-polypropylene oxide copolymers, polyethylene oxides, polymeric surfactants, polypropylene oxides, propoxylated alcs., propoxylated alkyl phenols, propoxylated fatty acids, protein-based surfactants, sarcosine derivs., silicone-based surfactants, sorbitan derivs., stearates, sucrose and glucose esters and derivs., and combinations thereof. For example, emulsion was prepared containing cyclosporin A 0.1%, castor oil 1%, clove oil 0.7%, Polysorbate-80 1%, diglycerol 0.7%, glycerin 2%, CM-cellulose 0.5%, sodium hydroxide to adjust pH (7.2) and water as needed.

OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)

REFERENCE COUNT: 89 THERE ARE 89 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 6 OF 14 CAPLUS COPYRIGHT 2014 ACS on STN

ACCESSION NUMBER: 2000:875740 CAPLUS

DOCUMENT NUMBER: 134:33000

TITLE: Emulsion preconcentrate comprising a cyclosporin, propylene carbonate, and glycerides

INVENTOR(S): Sherman, Bernard Charles

PATENT ASSIGNEE(S): Can.

SOURCE: U.S., 5 pp.
CODEN: USXXAM

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6159933	A	20001212	US 1998-66712	19980427
CA 2236131	A1	19981029	CA 1998-2236131	19980429

PRIORITY APPLN. INFO.: NZ 1997-314701 A 19970429

AB Pharmaceutical compns. in the form of an emulsion preconc. or microemulsion preconc. which comprise a cyclosporin as active ingredient, propylene carbonate as hydrophilic solvent, glycerides as lipophilic solvent, and a surfactant. An emulsion preconc. containing cyclosporin 1, Maisine 3.2, propylene carbonate 1.4, Cremophor RH40 3.8, and polysorbate 20 1.2 g was prepared, and 1 g of the preconc. was combined with 20 mL of warm water to form an emulsion or microemulsion.

OS.CITING REF COUNT: 5 THERE ARE 5 CAPLUS RECORDS THAT CITE THIS RECORD (5 CITINGS)

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 7 OF 14 CAPLUS COPYRIGHT 2014 ACS on STN

ACCESSION NUMBER: 2000:283997 CAPLUS

DOCUMENT NUMBER: 132:298857

TITLE: Pharmaceutical composition comprising cyclosporin in association with a carrier in a self-emulsifying drug

delivery system
INVENTOR(S): Mulye, Nirmal
PATENT ASSIGNEE(S): Pharmasolutions, Inc., USA
SOURCE: U.S., 8 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6057289	A	20000502	US 1999-303158	19990430
WO 2000066140	A1	20001109	WO 2000-US11624	20000428
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW				
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				
AU 2000046812	A	20001117	AU 2000-46812	20000428

PRIORITY APPLN. INFO.: US 1999-303158 A 19990430
WO 2000-US11624 W 20000428
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
AB The present invention is directed to a pharmaceutical composition comprising a pharmaceutically effective amount of cyclosporin in association with a pharmaceutical carrier, said carrier comprising a drug solubilizing effective amount of a fatty acid having 6-22 carbon atoms and a nonionic surfactant. An emulsion ready for encapsulation into a capsule contained cyclosporin 100, oleic acid 200, and polyoxyl 35 castor oil 200 mg.
OS.CITING REF COUNT: 12 THERE ARE 12 CAPLUS RECORDS THAT CITE THIS RECORD (12 CITINGS)
REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 8 OF 14 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 1999:594969 CAPLUS
DOCUMENT NUMBER: 131:219189
TITLE: Emulsion preconcentrates comprising a cyclosporin and glycerides
INVENTOR(S): Sherman, Bernard Charles
PATENT ASSIGNEE(S): Can.
SOURCE: PCT Int. Appl., 20 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9945946	A1	19990916	WO 1999-CA192	19990305
W: CA, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				

PRIORITY APPLN. INFO.: NZ 1998-329929 A 19980309
AB Pharmaceutical compns. in the form of an ethanol-free emulsion preconcs. which comprises a cyclosporin as active ingredient, a lipophilic solvent selected from glycerides, a hydrophilic solvent selected from propylene

glycol and polyethylene glycol, a surfactant selected from polyoxyethylene glycolated natural or hydrogenated vegetable oil, and a co-surfactant preferably selected from polyoxyethylene-sorbitan-fatty acid esters. A pharmaceutical emulsion contained cyclosporin 1.0, maisine 2.1, propylene glycol 2.6, Cremophor RH40 3.6, Polysorbate-80 1.0, and water q.s. 100%.

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 9 OF 14 CAPLUS COPYRIGHT 2014 ACS on STN

ACCESSION NUMBER: 1999:44999 CAPLUS
DOCUMENT NUMBER: 130:100683
TITLE: Pharmaceutical emulsions containing cyclosporins and surfactants
INVENTOR(S): Bhalani, Vinayak T.; Patel, Satishchandra P.
PATENT ASSIGNEE(S): Sidmak Laboratories, Inc., USA
SOURCE: U.S., 4 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5858401	A	19990112	US 1997-786314	19970122
US 7070802	B1	20060704	US 2001-797912	20010305
US 7988995	B1	20110802	US 2002-207146	20020730
US 20060188561	A1	20060824	US 2006-400585	20060407
US 8119157	B2	20120221		
US 20070259810	A1	20071108	US 2007-686555	20070315
US 7799340	B2	20100921		
US 20120135940	A1	20120531	US 2012-13349138	20120112

PRIORITY APPLN. INFO.:

US 1996-60010410	P	19960122
US 1997-786314	A2	19970122
US 1998-196353	B1	19981119
US 2001-797912	A1	20010305
US 2002-207146	A1	20020730
US 2006-400585	A1	20060407

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB A stable solution of cyclosporin forming a polar lipid self-emulsifying drug delivery system is disclosed. The composition typically consists of cyclosporin dissolved in a polar lipid, such as a medium chain monoglyceride of C6-12 fatty acids having a monoglyceride content of at least 50% and a surfactant. The composition provided here instantly forms a fine emulsion on exposure to water. The encapsulated dosage form of this composition needs neither a hydrophilic component nor air-tight blister packaging, and is particularly suitable for oral administration. Thus, 1.0 g of cyclosporin A was dissolved in 5.0 g of Capmul MCM at 25°-30°. Then 6.0 g of Tween 80 was added and mixed to achieve a homogeneous solution The mixture appeared as a clear solution to the naked eye, and a microscopic anal. revealed no crystals. The formulation was filled in a soft gelatin capsule such that each capsule contained 50 mg of cyclosporin.

OS.CITING REF COUNT: 15 THERE ARE 15 CAPLUS RECORDS THAT CITE THIS RECORD (15 CITINGS)

REFERENCE COUNT: 63 THERE ARE 63 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 10 OF 14 CAPLUS COPYRIGHT 2014 ACS on STN

ACCESSION NUMBER: 1998:719247 CAPLUS
DOCUMENT NUMBER: 129:347306
ORIGINAL REFERENCE NO.: 129:70613a,70616a

TITLE: Emulsion preconcentrate comprising a cyclosporin and acetylated monoglyceride
INVENTOR(S): Sherman, Bernard Charles
PATENT ASSIGNEE(S): Can.
SOURCE: PCT Int. Appl., 20 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9848779	A1	19981105	WO 1998-CA408	19980429
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, GW, 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, US, 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, ML, MR, NE, SN, TD, TG				
CA 2285983	A1	19981105	CA 1998-2285983	19980429
ZA 9803596	A	19981105	ZA 1998-3596	19980429
AU 9870248	A	19981124	AU 1998-70248	19980429
EP 981329	A1	20000301	EP 1998-916755	19980429
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, NL, SE, PT, IE, FI				
US 6258783	B1	20010710	US 1999-403660	19991027
US 20010027178	A1	20011004	US 2001-783969	20010216

PRIORITY APPLN. INFO.: NZ 1997-314702 A 19970429
WO 1998-CA408 W 19980429
US 1999-403660 A1 19991027

AB Pharmaceutical compns. in the form of an emulsion preconc. or microemulsion preconc. which comprise a cyclosporin as active ingredient, acetylated monoglyceride as lipophilic solvent, a surfactant, and optionally a hydrophilic solvent. One example contained cyclsporine 1.0, Myvacet 9-45 6.0, and Cremophor RH 40 3.7 parts.

OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 11 OF 14 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 1996:38846 CAPLUS
DOCUMENT NUMBER: 124:66660
ORIGINAL REFERENCE NO.: 124:12317a,12320a
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	A1	19951123	CA 1995-2190485	19950517
CA 2190485	C	20030415		
CA 2309033	A1	19951123	CA 1995-2309033	19950517
CA 2309033	C	20030826		
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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
CN 1229136	C	20051130		
BR 9507664	A	19971007	BR 1995-7664	19950517
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R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE				
AT 203911	T	20010815	AT 1995-921294	19950517
ES 2161895	T3	20011216	ES 1995-921294	19950517
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	KR 1996-706523	A3	19961118

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

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.

OS.CITING REF COUNT:	36	THERE ARE 36 CAPLUS RECORDS THAT CITE THIS RECORD (38 CITINGS)
REFERENCE COUNT:	2	THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 12 OF 14 CAPLUS

ACCESSION NUMBER: 1995:379416 CAPLUS
DOCUMENT NUMBER: 122:169924
ORIGINAL REFERENCE NO.: 122:31059a,31062a
TITLE: Cyclosporin A in fat emulsion carriers: experimental studies on pharmacokinetics and tissue distribution
AUTHOR(S): Tibell, A.; Lindholm, A.; Sawe, J.; Chen, G; Norrlind, B.
CORPORATE SOURCE: Department Transplantation Surgery, Karolinska Institute, Stockholm, Swed.
SOURCE: Pharmacology & Toxicology (Copenhagen) (1995), 76(2), 115-21
CODEN: PHTOEH; ISSN: 0901-9928
DIGITAL OBJECT ID: 10.1111/j.1600-0773.1995.tb00115.x
PUBLISHER: Munksgaard
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In the com. available i.v. formulation of cyclosporin A (Sandimmun), ethoxylated castor oil (Cremophor EL) is used as a solubilizing agent. The authors recently reported that the acute nephrotoxic effect of this drug was alleviated by replacing Cremophore EL with a soybean oil-based fat emulsion in a rat model. To further explore the potential of fat emulsions as carriers for cyclosporin A, data on the in vivo pharmacokinetics and tissue distribution are required. In this study in pigs, the pharmacokinetics of soybean oil-cyclosporin A was compared to that of Sandimmun. The 2 formulations seemed bioequivalent, as there were no significant differences in the systemic clearances, vols. of distribution or elimination half-lives. Moreover, the tissue distributions of soybean oil-cyclosporin A and Sandimmun were compared in rats. These studies also included two addnl. lipid-based carriers; one based on iodized ester of poppy seed oil and the other on a liposomal preparation The tissue distributions were similar regardless of the carriers used. Fat emulsion carriers seem to offer possibilities for preparing better tolerated i.v. formulations of cyclosporin A while maintaining the same characteristics concerning pharmacokinetics and tissue distribution.
OS.CITING REF COUNT: 15 THERE ARE 15 CAPLUS RECORDS THAT CITE THIS RECORD (15 CITINGS)

L2 ANSWER 13 OF 14 EMBASE
ACCESSION NUMBER: 1999105661 EMBASE
TITLE: Distribution of cyclosporin A in ocular tissues after topical administration to albino rabbits and beagle dogs.
AUTHOR: Acheampong, Andrew A., Dr. (correspondence); Shackleton, Martha; Tang-Liu, Diane D.-S.; Ding, Shulin; Stern, Mike E.; Decker, Robert
CORPORATE SOURCE: Allergan, Irvine, CA, United States. acheampong_andrew@Allergan.com
AUTHOR: Acheampong, Andrew A., Dr. (correspondence)
CORPORATE SOURCE: Allergan Inc., 2525 Dupont Drive, Irvine, CA 92715, United States. acheampong_andrew@Allergan.com
SOURCE: Current Eye Research, (Feb 1999) Vol. 18, No. 2, pp. 91-103.
Refs: 30
ISSN: 0271-3683 CODEN: CEYRDM
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 012 Ophthalmology
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
039 Pharmacy
LANGUAGE: English

SUMMARY LANGUAGE: English
ENTRY DATE: Entered Embase: 28 Apr 1999
Last Updated on Embase: 28 Apr 1999

AB Purpose. To determine the ocular pharmacokinetics of cyclosporin A after topical ophthalmic administration. Methods. Radiolabled cyclosporin A in either a castor oil-in-water emulsion or a corn oil ointment was applied to the eyes of beagle dogs or albino rabbits using the following paradigms: (i) single doses of 0.2% emulsion to rabbits and dogs, (ii) single doses of 0.05%, 0.2%, or 0.4% emulsion to rabbits, (iii) multiple doses of 0.2% emulsion to dogs, (iv) single and multiple doses of 0.2% ointment to rabbits. The distribution of cyclosporin A was determined by measuring the distribution of radioactivity. Results. After a single dose, cyclosporin A was rapidly absorbed into the conjunctiva (C(max): dogs, 1490 ng/g; rabbits, 1340 ng/g) and cornea (C(max): dogs, 311 ng/g; rabbits, 955 ng/g). High concentrations (> 300 ng/g) could be detected in the cornea up to 96 hours post-dose. Lower concentrations were found in the intraocular tissues, and systemic absorption was minimal. After multiple doses, there was some accumulation in the cornea, lens, lacrimal gland, and iris-cilliary body, but limited accumulation in the conjunctiva and sclera. Ocular tissue concentrations of cyclosporin A increased with increasing dose concentration; proportionally in lacrimal gland and intraocular tissues; less than proportionally in conjunctiva and cornea. The pharmacokinetic profile of the cyclosporin A corn oil ointment was similar to that of the emulsion. Conclusions. Topical ophthalmic cyclosporin A penetrated into extraocular tissues at concentrations adequate for local immunomodulation while penetration into intraocular tissues was much less and absorption into the blood was minimal.

L2 ANSWER 14 OF 14 MEDLINE ® on STN
ACCESSION NUMBER: 1999238168 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10223652
TITLE: Distribution of cyclosporin A in ocular tissues after topical administration to albino rabbits and beagle dogs.
AUTHOR: Acheampong A A
CORPORATE SOURCE: Allergan, Irvine, CA 92715, USA.
acheampong_andrew@Allergan.com
AUTHOR: Shackleton M; Tang-Liu D D; Ding S; Stern M E; Decker R
SOURCE: Current eye research, (1999 Feb) Vol. 18, No. 2, pp. 91-103.
Journal code: 8104312. ISSN: 0271-3683. L-ISSN: 0271-3683.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: MEDLINE; Priority Journals
FILE SEGMENT: Print
ENTRY MONTH: 199906
ENTRY DATE: Entered STN: 14 Jun 1999
Last Updated on STN: 14 Jun 1999
Entered Medline: 2 Jun 1999
OS.CITING REF COUNT: 3 There are 3 MEDLINE records that cite this record

AB PURPOSE: To determine the ocular pharmacokinetics of cyclosporin A after topical ophthalmic administration.

METHODS: Radiolabled cyclosporin A in either a castor oil-in-water emulsion or a corn oil ointment was applied to the eyes of beagle dogs or albino rabbits using the following paradigms: (i) single doses of 0.2% emulsion to rabbits and dogs, (ii) single doses of 0.05%, 0.2%, or 0.4% emulsion to rabbits, (iii) multiple doses of 0.2% emulsion to dogs, (iv) single and multiple doses of 0.2% ointment to rabbits. The distribution of cyclosporin A was determined by measuring the distribution of radioactivity.

RESULTS: After a single dose, cyclosporin A was rapidly absorbed into the conjunctiva (Cmax: dogs, 1490 ng/g; rabbits, 1340 ng/g) and cornea (Cmax: dogs, 311 ng/g; rabbits, 955 ng/g). High concentrations (>300 ng/g) could be detected in the cornea up to 96 hours post-dose. Lower concentrations were found in the intraocular tissues, and systemic absorption was minimal. After multiple doses, there was some accumulation in the cornea, lens, lacrimal gland, and iris-cilliary body, but limited accumulation in the conjunctiva and sclera. Ocular tissue concentrations of cyclosporin A increased with increasing dose concentration; proportionally in lacrimal gland and intraocular tissues; less than proportionally in conjunctiva and cornea. The pharmacokinetic profile of the cyclosporin A corn oil ointment was similar to that of the emulsion.

CONCLUSIONS: Topical ophthalmic cyclosporin A penetrated into extraocular tissues at concentrations adequate for local immunomodulation while penetration into intraocular tissues was much less and absorption into the blood was minimal.

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(FILE 'HOME' ENTERED AT 12:17:16 ON 16 JUN 2014)

FILE 'REGISTRY' ENTERED AT 12:17:22 ON 16 JUN 2014

FILE 'CAPLUS, EMBASE, BIOSIS, MEDLINE' ENTERED AT 12:17:32 ON 16 JUN 2014
L1 0 CYCLOSPORIN (10A) (TWICE OR TWO) (10A) (CASTOR OIL) (10A) (EMUL
L2 14 CYCLOSPORIN (10A) (CASTOR OIL) (10A) (EMULSION)

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COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	79.00	79.78

SESSION WILL BE HELD FOR 120 MINUTES
STN INTERNATIONAL SESSION SUSPENDED AT 12:19:01 ON 16 JUN 2014

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	14222478
	Filing Date	2014-03-21
	First Named Inventor	ANDREW ACHEAMPONG
	Art Unit	1621
	Examiner Name	TBD
	Attorney Docket Number	17618-US-CN6CN1-AP

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.M.C.G./

U.S.PATENTS						
Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
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	2	4388229		1983-06-14	Cherng-Chyi Fu	
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Receipt date: 03/28/2014	Application Number	14222478	14222478 - GAU: 1676
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**	Filing Date	2014-03-21	
	First Named Inventor	ANDREW ACHEAMPONG	
	Art Unit	1621	
	Examiner Name	TBD	
	Attorney Docket Number	17618-US-CN6CN1-AP	

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.M.C.G./

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Receipt date: 03/28/2014

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Application Number	14222478 14222478 - GAU: 1676
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Art Unit	1621
Examiner Name	TBD
Attorney Docket Number	17618-US-CN6CN1-AP

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.M.C.G./

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	21	5342625		1994-08-30	Hauer et al	
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Receipt date: 03/28/2014	Application Number	14222478	14222478 - GAU: 1676
INFORMATION DISCLOSURE STATEMENT BY APPLICANT	Filing Date	2014-03-21	
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	Art Unit	1621	
	Examiner Name	TBD	
	Attorney Docket Number	17618-US-CN6CN1-AP	

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.M.C.G./

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**	Filing Date	2014-03-21	
	First Named Inventor	ANDREW ACHEAMPONG	
	Art Unit	1621	
	Examiner Name	TBD	
	Attorney Docket Number	17618-US-CN6CN1-AP	

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.M.C.G./

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	Examiner Name	TBD	
	Attorney Docket Number	17618-US-CN6CN1-AP	

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	Examiner Name	TBD	
	Attorney Docket Number	17618-US-CN6CN1-AP	

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Receipt date: 03/28/2014	Application Number	14222478	14222478 - GAU: 1676
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	Art Unit	1621	
	Examiner Name	TBD	
	Attorney Docket Number	17618-US-CN6CN1-AP	

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	Examiner Name	TBD	
	Attorney Docket Number	17618-US-CN6CN1-AP	

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Receipt date: 03/28/2014	Application Number	14222478	14222478 - GAU: 1676
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	Art Unit	1621	
	Examiner Name	TBD	
	Attorney Docket Number	17618-US-CN6CN1-AP	

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.M.C.G./

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	105	8642556		2014-02-04	Acheampong et al	U.S. Application No. 13/967,189 and its entire prosecution history**
	106	8648048		2014-02-11	Acheampong et al	U.S. Application No. 13/967,168 and its entire prosecution history**

If you wish to add additional U.S. Patent citation information please click the Add button.

U.S.PATENT APPLICATION PUBLICATIONS

Receipt date: 03/28/2014

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(**Not for submission under 37 CFR 1.99)**

Application Number	14222478 14222478 - GAU: 1676
Filing Date	2014-03-21
First Named Inventor	ANDREW ACHEAMPONG
Art Unit	1621
Examiner Name	TBD
Attorney Docket Number	17618-US-CN6CN1-AP

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.M.C.G./

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
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	2	20010014665		2001-08-16	Fischer et al	
	3	20010036449		2001-11-01	Michael Garst	
	4	20020012680		2002-01-31	Patel et al	
	5	20020013272		2002-01-31	Cavanak et al	
	6	20020016290		2002-02-07	Floc'h et al	
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Receipt date: 03/28/2014	Application Number	14222478	14222478 - GAU: 1676
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**	Filing Date	2014-03-21	
	First Named Inventor	ANDREW ACHEAMPONG	
	Art Unit	1621	
	Examiner Name	TBD	
	Attorney Docket Number	17618-US-CN6CN1-AP	

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.M.C.G./

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☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

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☐ See attached certification statement.

☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ None

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Laura L. Wine/	Date (YYYY-MM-DD)	2014-03-27
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This collection of information is required by 37 CFR 1.97 and 1.98. 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 1 hour 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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The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S22	3690	ding.inv. and dry	US-PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2014/06/14 11:45
S23	41	ding.inv. and keratoconjunctivitis	US-PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2014/06/14 11:46
S24	19	ding.inv. and cyclosporin.clm.	US-PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2014/06/14 11:46
S25	118	cyclosporin same polysorbate same "castor oil"	US-PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2014/06/14 15:44
S26	24	cyclosporin same polysorbate same "castor oil".clm.	US-PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2014/06/14 15:44

EAST Search History (Interference)

< This search history is empty>

6/ 16/ 2014 12:15:00 PM
C:\ Users\ mgarcia\ Documents\ EAST\ Workspaces\ 12397834.wsp

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/222,478	03/21/2014	Andrew Acheampong	17618CON6CON1 (AP)	9616

51957 7590 05/09/2014

ALLERGAN, INC.
2525 DUPONT DRIVE, T2-7H
IRVINE, CA 92612-1599

EXAMINER	
CORDERO GARCIA, MARCELA M	
ART UNIT	PAPER NUMBER
1676	

NOTIFICATION DATE	DELIVERY MODE
05/09/2014	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
pair_allergan@firsttofile.com

Office Action Summary	Application No. 14/222,478	Applicant(s) ACHEAMPONG ET AL.	
	Examiner MARCELA M. CORDERO GARCIA	Art Unit 1676	AIA (First Inventor to File) Status No

-- 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 2 MONTHS 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 *3/21/2014*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ 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*

5)☒ Claim(s) *1-36* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☐ Claim(s) _____ is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☒ Claim(s) *1-36* are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ 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).

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).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

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) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

DETAILED ACTION

The present application is being examined under the pre-AIA first to invent provisions.

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 20.5.

II. Claims 21-36, drawn to a composition, classified, e.g., in class 514, subclass 11.

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, treating diseases such as corneal transplantation may be done with a cyclosporine solution in polymer or copolymer instead of an emulsion as instantly claimed (e.g., Lixin, Chinese Medical Journal 2002, cited in the IDS dated 3/28/2014).

Restriction for examination purposes as indicated is proper because all these inventions listed in this action are independent or distinct for the reasons given above and there would be a serious search and/or examination burden if restriction were not required because one or more of the following reasons apply:

A reference that would anticipate and/or make obvious one of the inventions would not necessarily anticipate and/or make obvious another invention.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of an invention to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected invention**.

The election of an invention 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. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable upon the elected invention.

Should applicant traverse on the ground that the inventions are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions 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 or pre-AIA 35 U.S.C. 103(a) of the other invention.

This application contains claims directed to the following patentably distinct species: (A) the many and multiple diseases to be treated (e.g., dry eye syndrome,

phacoanaphylactic endophthalmitis, uveitis, vernal conjunctivitis, atopic keratoconjunctivitis, corneal graft rejection); (B) the many and multiple hydrophobic components (e.g., vegetable oils, animal oilds, mineral oils, synthetic oils and mixtures thereof); (C) the many and multiple active agents: cyclosporin A, derivatives and mixtures thereof; (D) the many and multiple additional components (e.g., emulsifier component, tonicity component and/or polyelectrolyte component). The species are independent or distinct because they are drawn to different diseases having different symptoms and patient population and/or compounds having different molecular and physical-chemical properties. In addition, these species are not obvious variants of each other based on the current record.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species, or a single grouping of patentably indistinct species [i.e., for Group I: elect species for (A), (B), (C) and (D); for Group II: elect species of (B), (C) and (D)], for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, claims 1-36 are generic.

There is a search and/or examination burden for the patentably distinct species as set forth above because at least the following reason(s) apply: A reference that would anticipate and/or make obvious one of the species would not necessarily anticipate and/or make obvious another species.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing**

the elected species or grouping of patentably indistinct species, 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.

The election may be made with or without traverse. To preserve 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 election of species requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected species or grouping of patentably indistinct species.

Should applicant traverse on the ground that the species, or groupings of patentably indistinct species from which election is required, are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing them 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 species unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103 or pre-AIA 35 U.S.C. 103(a) of the other species.

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.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be corrected in compliance with 37 CFR 1.48(a) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. A request to correct inventorship under 37 CFR 1.48(a) must be accompanied by an application data sheet in accordance with 37 CFR 1.76 that identifies each inventor by his or her legal name and by the processing fee required under 37 CFR 1.17(i).

The examiner has required restriction between product or apparatus claims and process claims. Where applicant elects claims directed to the product/apparatus, and all product/apparatus claims are subsequently found allowable, withdrawn process claims that include all the limitations of the allowable product/apparatus claims should be considered for rejoinder. All claims directed to a nonelected process invention must include all the limitations of an allowable product/apparatus claim for that process invention to be rejoined.

In the event of rejoinder, the requirement for restriction between the product/apparatus 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/apparatus are found allowable, an otherwise proper restriction requirement between product/apparatus claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an

allowable product/apparatus claim will not be rejoined. See MPEP § 821.04. Additionally, in order for rejoinder to occur, applicant is advised that the process claims should be amended during prosecution to require the limitations of the product/apparatus claims. **Failure to do so may result in no 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.

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, Karlheinz R. Skowronek can be reached on (571)-272-9047. 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/
Primary Examiner, Art Unit 1676

MMCG 05/2014

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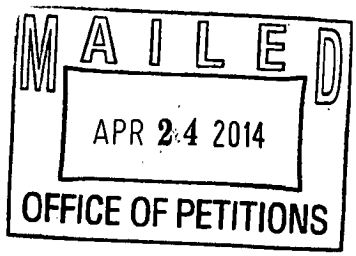

Doc Code: TRACK1.GRANT

Decision Granting Request for Prioritized Examination (Track I or After RCE)	Application No.: 14/222,478

1. THE REQUEST FILED March 21, 2014 IS **GRANTED**.

The above-identified application has met the requirements for prioritized examination

A. ☒ for an original nonprovisional application (Track I).
B. ☐ for an application undergoing continued examination (RCE).

2. **The above-identified application will undergo prioritized examination.** The application will be accorded special status throughout its entire course of prosecution until one of the following occurs:

A. filing a **petition for extension of time** to extend the time period for filing a reply;

B. filing an **amendment to amend the application to contain more than four independent claims, more than thirty total claims**, or a multiple dependent claim;

C. filing a **request for continued examination**;

D. filing a notice of appeal;

E. filing a request for suspension of action;

F. mailing of a notice of allowance;

G. mailing of a final Office action;

H. completion of examination as defined in 37 CFR 41.102; or

I. abandonment of the application.

Telephone inquiries with regard to this decision should be directed to Irvin Dingle at (571)272-3210, Office of Petitions.

Irvin Dingle
/Irvin Dingle/
[*Signature*]

Paralegal Specialist
(Title)

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 14/222,478

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	280
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	600
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	720
TOTAL CLAIMS (37 CFR 1.16(i))	27 minus 20 =	* 7			OR	x 80 =	560
INDEPENDENT CLAIMS (37 CFR 1.16(h))	4 minus 3 =	* 1				x 420 =	420
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 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).						0.00
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							0.00
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	2580

APPLICATION AS AMENDED - PART II

		(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($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT A	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	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE($)	ADDITIONAL FEE($)		RATE($)	ADDITIONAL FEE($)
AMENDMENT B	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 found in the appropriate box in column 1.

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
14/222,478	03/21/2014	1621	2580	17618CON6CON1 (AP)	27	4

CONFIRMATION NO. 9616

51957
ALLERGAN, INC.
2525 DUPONT DRIVE, T2-7H
IRVINE, CA 92612-1599

FILING RECEIPT

OC000000067802253

Date Mailed: 04/16/2014

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

Andrew Acheampong, Irvine, CA;
Diane D. Tang-Liu, Las Vegas, CA;
James N. Chang, Newport Beach, CA;
David F. Power, San Clemente, CA;

Applicant(s)

Allergan, Inc., Irvine, CA

Assignment For Published Patent Application

Allergan, Inc., Irvine, CA

Power of Attorney: The patent practitioners associated with Customer Number 51957

Domestic Priority data as claimed by applicant

This application is a CON of 13/961,828 08/07/2013 PAT 8685930
which is a CON of 11/897,177 08/28/2007 PAT 8618064
and is a CON of 10/927,857 08/27/2004 ABN
which claims benefit of 60/503,137 09/15/2003

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access - A proper **Authorization to Permit Access to Application by Participating Offices** (PTO/SB/39 or its equivalent) has been received by the USPTO.

If Required, Foreign Filing License Granted: 04/15/2014

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 14/222,478**

Projected Publication Date: 07/24/2014

Non-Publication Request: No

Early Publication Request: No

Title

METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS

Preliminary Class

514

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

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Electronic Acknowledgement Receipt

EFS ID:	18616805
Application Number:	14222478
International Application Number:	
Confirmation Number:	9616
Title of Invention:	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS
First Named Inventor/Applicant Name:	Andrew Acheampong
Customer Number:	51957
Filer:	Laura Lee Wine/Ken Dinh
Filer Authorized By:	Laura Lee Wine
Attorney Docket Number:	17618CON6CON1 (AP)
Receipt Date:	28-MAR-2014
Filing Date:	
Time Stamp:	16:55:06
Application Type:	Utility under 35 USC 111(a)

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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Non Patent Literature	PedersenExpertOpin1415_1436_2001.pdf	4262912 0ffbacdd587d316724d2c00a7e64fcdbc6ed49e4	no	22

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2	Non Patent Literature	Phillips_CyclosporineJOCP1_2000.pdf	1385594 63acdf4c243d41621f7001e9c76dbf167d4ec51d	no	10
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3	Non Patent Literature	Present_1993.pdf	1624134 baefc9d58e2e27ac5b6a99bd9151eb6a41e80d81	no	4
Warnings:					
Information:					
4	Non Patent Literature	Restasis_Increasing_tear_Production_2009.pdf	332259 0a1285bcf642f927562ba180ba3ba5446eb2afe4	no	3
Warnings:					
Information:					
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Warnings:					
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Warnings:					
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7	Non Patent Literature	RudingerPeptideHormones1_7_1976.pdf	2488192 b6fc18b6ad98c34de41f2d461a1f5736500be985	no	11
Warnings:					
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8	Non Patent Literature	Sall_2000.pdf	208829 065c18613831a6d2cf5a88066e70ae03daae1b29	no	9
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Information:					
26	Non Patent Literature	13961828.pdf	2596695 660e95b406b8f6ac91600605af4712d74c8677bb	no	34
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27	Non Patent Literature	90009944.pdf	1904560 4b5aa1ab68a1940d5930d4265e9053cf67203dc9	no	39
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	14222478
	Filing Date	2014-03-21
	First Named Inventor	ANDREW ACHEAMPONG
	Art Unit	1621
	Examiner Name	TBD
	Attorney Docket Number	17618-US-CN6CN1-AP

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Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
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	Examiner Name	TBD
	Attorney Docket Number	17618-US-CN6CN1-AP

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Attorney Docket Number	17618-US-CN6CN1-AP

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] ¡	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	19810655	DE		1999-09-16	Eberhard-Karls-Universitat Tubingen Universitatskl		☐
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	7	1995-031211	WO		1995-11-23	Allergan, Inc.		☐
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NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
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☐ See attached certification statement.

☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

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A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Laura L. Wine/	Date (YYYY-MM-DD)	2014-03-27
Name/Print	Laura L. Wine	Registration Number	68,681

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