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Table with 4 columns: APPLICATION NUMBER (14/493,903), FILING OR 371(C) DATE (09/23/2014), FIRST NAMED APPLICANT (Shirou SAWA), ATTY. DOCKET NO./TITLE (2014-1250)

CONFIRMATION NO. 7395

PUBLICATION NOTICE

513
WENDEROTH, LIND & PONACK, L.L.P.
1030 15th Street, N.W.,
Suite 400 East
Washington, DC 20005-1503



Title:AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID

Publication No.US-2015-0011634-A1

Publication Date:01/08/2015

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 Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101



APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/493,903	01/06/2015	8927606	2014-1250	7395

513                      7590                      12/17/2014  
WENDEROTH, LIND & PONACK, L.L.P.  
1030 15th Street, N.W.,  
Suite 400 East  
Washington, DC 20005-1503

### 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):

Shirou SAWA, Hyogo, JAPAN;  
SENJU PHARMACEUTICAL CO., LTD., Osaka, JAPAN, Assignee (with 37 CFR 1.172 Interest);  
Shuhei FUJITA, Hyogo, JAPAN;

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The USA offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to encourage and facilitate business investment. To learn more about why the USA is the best country in the world to develop technology, manufacture products, and grow your business, visit [SelectUSA.gov](http://SelectUSA.gov).

**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.

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.

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

513 7599 11/19/2014  
**WENDEROTH, LIND & PONACK, L.L.P.**  
 1030 15th Street, N.W.,  
 Suite 400 East  
 Washington, DC 20005-1503

**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.
14/493,903	09/23/2014	Shiroo SAWA	2014-1250	7395

TITLE OF INVENTION: AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID

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	02/19/2015

EXAMINER	ART UNIT	CLASS-SUBCLASS
SOROUSH, LAYLA	1627	514-619000

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. WENDEROTH, LIND & PONACK, L.L.P.

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: SENJU PHARMACEUTICAL CO., LTD.

(B) RESIDENCE: (CITY and STATE OR COUNTRY) OSAKA, JAPAN

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 23-0975 (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

Applicant asserting small entity status. See 37 CFR 1.27

Applicant changing to regular undiscounted fee status.

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.

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.

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 1.293 and 1.294 for signature requirements and certifications.

Warren M. Cheek, Jr. Digitally signed by Warren M. Cheek, Jr. DN: cn=Warren M. Cheek, o=Wenderoth, L.P., email=wcheek@wenderoth.com, c=US

Authorized Signature: Warren M. Cheek, Jr./ Date: 2014.11.21 13:01:08 -05'00'

Date: November 21, 2014

Typed or printed name: Warren M. Cheek Registration No. 33,367

## Electronic Patent Application Fee Transmittal

<b>Application Number:</b>	14493903
<b>Filing Date:</b>	23-Sep-2014
<b>Title of Invention:</b>	AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID
<b>First Named Inventor/Applicant Name:</b>	Shirou SAWA
<b>Filer:</b>	Warren M. Cheek Jr./Donna King
<b>Attorney Docket Number:</b>	2014-1250

Filed as Large Entity

### Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
<b>Basic Filing:</b>				
<b>Pages:</b>				
<b>Claims:</b>				
<b>Miscellaneous-Filing:</b>				
<b>Petition:</b>				
<b>Patent-Appeals-and-Interference:</b>				
<b>Post-Allowance-and-Post-Issuance:</b>				
Utility Appl Issue Fee	1501	1	960	960

**Extension of Time:**  
Page 4 of 306

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
<b>Miscellaneous:</b>				
<b>Total in USD (\$)</b>				<b>960</b>

## Electronic Acknowledgement Receipt

<b>EFS ID:</b>	20766046
<b>Application Number:</b>	14493903
<b>International Application Number:</b>	
<b>Confirmation Number:</b>	7395
<b>Title of Invention:</b>	AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID
<b>First Named Inventor/Applicant Name:</b>	Shirou SAWA
<b>Customer Number:</b>	513
<b>Filer:</b>	Warren M. Cheek Jr./maurice linder
<b>Filer Authorized By:</b>	Warren M. Cheek Jr.
<b>Attorney Docket Number:</b>	2014-1250
<b>Receipt Date:</b>	21-NOV-2014
<b>Filing Date:</b>	23-SEP-2014
<b>Time Stamp:</b>	14:19:12
<b>Application Type:</b>	Utility under 35 USC 111(a)

### Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	\$960
RAM confirmation Number	555
Deposit Account	230975
Authorized User	CHEEK JR., WARREN M.

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)	AttachA_IF.pdf	415516 ddf1617e8025bf921e65a2b7ad88412e8af7c2d1	no	1

### Warnings:

The PDF file has been signed with a digital signature and the legal effect of the document will be based on the contents of the file not the digital signature.

### Information:

2	Fee Worksheet (SB06)	fee-info.pdf	30663 1363e483d9503e897c14300d4941ebc9a139c76f	no	2
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### Warnings:

### Information:

**Total Files Size (in bytes):** 446179

**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.**



NOTICE OF ALLOWANCE AND FEE(S) DUE

513 7590 11/19/2014
WENDEROTH, LIND & PONACK, L.L.P.
1030 15th Street, N.W.,
Suite 400 East
Washington, DC 20005-1503

Table with 2 columns: EXAMINER (SOROUSH, LAYLA), ART UNIT (1627), PAPER NUMBER (7395)

DATE MAILED: 11/19/2014

Table with 5 columns: APPLICATION NO., FILING DATE, FIRST NAMED INVENTOR, ATTORNEY DOCKET NO., CONFIRMATION NO.

TITLE OF INVENTION: AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID

Table with 7 columns: APPLN. TYPE, ENTITY STATUS, ISSUE FEE DUE, PUBLICATION FEE DUE, PREV. PAID ISSUE FEE, TOTAL FEE(S) DUE, DATE DUE

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)

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.

513 7590 11/19/2014  
**WENDEROTH, LIND & PONACK, L.L.P.**  
 1030 15th Street, N.W.,  
 Suite 400 East  
 Washington, DC 20005-1503

**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.
14/493,903	09/23/2014	Shirou SAWA	2014-1250	7395

TITLE OF INVENTION: AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID

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	02/19/2015

EXAMINER	ART UNIT	CLASS-SUBCLASS
SOROUSH, LAYLA	1627	514-619000

<p>1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).</p> <p><input type="checkbox"/> Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.</p> <p><input type="checkbox"/> "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. <b>Use of a Customer Number is required.</b></p>	<p>2. For printing on the patent front page, list</p> <p>(1) The names of up to 3 registered patent attorneys or agents OR, alternatively, _____ 1</p> <p>(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. _____ 2</p> <p>_____ 3</p>
---	---

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

<p>4a. The following fee(s) are submitted:</p> <p><input type="checkbox"/> Issue Fee</p> <p><input type="checkbox"/> Publication Fee (No small entity discount permitted)</p> <p><input type="checkbox"/> Advance Order - # of Copies _____</p>	<p>4b. Payment of Fee(s): (<b>Please first reapply any previously paid issue fee shown above</b>)</p> <p><input type="checkbox"/> A check is enclosed.</p> <p><input type="checkbox"/> Payment by credit card. Form PTO-2038 is attached.</p> <p><input type="checkbox"/> 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).</p>
---	--

5. **Change in Entity Status** (from status indicated above)

Applicant certifying micro entity status. See 37 CFR 1.29

Applicant asserting small entity status. See 37 CFR 1.27

Applicant changing to regular undiscounted fee status.

**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.

**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.

**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. \_\_\_\_\_



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

Table with 5 columns: APPLICATION NO., FILING DATE, FIRST NAMED INVENTOR, ATTORNEY DOCKET NO., CONFIRMATION NO.
Values: 14/493,903, 09/23/2014, Shirou SAWA, 2014-1250, 7395

513 7590 11/19/2014
WENDEROTH, LIND & PONACK, L.L.P.
1030 15th Street, N.W.,
Suite 400 East
Washington, DC 20005-1503

Table with 2 columns: EXAMINER, ART UNIT, PAPER NUMBER
Values: SOROUGH, LAYLA, 1627

DATE MAILED: 11/19/2014

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.

**Notice of Allowability**

**Application No.**

14/493,903

**Examiner**

LAYLA SOROUGH

**Applicant(s)**

SAWA ET AL.

**Art Unit**

1627

**-- 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 the T.D filed on 11/5/14, 11/06/14 and approved on 11/6/14 and 11/7/14.
- 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 19-48.
- 4.  Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
  - a)  All    b)  Some\*    c)  None    of the:
    - 1.  Certified copies of the priority documents have been received.
    - 2.  Certified copies of the priority documents have been received in Application No. 10/525,006 .
    - 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.  A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.
  - 6.  CORRECTED DRAWINGS ( as "replacement sheets") must be submitted.
    - (a)  including changes required by the Notice of Draftsperson's Patent Drawing Review ( PTO-948) attached
      - 1)  hereto or 2)  to Paper No./Mail Date \_\_\_\_\_.
    - (b)  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).**
- 7.  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.  Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3.  Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 10/16/14; 9/23/14
- 4.  Examiner's Comment Regarding Requirement for Deposit of Biological Material
- 5.  Notice of Informal Patent Application
- 6.  Interview Summary (PTO-413), Paper No./Mail Date 10/22/14 .
- 7.  Examiner's Amendment/Comment
- 8.  Examiner's Statement of Reasons for Allowance
- 9.  Other \_\_\_\_\_.

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

***Acknowledgement of Receipt***

Applicant's response filed on 11/05/2014 is acknowledged.

***Claim Status***

Claims 19-48 are pending.

Claims 19-48 are allowed.

***Withdrawn Rejections***

The Double Patenting rejections over U.S. Patent No. 8129431, 8497304, 8669290, 8754131, 8871813, US App. No. 14502014, 14269692 is withdrawn in view of the TD's filed on 11/05/2014 and 11/06/2014; and approved on 11/06/2014 and 11/07/2014.

***Reasons for Allowance***

The following is an examiner's statement of reasons for allowance:

The method as claimed are found to be patentable over the prior art because the prior art does not teach or fairly suggest a method for treating an inflammatory disease of an eye, the method comprising administering to said eye a stable aqueous liquid preparation that comprises: (a) a first component; and (b) a second component; wherein the first component is 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, wherein the hydrate is at least one selected from a 1/2 hydrate, 1 hydrate, and 3/2 hydrate; the first component is

Art Unit: 1627

the sole pharmaceutical active ingredient contained in the preparation; the second component is tyloxapol and is present in said liquid preparation in an amount sufficient to stabilize said first component; wherein said stable liquid preparation is formulated for ophthalmic administration; and wherein said liquid preparation is administered to said eye at a dose and a frequency effective to treat said inflammatory disease.

The closest prior arts of record, namely Chen et al. (US 6383471), teach a pharmaceutical composition including a hydrophobic therapeutic agent having at least one ionizable functional group, and a carrier. The carrier includes an ionizing agent capable of ionizing the functional group, a surfactant, and optionally solubilizers, triglycerides, and neutralizing agents (abstract). The reference teaches a hydrophobic therapeutic agent to include bromfenac (2-amino-3-(4-bromobenzoyl)phenylacetic acid)(see claim 4). The hydrophobic therapeutic agent is used in less than about 1% by weight, and typically less than about 0.1% or 0.01% by weight (see col 4 lines 58-60) (renders obvious the limitation of claims 8 and 24). The reference further teaches surfactants inclusive of polyethylene glycol fatty acid esters and additionally teaches polyethylene glycol fatty acid monoesters such as peg-15 stearate, etc (see claims 21-22 24 and 27). The surfactants are selected from the group consisting of alcohols; polyoxyethylene alkylethers; fatty acids; glycerol fatty acid esters; acetylated glycerol fatty acid esters; lower alcohol fatty acids esters; polyethylene glycol fatty acids esters; polyethylene glycol glycerol fatty acid esters; polypropylene glycol fatty acid esters; polyoxyethylene glycerides; lactic acid derivatives of mono/diglycerides; propylene glycol diglycerides; sorbitan fatty acid esters; polyoxyethylene sorbitan fatty acid esters;

Art Unit: 1627

polyoxyethylene-polyoxypropylene block copolymers; transesterified vegetable oils; sterols; sterol derivatives; sugar esters; sugar ethers; sucroglycerides; polyoxyethylene vegetable oils; and polyoxyethylene hydrogenated vegetable oils. The pharmaceutical compositions of the present invention can be provided in the form of a solution concentrate; i.e., a composition as described above, and intended to be dispersed with water, either prior to administration, in the form of a drink, or dispersed in vivo (col 34 lines 63-68) (reads on an aqueous liquid preparation). The reference also teaches preservatives (see claim 64). Although formulations specifically suited to oral administration are presently preferred, the compositions of the present invention can also be formulated for topical, transdermal, ocular, pulmonary, vaginal, rectal, transmucosal or parenteral administration (col 35 lines 9-20). Chen et al. further teaches components that can be incorporated into the composition include inorganic acids inclusive of boric acid (col 46, line 6), solubilizer such as polyvinylpyrrolidone (claim 49), exemplifications of carriers comprising Edetate Disodium (col 4 table 20 formulations 65 and 66), and ionizing agents that deprotonate the acidic functional groups of the therapeutic agent are pharmaceutically acceptable organic or inorganic bases, inclusive of sodium hydroxide (col 11 lines 12-13) (reads on the limitations of claim 22).

However, Applicant presents excellent effects are clearly demonstrated by Experiments 1 to 3 of the present specification. Experiment 1 -- Stability of sodium 2-amino-3-(4-bromobenzoyl)phenyl acetate was evaluated. Namely, two eye drops of sodium 2-amino-3-(4-bromobenzoyl) phenylacetate comprising the components as

Art Unit: 1627

shown in Table 1 were prepared, filled respectively into a polypropylene container and subjected to a stability test at 60°C for 4 weeks. As is apparent from Table 1, the stability test was carried out under the conditions of pH 7.0 at 60°C for 4 weeks. Table 1 clearly shows that sodium 2-amino-3-(4-bromobenzoyl)phenylacetate in polyoxyl 40 stearate-containing preparation was more stable than that in polysorbate 80-containing preparation. As is apparent from Table 2, the remaining rate of sodium 2-amino-3-(4-bromobenzoyl)phenylacetate in the compositions A-07 and A-08 containing 0.02 w/v % and 0.05 w/v % of polyoxyl 40 stearate is not less than 90 % after storage at 60°C for 4 weeks. Table 2 clearly shows that the compositions containing 0.02 w/v % and 0.05 w/v % of polyoxyl 40 stearate have sufficient stability for eye drops.

The method as claimed are found to be patentable over the prior art because the prior art does not teach or fairly suggest a method for treating an inflammatory disease of an eye, the method comprising administering to said eye a stable aqueous liquid preparation that comprises: (a) a first component; and (b) a second component; wherein the first component is 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, wherein the hydrate is at least one selected from a 1/2 hydrate, 1 hydrate, and 3/2 hydrate; the first component is the sole pharmaceutical active ingredient contained in the preparation; the second component is tyloxapol and is present in said liquid preparation in an amount sufficient to stabilize said first component; wherein said stable liquid preparation is formulated for ophthalmic administration; and wherein said liquid preparation is administered to said eye at a dose and a frequency effective to treat said inflammatory disease.



Art Unit: 1627

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 LAYLA SOROUGH whose telephone number is (571)272-5008. The examiner can normally be reached on 8:30a.m.-5:00p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on (571)272-0629. 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.

/Layla Soroush/

Examiner, Art Unit 1627

<b>Examiner-Initiated Interview Summary</b>	<b>Application No.</b> 14/493,903	<b>Applicant(s)</b> SAWA ET AL.	
	<b>Examiner</b> LAYLA SOROUGH	<b>Art Unit</b> 1627	

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

- (1) LAYLA SOROUGH. (3)\_\_\_\_\_.
- (2) Warren Cheek. (4)\_\_\_\_\_.

Date of Interview: 22 October 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: \_\_\_\_\_.

Identification of prior art discussed: \_\_\_\_\_.

**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...)

In the interest of compact prosecution, a proposal was made to the Applicant to overcome the remaining issues and proceed to allowance. Applicant agreed and gave the Examiner authorization to make the appropriate claim amendments in an Examiner's Amendment.

**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

INFORMATION DISCLOSURE STATEMENT

FORM PTO/SB/08 A&B (modified)

U.S. DEPARTMENT OF COMMERCE  
PATENT AND TRADEMARK OFFICE

LIST OF REFERENCES CITED BY APPLICANT(S)  
(Use several sheets if necessary)

Date Submitted to PTO: September 23, 2014

ATTY DOCKET NO.  
2014-1250

SERIAL NO.  
NEW

FIRST NAMED INVENTOR  
Shirou SAWA

FILING DATE  
September 23, 2014

GROUP

U.S. PATENT DOCUMENTS

*EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
/L.S./	AA	5,603,929	2/1997	Desai et al.			
	AB	5,653,972	8/1997	Desai et al.			
	AC	4,910,225	3/1990	Ogawa et al.			
	AD	5,110,493	5/1992	Cheng-Chyi et al.			
	AE	6,383,471	5/2002	Chen et al.			
	AF	4,045,576	8/1977	Welstead, Jr. et al.			
	AG	4,683,242	7/1987	Poser			
	AH	6,319,513	11/2001	Dobrozsi			
	AI	2007/0082857	4/2007	Sawa			
	AJ	6,369,112	4/2002	Xia			
	AK	5,998,465	12/1999	Hellberg et al.			
	AL	5,597,560	1/1997	Bergamini et al.			
	AM	6,395,746	5/2002	Cagle et al.			
	AN	5,475,034	12/1995	Yanni et al.			
	AO	5,540,930	7/1996	Guy			
	AP	5,942,508	8/1999	Sawa			
	AQ	6,274,592	8/2001	Sawa			
	AR	2001/0056098	12/2001	Sawa			
	AS	6,274,609	8/2001	Yasueda et al.			
	AT	5,558,876	9/1996	Desai et al.			
	AU	6,162,393	12/2000	De Bruiju et al.			
	AV	8,129,431	3/2012	Sawa et al.			
	AW	6,107,343	8/2000	Sallmann et al.			
	AX	2,880,130	3/1959	Johnson			

## INFORMATION DISCLOSURE STATEMENT

FORM PTO/SB/08 A&B (modified)				ATTY DOCKET NO. 2014-1250			SERIAL NO. NEW	
U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE  LIST OF REFERENCES CITED BY APPLICANT(S) (Use several sheets if necessary)  Date Submitted to PTO: September 23, 2014				FIRST NAMED INVENTOR Shirou SAWA				
				FILING DATE September 23, 2014			GROUP	
/L.S./	AY	2,880,138	3/1959	Johnson				
/L.S./	AZ	6,071,904	6/2000	Ali et al.				
FOREIGN PATENT DOCUMENTS								
		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION/ADDITIONAL INFORMATION YES NO	
/L.S./	BA	9-503791	4/1997	JP				
	BB	2-124819	5/1990	JP				
	BC	1-104023	4/1989	JP				
	BD	00/59475	10/2000	WO				
	BE	11-228404	8/1999	JP			Yes	
	BF	5-223052	8/1993	JP			Abstract	
	BG	62-126124	6/1987	JP				No
	BH	96/14829	5/1996	WO				
	BI	01/15677	3/2001	WO				
	BJ	2 013 188	9/1990	CA				
	BK	02/13804	2/2002	WO				
	BL	707 119	9/1995	AU				
	BM	02083323	3/1990	JP				
	BN	2002-308764	10/2002	JP				
	BO	0 306 984	3/1989	EP				
	BP	22042/88	3/1989	AU				
	BQ	94/15597	7/1994	WO				
	BR	2 383 971	3/2001	CA				
	BS	0 274 870	7/1988	EP				
	BT	94/05298	3/1994	WO				
OTHER DOCUMENT(S) (Including Author, Title, Date, Pertinent Pages, Etc.)								
/L.S./	CA	New Drugs in Japan, 2001, 2001 Edition, Published by Yakuji Nippo Ltd., May 11, 2001, pp. 27-29, and its English translation of the material portions.						

FORM PTO/SB/08 A&B ( <i>modified</i> )		ATTY DOCKET NO. 2014-1250	SERIAL NO. NEW
U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE  LIST OF REFERENCES CITED BY APPLICANT(S) (Use several sheets if necessary)  Date Submitted to PTO: September 23, 2014		FIRST NAMED INVENTOR Shirou SAWA	
		FILING DATE September 23, 2014	GROUP
/L.S./	CB	ISTA Pharmaceuticals, "New Drug Applications: Xibrom", <a href="http://www.drugs.com/nda/xibrom_040525.html">http://www.drugs.com/nda/xibrom_040525.html</a> , accessed online 9/19/2007.	
	CC	Nolan et al., "The Topical Anti-Inflammatory and Analgesic Properties of Bromfenic in Rodents", Agents and Actions, Vol. 25, No. 1-2, pp. 77-85, August 1988.	
	CD	Corrected partial English translation of New Drugs in Japan, 2001, 2001 Edition, Published by Yakuji Nippo Ltd., May 11, 2001, pp. 27-29, previously submitted on April 11, 2005.	
	CE	Complete English translation of New Drugs in Japan, 2001, 2001 Edition, Published by Yakuji Nippo Ltd., May 11, 2001, pp. 27-29.	
	CF	Notice of Opposition dated February 19, 2009 issued by EPO in connection with the corresponding European patent application and Opposition.	
	CG	<a href="http://medical-dictionary.thefreedictionary.com/prophylactic">http://medical-dictionary.thefreedictionary.com/prophylactic</a> accessed 12/15/2009.	
	CH	Y. Hara, "Evaluation of New Drugs by Clinicians", Clinics & Drug Therapy, Vol. 19, No. 10, October 2000, pp. 1-2.	
	CI	G. Smolin, M.D., "New Drugs in Ophthalmology", International Ophthalmology Clinics, Vol. 36, No. 2, 1996, pp. 1-9.	
	CJ	ISTA News Release, XIBROM™, Bromfenac Ophthalmic Solution, 2007, p.1.	
	CK	S. Prince et al., "Analysis of Benzalkonium Chloride and its Homologs: HPLC Versus HPCE <sup>1</sup> ", Journal of Pharmaceutical and Biomedical Analysis, Vol. 19, pp. 877-882, 1999.	
	CL	M. Doughty, "Therapeutics: Medicines Update <i>p18</i> Side-Effects of Anti-Epilepsy Drugs", Optician, Vol. 223, No. 5853, May 31, 2002, pp. 16-22.	
	CM	I. Reddy, Ph.D., "Ocular Therapeutics and Drug Delivery", Technomics Publishing Co., Basel, pp. 42-43, 390, 1996.	
	CN	H. Schott, "Comparing the Surface Chemical Properties and the Effect of Salts on the Cloud Point of a Conventional Nonionic Surfactant, Octoxynol 9 (Triton X-100), and of its Oligomer, Tyloxapol (Triton WR-1339)", Journal of Colloid and Interface Science, Vol. 205, pp. 496-502, 1998.	
	CO	O. Regev, "Aggregation Behavior of Tyloxapol, a Nonionic Surfactant Oligomer, in Aqueous Solution", Journal of Colloid and Interface Science, Vol. 210, pp. 8-17, 1999.	
	CP	PDR 50th Edition 1996, Physicians' Desk Reference, p. 469.	
	CQ	PDR 54th Edition 2000, Physicians' Desk Reference, pp. 486-487, 491-492.	
	CR	V. A. Ostrovskii et al., "Acid-Base Properties of 5-Substituted Tetrazoles", Khimiya Get. Soc., pp. 412-416, 1981.	
	CS	LOTEMAX™ product brochure, Loteprednol Etabonate Ophthalmic Suspension, 0.5%, pp. 1-16, March 6, 1998.	

FORM PTO/SB/08 A&B ( <i>modified</i> )		ATTY DOCKET NO. 2014-1250	SERIAL NO. NEW
U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE		FIRST NAMED INVENTOR Shirou SAWA	
LIST OF REFERENCES CITED BY APPLICANT(S) (Use several sheets if necessary)		FILING DATE September 23, 2014	GROUP
Date Submitted to PTO: September 23, 2014			
/L.S./	CT	Webster's New World Dictionary of the American Language, Second College Edition, "monohydrate", Simon & Schuster, NY, p. 920, 1982.	
	CU	Pharmacopeia, R. S. Cook et al., "Edetic Acid", pp. 177-179, JT Steward, "Sodium Metabisulfide", pp. 451-453, 2000.	
	CV	Yakuji Nippo Limited, "Recent New Drugs 2001", Japanese Pharmacopoeia 2001 Edition, pp. 27-29, May 2001 (English translation).	
	CW	Sigma-Aldrich catalog, Biochemicals and Reagents for Life Science Research, p. 175, 2000.	
	CX	G. Patani et al., "Bioisosterism: A Rational Approach in Drug Design", Chemical Reviews, Vol. 96, No. 8, pp. 3147-3176, 1996.	
	CY	P. Deluca et al., "Interaction of Preservatives with Macromolecules IV, Binding of Quaternary Ammonium Compounds by Nonionic Agents", Journal of the American Pharmaceutical Association, Vol. 49, No. 7, pp. 430-437, July 1960.	
	CZ	D. Guttman et al., "Solubilization of Anti-Inflammatory Steroids by Aqueous Solutions of Triton WR-1339", Journal of Pharmaceutical Sciences, Vol. 50, No. 4, pp. 305-307, April 1961.	
	CCA	T. Fan et al., "Determination of Benzalkonium Chloride in Ophthalmic Solutions Containing Tyloxapol by Solid-Phase Extraction and Reversed-Phase High-Performance Liquid Chromatography", Journal of Pharmaceutical Sciences, Vol. 82, No. 11, pp. 1172-1174, November 1993.	
	CCB	FDA Website search of Orange Book (Patent and Exclusivity Search Results): Approved Drug Products with Therapeutic Equivalence Evaluations; Search Results for N203168, 2014.	
	CCC	FDA website search of Orange Book (Detail Record Search): Approved Drug Products with Therapeutic Equivalence Evaluations, Search Results for N203168, 2014.	
	CCD	Remington: The Science and Practice of Pharmacy, 20 <sup>th</sup> Edition, "Boric Acid", Lippincott, Williams, Baltimore MD, p. 1041, 2000.	
	CCE	PDR 52nd Edition 1998, Physicians' Desk Reference, "Duract", Method Economics Co., Monroville, NJ, pp. 3035-3037.	
	CCF	ALREX <sup>TM</sup> product package, Loteprednol Etabonate, Ophthalmic Suspension, 0.2%, pp. 1-13, 1998.	
	CCG	XIBROM <sup>TM</sup> product package, Bromfenac Ophthalmic Solution, 0.09%, pp. 3-6, 2000.	
	CCH	BROMDAY product package, Bromfenac Ophthalmic Solution, 0.09%, pp. 4-8, 1997.	
	CCI	PROLENSA <sup>TM</sup> product package, Bromfenac Ophthalmic Solution, 0.07%, pp. 4-9, 2013.	
	CCJ	PDR 54 Edition 2000, Physicians' Desk Reference, pp. 489-491, TOBRADEX®, Tobramycin and Dexamethasone Ophthalmic Suspension and Ointment.	
	CCK	FDA website description of VOLTAREN, Diclofenac Sodium, Ophthalmic Solution, 0.1%, pp. 1-2, 1991.	

## INFORMATION DISCLOSURE STATEMENT

FORM PTO/SB/08 A&B (modified)		<b>ATTY DOCKET NO.</b> 2014-1250	<b>SERIAL NO.</b> NEW
U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE  LIST OF REFERENCES CITED BY APPLICANT(S) (Use several sheets if necessary)  Date Submitted to PTO: September 23, 2014		<b>FIRST NAMED INVENTOR</b> Shirou SAWA	
		<b>FILING DATE</b> September 23, 2014	<b>GROUP</b>
/L.S./	CCL	ALREX™ product package, Loteprednol Etabonate, Ophthalmic Suspension, 0.2%, pp. 1-13, 1998.	
↓	CCM	The United States Pharmacopeia, The National Formulary, USP 24, NF 19, pp. 1809-1813, 1864-1866, 2000.	
↓	CCN	Dorset & Baber, Webster's New Twentieth Century Dictionary, Second Edition, "Ophthalmic" and "Ophthalmic" p. 1254, 1979.	
↓	CCO	BRONUCK® news release, Bromfenac Sodium Hydrate Ophthalmic Solution, p.1, 2005.	
EXAMINER		/Layla Soroush/	DATE CONSIDERED


**UNITED STATES PATENT AND TRADEMARK OFFICE**

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**United States Patent and Trademark Office**  
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 P.O. Box 1450  
 Alexandria, Virginia 22313-1450  
 www.uspto.gov

**BIB DATA SHEET**
**CONFIRMATION NO. 7395**

SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.	
14/493,903	09/23/2014	514	1627	2014-1250	
<b>APPLICANTS</b> SENJU PHARMACEUTICAL CO., LTD., Osaka, JAPAN, Assignee (with 37 CFR 1.172 Interest); <b>INVENTORS</b> Shirou SAWA, Hyogo, JAPAN; Shuhei FUJITA, Hyogo, JAPAN; <b>** CONTINUING DATA *****</b> This application is a DIV of 14/261,720 04/25/2014 PAT 8871813 which is a DIV of 14/165,976 01/28/2014 PAT 8754131 which is a DIV of 13/687,242 11/28/2012 PAT 8669290 which is a DIV of 13/353,653 01/19/2012 PAT 8497304 which is a DIV of 10/525,006 03/28/2005 PAT 8129431 which is a 371 of PCT/JP2004/000350 01/16/2004 <b>** FOREIGN APPLICATIONS *****</b> JAPAN 2003-012427 01/21/2003 <b>** IF REQUIRED, FOREIGN FILING LICENSE GRANTED **</b> 09/29/2014					
Foreign Priority claimed <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No 35 USC 119(a-d) conditions met <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No Verified and Acknowledged <u>/LAYLA SOROUGH/</u> <small>Examiner's Signature</small>	<input checked="" type="checkbox"/> Met after Allowance LS <small>Initials</small>	<b>STATE OR COUNTRY</b> JAPAN	<b>SHEETS DRAWINGS</b> 0	<b>TOTAL CLAIMS</b> 30	<b>INDEPENDENT CLAIMS</b> 3
<b>ADDRESS</b> WENDEROTH, LIND & PONACK, L.L.P. 1030 15th Street, N.W., Suite 400 East Washington, DC 20005-1503 UNITED STATES					
<b>TITLE</b> AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID					
<b>FILING FEE RECEIVED</b> 2400	FEES: Authority has been given in Paper No. _____ to charge/credit DEPOSIT ACCOUNT No. _____ for following:			<input type="checkbox"/> All Fees <input type="checkbox"/> 1.16 Fees (Filing) <input type="checkbox"/> 1.17 Fees (Processing Ext. of time) <input type="checkbox"/> 1.18 Fees (Issue) <input type="checkbox"/> Other _____ <input type="checkbox"/> Credit	



**Search Notes**




<b>Application/Control No.</b> 14/493,903	<b>Applicant(s)/Patent under Reexamination</b> SAWA ET AL.	
<b>Examiner</b> LAYLA SORROUSH	<b>Art Unit</b> 1627	

<b>SEARCHED</b>			
Class	Subclass	Date	Examiner
514	619	10/22/14	LS
514	535	10/22/14	LS
514	570	10/22/14	LS

<b>INTERFERENCE SEARCHED</b>			
Class	Subclass	Date	Examiner
514	618	10/22/14	LS

<b>SEARCH NOTES (INCLUDING SEARCH STRATEGY)</b>		
	DATE	EXMR
STIC (see also 13535653); and updated npl and EAST	10/22/14	LS
odp:SAWA, SHIROU and FUJITA, SHUHEI	10/22/14	LS

<b>Issue Classification</b> 	<b>Application/Control No.</b> 14/493,903	<b>Applicant(s)/Patent under Reexamination</b> SAWA ET AL.
	<b>Examiner</b> LAYLA SOROUGH	<b>Art Unit</b> 1627

ISSUE CLASSIFICATION												
ORIGINAL				INTERNATIONAL CLASSIFICATION								
CLASS		SUBCLASS		CLAIMED				NON-CLAIMED				
514		619		A	1	N	37	/18				/
CROSS REFERENCES				A	61	K	31	/165				/
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)											
514	535	570	618	A	1	N	37	/44				/
				A	61	K	31	/24				/
				A	1	N	37	/10				/
				A	61	K	31	/19				/
								/				/

(Assistant Examiner) (Date)	/Layla Soroush/ 11/7/14 (Primary Examiner) (Date)	<b>Total Claims Allowed: 30</b>  O.G. Print Claim(s) 1  O.G. Print Fig. NONE
(Legal Instruments Examiner) (Date)		

<input type="checkbox"/> Claims renumbered in the same order as presented by applicant				<input type="checkbox"/> CPA		<input type="checkbox"/> T.D.		<input type="checkbox"/> R.1.47	
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	7	19	37		67		97		127
	8	20	38		68		98		128
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INFORMATION DISCLOSURE STATEMENT

FORM PTO/SB/08 A&B (modified)

ATTY DOCKET NO.  
2014-1250

SERIAL NO.  
14/493,903

U.S. DEPARTMENT OF COMMERCE  
PATENT AND TRADEMARK OFFICE

FIRST NAMED INVENTOR  
Shirou SAWA

LIST OF REFERENCES CITED BY APPLICANT(S)  
(Use several sheets if necessary)

Date Submitted to PTO: October 16, 2014

FILING DATE  
September 23, 2014

GROUP

U.S. PATENT DOCUMENTS

*EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
/L.S./	AA	8,129,431	3/2012	Sawa et al.			
	AB	6,107,343	8/2000	Sallmann et al.			
	AC	4,910,225	3/1990	Ogawa et al.			
	AD	5,603,929	2/1997	Desai et al.			
	AE	5,475,034	12/1995	Yanni et al.			
	AF	5,558,876	9/1996	Desai et al.			
	AG	6,274,609	8/2001	Yasueda et al.			
	AH	5,540,930	7/1996	Guy et al.			
	AI	2,880,130	3/1959	Johnson			
	AJ	2,880,138	3/1959	Johnson			
	AK	6,071,904	6/2000	Ali et al.			
	AL	5,597,560	1/1997	Bergamini et al.			


FOREIGN PATENT DOCUMENTS


		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION/ADDITIONAL INFORMATION	
							YES	NO
/L.S./	BA	2 013 188	9/1990	CA				
	BB	22042/88	3/1989	AU				
	BC	94/15597	7/1994	WO				
	BD	2 383 971	3/2001	CA				
	BE	02/13804	2/2002	WO				
	BF	0 274 870	7/1988	EP				
	BG	94/05298	3/1994	WO				

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

/L.S./	CA	Y. Hara, "Evaluation of New Drugs by Clinicians", Clinics & Drug Therapy, Vol. 19, No. 10, October 2000, pp. 1-2.						
/L.S./	CB	G. Smolin, M.D., "New Drugs in Ophthalmology", International Ophthalmology Clinics, Vol. 36, No. 2, 1996, pp. 1-9.						

Sheet 2 of 3		INFORMATION DISCLOSURE STATEMENT	
FORM PTO/SB/08 A&B (modified)		ATTY DOCKET NO. 2014-1250	SERIAL NO. 14/493,903
U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE		FIRST NAMED INVENTOR Shirou SAWA	
LIST OF REFERENCES CITED BY APPLICANT(S) (Use several sheets if necessary)		FILING DATE September 23, 2014	GROUP
Date Submitted to PTO: October 16, 2014			
/L.S./	CC	ISTA News Release, XIBROM™, Bromfenac Ophthalmic Solution, 2007, p.1.	
	CD	S. Prince et al., "Analysis of Benzalkonium Chloride and its Homologs: HPLC Versus HPCE <sup>1</sup> ", Journal of Pharmaceutical and Biomedical Analysis, Vol. 19, pp. 877-882, 1999.	
	CE	M. Doughty, "Therapeutics: Medicines Update p18 Side-Effects of Anti-Epilepsy Drugs", Optician, Vol. 223, No. 5853, May 31, 2002, pp. 16-22.	
	CF	I. Reddy, Ph.D., "Ocular Therapeutics and Drug Delivery", Technomics Publishing Co., Basel, pp. 42-43, 390, 1996.	
	CG	H. Schott, "Comparing the Surface Chemical Properties and the Effect of Salts on the Cloud Point of a Conventional Nonionic Surfactant, Octoxynol 9 (Triton X-100), and of its Oligomer, Tyloxapol (Triton WR-1339)", Journal of Colloid and Interface Science, Vol. 205, pp. 496-502, 1998.	
	CH	O. Regev, "Aggregation Behavior of Tyloxapol, a Nonionic Surfactant Oligomer, in Aqueous Solution", Journal of Colloid and Interface Science, Vol. 210, pp. 8-17, 1999.	
	CI	PDR 50th Edition 1996, Physicans' Desk Reference, p. 469.	
	CJ	PDR 54th Edition 2000, Physicans' Desk Reference, pp. 486-487, 491-492.	
	CK	V. A. Ostrovskii et al., "Acid-Base Properties of 5-Substituted Tetrazoles", Khimiya Get. Soc., pp. 412-416, 1981.	
	CL	LOTEMAX™ product brochure, Loteprednol Etabonate Ophthalmic Suspension, 0.5%, pp. 1-16, March 6, 1998.	
	CM	Webster's New World Dictionary of the American Language, Second College Edition, "monohydrate", Simon & Schuster, NY, p. 920, 1982.	
	CN	Pharmacopeia, R. S. Cook et al., "Edetic Acid", pp. 177-179, JT Steward, "Sodium Metabisulfide", pp. 451-453, 2000.	
	CO	Yakuji Nippo Limited, "Recent New Drugs 2001", Japanese Pharmacopoeia 2001 Edition, pp. 27-29, May 2001 (English translation).	
	CP	Sigma-Aldrich catalog, Biochemicals and Reagents for Life Science Research, p. 175, 2000.	
	CQ	G. Patani et al., "Bioisosterism: A Rational Approach in Drug Design", Chemical Reviews, Vol. 96, No. 8, pp. 3147-3176, 1996.	
	CR	P. Deluca et al., "Interaction of Preservatives with Macromolecules IV, Binding of Quaternary Ammonium Compounds by Nonionic Agents", Journal of the American Pharmaceutical Association, Vol. 49, No. 7, pp. 430-437, July 1960.	
	CS	D. Guttman et al., "Solubilization of Anti-Inflammatory Steroids by Aqueous Solutions of Triton WR-1339", Journal of Pharmaceutical Sciences, Vol. 50, No. 4, pp. 305-307, April 1961.	
↓	CT	T. Fan et al., "Determination of Benzalkonium Chloride in Ophthalmic Solutions Containing Tyloxapol by Solid-Phase Extraction and Reversed-Phase High-Performance Liquid Chromatography", Journal of Pharmaceutical Sciences, Vol. 82, No. 11, pp. 1172-1174, November 1993.	

FORM PTO/SB/08 A&B ( <i>modified</i> )		ATTY DOCKET NO. 2014-1250	SERIAL NO. 14/493,903
U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE		FIRST NAMED INVENTOR Shirou SAWA	
LIST OF REFERENCES CITED BY APPLICANT(S) (Use several sheets if necessary)		FILING DATE September 23, 2014	GROUP
Date Submitted to PTO: October 16, 2014			
/L.S./	CU	FDA Website search of Orange Book (Patent and Exclusivity Search Results): Approved Drug Products with Therapeutic Equivalence Evaluations; Search Results for N203168, 2014.	
	CV	FDA website search of Orange Book (Detail Record Search): Approved Drug Products with Therapeutic Equivalence Evaluations, Search Results for N203168, 2014.	
	CW	Remington: The Science and Practice of Pharmacy, 20 <sup>th</sup> Edition, "Boric Acid", Lippincoh, Williams, Baltimore MD, p. 1041, 2000.	
	CX	PDR 52nd Edition 1998, Physicans' Desk Reference, "Duract", Method Economics Co., Montrale, NJ, pp. 3035-3037.	
	CY	ALREX <sup>TM</sup> product package, Loteprednol Etabonate, Ophthalmic Suspension, 0.2%, pp. 1-13, 1998.	
	CZ	XIBROM <sup>TM</sup> product package, Bromfenac Ophthalmic Solution, 0.09%, pp. 3-6, 2000.	
	CAA	BROMDAY product package, Bromfenac Ophthalmic Solution, 0.09%, pp. 4-8, 1997.	
	CAB	PROLENSA <sup>TM</sup> product package, Bromfenac Ophthalmic Solution, 0.07%, pp. 4-9, 2013.	
	CAC	PDR 54 Edition 2000, Physicans' Desk Reference, pp. 489-491, TOBRADEX®, Tobramycin and Dexamethasone Ophthalmic Suspension and Ointment.	
	CAD	FDA website description of VOLTAREN, Diclofenac Sodium, Ophthalmic Solution, 0.1%, pp. 1-2, 1991.	
	CAE	The United States Pharmacopeia, The National Formulary, USP 24, NF 19, pp. 1809-1813, 1864-1866, 2000.	
	CAF	Dorset & Baber, Webster's New Twentieth Century Dictionary, Second Edition, "Ophthalmic" and "Ophthalmitic" p. 1254, 1979.	
	CAG	BRONUCK® news release, Bromfenac Sodium Hydrate Ophthalmic Solution, p.1, 2005.	
	CAH	Petition for <i>Inter Partes</i> Review of USP 8,669,290 to Sawa et al., Metrics, Inc. v. Senju Pharmaceutical Co., Ltd, pp. 1-71.	
	CAI	Petition for <i>Inter Partes</i> Review of USP 8,129,431 to Sawa et al., Metrics, Inc. v. Senju Pharmaceutical Co., Ltd, pp. 1-71.	
EXAMINER	/Layla Soroush/		DATE CONSIDERED


<b>Application Number</b> 	<b>Application/Control No.</b> 14/493,903	<b>Applicant(s)/Patent under Reexamination</b> SAWA ET AL.

<b>Document Code - DISQ</b>	<b>Internal Document – DO NOT MAIL</b>
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<b>TERMINAL DISCLAIMER</b>	<input checked="" type="checkbox"/> <b>APPROVED</b>	<input type="checkbox"/> <b>DISAPPROVED</b>
Date Filed : 11/6/14	<b>This patent is subject to a Terminal Disclaimer</b>	

**Approved/Disapproved by:**

Janice Ford

<b>Application Number</b> 	<b>Application/Control No.</b> 14/493,903	<b>Applicant(s)/Patent under Reexamination</b> SAWA ET AL.

<b>Document Code - DISQ</b>	<b>Internal Document – DO NOT MAIL</b>
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<b>TERMINAL DISCLAIMER</b>	<input checked="" type="checkbox"/> <b>APPROVED</b>	<input type="checkbox"/> <b>DISAPPROVED</b>
Date Filed : 05 NOV 2014	<b>This patent is subject to a Terminal Disclaimer</b>	

**Approved/Disapproved by:**

Six TDs filed and approved.

JAB

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor : Attorney Docket No. 2014-1250  
Shirou SAWA : **Confirmation No. 7395**  
Serial No. 14/493,903 : **Group Art Unit Not Yet Assigned**  
Filed September 23, 2014 : **Examiner Not Yet Assigned**  
AQUEOUS LIQUID PREPARATION : **Mail Stop: AMENDMENT**  
CONTAINING 2-AMINO-3-(4-  
BROMOBENZOYL)PHENYLACETIC ACID

---

**RESPONSE**

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

Sir/Madam:

In response to the Examiner's request, we are enclosing herewith one additional Terminal Disclaimer to overcome the double patenting rejection over the claims for the above-identified application.

Respectfully submitted,

/Warren M.  
Cheek, Jr./

Digitally signed by /Warren M.  
Cheek, Jr./  
DN: cn=/Warren M. Cheek, Jr./, o, ou,  
email=wcheek@wenderoth.com,  
c=US  
Date: 2014.11.06 15:23:38 -05'00'

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Warren M. Cheek  
Registration No. 33,367  
Attorney for Applicant

WMC/dlk  
Washington, D.C. 20005-1503  
Telephone (202) 721-8200  
Facsimile (202) 721-8250  
November 6, 2014



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor : Attorney Docket No. 2014-1250  
Shirou SAWA : **Confirmation No. 7395**  
Serial No. 14/493,903 : **Group Art Unit Not Yet Assigned**  
Filed September 23, 2014 : **Examiner Not Yet Assigned**  
AQUEOUS LIQUID PREPARATION : **Mail Stop: AMENDMENT**  
CONTAINING 2-AMINO-3-(4-  
BROMOBENZOYL)PHENYLACETIC ACID

---

**TERMINAL DISCLAIMER UNDER 37 CFR 1.321**

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

Sir/Madam:

The owner, SENJU PHARMACEUTICAL CO., LTD., of 100% interest 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 defined in 35 USC 154 and 173, as shortened by any terminal disclaimer, of prior Patent No. 8,669,290, issued March 11, 2014. 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 any patent granted on the instant application that would extend to the expiration date of the full statutory term as defined in 35 USC 154 and 173 of the prior patent, as presently shortened by any terminal disclaimer, in the event that it 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 cancelled 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.

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.

[X] The undersigned is empowered to act on behalf of the organization.

[] The undersigned is an attorney of record.

November 6, 2014

**/Warren M.  
Cheek, Jr./**

Digitally signed by /Warren M. Cheek, Jr./  
DN: cn=/Warren M. Cheek, Jr., o, ou, email=wcheek@wenderoth.com, c=US  
Date: 2014.11.06 15:24:01 -05'00'

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Warren M. Cheek  
Reg. No. 33,367

Terminal disclaimer fee under 37 CFR 1.20(d) is included.

WMC/dlk  
Washington, D.C. 20005-1503  
Telephone (202) 721-8200  
Facsimile (202) 721-8250

## Electronic Patent Application Fee Transmittal

<b>Application Number:</b>	14493903
<b>Filing Date:</b>	23-Sep-2014
<b>Title of Invention:</b>	AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID
<b>First Named Inventor/Applicant Name:</b>	Shirou SAWA
<b>Filer:</b>	Warren M. Cheek Jr./Donna King
<b>Attorney Docket Number:</b>	2014-1250

Filed as Large Entity

### Utility under 35 USC 111(a) Filing Fees

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

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
<b>Miscellaneous:</b>				
Statutory or Terminal Disclaimer	1814	1	160	160
<b>Total in USD (\$)</b>				<b>160</b>

## Electronic Acknowledgement Receipt

<b>EFS ID:</b>	20627550
<b>Application Number:</b>	14493903
<b>International Application Number:</b>	
<b>Confirmation Number:</b>	7395
<b>Title of Invention:</b>	AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID
<b>First Named Inventor/Applicant Name:</b>	Shirou SAWA
<b>Customer Number:</b>	513
<b>Filer:</b>	Warren M. Cheek Jr./maurice linder
<b>Filer Authorized By:</b>	Warren M. Cheek Jr.
<b>Attorney Docket Number:</b>	2014-1250
<b>Receipt Date:</b>	06-NOV-2014
<b>Filing Date:</b>	23-SEP-2014
<b>Time Stamp:</b>	15:54:15
<b>Application Type:</b>	Utility under 35 USC 111(a)

### Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	\$160
RAM confirmation Number	2350
Deposit Account	230975
Authorized User	CHEEK JR., WARREN M.

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	Supplemental Response or Supplemental Amendment	AttachA_Response.pdf	173109 18dbd52236f1315064aa8ecf3aeb23cd3aa65ccf	no	1

**Warnings:**

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**Information:**

2	Terminal Disclaimer Filed	AttachB_TD.pdf	180139 1245809a9c91d4c7134a9bdd6c1e8b70059cd9f0	no	2
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**Information:**

3	Fee Worksheet (SB06)	fee-info.pdf	30859 8faf76fa40bd50bf910448aa52629cf0e9e0887f	no	2
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**Information:**

**Total Files Size (in bytes):** 384107

**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

First Named Inventor : Attorney Docket No. 2014-1250  
Shirou SAWA : **Confirmation No. 7395**  
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**RESPONSE**

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P.O. Box 1450  
Alexandria, VA 22313-1450

Sir/Madam:

In response to the Examiner's request, we are enclosing herewith six Terminal Disclaimers to overcome the double patenting rejection over the claims for the above-identified application.

Respectfully submitted,

/Warren M.  
Cheek, Jr./

Digitally signed by /Warren M. Cheek,  
Jr./  
DN: cn=/Warren M. Cheek, Jr./, o, ou,  
email=wcheek@wenderoth.com, c=US  
Date: 2014.11.05 13:02:14 -05'00'

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Warren M. Cheek  
Registration No. 33,367  
Attorney for Applicant

WMC/dlk  
Washington, D.C. 20005-1503  
Telephone (202) 721-8200  
Facsimile (202) 721-8250  
November 5, 2014

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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**TERMINAL DISCLAIMER UNDER 37 CFR 1.321**

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

Sir/Madam:

The owner, SENJU PHARMACEUTICAL CO., LTD., of 100% interest 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 defined in 35 USC 154 and 173, as shortened by any terminal disclaimer, of prior Patent No. 8,129,431, issued March 6, 2012. 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 any patent granted on the instant application that would extend to the expiration date of the full statutory term as defined in 35 USC 154 and 173 of the prior patent, as presently shortened by any terminal disclaimer, in the event that it 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 cancelled 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.

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.

[X] The undersigned is empowered to act on behalf of the organization.

[] The undersigned is an attorney of record.

November 5, 2014

**/Warren M.  
Cheek, Jr./**

Digitally signed by /Warren M. Cheek,  
Jr./  
DN: cn=/Warren M. Cheek, Jr./, o, ou,  
email=wcheek@wenderoth.com, c=US  
Date: 2014.11.05 13:03:38 -05'00'

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Warren M. Cheek  
Reg. No. 33,367

Terminal disclaimer fee under 37 CFR 1.20(d) is included.

WMC/dlk  
Washington, D.C. 20005-1503  
Telephone (202) 721-8200  
Facsimile (202) 721-8250

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor : Attorney Docket No. 2014-1250  
Shirou SAWA : **Confirmation No. 7395**  
Serial No. 14/493,903 : **Group Art Unit Not Yet Assigned**  
Filed September 23, 2014 : **Examiner Not Yet Assigned**  
AQUEOUS LIQUID PREPARATION : **Mail Stop: AMENDMENT**  
CONTAINING 2-AMINO-3-(4-  
BROMOBENZOYL)PHENYLACETIC ACID

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**TERMINAL DISCLAIMER UNDER 37 CFR 1.321**

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

Sir/Madam:

The owner, SENJU PHARMACEUTICAL CO., LTD., of 100% interest 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 defined in 35 USC 154 and 173 as shortened by any terminal disclaimer filed prior to the grant of any patent granted on pending second Application Number 14/269,692, filed May 5, 2014. 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 any patent granted on the second application are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon grantee, its successors or assigns.

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disclaimed under 37 CFR 1.321; has all claims cancelled by a reexamination certificate; is reissued; or is in any manner terminated prior to the expiration of its full statutory term as shortened by any terminal disclaimer filed prior to its grant.

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Telephone (202) 721-8200  
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## Electronic Patent Application Fee Transmittal

<b>Application Number:</b>	14493903
<b>Filing Date:</b>	23-Sep-2014
<b>Title of Invention:</b>	AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID
<b>First Named Inventor/Applicant Name:</b>	Shirou SAWA
<b>Filer:</b>	Warren M. Cheek Jr./Donna King
<b>Attorney Docket Number:</b>	2014-1250

Filed as Large Entity

### Utility under 35 USC 111(a) Filing Fees

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

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
<b>Miscellaneous:</b>				
Statutory or Terminal Disclaimer	1814	6	160	960
<b>Total in USD (\$)</b>				<b>960</b>

## Electronic Acknowledgement Receipt

<b>EFS ID:</b>	20613730
<b>Application Number:</b>	14493903
<b>International Application Number:</b>	
<b>Confirmation Number:</b>	7395
<b>Title of Invention:</b>	AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID
<b>First Named Inventor/Applicant Name:</b>	Shirou SAWA
<b>Customer Number:</b>	513
<b>Filer:</b>	Warren M. Cheek Jr./maurice linder
<b>Filer Authorized By:</b>	Warren M. Cheek Jr.
<b>Attorney Docket Number:</b>	2014-1250
<b>Receipt Date:</b>	05-NOV-2014
<b>Filing Date:</b>	23-SEP-2014
<b>Time Stamp:</b>	15:20:46
<b>Application Type:</b>	Utility under 35 USC 111(a)

### Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	\$960
RAM confirmation Number	1619
Deposit Account	230975
Authorized User	CHEEK JR., WARREN M.

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	Supplemental Response or Supplemental Amendment	AttachA.pdf	173152	no	1
			a516df9fd1395b60c15c9b3a41ba1193e9eab5cc		

### Warnings:

The PDF file has been signed with a digital signature and the legal effect of the document will be based on the contents of the file not the digital signature.

### Information:

2	Terminal Disclaimer Filed	AttachB.pdf	180109	no	2
			2427f748c76b5bb1fd58d57f4e1aed00196d6391		

### Warnings:

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### Information:

3	Terminal Disclaimer Filed	AttachC.pdf	180147	no	2
			d453db652b6cb4ec4c5d7c06aa052cbc12bc7866		

### Warnings:

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### Information:

4	Terminal Disclaimer Filed	AttachD.pdf	180126	no	2
			05fd548e549367278418d18963f541789d01af0a		

### Warnings:

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### Information:

5	Terminal Disclaimer Filed	AttachE.pdf	180121	no	2
			962157932fa039e651ef21f6be29945a08496f99		

### Warnings:

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### Information:

6	Terminal Disclaimer Filed	AttachF.pdf	180272	no	2
			38f01d5e92ff115cc59c23e7902b628f81f8b0fd		

### Warnings:

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**Information:**

7	Terminal Disclaimer Filed	AttachG.pdf	180225	no	2
			4287bb56a5569308bca6e83cd6c75104a0f15e51		

**Warnings:**

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**Information:**

8	Fee Worksheet (SB06)	fee-info.pdf	30986	no	2
			526f5fa19e03cf6073155a62d6e6eced75892fa5		

**Warnings:**

**Information:**

<b>Total Files Size (in bytes):</b>	1285138
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**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

First Named Inventor : Attorney Docket No. 2014-1250  
Shirou SAWA : **Confirmation No. 7395**  
Serial No. 14/493,903 : **Group Art Unit Not Yet Assigned**  
Filed September 23, 2014 : **Examiner Not Yet Assigned**  
AQUEOUS LIQUID PREPARATION : **Mail Stop: AMENDMENT**  
CONTAINING 2-AMINO-3-(4-  
BROMOBENZOYL)PHENYLACETIC ACID

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**TERMINAL DISCLAIMER UNDER 37 CFR 1.321**

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

Sir/Madam:

The owner, SENJU PHARMACEUTICAL CO., LTD., of 100% interest 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 defined in 35 USC 154 and 173, as shortened by any terminal disclaimer, of prior Patent No. 8,497,304, issued July 30, 2013. 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 any patent granted on the instant application that would extend to the expiration date of the full statutory term as defined in 35 USC 154 and 173 of the prior patent, as presently shortened by any terminal disclaimer, in the event that it 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 cancelled 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.

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

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[] The undersigned is an attorney of record.

November 5, 2014

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Digitally signed by /Warren M. Cheek, Jr./  
DN: cn=/Warren M. Cheek, Jr., o, ou, email=wcheek@wenderoth.com, c=US  
Date: 2014.11.05 13:03:22 -05'00'

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Warren M. Cheek  
Reg. No. 33,367

Terminal disclaimer fee under 37 CFR 1.20(d) is included.

WMC/dlk  
Washington, D.C. 20005-1503  
Telephone (202) 721-8200  
Facsimile (202) 721-8250

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Alexandria, VA 22313-1450

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Reg. No. 33,367

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Washington, D.C. 20005-1503  
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Facsimile (202) 721-8250

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In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term as defined in 35 USC 154 and 173 of the prior patent, as presently shortened by any terminal disclaimer, in the event that it 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 cancelled by a

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November 5, 2014

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DN: cn=/Warren M. Cheek, Jr./, o, ou,  
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Warren M. Cheek  
Reg. No. 33,367

Terminal disclaimer fee under 37 CFR 1.20(d) is included.

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Telephone (202) 721-8200  
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CONTAINING 2-AMINO-3-(4-  
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**INFORMATION DISCLOSURE STATEMENT**

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

Sir/Madam:

Pursuant to the provisions of 37 CFR 1.56, 1.97 and 1.98, Applicant requests consideration of the information listed on attached Form PTO/SB/08.

1a.  This Information Disclosure Statement is submitted:

within three months of the filing date (or of entry into the National Stage) of the above-entitled application, **or**

before the mailing of a first Office Action on the merits or the mailing of a first Office Action after the filing of an RCE,

**and thus no certification and/or fee is required.**

1b.  This Information Disclosure Statement is submitted

after the events of above paragraph 1a and prior to the mailing date of a final Office Action or a Notice of Allowance or an action which otherwise closes prosecution in the application, and thus:

- (1)  the certification of paragraph 2 below is provided, or
- (2)  the fee of \$180.00 (\$90.00 for small entity) specified in 37 CFR 1.17(p) is enclosed.

1c.  This Information Disclosure Statement is submitted:

after the mailing date of a final Office Action or Notice of Allowance or action which otherwise closes prosecution in the application, and prior to payment of the issue fee, and thus:

**the certification of paragraph 2 below is provided, and  
the fee of \$180.00 (\$90.00 for small entity) specified in 37 CFR 1.17(p) is enclosed.**

2. It is hereby certified

- a.  that each item of information contained in this 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 Statement (37 C.F.R. § 1.97(e)(1)), or
- b.  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, was known to any individual designated in §1.56(c) more than three months prior to the filing of the Statement (37 C.F.R. § 1.97(e)(2)).

3. For each non-English language reference listed on the attached Form PTO/SB/08, reference is made to one or more of the following:

- a.  a full or partial English language translation submitted herewith,
- b.  an International Search Report submitted herewith,
- c.  a foreign patent office search report or office action (in the English language) submitted herewith,

- d.  the concise explanation contained in the specification of the present application at page,
  - e.  the concise explanation set forth in the attached English language abstract,
  - f.  the concise explanation set forth below or on a separate sheet attached to the reference:
4.  A foreign patent office search report citing one or more of the references is enclosed.
5.  Statement Under 37 CFR 1.704(d) Each item of information contained in the information disclosure statement: (i) Was first cited in any communication from a patent office in a counterpart foreign or international application or from the office, and this communication was not received by any individual designated in § 1.56(c) more than thirty days prior to the filing of the information disclosure statement; or (ii) Is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office, and this communication was not received by any individual designated in § 1.56(c) more than thirty days prior to the filing of the information disclosure statement.

WMC/dlk  
Washington, D.C. 20005-1503  
Telephone (202) 721-8200  
Facsimile (202) 721-8250  
October 16, 2014

Respectfully submitted,  
**/Warren M.  
Cheek, Jr./**  
Digitally signed by /Warren M. Cheek,  
Jr./  
DN: cn=/Warren M. Cheek, Jr./, o, ou,  
email=wcheek@wenderoth.com,  
c=US  
Date: 2014.10.16 11:38:06 -04'00'

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Warren M. Cheek  
Registration No. 33,367  
Attorney for Applicant

## INFORMATION DISCLOSURE STATEMENT

FORM PTO/SB/08 A&amp;B (modified)

ATTY DOCKET NO.  
2014-1250SERIAL NO.  
14/493,903U.S. DEPARTMENT OF COMMERCE  
PATENT AND TRADEMARK OFFICEFIRST NAMED INVENTOR  
Shirou SAWALIST OF REFERENCES CITED BY APPLICANT(S)  
(Use several sheets if necessary)

Date Submitted to PTO: October 16, 2014

FILING DATE  
September 23, 2014

GROUP

## U.S. PATENT DOCUMENTS

*EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
	AA	8,129,431	3/2012	Sawa et al.			
	AB	6,107,343	8/2000	Sallmann et al.			
	AC	4,910,225	3/1990	Ogawa et al.			
	AD	5,603,929	2/1997	Desai et al.			
	AE	5,475,034	12/1995	Yanni et al.			
	AF	5,558,876	9/1996	Desai et al.			
	AG	6,274,609	8/2001	Yasueda et al.			
	AH	5,540,930	7/1996	Guy et al.			
	AI	2,880,130	3/1959	Johnson			
	AJ	2,880,138	3/1959	Johnson			
	AK	6,071,904	6/2000	Ali et al.			
	AL	5,597,560	1/1997	Bergamini et al.			

## FOREIGN PATENT DOCUMENTS


		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION/ADDITIONAL INFORMATION	
							YES	NO
	BA	2 013 188	9/1990	CA				
	BB	22042/88	3/1989	AU				
	BC	94/15597	7/1994	WO				
	BD	2 383 971	3/2001	CA				
	BE	02/13804	2/2002	WO				
	BF	0 274 870	7/1988	EP				
	BG	94/05298	3/1994	WO				

## OTHER DOCUMENT(S) (Including Author, Title, Date, Pertinent Pages, Etc.)

	CA	Y. Hara, "Evaluation of New Drugs by Clinicians", Clinics & Drug Therapy, Vol. 19, No. 10, October 2000, pp. 1-2.						
	CB	G. Smolin, M.D., "New Drugs in Ophthalmology", International Ophthalmology Clinics, Vol. 36, No. 2, 1996, pp. 1-9.						

Sheet 2 of 3		INFORMATION DISCLOSURE STATEMENT	
FORM PTO/SB/08 A&B (modified)		ATTY DOCKET NO. 2014-1250	SERIAL NO. 14/493,903
U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE		FIRST NAMED INVENTOR Shirou SAWA	
LIST OF REFERENCES CITED BY APPLICANT(S) (Use several sheets if necessary)		FILING DATE September 23, 2014	GROUP
Date Submitted to PTO: October 16, 2014			
CC	ISTA News Release, XIBROM™, Bromfenac Ophthalmic Solution, 2007, p.1.		
CD	S. Prince et al., "Analysis of Benzalkonium Chloride and its Homologs: HPLC Versus HPCE <sup>1</sup> ", Journal of Pharmaceutical and Biomedical Analysis, Vol. 19, pp. 877-882, 1999.		
CE	M. Doughty, "Therapeutics: Medicines Update <i>p18</i> Side-Effects of Anti-Epilepsy Drugs", Optician, Vol. 223, No. 5853, May 31, 2002, pp. 16-22.		
CF	I. Reddy, Ph.D., "Ocular Therapeutics and Drug Delivery", Technomics Publishing Co., Basel, pp. 42-43, 390, 1996.		
CG	H. Schott, "Comparing the Surface Chemical Properties and the Effect of Salts on the Cloud Point of a Conventional Nonionic Surfactant, Octoxynol 9 (Triton X-100), and of its Oligomer, Tyloxapol (Triton WR-1339)", Journal of Colloid and Interface Science, Vol. 205, pp. 496-502, 1998.		
CH	O. Regev, "Aggregation Behavior of Tyloxapol, a Nonionic Surfactant Oligomer, in Aqueous Solution", Journal of Colloid and Interface Science, Vol. 210, pp. 8-17, 1999.		
CI	PDR 50th Edition 1996, Physicans' Desk Reference, p. 469.		
CJ	PDR 54th Edition 2000, Physicans' Desk Reference, pp. 486-487, 491-492.		
CK	V. A. Ostrovskii et al., "Acid-Base Properties of 5-Substituted Tetrazoles", Khimiya Get. Soc., pp. 412-416, 1981.		
CL	LOTEMAX™ product brochure, Loteprednol Etabonate Ophthalmic Suspension, 0.5%, pp. 1-16, March 6, 1998.		
CM	Webster's New World Dictionary of the American Language, Second College Edition, "monohydrate", Simon & Schuster, NY, p. 920, 1982.		
CN	Pharmacopeia, R. S. Cook et al., "Edetic Acid", pp. 177-179, JT Steward, "Sodium Metabisulfide", pp. 451-453, 2000.		
CO	Yakuji Nippo Limited, "Recent New Drugs 2001", Japanese Pharmacopoeia 2001 Edition, pp. 27-29, May 2001 (English translation).		
CP	Sigma-Aldrich catalog, Biochemicals and Reagents for Life Science Research, p. 175, 2000.		
CQ	G. Patani et al., "Bioisosterism: A Rational Approach in Drug Design", Chemical Reviews, Vol. 96, No. 8, pp. 3147-3176, 1996.		
CR	P. Deluca et al., "Interaction of Preservatives with Macromolecules IV, Binding of Quaternary Ammonium Compounds by Nonionic Agents", Journal of the American Pharmaceutical Association, Vol. 49, No. 7, pp. 430-437, July 1960.		
CS	D. Guttman et al., "Solubilization of Anti-Inflammatory Steroids by Aqueous Solutions of Triton WR-1339", Journal of Pharmaceutical Sciences, Vol. 50, No. 4, pp. 305-307, April 1961.		
CT	T. Fan et al., "Determination of Benzalkonium Chloride in Ophthalmic Solutions Containing Tyloxapol by Solid-Phase Extraction and Reversed-Phase High-Performance Liquid Chromatography", Journal of Pharmaceutical Sciences, Vol. 82, No. 11, pp. 1172-1174, November 1993.		

Sheet 3 of 3		INFORMATION DISCLOSURE STATEMENT	
FORM PTO/SB/08 A&B ( <i>modified</i> )  U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE  LIST OF REFERENCES CITED BY APPLICANT(S) ( <i>Use several sheets if necessary</i> )  Date Submitted to PTO: October 16, 2014		<b>ATTY DOCKET NO.</b> 2014-1250	<b>SERIAL NO.</b> 14/493,903
		<b>FIRST NAMED INVENTOR</b> Shirou SAWA	
		<b>FILING DATE</b> September 23, 2014	<b>GROUP</b>
	CU	FDA Website search of Orange Book (Patent and Exclusivity Search Results): Approved Drug Products with Therapeutic Equivalence Evaluations; Search Results for N203168, 2014.	
	CV	FDA website search of Orange Book (Detail Record Search): Approved Drug Products with Therapeutic Equivalence Evaluations, Search Results for N203168, 2014.	
	CW	Remington: The Science and Practice of Pharmacy, 20 <sup>th</sup> Edition, "Boric Acid", Lippincott, Williams, Baltimore MD, p. 1041, 2000.	
	CX	PDR 52nd Edition 1998, Physicians' Desk Reference, "Duract", Method Economics Co., Monroton, NJ, pp. 3035-3037.	
	CY	ALREX <sup>TM</sup> product package, Loteprednol Etabonate, Ophthalmic Suspension, 0.2%, pp. 1-13, 1998.	
	CZ	XIBROM <sup>TM</sup> product package, Bromfenac Ophthalmic Solution, 0.09%, pp. 3-6, 2000.	
	CAA	BROMDAY product package, Bromfenac Ophthalmic Solution, 0.09%, pp. 4-8, 1997.	
	CAB	PROLENSA <sup>TM</sup> product package, Bromfenac Ophthalmic Solution, 0.07%, pp. 4-9, 2013.	
	CAC	PDR 54 Edition 2000, Physicians' Desk Reference, pp. 489-491, TOBRADEX®, Tobramycin and Dexamethasone Ophthalmic Suspension and Ointment.	
	CAD	FDA website description of VOLTAREN, Diclofenac Sodium, Ophthalmic Solution, 0.1%, pp. 1-2, 1991.	
	CAE	The United States Pharmacopeia, The National Formulary, USP 24, NF 19, pp. 1809-1813, 1864-1866, 2000.	
	CAF	Dorset & Baber, Webster's New Twentieth Century Dictionary, Second Edition, "Ophthalmic" and "Ophthalmic" p. 1254, 1979.	
	CAG	BRONUCK® news release, Bromfenac Sodium Hydrate Ophthalmic Solution, p.1, 2005.	
	CAH	Petition for <i>Inter Partes</i> Review of USP 8,669,290 to Sawa et al., Metrics, Inc. v. Senju Pharmaceutical Co., Ltd, pp. 1-71.	
	CAI	Petition for <i>Inter Partes</i> Review of USP 8,129,431 to Sawa et al., Metrics, Inc. v. Senju Pharmaceutical Co., Ltd, pp. 1-71.	
EXAMINER		DATE CONSIDERED	

(19)  Canadian  
Intellectual Property  
Office

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Industry Canada

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Intellectuelle  
du Canada

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d'Industrie Canada

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(72)

Fu, Cherng-Chyi Roger (US).  
Lidgate, Deborah M. (US).

(73)

Syntex (U.S.A.) Inc.  
3401 Hillview Avenue PALO ALTO XX (US).

(74)

DENNISON ASSOCIATES

(54) SYSTEME POUR CONSERVER LES PREPARATIONS OPHTALMIQUES

(54) PRESERVATIVE SYSTEM FOR OPHTHALMIC FORMULATIONS

(57)

Stable, clear, antimicrobially effective, ophthalmic formulations are disclosed which provide an antimicrobially effective preservative. The formulations include an ophthalmologically effective amount of a drug, which is a -COON group-containing non-steroidal anti-inflammatory drug (NSAID) in combination with an antibiotic drug, and a preservative system formed of a quaternary ammonium preservative and a nonionic polyoxyethylated octylphenol surfactant, all in an aqueous vehicle. The preservative system can be used with other formulations which require the preservative to be ophthalmologically acceptable and antimicrobially effective. These formulations are useful for treating diseases and/or conditions that are either caused by, associated with or accompanied by inflammatory processes, including, among others, glaucoma, cystoid macular edema, uveitis, diabetic retinopathy and conjunctivitis, or any trauma caused by eye surgery or eye injury. The ophthalmologically acceptable antibiotic is preferably tobramycin which has been found not to interfere with the rate of diffusion of the NSAID. The combination of the NSAID and antibiotic is particularly effective in simultaneously preventing and/or eliminating infection while preventing and/or eliminating inflammation.



(72) Fu, Cherng-Chyi Roger, US

(72) Lidgate, Deborah M., US

(73) Syntex (U.S.A.) Inc., US

(51) Int.Cl.<sup>5</sup> A61K 31/71, A61K 31/405, A61K 31/19

(30) 1989/03/28 (07/329,451) US

(54) **SYSTEME POUR CONSERVER LES PREPARATIONS  
OPHTALMIQUES**

(54) **PRESERVATIVE SYSTEM FOR OPHTHALMIC  
FORMULATIONS**

(57) Stable, clear, antimicrobially effective, ophthalmic formulations are disclosed which provide an antimicrobially effective preservative. The formulations include an ophthalmologically effective amount of a drug, which is a -COOH group-containing non-steroidal anti-inflammatory drug (NSAID) in combination with an antibiotic drug, and a preservative system formed of a quaternary ammonium preservative and a nonionic polyoxyethylated octylphenol surfactant, all in an aqueous vehicle. The preservative system can be used with other formulations which require the preservative to be ophthalmologically acceptable and antimicrobially effective. These formulations are useful for treating diseases and/or conditions that are either caused by, associated with or accompanied by inflammatory processes, including, among others, glaucoma, cystoid macular edema, uveitis, diabetic retinopathy and conjunctivitis, or any trauma caused by eye surgery or eye injury. The ophthalmologically acceptable antibiotic is preferably tobramycin which has been found not to interfere with the rate of diffusion of the NSAID. The combination of the NSAID and antibiotic is particularly effective in simultaneously preventing and/or eliminating infection while preventing and/or eliminating inflammation.





ABSTRACT OF THE DISCLOSURE

Stable, clear, antimicrobially effective,  
5 ophthalmic formulations are disclosed which provide an  
antimicrobially effective preservative. The  
formulations include an ophthalmologically effective  
amount of a drug, which is a -COOH group-containing  
10 non-steroidal anti-inflammatory drug (NSAID) in  
combination with an antibiotic drug, and a preservative  
system formed of a quaternary ammonium preservative and  
a nonionic polyoxyethylated octylphenol surfactant, all  
in an aqueous vehicle. The preservative system can be  
15 used with other formulations which require the  
preservative to be ophthalmologically acceptable and  
antimicrobially effective. These formulations are  
useful for treating diseases and/or conditions that are  
either caused by, associated with or accompanied by  
20 inflammatory processes, including, among others,  
glaucoma, cystoid macular edema, uveitis, diabetic  
retinopathy and conjunctivitis, or any trauma caused by  
eye surgery or eye injury. The ophthalmologically  
acceptable antibiotic is preferably tobramycin which has  
25 been found not to interfere with the rate of diffusion  
of the NSAID. The combination of the NSAID and  
antibiotic is particularly effective in simultaneously  
preventing and/or eliminating infection while preventing  
and/or eliminating inflammation.

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PRESERVATIVE SYSTEM FOR OPHTHALMIC FORMULATIONSFIELD OF THE INVENTION

10       The present invention relates to improved  
ophthalmic formulations which use an improved  
preservative system comprising a quaternary ammonium  
preservative and a stabilizing amount of a nonionic  
polyoxyethylated octylphenol surfactant for ophthalmic  
15 formulations of carboxyl ("COOH") group-containing  
non-steroidal anti-inflammatory drugs ("NSAIDs") and  
contain an ophthalmologically acceptable antibiotic,  
preferably tobramycin. The invention also relates to  
methods of using these formulations for treating  
20 diseases and/or conditions that are either caused by,  
associated with or accompanied by inflammatory  
processes, including, among others, glaucoma, cystoid  
macular edema, uveitis, diabetic retinopathy and  
conjunctivitis, or any trauma caused by eye surgery or  
25 eye injury. In addition, the formulation can be used to  
treat bacterial infection.

BACKGROUND OF THE INVENTION

To be ophthalmologically acceptable, a formulation  
30 must possess a number of characteristics to comply with

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the general FDA requirements of being safe and effective. In that eyes are quite sensitive to pain, the formulation must be developed such that it causes little to no discomfort or stinging when administered.

5 This feature is particularly important to insure user compliance and important in that such formulations are often administered in order to relieve pain or inflammation. The ophthalmic use of NSAID compounds was disclosed in U.S. Patent No. 4,454,151, where NSAID

10 compounds (such as those described in U.S. Patents 4,089,969; 4,232,038; 4,087,539 and 4,097,579) were exemplified in formulation with  $\text{NaH}_2\text{PO}_4 \cdot \text{H}_2\text{O}$ ,  $\text{Na}_2\text{HPO}_4 \cdot \text{H}_2\text{O}$ ,  $\text{NaCl}$ , benzalkonium chloride ("BAC") and sterilized water. While the formulations described

15 in the '151 patent were efficacious, a complex was found to form between the NSAID and the BAC.

Due to the formation of this complex, the formulations did not have the stability desired for shelf life in commercial applications. A reasonable

20 minimum shelf life is at least about one year, representing sufficient time to package, ship, and store a formulation without having to replace expired stock too frequently.

An ophthalmic suspension containing a particular

25 NSAID is disclosed in U.S. Patent No. 4,087,538 issued May 2, 1978. The suspension is aqueous based and can include benzalkonium chloride. Another ophthalmic formulation is disclosed in U.S. Patent No. 4,559,343 issued December 17, 1985. The formulation is aqueous

30 based and includes an NSAID and a benzalkonium chloride preservative. A somewhat similar ophthalmic formulation is disclosed in U.S. Patent No. 4,607,038 issued August 19, 1986. This formulation includes a specific NSAID

35 (pranoprofen) in an aqueous based formula with a known

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preservative. U.S. Patent No. 4,474,751 issued October 2, 1984 discloses ophthalmic formulations which gel in the eye in order to increase the bioavailability of the drug. The '751 patent discloses a large number of  
5 different active ingredients and excipient material. When this disclosure is taken in view of the other patents discussed above and the publications cited in each of them, the vast number of different ways of creating an ophthalmic formulation becomes apparent.  
10 Although there may be a considerable number of possible formulations and variations thereof, only certain specific formulations will meet all the requirements for being ophthalmologically acceptable.

In general, an ophthalmic formulation contains an  
15 active compound and various ophthalmologically acceptable excipients, in the form of a solution, an ointment, a suspension, etc. In order for an excipient to be ophthalmologically acceptable, it must be non-irritating to the eye in combination with other  
20 excipients and an active ingredient. The excipients must not prevent the active ingredient from penetrating the blood-aqueous barrier and/or diffusing through the various ocular substructures to the site where it is pharmacologically active. The excipients can interact  
25 with each other or the active drug. Accordingly, care in formulating is required in that so many materials may be used. These materials generally include a tonicifier, a preservative, a surfactant, a buffering system, a chelating agent, a viscosity agent as well as  
30 other stabilizing agents. Ophthalmic formulations must be sterile and must be preserved with an effective anti-microbial agent.

Organo-mercurials (e.g., thimerosal, phenylmercuric acetate and phenylmercuric nitrate) have been used  
35 extensively as the preservative in ophthalmic

solutions. These compounds, however, pose difficulties due to potential mercury toxicity as well as poor chemical stability. Benzalkonium chloride, a quaternary ammonium compound, has been widely used in ophthalmic solutions, and is considered to be the preservative of choice. However, BAC has typically been considered to be incompatible with anionic drugs (e.g., salicylates or nitrates, etc.) and can be inactivated by surfactants.

Many NSAIDs (such as ketorolac, indomethacin, flurbiprofen, diclofenac, and suprofen) are being developed for ocular use because of their activity as anti-inflammatory agents as well as their ability to prevent cystoid macular edema.

These NSAIDs have proven to be incompatible with quaternary ammonium compounds such as BAC because they can form a complex with them, rendering the preservative less available to serve its function, as is the case with other ophthalmic drugs that contain a -COOH group. Thus, less preferred preservatives have been used in such ophthalmic formulations. For example, Ocufen Ophthalmic solution, the first NSAID (flurbiprofen) approved by the FDA for ophthalmic use, incorporates thimerosal (with EDTA) as its preservative system.

European published application 306,984 (published March 15, 1989) discloses a stable, clear, antimicrobially effective, ophthalmic formulation containing an NSAID and a preservative system formed of a quaternary ammonium preservative and a nonionic surfactant all in an aqueous vehicle. Although the formulations of this European laid-open application are useful in treating diseases that are either caused by, associated with, or accompanied by inflammatory processes, there is no indication that the formulations of the European laid-open application are effective in preventing or eliminating infection.

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A need has continued to exist for a stable, clear, antimicrobial preservative effective ophthalmic formulation for NSAIDs with antibiotics using BAC as the preservative, and an improved preservative system for  
5 -COOH group containing ophthalmic drugs to overcome both inflammation and infection.

SUMMARY OF THE INVENTION

A primary object of the invention is to describe and disclose a formulation containing an  
10 ophthalmologically effective amount of an NSAID in combination with an antibiotic, a quaternary ammonium preservative and a stabilizing amount of a nonionic polyoxyethylated octylphenol surfactant, all in an aqueous vehicle.

15 A feature of the present invention is that it allows for the preparation of stable, i.e., clear and antimicrobially and antibioticly effective, NSAID-containing ophthalmic formulations without the need for an organo-mercurial preservative.

20 Another feature is that methods for treating ophthalmic diseases in mammals using the ophthalmic pharmaceutical formulations of the invention are provided.

An advantage of the present invention is that it is  
25 useful in the treatment of diseases or conditions associated with or accompanied by inflammatory processes, including, among others, glaucoma, cystoid macular edema, uveitis, diabetic retinopathy and conjunctivitis, or any trauma caused by eye surgery or  
30 eye injury and eliminating infection.

These and other objects, advantages and features of the present invention will become apparent to those persons skilled in the art upon reading the details of the composition, manufacture and usage as more fully set  
35 forth below. Reference being made to the accompanying

general structural formulae forming a part hereof wherein like symbols refer to like molecular moieties throughout.

5            DETAILED DESCRIPTION AND PREFERRED EMBODIMENTS

          Before the present compositions and processes for making and using such are disclosed and described, it is to be understood that this invention is not limited to the particular compositions, components or methods of use described as such compositions, components and methods may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting since the scope of the present invention will be limited only by the appended claims.

          It must be noted that as used in this specification and the appended claims, the singular forms "a", "an" and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a pharmaceutically acceptable salt" includes mixtures of salts, references to "an NSAID" includes reference to mixtures of such NSAIDS, reference to "the method of administration" includes one or more different methods of administration known to those skilled in the art.

Definitions

          As used herein, the term "NSAID" means an ophthalmologically acceptable carboxyl group containing non-steroidal anti-inflammatory drug. The NSAID's include, for example, flurbiprofen, ketorolac, diclofenac, indomethacin, suprofen, and the isomers, esters and pharmaceutically acceptable salts thereof.

35            As used herein, the term "q.s." means adding a

quantity sufficient to achieve a stated function, e.g., to bring a solution to the desired volume (i.e., 100%).

As used herein, the term "treatment" or "treating" means any treatment of a disease and/or condition in a

5 mammal, including:

(i) preventing the disease and/or condition, that is, causing the clinical symptoms of the disease not to develop;

10 (ii) inhibiting the disease and/or condition, that is, arresting the development of clinical symptoms; and/or

(iii) relieving the disease and/or condition, that is, causing the regression of clinical symptoms.

15 As used herein, the term "effective amount" means a dosage sufficient to provide treatment for the disease state being treated. This will vary depending on the patient, the disease and the treatment being effected.

20 As used herein, the term "antimicrobially effective" refers to the stability of the formulation prior to administration and means ability to withstand the U.S. Pharmacopia antimicrobial challenges put by a panel of microbes.

25 As used herein, the term "surfactant" means a nonionic surfactant, preferably ethoxylated octylphenol compounds as described below.

As used herein, the term "quarternary ammonium preservative" means a quarternary ammonium compound as described below.

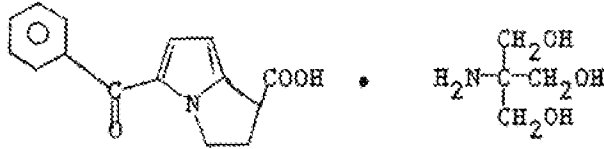
30 As used herein, the term "stabilizing" means keeping a formulation clear and antimicrobially effective for its minimum reasonable shelf life, e.g., at least one year.

35 "Ketorolac tromethamine" shall mean the compound ( $\pm$ )-5-benzoyl-1,2-dihydro-3H-pyrrolo-[1,2-a]-pyrrole-1-carboxylic acid 2-amino-2-hydroxymethyl-1,3-propanediol



salt, also known as (+)-5-benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1) having the following structural formula (1)

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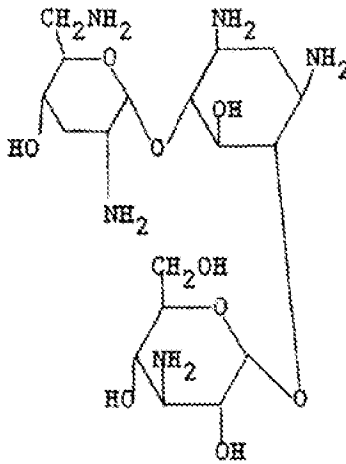


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"Tobramycin" shall mean the antibiotic produced by streptomyces tincenarius also known as 0-3-amino-3-deoxy- $\alpha$ -D-glucopyranosyl-(1 $\beta$ 6)-O-[2,6-diamino-2,3,6-trideoxy- $\alpha$ -D-ribo-hexopyranosyl-(1 $\beta$ 4)]-2-deoxy-D-streptamine. Tobramycin is represented by the following structural formula II:

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Tobramycin is a water soluble aminoglycosidic antibiotic having a broad spectrum of action against both gram negative and gram positive bacteria. Such

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aminoglycosidic antibiotics are useful in treating ocular infections and are used prophylactically before and after ocular surgery.

Formulations

5       The formulations of the present invention include an NSAID active agent in an effective amount for ophthalmic treatment, an ophthalmologically acceptable antibiotic as a second active agent in an effective amount for ophthalmic treatment, a quaternary ammonium  
10 preservative, a stabilizing amount of a nonionic polyoxyethylated octylphenol surfactant, optionally including other excipients such as a chelating agent, a tonicifier, a buffering system, a viscosity agent as well as other stabilizing agents.

15       The NSAID is preferably flurbiprofen, ketorolac, diclofenac, indomethacin, suprofen, and the isomers, esters, and pharmaceutically acceptable salts thereof. The antibiotic is preferably tobramycin.

20       Ophthalmic solutions and suspensions typically contain an aqueous vehicle rather than an oily vehicle. Ophthalmic formulations must be sterile, and if intended for multiple dosing regimens, must be antimicrobially effective for their minimum reasonable shelf life, e.g.,  
25 at least one year, and preferably two to three years or more. The ingredients used in the formulations of the present invention are typically commercially available or can be made by methods readily known to those skilled in the art.

30       Pharmaceutical ophthalmic formulations typically contain an effective amount, e.g., 0.001% to 10% wt/vol., preferably 0.002% to 5% wt/vol, most preferably 0.005% to 1% of an active ingredient (e.g., the NSAID of the present invention). The amount of active ingredient will vary with the particular formulation and the  
35 disease state for which it is intended. The total

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concentration of solutes should be such that, if possible, the resulting solution is isotonic with the lacrimal fluid (though this is not absolutely necessary) and has a pH in the range of 6 to 8.

5 The formulations of the present invention are prepared as solutions incorporating the above-described ingredients within the following approximate ranges:

	<u>Ingredient</u>	<u>Amount</u>
	Active Agent*	0.001% to 10.0% wt/vol.;
10	Preservative	0.001% to 1.0% wt/vol.;
	Surfactant	0.001% to 1.0% wt/vol.;
	Other Excipients	0% to 10.0% wt/vol.; and
	Purified Water	q.s. to 100%.

\*The active agent is the NSAID in combination with the  
15 antibiotic.

Optional other excipients, such as a chelating agent and a tonicifier, are used in the following approximate proportions:

	<u>Ingredient</u>	<u>Amount</u>
20	Chelating agent	0.01% to 1.0%wt/vol.;
	Tonicifier	q.s. to achieve isotonicity with lacrimal fluid; and
25	1N NaOH or 1N HCl	q.s. to adjust pH to 6.0 to 8.0.

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In a preferred ophthalmic NSAID solution, the ingredients are combined in the following proportions:

	Ingredient	Amount
	NSAID	0.50% wt/vol.;
5	Antibiotic	0.30% wt/vol.;
	BAC	0.02% wt/vol.;
	(50% aq. soln.)	
	Octoxynol 40	0.01% wt/vol.;
	(70% aq. soln.)	
10	EDTA Na <sub>2</sub>	0.10% wt/vol.;
	NaCl/ boric acid/	q.s. for isotonicity with
	Na borate	lacrimal fluid;
	1N NaOH or 1N HCl	q.s. to adjust pH to
		7.4±0.4; and
15	Purified Water	q.s. to 100%.

The invention relates primarily to formulations having as the active agent ophthalmologically acceptable drugs (including the esters and pharmaceutically acceptable salts thereof) that can form a complex with a quaternary ammonium compound, particularly carboxyl group-containing NSAIDs.

NSAIDs useful in the practice of this invention include, for example, ketorolac (and the other compounds described as being ophthalmologically effective in U.S. Patent No. 4,454,151 to Waterbury, issued June 12, 1984, the pertinent portions of which are incorporated herein by reference), indomethacin, flurbiprofen sodium, diclofenac, and suprofen, including the esters and pharmaceutically acceptable salts thereof.

In addition to the NSAID there is another active ingredient in the form of an ophthalmologically acceptable antibiotic, preferably tobramycin. The antibiotic is present in an effective amount for ophthalmic treatment. The antibiotic tobramycin does not interfere with the corneal permeability of the NSAID.

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Preservatives useful in the formulations of the present invention include quaternary ammonium compounds, such as cetyltrimethylammonium bromide, cetylpyridinium chloride and preferably, benzalkonium chloride.

5       The nonionic surfactants useful in the formulations of the present invention are preferably polyoxyethylated octylphenol surfactants including polyoxyethylene hydrogenated vegetable oils, such as polyethylene 60 hydrogenated castor oil, manufactured and sold by Kao  
10 Corp. of Japan under the trade name Emanon CH-60, and preferably ethoxylated octylphenol compounds, such as Octoxynol 10 and most preferably Octoxynol 40, manufactured and sold by GAF under the trade name Igepal  
15 CAS97 (a 70% aqueous solution of Octoxynol 40). Octoxynol 40 is a nonionic polymeric surfactant material. More specifically, it is a nonionic polyoxyethylated octylphenol surfactant material sold commercially by GAF.

20       Among the optional excipients, the chelating agents useful in the formulations of the present invention include 8-hydroxyquinoline sulfate, citric acid, and preferably disodium edetate. Under certain conditions, the chelating agent may also enhance the anti-microbial effect due to its ability to render essential metal ions  
25 unavailable to the microbes.

Buffering systems optionally useful in the formulations of the present invention are based on, for example, citrate, borate, or phosphate.

30       Tonicifiers optionally useful in the formulations of the present invention include dextrose, potassium chloride and/or sodium chloride, preferably sodium chloride.

35       Viscosity agents optionally useful in the formulations of the present invention include the cellulose derivatives such as hydroxypropylmethyl

3374M

26280/2 FF

cellulose, sodium carboxymethylcellulose, and hydroxyethylcellulose.

Other optional excipients useful in the formulations of the present invention include  
5 stabilizing agents such as antioxidants, e.g., sodium metabisulfate and ascorbic acid, depending on the NSAID used.

These formulations are prepared by dissolving the solutes (e.g., the NSAID, the preservative, the  
10 surfactant, the chelating agent, and the buffering agent) in a suitable quantity of water, adjusting the pH to about 6 to 8, preferably 6.8 to 8.0 and most preferably 7.4, making a final volume adjustment to 100% with additional water, and sterilizing the preparation  
15 using any suitable method known to those in the art.

Ophthalmic formulations incorporating the preservative system of the invention are physically stable (i.e., remain clear) and functionally stable (i.e., remain antimicrobially effective) for at  
20 least the minimum reasonable shelf life of such products. The inclusion of an antibiotic in the formulation does not effect the rate of diffusion of the NSAID.

#### 25 Preferred Formulations

The preferred ophthalmic formulation of the invention includes a NSAID active agent in an effective amount for ophthalmic treatment and an antimicrobially effective amount of the above-described preferred  
30 preservative system.

The preferred preservative of the invention is benzalkonium chloride.

The preferred surfactant of the invention is Octoxynol 40, especially when combined with benzalkonium  
35 chloride.

3374M

26280/2 FF

- 14 -

The preferred chelating agent of the invention is disodium edetate, especially when combined with benzalkonium chloride and Octoxynol 40.

The preferred antibiotic is one which does not interfere with the corneal permeability of the NSAID. Tobramycin is a preferred antiobiotic.

The preferred ophthalmic solutions of the invention include a NSAID, benzalkonium chloride, Octoxynol 40 and disodium edetate and, as a second active agent, tobramycin.

A preferred ophthalmic NSAID/antibiotic solution has the following formulation:

	Ingredient	Amount
	NSAID	0.50% wt/vol.
15	antibiotic	0.30% wt/vol.
	BAC	0.02% wt/vol.
	(50% aq. soln.)	
	Octoxynol 40	0.01% wt/vol.
	(70% aq. soln.)	
20	EDTA Na <sub>2</sub>	0.10% wt/vol.
	(NaCl/boric acid/ Na borate)	q.s. for isotonicity with lacrimal fluid
	1N NaOH or 1N HCl	q.s. to adjust pH to 7.4±0.4
25	Purified Water	q.s. to 100%

Most preferred is the ophthalmic solution according to the above formulations is wherein the NSAID is Ketorolac Tromethamine and when the antibiotic is present it is tobramycin.

30

#### Utility and Administration

This invention is directed to NSAID ophthalmic formulations and a method useful for treating ophthalmic diseases in mammals. These diseases are either caused by, associated with or accompanied by inflammatory

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3374M

26280/2 FF

processes, including, among others, glaucoma, cystoid macular edema, uveitis, diabetic retinopathy and conjunctivitis, or any trauma caused by eye surgery or eye injury.

5       The method of this invention is both curative and preventative. Where applied, for example, pre-surgically or immediately post-traumatically, i.e. before inflammation develops, it prevents development of inflammation. When applied directly to the eye  
10 suffering from any of the named ophthalmic diseases, it supresses already developed inflammatory processes.

The formulation of the invention includes an antibiotic such as tobramycin, providing antibacterial properties useful in eliminating and/or preventing a  
15 bacterial infection.

Ophthalmic formulations are typically administered by topical application to the eyelids or for instillation into the space (cul-de-sac) between the eyeball and the eyelids, by topically applied ophthalmic  
20 solutions, suspensions or ointments, or by subconjunctival injection.

The dosage level will, of course, depend on the concentration of the drops, the condition of the subject and the individual magnitude of responses to treatment.  
25 However, typical dosage ranges might be about 2 to 10 drops of solution of active ingredient per day wherein the solution includes 0.5 wt/vol.% of Ketorolac trimethamine and 0.3 wt/vol.% of tobramycin.

For a more detailed discussion of ophthalmic  
30 formulations, their preparation and administration, see Remington's Pharmaceutical Sciences, 15th Ed., pages 1489-1504, (1975).

#### Testing

35       Ophthalmic formulations such as the solutions of



the present invention are typically tested for physical stability, chemical stability, and preservative efficacy, both when they are first manufactured and after a fixed period of time (e.g., after two years).

- 5 They are generally considered to be safe and clinically acceptable if proven to be well tolerated in the eye.

Physical stability is determined by observation of a solution after expiration of a fixed period of time. A solution is considered to be physically stable if its  
10 appearance (e.g., color and clarity) does not change and if the pH remains constant, within acceptable limits. Chemical stability involves a routine chemical analysis of the solution, to be sure that its active  
15 ingredient(s), preservatives and the excipients have not changed after a fixed period of time.

Preservative efficacy of the formulation prior to administration is tested by the procedure described in the U.S. Pharmacopia Compendiary, whereby a solution is challenged with a panel of microbes and a determination  
20 is made as to whether a given microbe survives in it.

#### EXAMPLES

The following examples are given to enable those  
25 skilled in the art to more clearly understand and to practice the present invention. They should not be considered as a limitation on the scope of the invention, but merely as being illustrative and representative thereof.

30

#### EXAMPLE 1

This example illustrates the preparation of a representative pharmaceutical formulation for ophthalmic administration containing the NSAID Ketorolac  
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3374M

26280/2 FF

Tromethamine and the antibiotic tobramycin.

	<u>Ingredient</u>	<u>Amount</u>
	ketorolac tromethamine	0.50% wt/vol.
5	tobramycin	0.30% wt/vol.
	BAC	0.02% wt/vol.
	(50% aq. soln.)	
	Octoxynol 40	0.01% wt/vol.
	(70% aq. soln.)	
10	EDTA Na <sub>2</sub>	0.10% wt/vol.
	NaCl	0.18% wt/vol.
	Boric Acid	0.9% wt/vol.
	Na Borate	0.45% wt/vol.

15 The above ingredients are mixed, adding purified water until they are dissolved, the pH is adjusted to 7.4±0.4 and the balance of the formulation is made up with purified water, adding a quantity sufficient to make 100% volume. The solution is then sterilized.

20 Other NSAIDs, such as those described above, can be used as the active compound in the preparation of the formulation of this example.

#### EXAMPLE 2

25 This example illustrates the preparation of a general pharmaceutical formulation for ophthalmic

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3374M

26280/2 FF

- 18 -

administration containing an NSAID and an antibiotic.

	Ingredient	Amount
	NSAID	0.50% wt/vol.
5	antibiotic	0.3% wt/vol.
	BAC	0.01% wt/vol.
	(50% aq. soln.)	
	Octoxynol 40	0.02% wt/vol.
	(70% aq. soln.)	
10	EDTA Na <sub>2</sub>	0.20% wt/vol.
	NaCl	0.18% wt/vol.
	Boric Acid	0.9% wt/vol.
	Na Borate	0.45% wt/vol.

15

EXAMPLE 3

This example illustrates the preparation of a representative pharmaceutical formulation for ophthalmic administration containing the NSAID ketorolac tromethamine and tobramycin.

	Ingredient	Amount
	ketorolac tromethamine	0.50% wt/vol.
	tobramycin	0.30% wt/vol.
25	BAC	0.01% wt/vol.
	(50% aq. soln.)	
	Octoxynol 40	0.01% wt/vol.
	(70% aq. soln.)	
30	EDTA Na <sub>2</sub>	0.20% wt/vol.
	NaCl	0.18% wt/vol.
	Boric Acid	0.9% wt/vol.
	Na Borate	0.45% wt/vol.

Other NSAIDs, such as those described above, can be used as the active compound in the preparation of the

3374M

26280/2 FF

formulation of any of these examples.

EXAMPLE 4

This example illustrates the preparation of a  
 5 representative pharmaceutical formulation for ophthalmic  
 administration containing the NSAID flurbiprofen sodium.

	<u>Ingredient</u>	<u>Amount</u>
	Flurbiprofen Sodium	0.03% wt/vol.
10	BAC	0.02% wt/vol.
	(50% aq. soln.)	
	Octoxynol 40	0.01% wt/vol.
	(70% aq. soln.)	
	EDTA Na <sub>2</sub>	0.10% wt/vol.
15	NaCl	0.18% wt/vol.
	Boric Acid	0.9% wt/vol.
	Na Borate	0.45% wt/vol.

The above ingredients are mixed, adding purified  
 20 water until they are dissolved, the pH is adjusted to  
 7.4±0.4 and the balance of the formulation is made up  
 with purified water, adding a quantity sufficient to make  
 100% volume. The solution is then sterilized.

Other ophthalmic drugs and NSAIDs, such as those  
 25 described above, can be used as the active compound in  
 the preparation of the formulation of this example.

EXAMPLE 5

Physical stability of the formulations of the  
 30 present invention is measured by preparing clear  
 formulations, e.g., according to the foregoing Examples,  
 sealing them in sterilized containers, and observing the  
 clarity of the solution after a period of one month and  
 again after five months. Solutions that remain clear are  
 35 considered stable in this procedure.

3374M

26280/2 FF

The formulations of the present invention have proven to be stable when tested in accordance with the above procedure. Formulations using surfactants other than the nonionic surfactants of the invention did not  
5 remain clear and were not stable.

Preservative efficacy of the formulations of the present invention is measured by preparing formulations, e.g., according to the foregoing Examples, and subjecting them to the U.S. Pharmacopia antimicrobial challenge.

10 The formulations of the present invention demonstrate preservative efficacy when tested in accordance with the above procedure.

Formulations of the present invention are freely flowable liquids which can be administered directly to  
15 the eye using a conventional means such as eyedroppers. The amount of active ingredient administered will vary with the individual and/or the type of disease or condition being treated. The NSAID's such as ketorolac and antibiotics such as tobramycin are generally  
20 administered in an amount of about 1 to 2 drops per eye with drops containing about 25 microliters of formulation. The drops are generally administered 3 to 4 times per day.

25

EXAMPLE 6

In vitro rabbit corneal penetration of ketorolac was evaluated in the presence of tobramycin to determine if tobramycin alters penetration of ketorolac through rabbit  
30 corneas. Two sets of studies were performed to evaluate tobramycin's effect on ketorolac penetration.

Apparatus - A modified Franz diffusion cell consisting of an 8.0 ml glass receptor cell along with a teflon donor cell were used for the penetration  
35 experiments. A side arm allowed sampling of the receptor

3374M

26280/2 FF

phase. The donor cell was recessed to accommodate corneal curvature. A 0.3 ml volume of donor solution was placed on the epithelial side of the cornea, and evaporation of this donor solution was diminished by sealing a glass coverslip over the opening of the donor cell with silicon grease. To ensure corneal curvature throughout the course of the experiment, a 1.0 ml latex bulb was placed over the sampling port of the glass diffusion cell. By so doing, enough pressure was exerted under the cornea to maintain a curved, wrinkle-free membrane. Water at 37° C was circulated through the water jacket surrounding the receptor cell. A magnetic stir bar placed in the bottom of the receptor cell maintained homogeneity within the receptor solution.

Cornea Preparation - New Zealand white rabbits weighing 3.5 to 4 kg were used for the studies. Rabbits were sacrificed by rapid injection of 1.25 ml/kg of T-61 Euthanasia Solution (American Hoechst Corp. Animal Health Division, Somerville, NJ) into a marginal ear vein. The cornea were carefully removed along with 2-4 mm of surrounding scleral tissue then placed in a buffer containing: 0.57% sodium chloride, 0.361% sodium bicarbonate, 0.04% potassium chloride, 0.023% potassium phosphate dibasic, 0.007% magnesium sulfate, 0.08% calcium chloride, and 0.133% adenosine in water, adjusted to pH 7.4. This buffer was used as receptor solution for all studies; its selection was based on the ability to maintain corneal integrity throughout the diffusion studies.

Experimental Procedure - A fresh cornea was placed between the top and bottom of the teflon donor cell; this unit was then clamped onto the glass receptor cell. The receptor cell was filled with sterile, degassed buffer solution; all air bubbles were expelled from beneath the cornea by inverting the entire diffusion cell and

3374M

26280/2 FF

allowing bubbles to travel out the sampling port. After donor solution was placed on the cornea, a 0.3 ml sample of receptor solution was collected at the following time points: 15, 30, 45, 60 and 120 minutes. The 0.3 ml  
5 aliquot was replaced at each time point with fresh buffer solution.

Preparation of Test Solutions - 1. To determine ketorolac corneal diffusion in the presence of tobramycin, and to determine a dose effect, a saline  
10 vehicle was utilized to avoid potential complications by excipients. The following solutions were isotonic and prepared at pH 7.4: (a) 0.5% ketorolac tromethamine, 0.79% sodium chloride, purified water; (b) solution (a) with 0.15% tobramycin; (c) solution (a) with 0.30%  
15 tobramycin; and (d) solution (a) with 0.60% tobramycin.

2. To evaluate whether 0.30% tobramycin (a clinically acceptable and efficacious concentration) has an effect on ketorolac corneal diffusion when administered in a more complex vehicle, an isotonic  
20 solution at pH 7.4 was made which contained the following: (a) 0.5% ketorolac tromethamine, 0.79% sodium chloride, edetate disodium, benzalkonium chloride, purified water; (b) solution (a) with 0.30% tobramycin.

<sup>14</sup>C-glycerol Penetration - To monitor corneal  
25 integrity throughout the course of the permeability studies, <sup>14</sup>C-glycerol penetration was evaluated (<sup>14</sup>C-glycerol 15.76 mCi/mole was obtained from NEN with a radiochemical purity of 98%). Nonionized  
<sup>14</sup>C-glycerol was incorporated into selected test  
30 solutions (1a and d, above). For controls, two additional isotonic test solutions were made at pH 7.4: (1) phosphate buffered saline; (2) 0.6% tobramycin in phosphate buffered saline. To a 2.0 ml aliquot of each test solution, 10 µl of <sup>14</sup>C-glycerol was added. At  
35 designated time intervals, 0.3 ml of receptor solution

was sampled for scintillation counting (Beckman model LS 8100).

Analytical Methods - 1. Quantitation of ketorolac was performed by HPLC. The mobile phase was composed of 5 methanol, water and glacial acetic acid (65:34:1). The equipment included: a Spectra-Physics 8440 UV/Vis detector; a Spectra-Physics 4270 integrator; a Spectra-Physics 8700 solvent delivery system; a Dynatech autosampler; and a Whatman Partisil ODS 3, 10 micron 10 column. The mobile phase flow rate was 1.0 ml/min; the sample injection volume was 50  $\mu$ l; and the absorbance wavelength was 254 nm. A 100  $\mu$ l aliquot of each sample was diluted with 150  $\mu$ l of mobile phase.

2. Quantitation of tobramycin was performed using 15 the Syva EMIT tobramycin assay kit. The assay is an enzyme immunoassay intended to quantitatively analyze tobramycin in human serum or plasma; the limit of detection is 1.0  $\mu$ g/ml. The assay is based on competition for antibody sites between free drug in 20 sample and drug labeled with glucose-6-phosphate dehydrogenase (G-6-P-DH). Since G-6-P-DH activity decreases upon binding with antibody, tobramycin concentration can be measured in terms of enzyme activity. Active enzyme converts oxidized nicotinamide 25 adenine dinucleotide (NAD) to NADH. This conversion results in an absorbance change that is measured spectrophotometrically.

Each experiment was performed with matched controls; that is, from a single rabbit, one cornea was treated 30 with a ketorolac (control) solution, and the other cornea was treated with the ketorolac and tobramycin solution. Each test solution containing tobramycin was evaluated in triplicate. For the study using the simple isotonic vehicle, data for nine control corneas were generated. 35 Since these were control cornea, each is from a different

3374M

26280/2 FF



rabbit; hence, the deviation shown at each time point gives an indication of both the biological as well as experimental deviation inherent to this type of study.

An indication of corneal integrity throughout the course of these studies was determined by penetration of  $^{14}\text{C}$ -glycerol. Changes in the permeability profile of  $^{14}\text{C}$ -glycerol can be attributed to corneal alteration or damage. Select vehicles were chosen to evaluate whether corneal damage could be attributed to a particular compound or combination. With phosphate buffered saline serving as control, a two or three-fold increase in  $^{14}\text{C}$ -glycerol penetration would indicate substantial corneal alteration. Table I shows that  $^{14}\text{C}$ -glycerol penetration in a solution containing ketorolac tromethamine, or 0.6% tobramycin, or their combination, does not differ from its penetration in buffer alone. These results suggest that corneal integrity is not altered by ketorolac tromethamine or tobramycin.

20

TABLE I

Preparation	Percent of Initial Counts per Minute	
	at 60 min	at 120 min
25 Phosphate Buffered Saline	2.10	7.36
Ketorolac tromethamine in Saline	2.47	8.60
Tobramycin (0.6%) in Phosphate buffered saline	1.83	7.08
30 Ketorolac tromethamine and Tobramycin (0.6%) in Saline	2.01	6.03

The average total milligrams of ketorolac penetrating the cornea at each time point for the simple solutions containing ketorolac alone and solutions

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3374M

26280/2 FF

containing either 0.15%, 0.30% or 0.60% tobramycin, respectively, were compared. In all cases, the solutions containing tobramycin were equivalent to the control solution.

5       A comparison of the average total milligrams of ketorolac penetrating the cornea at each time point for the ophthalmic formulation with and without 0.30% tobramycin was made. Again, the test solution and the control solution were equivalent. Studies with the  
10 formulation demonstrated that after 60 minutes, there occurs a two to three fold increase in ketorolac diffusion, that is, enhanced penetration.

While the present invention has been described with  
15 reference to the specific embodiments thereof, it should be understood by those skilled in the art that various changes may be made and equivalents may be substituted without departing from the true spirit and scope of the invention. In addition, many modifications may be made  
20 to adapt a particular situation, material, composition of matter, process, process step or steps, to the objective, spirit and scope of the present invention. All such modifications are intended to be within the scope of the claims appended hereto.

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3374M

26280/2 FF

WHAT IS CLAIMED IS:

1. An ophthalmologically acceptable non-steroidal anti-inflammatory drug formulation, comprising:
- 5 an ophthalmologically acceptable non-steroidal anti-inflammatory carboxyl group-containing drug in an effective amount for ophthalmic treatment;
- an ophthalmologically acceptable antibiotic in an effective amount for ophthalmic treatment;
- 10 a quaternary ammonium preservative;
- a stabilizing amount of a nonionic polyoxyethylated octylphenol surfactant; and
- an aqueous vehicle.
- 15 2. The ophthalmologically acceptable non-steroidal anti-inflammatory drug formulation of Claim 1 wherein said quaternary ammonium preservative is benzalkonium chloride.
- 20 3. The ophthalmologically acceptable non-steroidal anti-inflammatory drug formulation of Claim 1 wherein said nonionic polyoxyethylated octylphenol surfactant is Octoxynol 40 and the antibiotic is tobramycin.
- 25 4. The ophthalmologically acceptable non-steroidal anti-inflammatory drug formulation of Claim 1 including disodium edetate.
5. The ophthalmologically acceptable
- 30 non-steroidal anti-inflammatory drug formulation of Claim 1 wherein said ophthalmologically acceptable non-steroidal anti-inflammatory carboxyl group-containing drug is selected from the group: ketorolac, indomethacin, flurbiprofen, diclofenac, and suprofen.
- 35

6. The ophthalmologically acceptable non-steroidal anti-inflammatory drug formulation of Claim 5 wherein said ophthalmologically acceptable non-steroidal anti-inflammatory carboxyl group-containing drug is ketorolac tromethamine.

7. The ophthalmologically acceptable non-steroidal anti-inflammatory drug formulation of Claim 1 comprising:

10	NSAID	0.001% to 10.0% wt/vol.;
	Antibiotic	0.001% to 10.0% wt/vol.;
	Preservative	0.001% to 1.0% wt/vol.;
	Surfactant	0.001% to 1.0% wt/vol.;
		and
15	Purified Water	q.s. to 100%.

8. The ophthalmologically acceptable non-steroidal anti-inflammatory drug formulation of Claim 7 comprising:

20	ketorolac tromethamine	0.001% to 10.0% wt/vol.;
	tobramycin	0.001% to 10.0% wt/vol.;
	Preservative	0.001% to 1.0% wt/vol.;
	Surfactant	0.001% to 1.0% wt/vol.; and
25	Purified Water	q.s. to 100%.

9. The ophthalmologically acceptable non-steroidal anti-inflammatory drug formulation of Claim 7 wherein said preservative is benzalkonium chloride, and the surfactant is Octoxynol 40.

10. The ophthalmologically acceptable non-steroidal anti-inflammatory drug formulation of

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Claim 8, further comprising:

5 Chelating agent 0.01% to 1.0% wt/vol.;  
 Tonicifier q.s. to achieve isotonicity  
 with lacrimal fluid; and  
 1N NaOH or 1N HCl q.s. to adjust pH to  
 7.4±0.4.

11. The ophthalmologically acceptable  
 10 non-steroidal anti-inflammatory drug formulation of  
 Claim 9 comprising:

ketorolac tromethamine 0.50% wt/vol.;  
 Tobramycin 0.30% wt/vol.;  
 BAC 0.02% wt/vol.;  
 15 (50% aq. soln.)  
 Octoxynol 40 0.01% wt/vol.;  
 (70% aq. soln.)  
 EDTA Na<sub>2</sub> 0.10% wt/vol.;  
 NaCl 0.18% wt/vol.;  
 20 Boric Acid 0.9% wt/vol.  
 Na Borate 0.45% wt/vol.  
 1N NaOH or 1N HCl q.s. to adjust pH to  
 7.4±0.4; and  
 Purified Water q.s. to 100%.  
 25

12. The use of a formulation comprising: an  
 ophthalmologically acceptable non-steroidal anti-  
 inflammatory carboxyl group-containing drug in an effective  
 amount for ophthalmic treatment, an antibiotic in an  
 effective amount for ophthalmic treatment, a quaternary  
 ammonium preservative, a stabilizing amount of a nonionic  
 polyoxyethylated octylphenol surfactant, and an aqueous

vehicle for treating ophthalmic disease in a mammal suffering therewith.

13. The use of Claim 12 wherein said preservative is benzalkonium chloride and said surfactant is Octoxynol 40.

14. The use of Claim 12 wherein said ophthalmologically acceptable non-steroidal anti-inflammatory carboxyl group-containing drug is selected from the group: ketorolac, indomethacin, flurbiprofen, diclofenac, and suprofen.

15. The use of Claim 12 wherein said ophthalmologically acceptable non-steroidal anti-inflammatory carboxyl group-containing drug is Ketorolac Tromethamine and the antibiotic is tobramycin.

16. The use of Claim 15 wherein said ophthalmologically acceptable non-steroidal anti-inflammatory drug formulation comprises:

	ketorolac tromethamine	0.50% wt/vol.;
	Tobramycin	0.30% wt/vol.;
25	BAC	0.01% wt/vol.;
	(50% aq. soln.)	
	Octoxynol 40	0.01% wt/vol.;
	(70% aq. soln.)	
	EDTA Na <sub>2</sub>	0.10% wt/vol.;
30	NaCl	0.18% wt/vol.;
	Boric Acid	0.9% wt/vol.
	Na Borate	0.45% wt/vol.
	1N NaOH or 1N HCl	to adjust pH to
		7.4±0.4; and
35	Purified Water	q.s. to 100%.

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**B**

(54) Title  
**PRESERVATIVE SYSTEM FOR OPHTHALMIC FORMULATIONS**

International Patent Classification(s)  
(51)<sup>a</sup> A61K 031/40 A61K 031/13 A61K 031/19 A61K 031/195  
A61K 031/405

(51)<sup>b</sup> A61K 047/10 A61K 047/18

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(71) Applicant(s)  
SYNTEX (U.S.A.) INC.

(72) Inventor(s)  
CHERNG-CHYI ROGER FU; DEBORAH M. LIDGATE

(74) Attorney or Agent  
WATERMARK PATENT & TRADEMARK ATTORNEYS , Locked Bag 5, HAWTHORN VIC 3122

(57) Claim

1. An ophthalmic NSAID formulation comprising:  
a NSAID in an effective amount for ophthalmic treatment,  
a quaternary ammonium preservative, a stabilizing amount  
of a nonionic ethoxylated octylphenol surfactant, and an  
aqueous vehicle.

22. An antimicrobially effective ophthalmologically acceptable preservative system  
for ophthalmologically acceptable, carboxyl group-containing drugs, said preservative  
system comprising a quaternary ammonium preservative and a stabilizing amount of a  
nonionic ethoxylated octylphenol surfactant.

# COMPLETE SPECIFICATION

(ORIGINAL)

# 626798

Class

Int. Class

Application Number:  
Lodged:

Complete Specification Lodged:  
Accepted:  
Published:

Priority:

Related Art:

Name of Applicant: SYNTEX (U.S.A.) INC.

Address of Applicant: 3401 Hillview Avenue, Palo Alto, California 94304, United States of America

Actual Inventor: CHERNG-CHYI ROGER FU and DEBORAH M. LIDGATE

Address for Service: EDWD. WATERS & SONS,  
59 QUEEN STREET, MELBOURNE, AUSTRALIA, 3000.

Complete Specification for the invention entitled:

PRESERVATIVE SYSTEM FOR OPHTHALMIC FORMULATIONS

The following statement is a full description of this invention, including the best method of performing it known to the US



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-19-

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PRESERVATIVE SYSTEM FOR OPHTHALMIC FORMULATIONS

BACKGROUND OF THE INVENTION

15

The present invention relates to improved ophthalmic formulations, particularly to ophthalmic formulations for anti-inflammatory drugs, and specifically to an improved preservative system for ophthalmic formulations of carboxyl ("COOH") group-containing drugs, especially non-steroidal anti-inflammatory drugs ("NSAIDs").

20

The invention also relates to methods of using these formulations for treating diseases that are either caused by, associated with or accompanied by inflammatory processes, including, among others, glaucoma, cystoid macular edema, uveitis, diabetic retinopathy, and conjunctivitis, or any trauma caused by eye surgery or eye injury.

25

30

The topical use of NSAIDs, particularly pyrrolo pyrroles, in the treatment of ophthalmic diseases was first taught in U.S. Patent No. 4,454,151, where NSAID compounds (such as those described in U.S. Patents 4,089,969; 4,232,038; 4,087,539 and 4,097,579) were exemplified in formulation with  $\text{NaH}_2\text{PO}_4 \cdot \text{H}_2\text{O}$ ,  $\text{Na}_2\text{HPO}_4 \cdot \text{H}_2\text{O}$ , NaCl, benzalkonium chloride ("BAC") and sterilized water. While the formulations described

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in the '151 patent were efficacious, an insoluble complex was found to form between the NSAID and the BAC. The formulations became cloudy or turbid and did not, therefore, have the stability desired for shelf life in commercial applications. A reasonable minimum shelf life (that is, the time during which a solution remains clear and retains its pharmaceutical activity) is at least about one year, representing sufficient time to package, ship, and store a formulation without having to replace expired stock too frequently. The solutions of the present invention have shown a shelf life of at least one year. Thus, the present invention entails an improvement over the formulations described in the '151 patent.

In general, an ophthalmic formulation contains an active compound and various ophthalmologically acceptable excipients, in the form of a solution, an ointment, a suspension, etc. An excipient is ophthalmologically acceptable if it is non-irritating to the eye and if its active ingredient penetrates the blood-aqueous barrier and/or diffuses through the various ocular substructures to the site where it is pharmacologically active. The excipients can include a tonicifier, a preservative, a surfactant, a buffering system, a chelating agent, a viscosity agent as well as other stabilizing agents. Ophthalmic formulations must be sterile, and if intended for multiple dosing regimens, must be preserved with an effective anti-microbial agent.

Organo-mercurials (e.g., thimerosal, phenylmercuric acetate and phenylmercuric nitrate) have been used extensively as the preservative in ophthalmic solutions. These compounds, however, pose difficulties due to potential mercury toxicity as well as poor chemical stability. Benzalkonium chloride, a quaternary ammonium compound, has been widely used in ophthalmic solutions, and is considered to be the preservative of choice.

However, BAC has typically been considered to be incompatible with anionic drugs (e.g., salicylates or nitrates, etc.), forming insoluble complexes which cause the solution to become cloudy or turbid. Such a complex  
5 between the anionic drug and benzalkonium chloride can cause a decrease in the pharmaceutical activity of the anionic drug.

Many NSAIDs (such as ketorolac, indomethacin, flurbiprofen and diclofenac) are being developed for  
10 ocular use because of their activity as anti-inflammatory agents including their ability to prevent cystoid macular edema.

In the past, as in the case with other ophthalmic drugs that contain a -COOH group, antiinflammatory  
15 solutions of NSAIDs for ocular use have proven to be incompatible with quaternary ammonium compounds such as BAC. This incompatibility is due to the fact that the -COOH group can form a complex with the quaternary ammonium compounds, rendering the preservative less  
20 available to serve its function, and reducing the activity of the active ingredient. Indomethacin ophthalmic formulations have been prepared, however, these are suspensions, not solutions. Ocufen Ophthalmic solution, an NSAID (flurbiprofen) approved by the FDA for  
25 ophthalmic use, incorporates thimerosal (with EDTA) as its preservative system. In U.S. patent 4,454,151 there is a disclosure of an ophthalmic formulation using ketorolac, benzalkonium chloride (as the preservative) and polysorbate 80, however the solution became cloudy or  
30 turbid after a short period of time.

It has remained desired to provide a stable, clear, antimicrobially effective ophthalmic formulation with a prolonged shelf life for -COOH group containing ophthalmic drugs, especially NSAIDs, using BAC as the  
35 preservative.

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SUMMARY OF THE INVENTION

It has now been discovered that stable, clear and antimicrobially effective, NSAID-containing ophthalmic formulations can be prepared which include a quaternary ammonium preservative. These solutions have an improved shelf life, exhibiting no cloudiness or turbidity over extended periods.

In one aspect of the invention, these compositions include an ophthalmologically effective amount of a NSAID, a quaternary ammonium preservative and a stabilizing amount of an ethoxylated octylphenol as a nonionic surfactant, all in an aqueous vehicle.

Another aspect is an ophthalmic composition including an ophthalmologically effective amount of a NSAID, a quaternary ammonium preservative and a stabilizing amount of an ethoxylated octylphenol as a nonionic surfactant.

Another aspect is an ophthalmic composition including an ophthalmologically effective amount of a NSAID, benzalkonium chloride as a preservative and a stabilizing amount of an ethoxylated octylphenol as a nonionic surfactant.

Another aspect is an ophthalmic composition including an ophthalmologically effective amount of a NSAID, benzalkonium chloride as a preservative and a stabilizing amount of Octoxynol 40 as a nonionic surfactant.

Another aspect is an ophthalmic composition including an ophthalmologically effective amount of ketorolac or an isomer, an ester, or a pharmaceutically acceptable salt thereof, benzalkonium chloride as a preservative and a stabilizing amount of Octoxynol 40 as a nonionic surfactant.

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In another aspect of the invention, methods for treating ophthalmic diseases in mammals using the ophthalmic pharmaceutical formulations of the invention are also disclosed. These diseases are those that are either caused by, associated with or accompanied by inflammatory processes, including, among others, glaucoma, cystoid macular edema, uveitis, diabetic retinopathy and conjunctivitis, or any trauma caused by eye surgery or eye injury.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Definitions

As used herein, the term "NSAID" means an ophthalmologically acceptable non-steroidal anti-inflammatory drug. The NSAID's include, for example, flurbiprofen, ketorolac, diclofenac, indomethacin, and the isomers, esters, and pharmaceutically acceptable salts thereof.

As used herein, the term "q.s." means adding a quantity sufficient to achieve a stated function, e.g., to bring a solution to the desired volume (i.e., 100%).

As used herein, the term "treatment" or "treating" means any treatment of a disease in a mammal, including:

- (i) preventing the disease, that is, causing the clinical symptoms of the disease not to develop;
- (ii) inhibiting the disease, that is, arresting the development of clinical symptoms; and/or
- (iii) relieving the disease, that is, causing the regression of clinical symptoms.

As used herein, the term "effective amount" means a dosage sufficient to provide treatment for the disease state being treated. This will vary depending on the patient, the disease and the treatment being effected.

As used herein, the term "antimicrobially effective" means ability to withstand the U.S. Pharmacopia antimicrobial challenge.

As used herein, the term "surfactant" means a  
5 nonionic surfactant, preferably ethoxylated octylphenol compounds as described below.

As used herein, the term "quaternary ammonium preservative" means a quaternary ammonium compound such as described below.

10 As used herein, the term "stabilizing" means keeping a formulation clear and antimicrobially effective for its minimum reasonable shelf life, e.g., at least one year.

#### Formulations

15 The formulations of the present invention include an NSAID active agent in an effective amount for ophthalmic treatment, a quaternary ammonium preservative, a stabilizing amount of an ethoxylated octylphenol as a nonionic surfactant, optionally including other  
20 excipients such as a chelating agent, a tonicifier, a buffering system, a viscosity agent as well as other stabilizing agents. Ophthalmic solutions and suspensions typically contain an aqueous vehicle rather than an oily vehicle. Ophthalmic formulations must be sterile, and if  
25 intended for multiple dosing regimens, must be antimicrobially effective for their minimum reasonable shelf life, e.g., at least one year, and preferably two to three years or more. The ingredients used in the formulations of the present invention are typically  
30 commercially available or can be made by methods readily known to those skilled in the art.

Pharmaceutical ophthalmic formulations typically contain an effective amount, e.g., 0.001% to 10% wt/vol., preferably 0.002% to 5% wt/vol, most preferably 0.005% to  
35 1% wt/vol of an active ingredient (e.g., the NSAID of the

present invention). The amount of active ingredient will vary with the particular formulation and the disease state for which it is intended. The total concentration of solutes should be such that, if possible, the resulting solution is isotonic with the lacrimal fluid (though this is not absolutely necessary) and has a pH in the range of 6 to 8.

The formulations of the present invention are prepared as solutions incorporating the above-described ingredients within the following approximate ranges:

	<u>Ingredient</u>	<u>Amount</u>
	Active Agent	0.001% to 10.0% wt/vol.;
	Preservative	0.001% to 1.0% wt/vol.;
	Surfactant	0.001% to 1.0% wt/vol.;
15	Other Excipients	0% to 10.0% wt/vol.; and
	Purified Water	q.s. to 100%.

Optional other excipients, such as a chelating agent and a tonicifier, are used in the following approximate proportions:

	<u>Ingredient</u>	<u>Amount</u>
20	Chelating agent	0.01% to 1.0%wt/vol.;
	Tonicifier	q.s. to achieve isotonicity with lacrimal fluid; and
25	1N NaOH or 1N HCl	q.s. to adjust pH to 6.0 to 8.0.

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26280-FF

In a preferred ophthalmic NSAID solution, the ingredients are combined in the following proportions:

	<u>Ingredient</u>	<u>Amount</u>
5	NSAID	0.002% to 5.0% wt/vol.;
	BAC	0.002% to 1.0% wt/vol.;
	(50% aq. soln.)	
	Octoxynol 40	0.001% to 1.0% wt/vol.;
	(70% aq. soln.)	
10	EDTA Na <sub>2</sub>	0.01% to 1.0% wt/vol.;
	NaCl	q.s. for isotonicity with lacrimal fluid;
	1N NaOH or 1N HCl	q.s. to adjust pH to 7.4±0.4; and
	Purified Water	q.s. to 100%.

In another preferred ophthalmic NSAID solution, the ingredients are combined in the following proportions:

	<u>Ingredient</u>	<u>Amount</u>
20	NSAID	0.005% to 1.0% wt/vol.;
	BAC	0.002% to 1.0% wt/vol.;
	(50% aq. soln.)	
	Octoxynol 40	0.001% to 1.0% wt/vol.;
	(70% aq. soln.)	
25	EDTA Na <sub>2</sub>	0.01% to 1.0% wt/vol.;
	NaCl	q.s. for isotonicity with lacrimal fluid;
	1N NaOH or 1N HCl	q.s. to adjust pH to 7.4±0.4; and
	Purified Water	q.s. to 100%.



In a more preferred ophthalmic NSAID solution, the ingredients are combined in the following proportions:

	<u>Ingredient</u>	<u>Amount</u>
	NSAID	0.50% wt/vol.;
5	BAC (50% aq. soln.)	0.02% wt/vol.;
	Octoxynol 40 (70% aq. soln.)	0.01% wt/vol.;
	EDTA Na <sub>2</sub>	0.10% wt/vol.;
10	NaCl	q.s. for isotonicity with lacrimal fluid;
	1N NaOH or 1N HCl	q.s. to adjust pH to 7.4 ± 0.4; and
	Purified Water	q.s. to 100%.

15 The invention relates primarily to formulations having as the active agent ophthalmologically acceptable drugs (including the isomers (as either the (d)- or (l)-isomer) esters and pharmaceutically acceptable salts thereof) that can form a complex with a quaternary ammonium compound, particularly NSAIDs and drugs with a carboxyl group.

20 NSAIDs useful in the practice of this invention include, for example, ketorolac (and the other compounds described as being ophthalmologically effective in U.S. Patent No. 4,454,151 to Waterbury, issued June 12, 1984, the pertinent portions of which are incorporated herein by reference), indomethacin, flurbiprofen sodium, and diclofenac, including the isomers, esters and pharmaceutically acceptable salts thereof.

25 Preservatives useful in the formulations of the present invention include quaternary ammonium compounds, such as cetyltrimethylammonium bromide, cetylpyridinium chloride and benzalkonium chloride, preferably, benzalkonium chloride.



The nonionic surfactants useful in the formulations of the present invention are preferably ethoxylated octylphenol compounds, such as octylphenoxypoly-(ethyleneoxy)ethanols, more preferably, a homologous series of surfactants sold under the trade name Igepal CA with a numerical suffix indicating the mole ratio of ethylene oxide to octylphenol, the ratio being 3 to 40. Examples include Octoxynol 9, Octoxynol 12, Octoxynol 13, and Octoxynol 40, and most preferably Octoxynol 40, manufactured and sold by GAF under the trade name Igepal CA897 (a 70% aqueous solution of Octoxynol 40).

Among the optional excipients, the chelating agents useful in the formulations of the present invention include 8-hydroxyquinoline sulfate, citric acid, and preferably disodium edetate. Under certain conditions, the chelating agent may also enhance the anti-microbial effect due to its ability to render essential metal ions unavailable to the microbes.

Buffering systems optionally useful in the formulations of the present invention are based on, for example, citrate, borate, or phosphate.

Tonicifiers optionally useful in the formulations of the present invention include dextrose, potassium chloride and/or sodium chloride, preferably sodium chloride.

Viscosity agents optionally useful in the formulations of the present invention include the cellulose derivatives such as hydroxypropylmethyl cellulose, sodium carboxymethylcellulose, and hydroxyethylcellulose.

Other optional excipients useful in the formulations of the present invention include stabilizing agents such as antioxidants, e.g., sodium metabisulfate and ascorbic acid, depending on the NSAID used.

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26280-FF

These formulations are prepared by dissolving the solutes (e.g., the NSAID, the preservative, the surfactant, the chelating agent, and the buffering agent) in a suitable quantity of water, adjusting the pH to about 6 to 8, preferably 6.8 to 8.0 and most preferably 7.4, making a final volume adjustment to 100% with additional water, and sterilizing the preparation using any suitable method known to those in the art.

It has been discovered that ophthalmic formulations incorporating the preservative system of the invention are physically stable (i.e., remain clear) and functionally stable (i.e., remain antimicrobially effective) for at least the minimum reasonable shelf life of such products.

15 Preferred Formulations

The preferred preservative system of the invention includes a quaternary ammonium preservative and a stabilizing amount of a nonionic surfactant.

The preferred ophthalmic formulation of the invention includes a NSAID active agent in an effective amount for ophthalmic treatment and an antimicrobially effective amount of the above-described preferred preservative system.

The preferred preservative of the invention is benzalkonium chloride.

The preferred surfactant of the invention is Octoxynol 40, especially when combined with benzalkonium chloride as the preservative.

The preferred chelating agent of the invention is disodium edetate, especially when combined with benzalkonium chloride as the preservative and Octoxynol 40 as the nonionic surfactant.

The preferred ophthalmic solutions of the invention include a NSAID, benzalkonium chloride, Octoxynol 40 and disodium edetate.

A preferred ophthalmic NSAID solution, the ingredients are combined in the following proportions:

	<u>Ingredient</u>	<u>Amount</u>
	NSAID	0.002% to 5.0% wt/vol.;
5	BAC (50% aq. soln.)	0.002% to 1.0% wt/vol.;
	Octoxynol 40 (70% aq. soln.)	0.001% to 1.0% wt/vol.;
	EDTA Na <sub>2</sub>	0.01% to 1.0% wt/vol.;
10	NaCl	q.s. for isotonicity with lacrimal fluid;
	IN NaOH or IN HCl	q.s. to adjust pH to 7.4 ± 0.4; and
	Purified Water	q.s. to 100%.

Another preferred ophthalmic NSAID solution, the ingredients are combined in the following proportions:

	<u>Ingredient</u>	<u>Amount</u>
	NSAID	0.005% to 1.0% wt/vol.;
20	BAC (50% aq. soln.)	0.002% to 1.0% wt/vol.;
	Octoxynol 40 (70% aq. soln.)	0.001% to 1.0% wt/vol.;
	EDTA Na <sub>2</sub>	0.01% to 1.0% wt/vol.;
25	NaCl	q.s. for isotonicity with lacrimal fluid;
	IN NaOH or IN HCl	q.s. to adjust pH to 7.4 ± 0.4; and
	Purified Water	q.s. to 100%.

30

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A preferred ophthalmic NSAID solution has the following formulation:

	<u>Ingredient</u>	<u>Amount</u>
	NSAID	0.50% wt/vol.
5	BAC (50% aq. soln.)	0.02% wt/vol.
	Octoxynol 40 (70% aq. soln.)	0.01% wt/vol.
	EDTA Na <sub>2</sub>	0.10% wt/vol.
10	NaCl	q.s. for isotonicity with lacrimal fluid
	1N NaOH or 1N HCl	q.s. to adjust pH to 7.4±0.4
	Purified Water	q.s. to 100%

15

Most preferred is the ophthalmic solution according to the above formulation wherein the NSAID is Ketorolac Tromethamine or an isomer thereof.

20 Utility and Administration

This invention is directed to NSAID ophthalmic formulations and a method useful for treating ophthalmic diseases in mammals. These diseases are either caused by, associated with or accompanied by inflammatory processes, including, among others, glaucoma, cystoid macular edema, uveitis, diabetic retinopathy and conjunctivitis, or any trauma caused by eye surgery or eye injury.

The method of this invention is both curative and preventative. Where applied, for example, pre-surgically or immediately post-traumatically, i.e. before inflammation develops, it prevents development of inflammation. When applied directly to the eye suffering from any of the named ophthalmic diseases, it suppresses already developed inflammatory processes.

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26280-FF

Ophthalmic formulations are typically administered by topical application to the eyelids or for instillation into the space (cul-de-sac) between the eyeball and the eyelids, of topically applied ophthalmic solutions, suspensions or ointments, or by subconjunctival injection.

The dosage level will, of course, depend on the concentration of the drops, the condition of the subject and the individual magnitude of responses to treatment. However, typical dosage ranges might be about 2 to 10 drops of 0.5% solution of active ingredient per day.

For a more detailed discussion of ophthalmic formulations, their preparation and administration, see Remington's Pharmaceutical Sciences, 15th Ed., pages 1489-1504, (1975).

15

#### Testing

Ophthalmic formulations such as the solutions of the present invention are typically tested for physical stability, chemical stability, and preservative efficacy, both when they are first manufactured and after a fixed period of time (e.g., after two years). They are generally considered to be safe and clinically acceptable if proven to be well tolerated in the eye.

Physical stability is determined by observation of a solution after expiration of a fixed period of time. A solution is considered to be physically stable if its appearance (e.g., color and clarity) does not change and if the pH remains constant, within acceptable limits. Chemical stability involves a routine chemical analysis of the solution, to be sure that its active ingredient and the excipients have not changed after a fixed period of time.

Preservative efficacy is tested by the procedure described in the U.S. Pharmacopia Compendiary, whereby a

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26280-FF

solution is challenged with a microbe and a determination is made as to whether the microbe survives in it.

EXAMPLES

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The following examples are given to enable those skilled in the art to more clearly understand and to practice the present invention. They should not be considered as a limitation on the scope of the invention, but merely as being illustrative and representative thereof.

EXAMPLE 1

15

This example illustrates the preparation of a representative pharmaceutical formulation for ophthalmic administration containing the NSAID Ketorolac Tromethamine.

20

<u>Ingredient</u>	<u>Amount</u>
Ketorolac Tromethamine	0.50% wt/vol.
BAC (50% aq. soln.)	0.02% wt/vol.
Octoxynol 40 (70% aq. soln.)	0.01% wt/vol.
EDTA Na <sub>2</sub>	0.10% wt/vol.
NaCl	0.79% wt/vol.

25

The above ingredients are mixed, adding purified water until they are dissolved, the pH is adjusted to 7.4±0.4 and the balance of the formulation is made up with purified water, adding a quantity sufficient to make 100% volume. The solution is then sterilized.

Other NSAIDs or their isomers, salts or esters, such as those described above, can be used as the active

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compound in the preparation of the formulation of this example.

EXAMPLE 2

5

This example illustrates the preparation of a representative pharmaceutical formulation for ophthalmic administration containing the NSAID Ketorolac Tromethamine.

10

<u>Ingredient</u>	<u>Amount</u>
Ketorolac Tromethamine	0.50% wt/vol.
BAC (50% aq. soln.)	0.02% wt/vol.
15 Octoxynol 40 (70% aq. soln.)	0.02% wt/vol.
EDTA Na <sub>2</sub>	0.20% wt/vol.
NaCl	0.79% wt/vol.

20

The above ingredients are mixed, adding purified water until they are dissolved, the pH is adjusted to 7.4±0.4 and the balance of the formulation is made up with purified water, adding a quantity sufficient to make 100% volume. The solution is then sterilized.

25

Other NSAIDs or their isomers, salts or esters, such as those described above, can be used as the active compound in the preparation of the formulation of this example.

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EXAMPLE 3

This example illustrates the preparation of a representative pharmaceutical formulation for ophthalmic

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26280-FF



administration containing the NSAID Ketorolac Tromethamine.

	<u>Ingredient</u>	<u>Amount</u>
5	Ketorolac Tromethamine	0.10% wt/vol.
	BAC	0.004% wt/vol.
	(50% aq. soln.)	
	Octoxynol 40	0.004% wt/vol.
	(70% aq. soln.)	
10	EDTA Na <sub>2</sub>	0.05% wt/vol.
	NaCl	0.88% wt/vol.

The above ingredients are mixed, adding purified water until they are dissolved, the pH is adjusted to 7.4 ± 0.4 and the balance of the formulation is made up with purified water, adding a quantity sufficient to make 100% volume. The solution is then sterilized.

Other NSAIDs their isomers, salts or esters, such as those described above, can be used as the active compound in the preparation of the formulation of this example.

EXAMPLE 4

This example illustrates the preparation of a representative pharmaceutical formulation for ophthalmic administration containing the NSAID flurbiprofen sodium.

	<u>Ingredient</u>	<u>Amount</u>
	Flurbiprofen Sodium	0.03% wt/vol.
	BAC	0.02% wt/vol.
	(50% aq. soln.)	
30	Octoxynol 40	0.01% wt/vol.
	(70% aq. soln.)	
	EDTA Na <sub>2</sub>	0.10% wt/vol.
	NaCl	0.90% wt/vol.

The above ingredients are mixed, adding purified

water until they are dissolved, the pH is adjusted to 7.4±0.4 and the balance of the formulation is made up with purified water, adding a quantity sufficient to make 100% volume. The solution is then sterilized.

- 5 Other ophthalmic drugs and NSAIDs, such as those described above, can be used as the active compound in the preparation of the formulation of this example.

EXAMPLE 5

10

Physical stability of the formulations of the present invention is measured by preparing clear formulations, in the concentrations shown in the table below, sealing them in sterilized containers, and  
15 observing the clarity of the solution after a period of one month and again after five months. Solutions that remain clear are considered stable in this procedure.

The formulations of the present invention have proven to be stable when tested in accordance with the  
20 above procedure. Formulations using surfactants other than the nonionic surfactants of the invention did not remain clear and were not stable.

Three surfactants were evaluated for their ability to dissolve the ketorolac - benzalkonium chloride complex and maintain a physically clear solution over an extended  
25 period of time. The three surfactants tested were: Octoxynol 40; Polysorbate 80 (Tween 80); and Myrj 52. Two concentrations of each surfactant were incorporated into the ophthalmic formulation, and these were placed at  
30 various temperatures for future visual observations.

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8408Y

26280-FF

		<u>Octoxynol 40</u>		<u>Tween 80</u>		<u>Myrj 52</u>	
		0.004%	0.02%	0.0035%	0.01%	0.0015%	0.01%
	<u>1 month</u>						
5	60°C	clear	clear	clear	clear	clear	clear
	40°C	clear	clear	very turbid	very turbid	turbid	turbid
	RT	clear	clear	turbid	turbid	clear	clear
	4-40°C	clear	clear	turbid	turbid	clear	clear
10	<u>5 month</u>						
	60°C	clear	clear	clear	clear	clear	clear
	40°C	clear	clear	turbid	turbid	turbid	turbid
	RT	clear	clear	turbid	turbid	turbid	turbid

15

At the 5 month time period it was apparent that the Octoxynol 40 surfactant was superior to the other two surfactants. At 5 months, Tween 80 and Myrj 52 displayed turbidity when stored at RT. The presence of turbidity suggested the inability to solubilize a precipitate formation between the Ketorolac moiety and benzalkonium chloride.

20

A further study has shown a 2 year shelf life for the ophthalmic formulation. Precipitate formation and turbidity are not a problem with this formulation. Preservative efficacy is maintained throughout the 2 year shelf life.

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EXAMPLE 6

Preservative efficacy of the formulations of the present invention is measured by preparing formulations, e.g., according to the foregoing Examples, and subjecting them to the U.S. Pharmacopia antimicrobial challenge.

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26280-FF

The formulations of the present invention demonstrate preservative efficacy when tested in accordance with the above procedure.

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EXAMPLE 7

The objective of this clinical efficacy study was to compare the effectiveness and safety of ketorolac with a control solution in reducing inflammation following  
10 cataract removal and intraocular lens implantation. All patients underwent an extracapsular cataract extraction with intraocular lens implantation 1 day following initiation of treatment.

Ophthalmic examinations were performed  
15 preoperatively (within 3 weeks of surgery) and during the first week (postoperative days 1 to 3), second week (postoperative days 4 through 12), and third week (postoperative days 15 through 27) of treatment. Particular attention was given to signs and symptoms  
20 consistent with inflammation. Among the ocular characteristics assessed on a scale of none, mild, moderate, or severe were: lid edema, corneal edema, conjunctival injections, ciliary flush, and the presence of cells and flare in the anterior chamber.

Fluorophotometry: Anterior segment inflammation  
25 (i.e., iritis, cyclitis, iridocyclitis) is by definition a disruption of the blood-aqueous barrier. When inflammation is present, a careful slit lamp examination will reveal cells and flare within the anterior chamber  
30 of the eye. The clinical grading of cells and flare is a measure of degree of anterior segment inflammation; but consistent grading of these observations is difficult, even by experts.

Ocular fluorophotometry is based on the fact that  
35 the blood-aqueous barrier becomes permeable to

8408Y

26280-FF

intravascular cells and proteinaceous fluid (explaining the observed cells and flare) and also to intravascular fluorescein. Furthermore, the appearance of fluorescein within the anterior chamber is a more sensitive  
5 indication of the breakdown of the blood-aqueous barrier than the gross observation of cells and flare, and is consistently quantifiable. For these reasons, a Flurortron\* Master (Coherent, Sunnyvale, California), complete with software modifications designed for this  
10 study was used. Following oral administration of fluorescein, the fluorophotometer was used to determine the integrity of the aqueous barrier by measuring the concentration of fluorescein in the anterior chamber.

The fluorophotometry data were analyzed using the  
15 Wilcoxon Rank Sum Test or analysis of variance (ANOVA) of rank-transformed data by calculating the percentage difference in fluorescein concentration between the patient's two eyes, according to the formula:

Percent difference = [(fluorescein concentration of  
20 operated eye - fluorescein concentration of unoperated eye)/fluorescein concentration of unoperated eye] x 100.

This calculation allowed and corrected for any  
interpatient variation in the timing and concentration of  
25 fluorescein administered.

129 patients began treatment for 21 days with either ketorolac or vehicle. In this study, the ketorolac formulation used was that illustrated in Example 1 above. During the first week 118 patients and during the  
30 second week 110 patients were evaluated for postoperative inflammation with ophthalmic examinations and fluorophotometry. During the third week, 83 patients were evaluated with ophthalmic examinations alone. At 2 weeks ketorolac provide significantly greater  
35 anti-inflammatory activity than the vehicle as measured

by fluorophotometry ( $p = 0.019$ ). When patients were excluded who had greater than 40% difference in fluorescein concentration between eyes at baseline, the  $p$ -value during week 2 rose to 0.06. In addition, the  
5 vehicle-treated patients had more ocular inflammation seen on slit lamp examination, e.g., eyelid edema ( $p = 0.001$ ), conjunctival injection ( $p = 0.001$ ), and Descemet folds ( $p = 0.002$ ) than did the ketorolac-treated  
10 patients. Finally, there were significantly more complaints ( $p = 0.01$ ) and more severe complaints consistent with ocular inflammation (photophobia, iritis, conjunctival injection) in the vehicle-treated group than in the ketorolac-treated group.

In summary, ketorolac solutions proved significantly  
15 superior to vehicle in treating postoperative inflammation as quantitated by fluorophotometry, by routine slit lamp examination, by patients having fewer and milder adverse events, and by infrequent need of additional corticosteroid therapy to control inflammation.

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#### EXAMPLE 8

This was a double-blind, parallel comparison with  
vehicle to evaluate the efficacy of ketorolac 0.5%  
25 ophthalmic solution in reducing signs and symptoms of allergic conjunctivitis. Ketorolac 0.5% solution or a vehicle solution of the same pH and tonicity were instilled four times daily into the eyes of patients with allergic conjunctivitis (ocular itching with and without  
30 eosinophils seen on conjunctival scrapings) for 7 days.

Thirty patients with allergic conjunctivitis participated in the study. Following admission to the study, patients reported to the investigator for  
baseline, mid-week, and final one-week examinations. At  
35 each of these visits, patients received ophthalmic

8408Y

26280-FF

examinations (visual acuity, external eye exam using slit lamp biomicroscopy, measurement of intraocular pressure, and undilated ophthalmoscopic examination). Laboratory tests included a conjunctival scraping performed at  
5 baseline and the final exam.

All patients completed the study. There were no adverse events or toxicities in patients treated with vehicle while stinging on one occasion was reported from ketorolac 0.5% ophthalmic solution. Ketorolac treatment  
10 was associated with a decrease in free eosinophilic granules as compared to vehicle ( $p = 0.025$  Fisher's Exact Test, two-tailed).

The results of this study show that ketorolac 0.5% ophthalmic solution applied four times daily for seven  
15 days produces a decrease in eosinophilic granules as compared to vehicle in the treatment of allergic conjunctivitis.

EXAMPLE 9

20 This study was a double-blind, paired comparison design trial to evaluate the tolerance of ketorolac 0.5% ophthalmic solution and its vehicle in 26 healthy subjects. Solutions were instilled three times daily for  
25 21 days. Complete ophthalmic examinations were done pretreatment and on days 3, 10, 17, 24 (2 days after ending treatment), and 45 (23 days after ending treatment). No statistically significant difference in symptoms (burning, stinging, itchiness, scratchiness,  
30 photophobia) or signs (tearing, ocular discharge, conjunctival vasodilation, chemosis, keratitis, fluorescein staining, Rose Bengal staining) was found between ketorolac and vehicle.

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EXAMPLE 10

5 An ocular formulation containing 5 mg/ml ketorolac  
tromethamine was administered at a dose of 0.1 ml/eye  
every one-half hour for a total of 12 doses to both eyes  
of 6 New Zealand albino rabbits. The formulation  
contained benzalkonium chloride as the preservative  
system. Two additional groups of animals served as  
saline and vehicle controls, respectively.

10 Eyes were examined after the last dose was  
administered and on days 1, 2, 3, and 6 following  
dosing. Results indicated that no eye irritation or  
toxicity resulted from ketorolac tromethamine  
administration.

15 While the present invention has been described with  
reference to the specific embodiments thereof, it should  
be understood by those skilled in the art that various  
changes may be made and equivalents may be substituted  
20 without departing from the true spirit and scope of the  
invention. In addition, many modifications may be made  
to adapt a particular situation, material, composition of  
matter, process, process step or steps, to the objective,  
spirit and scope of the present invention. All such  
25 modifications are intended to be within the scope of the  
claims appended hereto.

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~~WHATXESXCLANDMEEXXESX~~

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. An ophthalmic NSAID formulation comprising:  
a NSAID in an effective amount for ophthalmic treatment,  
5 a quaternary ammonium preservative, a stabilizing amount  
of a nonionic ethoxylated octylphenol surfactant, and an  
aqueous vehicle.
  
2. The ophthalmic NSAID formulation of Claim 1  
10 wherein said quaternary ammonium preservative is  
benzalkonium chloride.
  
3. The ophthalmic NSAID formulation of Claim 1  
wherein said nonionic ethoxylated octylphenol surfactant  
15 is an octylphenoxypoly(ethyleneoxy)ethanol with a mole  
ratio of ethylene oxide to octylphenol of between 3:1 and  
40:1.
  
4. The ophthalmic NSAID formulation of Claim 3  
20 wherein said nonionic ethoxylated octylphenol surfactant  
is Octoxynol 40.
  
5. The ophthalmic NSAID formulation of Claim 4  
including disodium edetate.  
25
  
6. The ophthalmic NSAID formulation of Claim 1  
wherein said NSAID is selected from the group:  
ketorolac, indomethacin, flurbiprofen, and diclofenac, or  
their isomers, pharmaceutically acceptable salts, or  
30 esters.
  
7. The ophthalmic NSAID formulation of Claim 6  
wherein said NSAID is Ketorolac Tromethamine.

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8. The ophthalmic NSAID formulation of Claim 6 wherein said NSAID is the (1)-isomer of ketorolac or one of its pharmaceutically acceptable salts.

5 9. The ophthalmic NSAID formulation of Claim 1 comprising:

	NSAID	0.001% to 10.0% wt/vol.;
	Preservative	0.001% to 1.0% wt/vol.;
	Surfactant	0.001% to 1.0% wt/vol.;
10		and
	Purified Water	q.s. to 100%.

10. The ophthalmic NSAID formulation of Claim 9 wherein said preservative is benzalkonium chloride.

15 11. The ophthalmic NSAID formulation of Claim 10 wherein said surfactant is Octoxynol 40.

20 12. The ophthalmic NSAID formulation of Claim 11 wherein said NSAID is Ketorolac Tromethamine.

25 13. The ophthalmic NSAID formulation of Claim 9 including:

	Chelating agent	0.01% to 1.0%wt/vol.;
	Tonicifier	q.s. to achieve isotonicity with lacrimal fluid; and
	1N NaOH or 1N HCl	q.s. to adjust pH to 6.0 to 8.0.

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14. The ophthalmic NSAID formulation of Claim 13 comprising:

	NSAID	0.50% wt/vol.;
	BAC	0.02% wt/vol.;
5	(50% aq. soln.)	
	Octoxynol 40	0.01% wt/vol.;
	(70% aq. soln.)	
	EDTA Na <sub>2</sub>	0.10% wt/vol.;
	NaCl	0.79% wt/vol.;
10	1N NaOH or 1N HCl	q.s. to adjust pH to 7.4±0.4; and
	Purified Water	q.s. to 100%.

15 15. The ophthalmic NSAID formulation of Claim 14 wherein said NSAID is Ketorolac Tromethamine.

16 16. A method of treating ophthalmic disease comprising administering to a mammal suffering therewith a formulation comprising: a NSAID in an effective amount  
20 for ophthalmic treatment, a quaternary ammonium preservative, a stabilizing amount of a nonionic surfactant, and an aqueous vehicle.

25 17. The method of treating ophthalmic diseases of Claim 16 wherein said preservative is benzalkonium chloride.

30 18. The method of treating ophthalmic diseases of Claim 17 wherein said surfactant is Octoxynol 40.

35 19. The method of treating ophthalmic diseases of Claim 16 wherein said NSAID is selected from the group: ketorolac, indomethacin, flurbiprofen, and diclofenac, or their isomers, pharmaceutically acceptable salts, or esters.

20. The method of treating ophthalmic diseases of Claim 19 wherein said NSAID is Ketorolac Tromethamine.

21. The method of treating ophthalmic diseases of Claim 20 wherein said ophthalmic NSAID formulation comprises:

Ketorolac Tromethamine	0.50% wt/vol.;
BAC	0.02% wt/vol.;
(50% aq. soln.)	
Octoxynol 40	0.01% wt/vol.;
(70% aq. soln.)	
EDTA Na <sub>2</sub>	0.10% wt/vol.;
NaCl	0.79% wt/vol.;
1N NaOH or 1N HCl	to adjust pH to $7.4 \pm 0.4$ ; and
Purified Water	q.s. to 100%.

22. An antimicrobially effective ophthalmologically acceptable preservative system for ophthalmologically acceptable, carboxyl group-containing drugs, said preservative system comprising a quaternary ammonium preservative and a stabilizing amount of a nonionic ethoxylated octylphenol surfactant.

23. The preservative system of Claim 22 wherein said ophthalmologically acceptable preservative is benzalkonium chloride and said surfactant is Octoxynol 40.

~~24. The use of a formulation of Claim 1 for the treatment or prevention of ocular inflammatory diseases.~~

24. The use of a preservative system of Claim 22 for the treatment or prevention of ocular inflammatory diseases.



25. A process for the preparation of an ophthalmic NSAID formulation which comprises mixing  
0.001% to 10.0% wt/vol. of an NSAID,  
0.001% to 1.0% wt/vol. of a preservative,  
0.001% to 1.0% wt/vol. of a nonionic ethoxylated octylphenol surfactant, q.s. of 1N NaOH  
or 1N HCl to adjust pH to 6.0 to 8.0 and  
Purified Water q.s. to 100%.

26. The process of Claim 25 which further comprises mixing  
0.01% to 1.0% wt/vol. of a chelating agent,  
q.s. of a tonicifier to achieve isotonicity with lacrimal fluid.

DATED this 14th day of August, 1991.

SYNTEX (U.S.A.) INC.

WATERMARK PATENT & TRADEMARK ATTORNEYS  
THE ATRIUM  
290 BURWOOD ROAD  
HAWTHORN VICTORIA 3122  
AUSTRALIA

IAS:JZ





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

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<p>(21) International Application Number: PCT/US94/00188</p> <p>(22) International Filing Date: 6 January 1994 (06.01.94)</p> <p>(30) Priority Data: 08/003,107      11 January 1993 (11.01.93)      US</p> <p>(71) Applicant: ALLERGAN, INC. [US/US]; 2525 Dupont Drive, P.O. Box 19534, Irvine, CA 92713-9534 (US).</p> <p>(72) Inventor: WONG, Michelle, P.; 15662 Myrtle Avenue, Tustin, CA 92680 (US).</p> <p>(74) Agents: BARAN, Robert, J. et al.; Allergan, Inc., 2525 Dupont Drive, P.O. Box 19534, Irvine, CA 92713-9534 (US).</p>	<p>(81) Designated States: AU, CA, JP, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).</p> <p><b>Published</b> <i>With international search report.</i></p>	
(54) Title: OPTHALMIC COMPOSITIONS COMPRISING BENZYLLAURYLDIMETHYLAMMONIUM CHLORIDE		
<p>(57) Abstract</p> <p>An ophthalmic solution generally includes an ophthalmologically acceptable drug formulation incompatible with benzalkonium chloride and lauralkonium chloride present in an anti-microbially effective amount. The incompatibility of the ophthalmologically acceptable drug manifests itself by forming insoluble ion pairs with the benzalkonium chloride. It has been found that lauralkonium chloride which is the C<sub>12</sub> homolog of benzalkonium chloride is effective as a preservative without apparent interaction with the acidic ophthalmologically acceptable drug and formulations maintain their antimicrobial efficiency over periods of up to one year or more.</p>		

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## OPHTHALMIC COMPOSITIONS COMPRISING BENZYLLAURYLDIMETHYLAMMONIUM CHLORIDE

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The present invention generally relates to improved ophthalmic formulations and solutions and more particularly to improved preservative systems for ophthalmologically acceptable drug formulations which have an incompatibility with benzalkonium chloride. More specifically, the present invention pertains to the preservative for an anti-inflammatory drug such as sodium flurbiprofen (Ocufen®).

10

Ophthalmologically acceptable drug formulations generally contain effective compounds and a number of ophthalmologically acceptable excipients. Such excipients generally include solutions, ointments, and suspensions, etc. More specifically, such excipients include stabilizing agents, surfactants, buffering systems, chelating systems, viscosity agents, and, importantly, a preservative.

15

20

Ophthalmic formulations, understandably, must be sterile and if a multi-dose regime is intended, the formulation must be preserved with an effective antimicrobial agent.

25

As discussed in U.S. Patent No. 5,110,493, organo-mercurials have been used extensively as the preservatives in ophthalmic solutions. As reported in this reference, these compounds pose difficulties due to potential mercury toxicity as well as poor chemical stability.



-2-

Therefore, benzalkonium chloride, which is a quaternary ammonium compound, has been widely used in ophthalmic solutions. It is also well-known, however, that benzalkonium chloride is considered incompatible with anionic drugs, forming insoluble compounds which cause the solution to turn cloudy.

This is because of the fact that many acidic drug entities carry a negative charge at physiological pH. In fact, all acidic drug entities will carry a negative charge at all pH above their pKa.

In the case of benzalkonium chloride, which is a positively charged preservative, ion pairs can be formed with negatively charged drug compounds, forming an insoluble ion pair which causes the drug to precipitate out of solution. Concomitant with the removal of the drug from solution is the removal of benzalkonium chloride, thereby rendering this quaternary germicide incapable of performing its function as an antimicrobial agent.

Benzalkonium chloride is a mixture of alkyldimethylbenzylammonium chloride of the general formula as shown below in which R represents a mixture of the alkyls from  $C_8H_{17}$  to  $C_{18}H_{37}$

As hereinbefore noted, it is well-known that benzalkonium chloride is generally incompatible with anionic detergents or anionic drug compounds.

See U.S. Patent No. 5,110,493, and The Merck Index, 11th Edition, Merck & Co., Inc., 1989.

5 The present invention specifically relates to the discovery that a particular member of a group of compounds, generally known as benzalkonium chloride, exhibits properties totally different from other members of the group and different from the gross properties of the mixture known as benzalkonium chloride.

10 This discovery by the applicant must be taken in the context that all compositions are made of the same substances, retaining their fixed chemical properties. The elements are capable of an infinity of permutations, and selection of that group or element of a group which proves serviceable to a given need requires a high degree of originality.  
15 This general premise relates to the invention at hand. The applicant has discovered that lauralkonium chloride, which is the  $C_{12}$  homolog of benzalkonium chloride, is compatible with acidic drug entities with apparently no insoluble ion pairs being formed therewith. This is contrary to the properties of the mixture of alkyldimethylbenzylammonium chloride,  
20 known as benzalkonium chloride, which includes a mixture of the alkyls from  $C_8H_{17}$  to  $C_{18}H_{37}$ .

#### SUMMARY OF THE INVENTION

25 An ophthalmic solution, in accordance with the present invention, generally includes an ophthalmologically acceptable drug formulation incompatible with benzalkonium chloride and lauralkonium chloride present in an antimicrobially effective amount. More specifically, flurbiprofen is an example of an acidic drug that forms an insoluble ion-

pair with benzalkonium chloride. However, when combined with lauralkonium chloride, no apparent insoluble ion pairs are formed.

5 More particularly, in accordance with the present invention, the ophthalmic solution may further include citric acid monohydrate, sodium citrate dihydrate, polyvinyl alcohol, edetate disodium dihydrate, sodium chloride, potassium chloride and water.

10 The amount of lauralkonium chloride is any antimicrobially effective amount and preferably may be up to about 0.005% by weight per volume of the solution, and the amount of sodium flurbiprofen may be present in any effective amount and preferably about 0.03% by weight per volume.

15 The combination of lauralkonium chloride is further emphasized in that it can be combined with an acidic ophthalmologically acceptable drug formulation having a negative charge at physiological pH, and further the fact that the acidic ophthalmologically acceptable drug is capable of forming an insoluble ion-pair with benzalkonium chloride, no apparent  
20 insoluble ion-pairs are produced when the drug is in combination with lauralkonium chloride, taken itself.

25 Further, the invention includes a method for preserving an acidic ophthalmologically acceptable drug solution, comprising adding to the ophthalmologically acceptable drug solution an antimicrobially effective amount of lauralkonium chloride.

### DETAILED DESCRIPTION

Flurbiprofen is a classic example of an acidic drug that forms an insoluble ion-pair with benzalkonium chloride. It has been discovered that  
5 this interaction (insoluble ion-pair formation) can be overcome by formulating the flurbiprofen with the  $C_{12}$  homolog of benzalkonium chloride and lauralkonium chloride.

The lauralkonium chloride utilized will comprise at least 95% and  
10 preferably about 97.8% of the  $C_{12}$  homolog, 1.5% of the  $C_{14}$  homolog, and 0.7% of the  $C_{16}$  homolog.

The following examples, illustrating the utility of lauralkonium chloride as opposed to benzalkonium chloride, include the preparation or  
15 compounding of flurbiprofen formulations as follows.

Compounding occurs in two parts:

Part 1: Disperse polyvinyl alcohol in rapidly stirring purified water  
20 and heat to 85°C. Maintain temperature and stirring for one hour to dissolve the polyvinyl alcohol.

Part 2: While mixing a bulk of purified water of at least 50% of  
25 the final lot volume, add edetate disodium, benzalkonium chloride or lauralkonium chloride, potassium chloride, sodium chloride, sodium citrate and citric acid allowing each to dissolve or mix well before adding the next. Adjust the pH to 6.4-6.6 with dilute sodium hydroxide and/or hydrochloric acid. Add sodium flurbiprofen to the bulk and mix well.

-6-

While mixing Part 2, add Part 1 and mix thoroughly. Adjust the pH to 6.4-6.6 with dilute sodium hydroxide and/or hydrochloric acid. Sterilize the lot by filtration (0.22 $\mu$ ) and aseptically fill units into pre-sterilized containers.

5

The benzalkonium chloride and the lauralkonium chloride utilized in the present examples were obtained from E.M. Industries, Inc. of Hawthorne, NY and Triple Crown Ammerica, Inc. of Perkasio, PA, respectively.

10

### Example

Table 1 shows the ingredients for Examples A and B, with the formulations being identical, except that Example A utilizes benzalkonium chloride and Example B utilizes lauralkonium chloride in the same amounts, i.e., 0.005%, by weight per volume.

15

TABLE 1

20

### OCULEN® FORMULATIONS

Ingredient	Example A	Example B
	% w/v	% w/v
Sodium flurbiprofen	0.03	0.03
Benzalkonium chloride	0.005	-
Lauralkonium chloride	-	.005
Citric acid monohydrate USP	0.05	0.05
Sodium citrate dihydrate USP	0.45	0.45
Polyvinyl alcohol 20-90 Grade	1.4	1.4
Edetate disodium dihydrate USP	0.0127	0.0127

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-7-

	Sodium chloride USP	0.65	0.65
	Potassium chloride USP	0.075	0.075
	Purified water USP	qs to 100	qs to 100
	Sodium hydroxide NF	pH 6.4 to 6.6	pH 6.4 to 6.6
5	Hydrochloric acid NF	pH 6.4 to 6.6	pH 6.4 to 6.6

Example A results in a cloudy solution with precipitate and loss of antimicrobial efficacy while Example B remains as a solution and the solution maintains its antimicrobial efficacy. Example A failed to pass the preservative effectiveness test as described in the British Pharmacopoeia while Example B passes the British Pharmacopoeia preservative effectiveness test.

In addition, the ability of lauralkonium chloride to stay in solution and to maintain its antimicrobial effectiveness as a function of time was also monitored. Table 2 shows the concentration of lauralkonium chloride in the formulation described in Example B. Table 3 shows the ability of lauralkonium chloride to maintain its antimicrobial efficacy over a period of up to one year or more.

TABLE 2

No. of Days	Lauralkonium chloride - ppm
13	46.0
32	46.0
75	45.8
115	45.0
192	47.7

-8-

370	48.2
-----	------

TABLE 3

No. of Days	Microbiology Results
13	Pass BP-88
370	Pass BP-88

5

10

15

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

**WHAT IS CLAIMED IS:**

1. An ophthalmic solution comprising:  
an ophthalmologically acceptable drug formulation  
incompatible with benzalkonium chloride; and  
a preservative consisting essentially of lauralkonium  
chloride and present in an antimicrobially effective amount.
2. The ophthalmic solution according to Claim 1 wherein said  
ophthalmologically acceptable drug formulation comprises sodium  
flurbiprofen.
3. The ophthalmic solution according to claim 2 further  
comprising citric acid monohydrate, sodium citrate dihydrate, polyvinyl  
alcohol, edetate disodium dihydrate, sodium chloride, potassium chloride,  
and water.
4. The ophthalmic solution according to Claims 1, 2 or 3  
wherein said lauralkonium chloride is present in an amount up to about  
0.005% by weight per volume of the solution.
5. The ophthalmic solution according to claim 2 or 3 wherein  
the sodium flurbiprofen is present in an amount up to about 0.03% by  
weight per volume of the solution and the lauralkonium chloride is present  
in an amount up to about 0.005% by volume of the solution.
6. An ophthalmic solution comprising:  
an acidic ophthalmologically acceptable drug  
formulation having a negative charge at physiological pH;  
and



5 a preservative consisting essentially of lauralkonium chloride and present in an antimicrobially effective amount.

7. The ophthalmic solution according to Claim 6 wherein said ophthalmologically acceptable drug formulation comprises sodium flurbiprofen.

8. The ophthalmic solution according to Claim 7 further comprising citric acid monohydrate, sodium citrate dihydrate, polyvinyl alcohol, edetate disodium dihydrate, sodium chloride, potassium chloride, and water.

9. The ophthalmic solution according to Claims 6, 7 or 8 wherein said lauralkonium chloride is present in an amount up to about 0.005% by weight per volume of the solution.

10. The ophthalmic solution according to Claim 7 or 8 wherein the sodium flurbiprofen is present in an amount up to about 0.03% by weight per volume of the solution and the lauralkonium chloride is present in an amount up to about 0.005% by volume of the solution.

11. A method for preserving an acidic ophthalmically acceptable drug solution comprising adding to said ophthalmically acceptable drug solution an antimicrobially effective amount of lauralkonium chloride.

12. An ophthalmic solution comprising:  
an acidic ophthalmologically acceptable drug capable of forming an insoluble ion-pair with benzalkonium chloride;  
and

5

a preservative consisting essentially of lauralkonium chloride and present in an antimicrobially effective amount.

INTERNATIONAL SEARCH REPORT

Inter. Appl. Application No  
PCT/US 94/00188

<p>A. CLASSIFICATION OF SUBJECT MATTER IPC 5 A61K31/19 A61K9/00 A61K47/18</p> <p>According to International Patent Classification (IPC) or to both national classification and IPC</p>											
<p>B. FIELDS SEARCHED</p> <p>Minimum documentation searched (classification system followed by classification symbols) IPC 5 A61K</p> <p>Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched</p> <p>Electronic data base consulted during the international search (name of data base and, where practical, search terms used)</p>											
<p>C. DOCUMENTS CONSIDERED TO BE RELEVANT</p> <table border="1"> <thead> <tr> <th>Category *</th> <th>Citation of document, with indication, where appropriate, of the relevant passages</th> <th>Relevant to claim No.</th> </tr> </thead> <tbody> <tr> <td>X</td> <td>CHEMICAL ABSTRACTS, vol. 112, no. 16, 16 April 1990, Columbus, Ohio, US; abstract no. 145590h, see abstract &amp; JP,A,01 246 227 (SANTEN PHARMACEUTICAL CO.,LTD.) 2 October 1989</td> <td>1,3,4,6, 8,9,11, 12</td> </tr> <tr> <td>A</td> <td>DATABASE WPI Week 8231, Derwent Publications Ltd., London, GB; AN 82-64749E (31) see abstract &amp; JP,A,57 102 817 (KAKENYAKU KAKO KK) 26 June 1982</td> <td>2,5,7,10</td> </tr> </tbody> </table>			Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	X	CHEMICAL ABSTRACTS, vol. 112, no. 16, 16 April 1990, Columbus, Ohio, US; abstract no. 145590h, see abstract & JP,A,01 246 227 (SANTEN PHARMACEUTICAL CO.,LTD.) 2 October 1989	1,3,4,6, 8,9,11, 12	A	DATABASE WPI Week 8231, Derwent Publications Ltd., London, GB; AN 82-64749E (31) see abstract & JP,A,57 102 817 (KAKENYAKU KAKO KK) 26 June 1982	2,5,7,10
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<p><input type="checkbox"/> Further documents are listed in the continuation of box C. <input type="checkbox"/> Patent family members are listed in annex.</p>											
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<p>Date of the actual completion of the international search 11 April 1994</p>		<p>Date of mailing of the international search report 25.10.94</p>									
<p>Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016</p>		<p>Authorized officer Scarponi, U</p>									

# INTERNATIONAL SEARCH REPORT

Information on patent family members

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Chuo-ku, Osaka-shi  
541-0046, OSAKA, XX (JP).

(71)

ONO PHARMACEUTICAL CO., LTD.,  
1-6, Doshomachi 2-chome  
Chuo-ku  
Osaka-shi  
541-8526, OSAKA, XX (JP).  
SENJU PHARMACEUTICAL CO., LTD.,  
5-8 Hiranomachi 2-chome

(72)

KAWABATA, KAZUHITO (JP).  
NAKA, HIROAKI (JP).  
TOKUSHIGE, HIDEKI (JP).

(74)

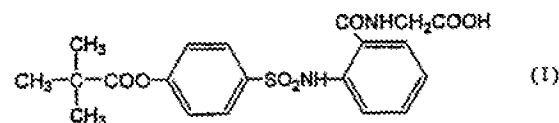
FETHERSTONHAUGH & CO.

(54) MEDICAMENTS THERAPEUTIQUE ET PROPHYLACTIQUE POUR TRAITER LES MALADIES OPHTALMIQUES

(54) PROPHYLACTIC AND THERAPEUTIC MEDICAMENTS FOR OPHTHALMIC DISEASES

(57)

Preventive and therapeutic agents for eye diseases,  
particularly inflammatory eye diseases and corneal  
ulcer, containing as the active ingredient the  
compound of formula (I), pharmacologically acceptable  
salts thereof, or hydrates of both.



(I)



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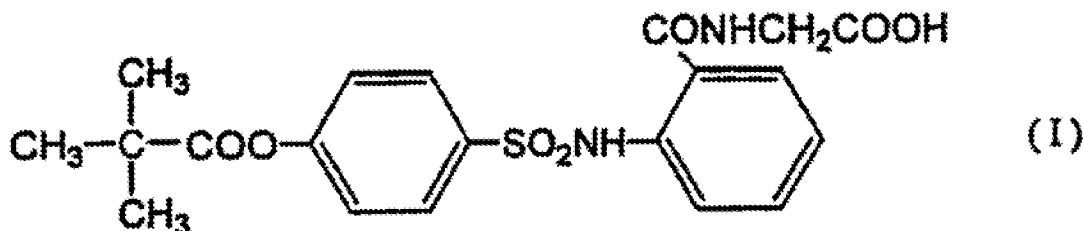
(71) Demandeurs/Applicants:  
SENJU PHARMACEUTICAL CO., LTD., JP;  
ONO PHARMACEUTICAL CO., LTD., JP

(72) Inventeurs/Inventors:  
NAKA, HIROAKI, JP;  
KAWABATA, KAZUHITO, JP;  
TOKUSHIGE, HIDEKI, JP

(74) Agent: FETHERSTONHAUGH & CO.

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(54) Title: PROPHYLACTIC AND THERAPEUTIC MEDICAMENTS FOR OPHTHALMIC DISEASES



(57) Abrégé/Abstract:

Preventive and therapeutic agents for eye diseases, particularly inflammatory eye diseases and corneal ulcer, containing as the active ingredient the compound of formula (I), pharmacologically acceptable salts thereof, or hydrates of both.

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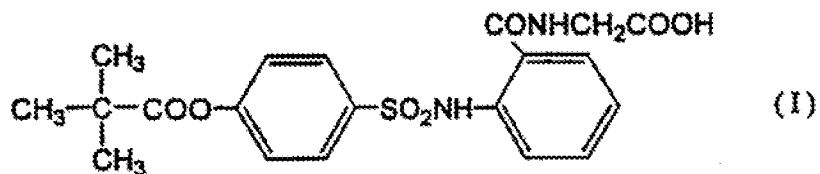
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## Abstract of the disclosure:

The present invention provides a prophylactic and therapeutic medicament for ophthalmic diseases, especially ophthalmic inflammatory diseases and corneal ulcer, comprising as an active ingredient a compound represented by the formula (I):



or a pharmacologically acceptable salt or hydrate thereof.

PROPHYLACTIC AND THERAPEUTIC MEDICAMENTS FOR OPHTHALMIC  
DISEASES

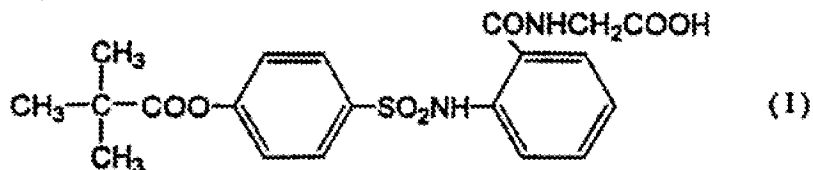
5 TECHNICAL FIELD

The present invention relates to a prophylactic  
and therapeutic medicament for ophthalmic diseases  
having a leukocyte (neutrophil)-derived elastase  
inhibitory activity.

10

BACKGROUND OF THE INVENTION

JP-B 5-81586 and JP-A 5-194366 (corresponding to  
EP-A 539223) disclose a compound represented by the  
formula (I):



15

(hereinafter referred to as a compound of Formula (I))  
and a salt or hydrate thereof, which has a human  
neutrophil-derived elastase inhibitory activity and is  
20 effective for preventing and treating diseases such as  
pulmonary emphysema, atherosclerosis and rheumatoid  
arthritis.

On the other hand, the ophthalmologic field also



involves various diseases relating to leukocytes and their elastases. For example, ophthalmic infections, corneal traumas, corneal ulcers and uveitis may be mentioned. In an ophthalmic infection, the cellular infiltration of leukocytes results in an intraocular abscess [Invest. Ophthalmol. Vis. Sci., 40, 385-391 (1999)]. An alkaline trauma (erosion) which is one of corneal traumas allows leukocytes to be infiltrated into corneal stromal cells at an early stage of the alkaline erosion, two to three weeks after which the elevation of leukocyte elastase activity is observed [Ophthalmic. Res., 29, 154-160 (1997)]. Also in a case of corneal ulcers, a corneal wound or detachment results in the infiltration of leukocytes into a corneal stroma, which leads to the release or secretion of a protease such as an elastase or collagen [Klin. Monatsbl. Augenheilkd, 188, 593-595 (1986)]. An uveitis, especially Behcet's disease, was reported to undergo an increase in a plasma leukocyte elastase [Clin. Chim. Acta 236:129-134 (1995), Acta, Ophthalmol. Scand. 75:287-289 (1997), J.Reumatol. 25: 326-328 (1998)]. While leukocytes or their elastases were reported to be involved in the ophthalmic diseases mentioned above, no actual effect of the administration of an elastase inhibitor was reported.

While in JP-A 5-221872 (corresponding to EP-A  
519354) and JP-A 6-509232 (corresponding to EP-A  
596118), a microbe-derived substance having human  
leukocyte elastase inhibitory activity is described  
5 generally to be useful as a prophylactic and  
therapeutic medicament against a corneal scar tissue  
formation or a fibroblast proliferation [eye  
solidification (burn, mechanical or chemical damage,  
keratoconjunctivitis) and the like], it was not  
10 administered actually to verify its effect, and is  
different totally from a compound of Formula (I).

#### OBJECTS OF THE INVENTION

An objective of the present invention is to  
15 develop a prophylactic and therapeutic medicament for  
ophthalmic diseases containing as an active ingredient  
a compound of Formula (I).

This objective as well as other objectives and  
advantages of the present invention will be explained  
20 hereinafter with reference to the attached drawings.

#### BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a graph showing the effect of an eye  
drop formulation of N-[o-(p-pivaloyloxybenzenesulfonyl-  
25 amino)benzoyl]glycine monosodium salt tetrahydrate

(hereinafter referred to as Compound A) on an  
endotoxin-induced keratitis (effect on a corneal  
opacity). Each symbol represents a mean  $\pm$  standard  
deviation (n=4). A statistically significant  
5 difference from a control is analyzed with  $p < 0.05$   
(Wilcoxon test, one-sided).

Fig. 2 is a graph showing the effect of a Compound  
A eye drop formulation on an endotoxin-induced  
keratitis (effect on a corneal ulcer). Each symbol  
10 represents a mean  $\pm$  standard deviation (n=4). A  
statistically significant difference from a control is  
analyzed with  $p < 0.05$  (Wilcoxon test, one-sided).

Fig. 3 is a graph showing the effect of a Compound  
A eye drop formulation on an endotoxin-induced  
15 keratitis (effect on a vascularization). Each symbol  
represents a mean  $\pm$  standard deviation (n=4).

Fig. 4 shows the effect of a Compound A eye drop  
formulation 15 days after the challenge on an  
endotoxin-induced keratitis. Each column represents a  
20 mean  $\pm$  standard deviation (n=4). A statistically  
significant difference from a control is analyzed with  
 $p < 0.05$  (Wilcoxon test, one-sided).

Fig. 5 is a graph showing the effect of a Compound  
A eye drop formulation on an alkaline erosion keratitis  
25 (effect on a corneal opacity). Each symbol represents

a mean  $\pm$  standard deviation (n=4).

Fig. 6 is a graph showing the effect of a Compound A eye drop formulation on an alkaline erosion keratitis (effect on a corneal ulcer). Each symbol represents a mean  $\pm$  standard deviation (n=4). A statistically significant difference from a control is analyzed with  $p < 0.05$  (Wilcoxon test, one-sided).

Fig. 7 is a graph showing the effect of a Compound A eye drop formulation on an alkaline erosion keratitis (effect on a vascularization). Each symbol represents a mean  $\pm$  standard deviation (n=4).

Fig. 8 is a graph showing the effect of a Compound A eye drop formulation on a pyocyanic corneal ulcer immediately after the inoculation of the microbe. Each symbol represents a mean  $\pm$  standard deviation (n=6). A statistically significant difference from a control is analyzed with  $p < 0.05$  (Wilcoxon test, one-sided).

Fig. 9 is a graph showing the effects of the instillation of Compound A and lomefloxacin on a pyocyanic corneal ulcer one day after the inoculation of the microbe and later. Each symbol represents a mean  $\pm$  standard deviation (n=5-6). A statistically significant difference from a control is analyzed with \*  $p < 0.05$  and \*\*  $p < 0.01$  (Steel test, one-sided).

## SUMMARY OF THE INVENTION

The present inventors found out that a compound represented by Formula (I) or a pharmacologically acceptable salt or hydrate thereof exhibits a marked prophylactic and therapeutic effect against various ophthalmic diseases.

Thus, the present invention provides a prophylactic and therapeutic medicament for ophthalmic diseases, especially ophthalmic inflammatory diseases and corneal ulcer, comprising as an active ingredient a compound represented by Formula (I) or a pharmacologically acceptable salt or hydrate thereof.

The present invention also provides a method for preventing and treating an ophthalmic disease which comprises administering an active ingredient mentioned above to a mammal in need of a treatment for such ophthalmic disease.

Furthermore, the present invention provides use of an active ingredient mentioned above in the manufacture of a prophylactic and therapeutic medicament for ophthalmic diseases.

Moreover, the present invention provides an eye drop formulation in the form of an aqueous suspension of an active ingredient described above.

25

## DETAILED DESCRIPTION OF THE INVENTION

The prophylactic and therapeutic medicament according to the present invention is preferably in a dosage form for a local administration such as an eye drop formulation or an ophthalmic ointment, which is useful for preventing and treating various ophthalmic diseases such as ophthalmic infections (for example, corneal herpes, bacterial keratitis, bacterial conjunctivitis, mycotic keratitis, acanthamebic keratitis, infectious endophthalmitis, infectious corneal ulcer and the like), corneal trauma, cicatricial keratoconjunctival diseases (for example, alkaline erosive keratoconjunctivitis, Stevens-Johnson syndrome, ophthalmic pemphigoid and the like), corneal ulcer (for example, Mooren's ulcer, corneal ulcer subsequent to chronic rheumatoid arthritis or collagen disease, Terrien's margine degeneration, catarrhal corneal ulcer, infectious corneal ulcer and the like), vitamin A insufficiency-induced keratomalacia, necrotic keratitis, neuroparalytic keratitis, diabetic keratopathy, keratoconjunctiva sicca, contact lens-induced keratoconjunctivitis, vernal conjunctivitis, allergic conjunctivitis, uveitis, Behcet's syndrome, inflammation after cataract surgery and pseudopterygium, especially a keratoconjunctival inflammatory disease

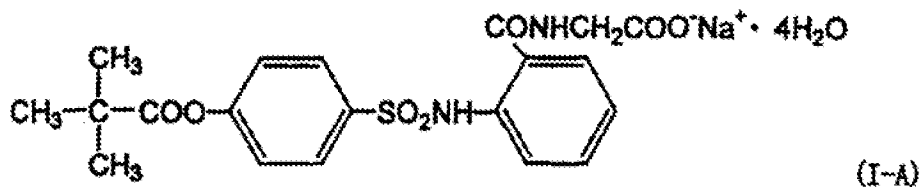
(for example, corneal herpes, bacterial keratitis, bacterial conjunctivitis, mycotic keratitis, acanthamebic keratitis, corneal trauma, alkaline erosive keratoconjunctivitis, corneal ulcer, vitamin A  
5 insufficiency-induced keratomalacia, necrotic keratitis, neuroparalytic keratitis, diabetic keratopathy, keratoconjunctiva sicca, contact lens-induced keratoconjunctivitis, vernal conjunctivitis, allergic conjunctivitis and the like). It is useful also for  
10 preventing and treating corneal ulcer (including various corneal ulcers described above and those induced otherwise), especially an infectious corneal ulcer.

A compound of Formula (I) used as an active  
15 ingredient according to the present invention or a pharmacologically acceptable salt thereof is a known compound described in JP-B 5-81586, and can be produced, in accordance with the procedure described therein, by the amidation of p-pivaloyloxybenzenesulfonyl chloride  
20 followed by the conversion into a salt by a known method. The resultant compound may also be converted into a hydrate by a known method.

A pharmacologically acceptable salt of a compound of Formula (I) may for example be an inorganic salt  
25 such as hydrochloride, hydrobromide, hydroiodide,

sulfate, phosphate and nitrate, an organic salt such as acetate, lactate, tartarate, benzoate, citrate, methanesulfonate, ethanesulfonate, benzenesulfonate, toluenesulfonate, isethionate, glucuronate and gluconate, an alkaline metal salt (sodium salt, potassium salt and the like), an alkaline earth metal salt (calcium salt, magnesium salt and the like), an ammonium salt, a pharmacologically acceptable amine salt (tetramethylammonium salt, triethylamine salt, methylamine salt, dimethylamine salt, cyclopentylamine salt, benzylamine salt, phenethylamine salt, piperidine salt, monoethanolamine salt, diethanolamine salt, tris(hydroxymethyl)aminomethane salt, lysine salt, arginine salt, N-methyl-D-glucamine salt and the like).

One preferred especially as an active ingredient used in the present invention is a sodium salt tetrahydrate of a compound of Formula (I), i.e., N-[o-(p-pivaloyloxybenzenesulfonylamino)benzoyl]glycine monosodium salt tetrahydrate (described in Example 3 in JP-A 5-194366 corresponding to EP-A 539223) represented by Formula (I-A):





The prophylactic and therapeutic medicament for ophthalmic diseases according to the present invention, on the basis of its leukocyte-derived elastase inhibitory activity, is useful in preventing and  
5 treating various ophthalmic diseases such as an ophthalmic infections (for example, corneal herpes, bacterial keratitis, bacterial conjunctivitis, mycotic keratitis, acanthamebic keratitis, infectious endophthalmitis, infectious corneal ulcer and the like),  
10 corneal trauma, cicatricial keratoconjunctival diseases (for example, alkaline erosive keratoconjunctivitis, Stevens-Johnson syndrome, ophthalmic pemphigoid and the like), corneal ulcer (for example, Mooren's ulcer, corneal ulcer subsequent to chronic rheumatoid  
15 arthritis or collagen disease, Terrien's margine degeneration, catarrhal corneal ulcer, infectious corneal ulcer and the like), vitamin A insufficiency-induced keratomalacia, necrotic keratitis, neuroparalytic keratitis, diabetic keratopathy,  
20 keratoconjunctiva sicca, contact lens-induced keratoconjunctivitis, vernal conjunctivitis, allergic conjunctivitis, uveitis, Behcet's syndrome, inflammation after cataract surgery and pseudopterygium, especially a keratoconjunctival inflammatory disease  
25 (for example, corneal herpes, bacterial keratitis,

bacterial conjunctivitis, mycotic keratitis,  
acanthamebic keratitis, corneal trauma, alkaline  
erosive keratoconjunctivitis, corneal ulcer, vitamin A  
insufficiency-induced keratomalacia, necrotic keratitis,  
5 neuroparalytic keratitis, diabetic keratopathy,  
keratoconjunctiva sicca, contact lens-induced  
keratoconjunctivitis, vernal conjunctivitis, allergic  
conjunctivitis and the like). It is useful also for  
preventing and treating corneal ulcer (including  
10 various corneal ulcers described above and those  
induced otherwise), especially infectious corneal ulcer.

The prophylactic and therapeutic medicament for  
ophthalmic diseases according to the present invention  
can be mixed with a pharmacologically acceptable  
15 carrier, excipient or diluent which is known per se and  
formulated by a method known per se into a  
pharmaceutical or a veterinary medicine in various oral  
or parenteral dosage forms such as tablets, capsules,  
granules, injection solutions, eye drops and ophthalmic  
20 ointments, and it is especially preferred to be used in  
a local dosage form, preferably an eye drop formulation  
or an ophthalmic ointment.

The eye drop formulation may for example be  
aqueous formulations such as aqueous eye drops, aqueous  
25 suspension eye drops, viscous eye drops and solubilized

eye drops as well as non-aqueous formulations such as non-aqueous eye drops and non-aqueous suspension eye drops, with an aqueous formulation being preferred. One preferred especially is an aqueous suspension eye drop formulation.

The aqueous eye drop formulation may contain various additives incorporated ordinarily, such as buffering agents (e.g., phosphate buffers, borate buffers, citrate buffers, tartarate buffers, acetate buffers, amino acids, sodium acetate, sodium citrate and the like), isotonicities (e.g., saccharides such as sorbitol, glucose and mannitol, polyhydric alcohols such as glycerin, concentrated glycerin, polyethylene glycol and propylene glycol, salts such as sodium chloride), preservatives or antiseptics (e.g., benzalkonium chloride, benzethonium chloride, p-oxybenzoates such as methyl p-oxybenzoate or ethyl p-oxybenzoate, benzyl alcohol, phenethyl alcohol, sorbic acid or its salt, thimerosal, chlorobutanol and the like), solubilizing aids or stabilizing agents (e.g., cyclodextrins and their derivative, water-soluble polymers such as polyvinyl pyrrolidone, surfactants such as polysorbate 80 (Tween 80)), pH modifiers (e.g., hydrochloric acid, acetic acid, phosphoric acid, sodium hydroxide, potassium hydroxide, ammonium hydroxide and

the like), thickening agents (e.g., hydroxyethyl cellulose, hydroxypropyl cellulose, methyl cellulose, hydroxypropylmethyl cellulose, carboxymethyl cellulose and their salts), chelating agents (e.g., sodium edetate, sodium citrate, condensed sodium phosphate) and the like.

The eye drop formulation in the form of an aqueous suspension may also contain suspending agents (e.g., polyvinyl pyrrolidone, glycerin monostearate) and dispersing agents (e.g., surfactants such as tyloxapol and polysorbate 80, ionic polymers such as sodium alginate) in addition to the additives listed above, whereby ensuring that the eye drop formulation is a further uniform microparticulate and satisfactorily dispersed aqueous suspension.

When the eye drop formulation in the form of an aqueous suspension is produced, it is preferable to use a pH modifier to make the formulation acidic pH (pH4 to 5.5). A preferred pH modifier is hydrochloric acid.

The eye drop formulation in the form of an aqueous suspension preferably contains sodium citrate or sodium acetate as a buffering agent, concentrated glycerin and/or propylene glycol as an isotonicity and polyvinyl pyrrolidone as a suspending agent. A preferred dispersing agent is a surfactant and/or sodium alginate.

Such surfactant is preferably tyloxapol or polysorbate 80.

The ophthalmic ointment may employ an ointment base known per se, such as purified lanolin, petrolatum, 5 plastibase, liquid paraffin, polyethylene glycol and the like.

The prophylactic and therapeutic medicament of the present invention may be administered to a mammal which is or may be suffered from an ophthalmic disease (e.g., 10 human, rabbit, dog, cat, cattle, horse, monkey). While the administration route and the dose may vary depending on a symptom, age and body weight of a subject, the concentration is about 0.001 to 5 (w/v) %, preferably about 0.01 to 3 (w/v) % as a free form of a 15 compound of Formula (I) contained in an aqueous eye drop formulation when given to an adult, and is given preferably 1 to 8 times a day with a single dose being one to several drops.

When given as the ophthalmic ointment, the dose is 20 about 0.001 to 5 (w/v) %, preferably about 0.01 to 3 (w/v) % as a free form of a compound of Formula (I), and is given preferably 1 to 4 times a day as appropriate in view of the symptom.

Unless the intended purpose of use is affected 25 adversely, the prophylactic and therapeutic medicament

of the present invention may contain or may be used together with other appropriate pharmacologically effective substances, for example, steroidal anti-inflammatory agents (dexamethasone, prednisolone and the like), non-steroidal anti-inflammatory agents (diclofenac sodium, pranoprofen and the like), antiallergic agents (tranilast, ketotifen fumarate, sodium cromoglicate and the like), antihistamic agents (diphenhydramine hydrochloride and the like), glaucoma-treating agents (pilocarpine hydrochloride, physostigmine salicylate, timolol, isopropylunoprostone and the like), antibiotics (gentamycin sulfate, fradiomycin sulfate, tobramycin, sulbenicillin, cefmenoxime, erythromycin, colistin, oxytetracycline, polymyxin B, chloramphenicol, micronomicin, dibekacin, sisomicin and the like), antibacterial agents (sulfamethizole, sulfamethoxazole, ofloxacin, norfloxacin, lomefloxacin hydrochloride, enoxacin, ciprofloxacin hydrochloride, cinoxacin, sparfloxacin, tosufloxacin tosylate, nalidixic acid, pipemidic acid trihydrate, pipemidic acid, fleroxacin, levofloxacin and the like), and antiviral agents (idoxuridine, acyclovir and the like), and antimycotic agents (pimaricin, fluconazole, miconazole, amphotericin B, flucytosine, itraconazole and the like).

The prophylactic and therapeutic medicament of the present invention is used preferably together with at least one selected from the antibiotic, antibacterial, antiviral and antimycotic agents listed above in

5 prophylaxis or therapy especially for an ophthalmic infection-induced inflammation or corneal ulcer. In such case, any of the antibiotic, antibacterial, antiviral and antimycotic agents can be combined with the prophylactic and therapeutic medicament of the

10 present invention in a single formulation, or may be instilled separately. When being instilled separately, the prophylactic and therapeutic medicament of the present invention may be instilled simultaneously with any of the antibiotic, antibacterial, antiviral and

15 antimycotic agents, or successively at a certain interval. When being instilled simultaneously, any of the prophylactic and therapeutic medicament of the present invention and the antibiotic, antibacterial, antiviral and antimycotic agents is first instilled and

20 then preferably after a certain time period another agent is instilled whereby avoiding any escape of the agent given previously. Any of the antibiotic, antibacterial, antiviral and antimycotic agents listed above may also be given systemically by means of an

25 oral or intravenous formulation.

The present invention is further illustrated in detail by the following Experiments and Examples, which are not construed to limit the scope of the present invention.

5

## EXPERIMENT 1

The effect of Compound A on an ophthalmic inflammatory disease was investigated as described below.

10 The effect of Compound A when given as eye drops was investigated in a rabbit keratitis model using an endotoxin derived from *Pseudomonas aeruginosa* detected frequently in an ophthalmic infection as well as in a rabbit corneal alkaline erosion model.

## 15 MATERIALS AND METHODS

## (1) Animals

Male Japanese albino rabbits each weighing about 2 to 2.5 kg purchased from FUKUZAKI rabbit-raising association were used. Each animal was maintained at a  
20 temperature of  $24 \pm 4^{\circ}\text{C}$  and a humidity of  $55 \pm 15\%$ .

## (2) Test substances

Compound A was given as a 1.0 % Compound A eye drop formulation prepared by suspending Compound A in a formulation base (0.1 %  $\text{NaH}_2\text{PO}_4$ , 0.1 % polysorbate 80  
25 and 0.9 %  $\text{NaCl}$ , pH 5.0). As a positive control, a



0.1 % betamethasone eye drop formulation (Rinderon™ solution, Sionogi) was used. In a control group, the formulation base was given.

(3) Methods

5 1) Effect on endotoxin-induced keratitis

16 Male Japanese albino rabbits each weighing 2 to 2.5 kg were used. The rabbits were divided into four groups each having 4 animals, which were anesthetized systemically by an intramuscular administration each of 10 1 ml/kg of an equal volume mixture of 5 % ketamine hydrochloride and 2 % xylazine hydrochloride. Each 10 µl of a 1 % solution of Pseudomonas aeruginosa-derived endotoxin in physiological saline was infused into each corneal stroma of a rabbit. An anterior part of an eye 15 was observed using a slit lamp every 5 days over a period from the day after the endotoxin infusion through the 30th day, and examined for the corneal opacity, the corneal ulcer and the vascularization, which were scored in accordance with the criteria shown 20 in Table 1. Each test substance was started to be instilled immediately after the endotoxin infusion, and then given 4 times a day in the volume of 20 µl every 2 hours.

2) Effects on alkaline erosive keratitis

25 16 Male Japanese albino rabbits each weighing 2 to

2.5 kg were used. The rabbits were divided into four groups each having 4 animals, which were anesthetized systemically by an intramuscular administration each of 1 ml/kg of an equal volume mixture of 5 % ketamine hydrochloride and 2 % xylazine hydrochloride and also locally by an instillation of oxybuprocaine hydrochloride. A filter paper whose diameter was 10 mm and which had been immersed in 2N NaOH was brought into contact with the center of the right cornea of a rabbit for 1 minute to establish an alkaline erosion, and then the eye was rinsed immediately with 10 mL or more of physiological saline. The depth of the corneal ulcer and the vascularization were observed using a slit lamp every 5 days over a period from 5 days after the alkaline erosion through the 30th day, and scored in accordance with the criteria shown in Table 1. Each test substance was started to be instilled immediately after the alkaline erosion, and then given 4 times a day in the volume of 20  $\mu$ l every 2 hours.

Table 1

Rabbit keratitis scoring criteria

\* Corneal opacity<sup>remarks 1)</sup>

A) Degree

0: No opacity

1: Mild opacity but distinguishable anterior chamber

- 2: Difficulty in distinguishing details of iris
- 3: Almost no transparency in anterior chamber
- B) Corresponding size of corneal region
- 1: 1/3 or less of entire
- 5 2: 1/3 to 2/3 of entire
- 3: 2/3 or more of entire
- \* Corneal ulcer
- 0: No corneal ulcer
- 1: Ulcer of less than 1/3 in depth from corneal surface
- 10 toward inside of anterior chamber
- 2: Ulcer of 1/3 or more and less than 2/3 in depth from corneal surface toward inside of anterior chamber
- 3: Ulcer of 2/3 or more in depth from corneal surface toward inside of anterior chamber
- 15 4: Perforation in cornea
- \* Vascularization<sup>remarks 1)</sup>
- A) Length
- 0: No vascularization into cornea
- 1: Less than 1/3 from corneal limbus through center
- 20 2: Less than 2/3 from corneal limbus through center
- 3: 2/3 or more from corneal limbus through center
- B) Region
- 0.5: Less than 1/3 of corneal circumference
- 1: 1/3 or more and less than 2/3 of corneal
- 25 circumference

2: 2/3 or more of corneal circumference

Remarks 1) Each as score A x score B

#### RESULTS AND DISCUSSION

5 1) Effects on endotoxin-induced keratitis

Figs. 1 to 3 show the change in the keratitis symptoms over a period from 5 to 30 days after the endotoxin infusion. In the control group, the severity of each symptom peaked on the 15th day, and then a gradual recovery was observed until the 30th day when almost all disappeared. In Compound A instillation group, inhibitory effects were observed on all of the evaluation items, i.e., the corneal opacity, the corneal ulcer and the vascularization, when compared with the control group. In the 0.1 % betamethasone phosphate instillation group used as the positive control, the onset of the keratitis was inhibited almost completely over the observation period. Fig. 4 shows the total score in each group on the 15th day when the severity of each symptom peaked, and revealed that the % inhibition in the Compound A instillation group when compared with the control group was 59.4 %, with a statistically significant difference.

Based on the results described above, the Compound A eye drop formulation was proven to be effective

against various symptoms of the keratitis during an ophthalmic infection.

While betamethasone phosphate used here as a positive control exhibited an extremely potent anti-inflammatory activity, its use is limited frequently in view of a side effect experienced as the exacerbation of an infection over a prolonged therapy with a steroid in a clinical case of the ophthalmic infections.

Accordingly, the Compound A eye drop formulation expected to have a less risk of the exacerbation of an infection can serve as a hopeful agent against the ophthalmic infections.

#### 2) Effects on alkaline erosive keratitis

Figs. 5 to 7 show the change in the keratitis symptoms over a period from 5 to 30 days after the corneal alkaline exposure. In the control group, the severity peaked on the 20 to 25th day after the corneal alkaline exposure. In Compound A instillation group, a significant inhibitory effect on the corneal ulcer was observed on the 20th day, but no effects were noted on the vascularization or the corneal opacity. In the 0.1 % betamethasone phosphate instillation group used as the positive control, a significant inhibitory effect was observed on the vascularization on the 15th day.

## EXPERIMENT 2

## MATERIALS AND METHODS

## (1) Animals

5 Male Japanese albino rabbits each weighing about 2 kg purchased from KITAYAMA LABES CO., LTD. were used. Each animal was maintained at a temperature of  $23 \pm 3^{\circ}\text{C}$  and a humidity of  $55 \pm 10 \%$ .

## (2) Test substances

10 Compound A was given as a 1.0 % Compound A eye drop formulation prepared by suspending Compound A in a formulation base (0.1 % sodium acetate, 0.1 % polysorbate 80 and 0.9 % NaCl, pH 5.0). A 0.3 % lomefloxacin (LFLX) hydrochloride was used as an  
15 antibacterial agent, and physiological saline was used as a control.

## (3) Methods

## 1) Excision of nictitating membrane

After instilling 0.4 % oxybuprocaine hydrochloride  
20 for a local anesthesia, a nictitating membrane was excised.

## 2) Inoculation

A causative microorganism used was a clinical isolate *Pseudomonas aeruginosa* strain No. ho-134. A  
25 rabbit was anesthetized systemically with 5 % ketamine

hydrochloride and 2 % xylazine hydrochloride (equal volume mixture), and then inoculated by an infusion of 30  $\mu$ l of a  $3.9 \times 10^4$  CFU/ml cell suspension ( $1.17 \times 10^3$  CFU/cornea) using a 100  $\mu$ l microsyringe fitted with a 30G needle into one corneal stroma of a rabbit.

### 3) Instillation

An animal which had received an infusion of the cell suspension into the corneal stroma and whose inoculation was surely successful was grouped into one of [1] physiological saline instillation group (control, n=6) and [2] 1.0 % Compound A instillation group (Compound A group, n=6) as groups whose therapy was started immediately after the inoculation, and [3] 1.0 % Compound A instillation group (late Compound A group, n=5), [4] 0.3 % LFLX instillation group (LFLX group, n=6) and [5] 1.0 % Compound A instillation - 0.3 % LFLX instillation combination group (Compound A - LFLX combination group, n=6) as groups whose therapy was started 1 day after the inoculation (after onset of corneal ulcer), and 50  $\mu$ l of each substance was given four times a day immediately after the inoculation or 1 day after the inoculation (after onset of corneal ulcer). In the Compound A - LFLX combination group, the 1.0 % Compound A eye drop formulation was instilled about 10 minutes after the instillation of the 0.3 %

LFLX eye drop formulation.

4) Observation of infectious symptoms

Each animal was examined for the corneal ulcer every 24 hours after the inoculation and scored in accordance with the rabbit corneal lesion scoring criteria (Barletta J.P. et al., Invest Ophthalmol Vis Sic 37:20-28, 1996) shown in Table 2.

Table 2

Rabbit corneal lesion scoring criteria

10 \* Corneal ulcer

0:No corneal ulcer

1:Ulcer of less than 1/4 of entire cornea

2:Ulcer of 1/4 or more and less than 1/2 of entire cornea

15 3:Ulcer of 1/2 or more and less than 3/4 of entire cornea

4:Ulcer of 3/4 or more of entire cornea

RESULTS AND DISCUSSION

20 1) Effects on pyocyanic corneal ulcer - effect of instillation started immediately after inoculation

The results of the instillation started immediately after the inoculation are shown in Fig. 8. The corneal ulcer was exacerbated gradually in the control group (physiological saline group) toward an

25



extensive corneal ulcer 5 days after the inoculation. On the contrary, the corneal ulcer formation was started to be inhibited 3 days after the inoculation in the Compound A group, with a statistically significant difference (Fig. 8).

2) Effects on pyocyanic corneal ulcer - effect of instillation started one day after inoculation

In the late Compound A group in which the instillation was started 1 day after the inoculation, the corneal ulcer formation was started to be inhibited 3 days after the inoculation. The LFLX group exhibited the change similar to that in the control group, with no inhibition of the corneal ulcer formation being noted (Fig. 9). In the Compound A - LFLX combination group, the corneal ulcer formation was started to be inhibited potently 3 days after the inoculation, with a statistically significant difference (Fig. 9).

Based on the results observed as described above, Compound A as an elastase inhibitor was proven to be effective against the corneal ulcer induced by bacterial infection. It was also proven that a combination of an elastase inhibitor with an antibacterial agent was more markedly effective against the corneal ulcer of a bacterial infection than each agent used alone.

## EXAMPLE 1

An aqueous eye drop formulation was prepared using the following composition.

5	Component	Quantity
	Compound A	0.1 g
	Sodium chloride	0.9 g
	Sodium acetate	0.1 g
	Benzalkonium chloride	0.005 g
10	Hydrochloric acid	As appropriate
	Sodium hydroxide	As appropriate
	Sterilized purified water	to 100 mL (pH 6.0)

In about 80 ml of purified water, Compound A, sodium chloride, sodium acetate and benzalkonium chloride were dissolved. The solution was adjusted at pH 6.0 using hydrochloric acid and sodium hydroxide. Sterilized purified water was added to make the entire volume 100 mL, whereby obtaining an aqueous eye drop formulation.

20

## EXAMPLE 2

An eye drop formulation as an aqueous suspension was prepared using the following composition.

25	Component	Quantity
	Compound A	1.0 g

	Sodium chloride	0.9 g
	Sodium acetate	0.1 g
	Polysorbate 80	0.2 g
	Benzalkonium chloride	0.005 g
5	Hydrochloric acid	As appropriate
	Sodium hydroxide	As appropriate
	Sterilized purified water	to 100 mL (pH 5.0)

In about 80 ml of purified water, sodium chloride, sodium acetate, polysorbate 80 and benzalkonium  
 10 chloride were dissolved. The solution was adjusted at pH 5.0 using hydrochloric acid and sodium hydroxide, and then Compound A was added and suspended uniformly using a homogenizer. Sterilized purified water was added to make the entire volume 100 mL, whereby  
 15 obtaining an eye drop formulation as an aqueous suspension.

### EXAMPLE 3

An eye drop formulation as an aqueous suspension  
 20 was prepared using the following composition.

	Component	Quantity
	Compound A	0.5 g
	Concentrated glycerin	2.6 g
	Sodium acetate	0.1 g
25	Hydroxypropylmethyl cellulose	0.2 g

	Methyl p-oxybenzoate	0.03 g
	Propyl p-oxybenzoate	0.02 g
	Hydrochloric acid	As appropriate
	Sodium hydroxide	As appropriate
5	Sterilized purified water	to 100 mL (pH 5.0)

About 80 ml of purified water was warmed and methyl p-oxybenzoate and propyl p-oxybenzoate were dissolved. In this solution, hydroxypropylmethyl cellulose was dispersed and then cooled to room  
 10 temperature for dissolution. To this solution, concentrated glycerin and sodium acetate were added, and then the pH was adjusted at 5.0 using hydrochloric acid and sodium hydroxide. To this solution, Compound A was added and suspended uniformly using a homogenizer.  
 15 Sterilized purified water was added to make the entire volume 100 mL, whereby obtaining an eye drop formulation as an aqueous suspension.

#### Example 4

20 The following composition was used to make an ophthalmic ointment

	Component	Quantity
	Compound A	2.0 g
	Liquid paraffin	2.0 g
25	White petrolatum	to 100 g

Liquid paraffin and white petrolatum were sterilized previously by heating. Subsequently, Compound A was mixed thoroughly with liquid paraffin, and then kneaded with the white petrolatum to obtain an ophthalmic ointment.

## EXAMPLE 5

An eye drop formulation as an aqueous suspension was prepared using the following composition.

10	Component	Quantity
	Compound A	1.0 g
	Sodium citrate	0.1 g
	Concentrated glycerin	1.2 g
	Methyl p-oxybenzoate	0.026 g
15	Propyl p-oxybenzoate	0.014 g
	Propylene glycol	1.0 g
	Polyvinyl pyrrolidone (K-25)	0.5 g
	Sodium alginate	0.2 g
	Hydrochloric acid	As appropriate
20	Sterilized purified water	to 100 mL (pH 5.0)

In about 80 ml of purified water, sodium citrate, concentrated glycerin, methyl p-oxybenzoate, propyl p-oxybenzoate, propylene glycol and polyvinyl pyrrolidone were dissolved. In this solution, Compound A was dissolved and the solution was filtered through a 0.22

µm membrane filter, adjusted at pH 5.0 with  
 hydrochloric acid, whereby precipitating a fine crystal  
 (2 to 3 µm) of Compound A. Sodium alginate was  
 dissolved, and purified water was added to make the  
 5 entire volume 100 mL, whereby obtaining an eye drop  
 formulation as an aqueous suspension.

After a storage for 4 weeks at 60°C, the eye drop  
 formulation as an aqueous suspension contained 101.7 %  
 of Compound A, and exhibited a satisfactory re-  
 10 dispersion performance without any aggregation.

#### EXAMPLE 6

An eye drop formulation as an aqueous suspension  
 was prepared using the following composition.

15	Component	Quantity
	Compound A	1.0 g
	Sodium citrate	0.1 g
	Concentrated glycerin	1.2 g
	Methyl p-oxybenzoate	0.026 g
20	Propyl p-oxybenzoate	0.014 g
	Propylene glycol	1.0 g
	Polyvinyl pyrrolidone (K-25)	0.5 g
	Sodium alginate	0.2 g
	Tyloxapol	0.1 g
25	Hydrochloric acid	As appropriate

Sterilized purified water to 100 mL (pH 5.0)

In about 80 ml of purified water, sodium citrate, concentrated glycerin, methyl p-oxybenzoate, propyl p-oxybenzoate, propylene glycol and polyvinyl pyrrolidone were dissolved. In this solution, Compound A was dissolved and the solution was filtered through a 0.22  $\mu$ m membrane filter, adjusted at pH 5.0 with hydrochloric acid, whereby precipitating a fine crystal (2 to 3  $\mu$ m) of Compound A. Sodium alginate and tyloxapol were dissolved, and purified water was added to make the entire volume 100 mL, whereby obtaining an eye drop formulation as an aqueous suspension.

After a storage for 2 weeks at 60°C, the eye drop formulation as an aqueous suspension contained 102.5 % of Compound A, and exhibited a satisfactory re-dispersion performance without any aggregation.

#### EXAMPLE 7

An eye drop formulation as an aqueous suspension was prepared using the following composition.

Component	Quantity
Compound A	1.0 g
Sodium citrate	0.1 g
Concentrated glycerin	1.2 g
Methyl p-oxybenzoate	0.026 g

	Propyl p-oxybenzoate	0.014 g
	Polyvinyl pyrrolidone (K-25)	0.5 g
	Sodium alginate	0.2 g
	Tyloxapol	0.1 g
5	Hydrochloric acid	As appropriate
	Sterilized purified water	to 100 mL (pH 5.0)

In about 80 ml of purified water, sodium citrate, concentrated glycerin, methyl p-oxybenzoate, propyl p-oxybenzoate and polyvinyl pyrrolidone were dissolved.

10 In this solution, Compound A was dissolved and the solution was filtered through a 0.22  $\mu$ m membrane filter, adjusted at pH 5.0 with hydrochloric acid, whereby precipitating a fine crystal (2 to 3  $\mu$ m) of Compound A. Sodium alginate and tyloxapol were dissolved, and

15 purified water was added to make the entire volume 100 mL, whereby obtaining an eye drop formulation as an aqueous suspension.

#### EXAMPLE 8

20 An eye drop formulation as an aqueous suspension was prepared using the following composition.

	Component	Quantity
	Compound A	1.0 g
25	Sodium citrate	0.1 g



	Concentrated glycerin	1.2 g
	Benzalkonium chloride	0.005 g
	Polyvinyl pyrrolidone (K-25)	0.5 g
	Sodium alginate	0.2 g
5	Tyloxapol	0.1 g
	Hydrochloric acid	As appropriate
	Sterilized purified water	to 100 mL (pH 5.0)

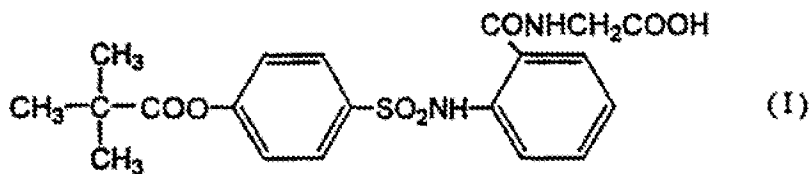
In about 80 ml of purified water, sodium citrate, concentrated glycerin and polyvinyl pyrrolidone were dissolved. In this solution, Compound A was dissolved and the solution was filtered through a 0.22  $\mu$ m membrane filter, adjusted at pH 5.0 with hydrochloric acid, whereby precipitating a fine crystal (2 to 3  $\mu$ m) of Compound A. Sodium alginate and tyloxapol were dissolved, and then benzalkonium chloride was dissolved. Purified water was added to make the entire volume 100 mL, whereby obtaining an eye drop formulation as an aqueous suspension.

## 20 INDUSTRIAL APPLICABILITY

According to the present invention, the pharmaceutical or a veterinary medicine which is effective in preventing or treating ophthalmic diseases, especially ophthalmic inflammatory diseases and corneal ulcer, can be provided.

What is claimed is:

1. A prophylactic and therapeutic medicament for ophthalmic diseases comprising as an active ingredient a compound represented by the formula (I):



or a pharmacologically acceptable salt or hydrate thereof.

2. The prophylactic and therapeutic medicament according to Claim 1, wherein the active ingredient is N-[o-(p-pivaloyloxybenzenesulfonylamino)benzoyl]glycine monosodium salt tetrahydrate.

3. The prophylactic and therapeutic medicament according to Claim 1 which is in a dosage form for local administration.

4. The prophylactic and therapeutic medicament according to Claim 3 which is an eye drop formulation.

5. The prophylactic and therapeutic medicament according to Claim 4 which is an eye drop formulation in the form of an aqueous suspension.

6. The prophylactic and therapeutic medicament according to Claim 3 which is an ophthalmic ointment.

7. The prophylactic and therapeutic medicament

according to Claim 1 which is in a prophylactic and therapeutic medicament for ophthalmic inflammatory diseases.

8. The prophylactic and therapeutic medicament according to Claim 7 which is in a prophylactic and therapeutic medicament for keratoconjunctival inflammatory diseases.

9. The prophylactic and therapeutic medicament according to Claim 1 which is in a prophylactic and therapeutic medicament for corneal ulcer.

10. The prophylactic and therapeutic medicament according to Claim 9 which is in a prophylactic and therapeutic medicament for infectious corneal ulcer.

11. The prophylactic and therapeutic medicament according to any one of Claims 1 to 10 which is used together with at least one of antibiotics, antibacterial agents, antiviral agents and antimycotic agents.

12. A method for preventing and treating ophthalmic diseases which comprises administering an effective amount of a compound represented by the formula (I) or a pharmacologically acceptable salt or hydrate thereof to a mammal in need of a treatment for such ophthalmic disease.

13. The method according to Claim 12, wherein N-

[o-(p-pivaloyloxybenzenesulfonylamino)benzoyl]glycine  
monosodium salt tetrahydrate is administered.

14. The method according to Claim 12, wherein the  
ophthalmic disease is an ophthalmic inflammatory  
5 disease.

15. The method according to Claim 14, wherein the  
ophthalmic inflammatory disease is a keratoconjunctival  
inflammatory disease.

16. The method according to Claim 12, wherein the  
10 ophthalmic disease is corneal ulcer.

17. The method according to Claim 16, wherein the  
corneal ulcer is an infectious corneal ulcer.

18. The method according to Claim 12, wherein at  
least one of antibiotics, antibacterial agents,  
15 antiviral agents and antimycotic agents is used  
together.

19. Use of a compound represented by the formula  
(I) or a pharmacologically acceptable salt or hydrate  
thereof in the manufacture of a prophylactic and  
20 therapeutic medicament for ophthalmic diseases.

20. Use according to Claim 19, wherein N-[o-(p-  
pivaloyloxybenzenesulfonylamino)benzoyl]glycine  
monosodium salt tetrahydrate is used.

21. Use according to Claim 19, wherein the  
25 ophthalmic disease is an ophthalmic inflammatory

disease.

22. Use according to Claim 21, wherein the ophthalmic inflammatory disease is a keratoconjunctival inflammatory disease.

5 23. Use according to Claim 19, wherein the ophthalmic disease is a corneal ulcer.

24. Use according to Claim 23, wherein the corneal ulcer is an infectious corneal ulcer.

10 25. Use according to Claim 19, wherein at least one of antibiotics, antibacterial agents, antiviral agents and antimycotic agents is used together.

26. An eye drop formulation in the form of an aqueous suspension of a compound represented by the formula (I) or a pharmacologically acceptable salt or hydrate thereof which is adjusted at pH 4 to 5.5 using at least one pH modifier.

27. The eye drop formulation in the form of an aqueous suspension according to Claim 26, wherein the pH modifier is hydrochloric acid or hydrochloric acid in combination with sodium hydroxide.

28. The eye drop formulation in the form of an aqueous suspension according to Claim 26 comprising a buffering agent, an isotonicity, a suspending agent and a dispersing agent.

25 29. The eye drop formulation in the form of an

aqueous suspension according to Claim 28, wherein the buffering agent is sodium citrate or sodium acetate.

30. The eye drop formulation in the form of an aqueous suspension according to Claim 28, wherein the isotonicity is concentrated glycerin and/or propylene glycol.

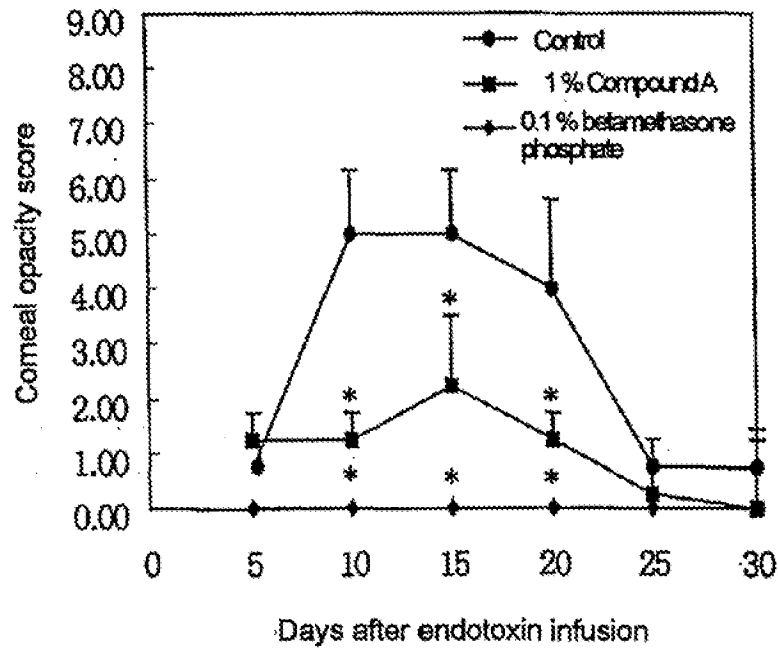
31. The eye drop formulation in the form of an aqueous suspension according to Claim 28, wherein the suspending agent is polyvinyl pyrrolidone.

10 32. An eye drop formulation in the form of an aqueous suspension according to Claim 28, wherein the dispersing agent is a surfactant and/or sodium alginate.

33. The eye drop formulation in the form of an aqueous suspension according to the above-mentioned Claim 15 32 wherein the surfactant is tyloxapol or polysorbate 80.

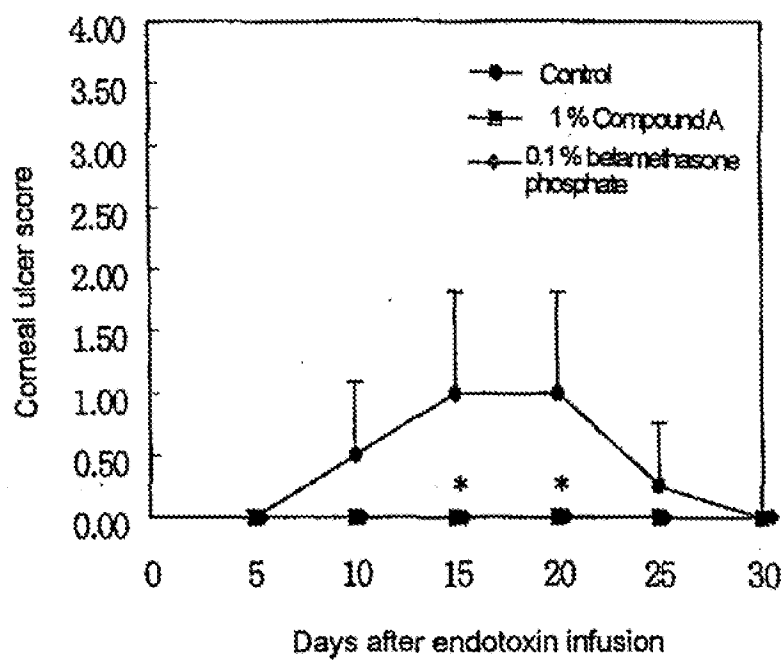
Fetherstonhaugh & Co.  
Ottawa, Canada  
Patent Agents

Fig. 1



2/9

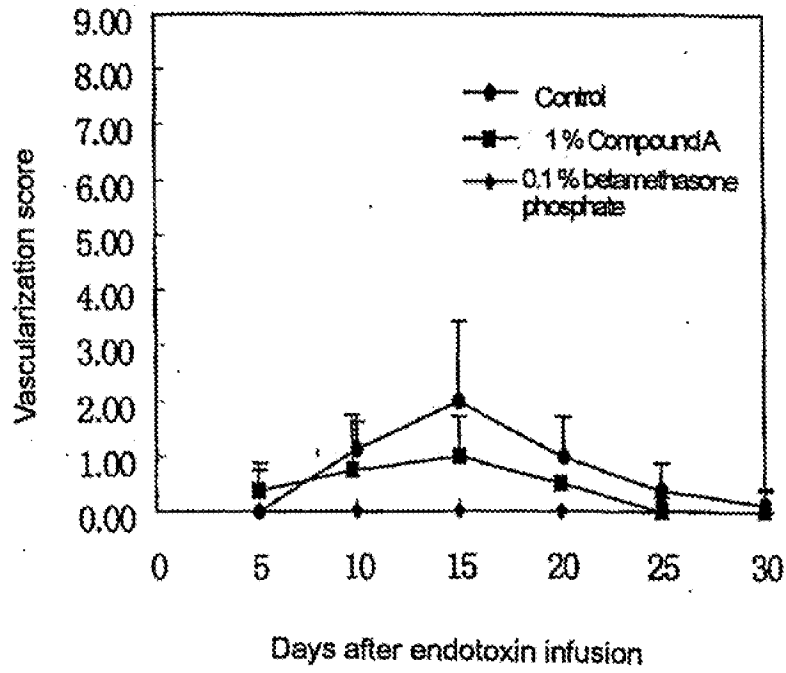
Fig. 2





3/9

Fig. 3



4/9

Fig. 4

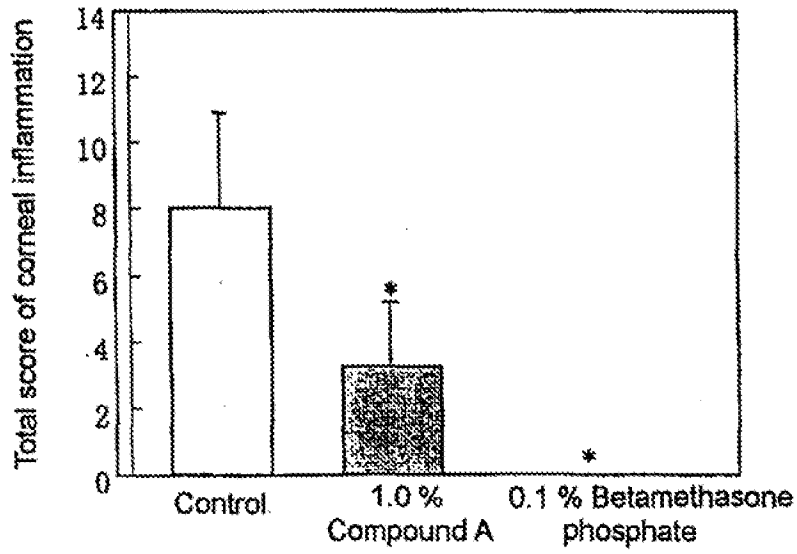


Fig. 5

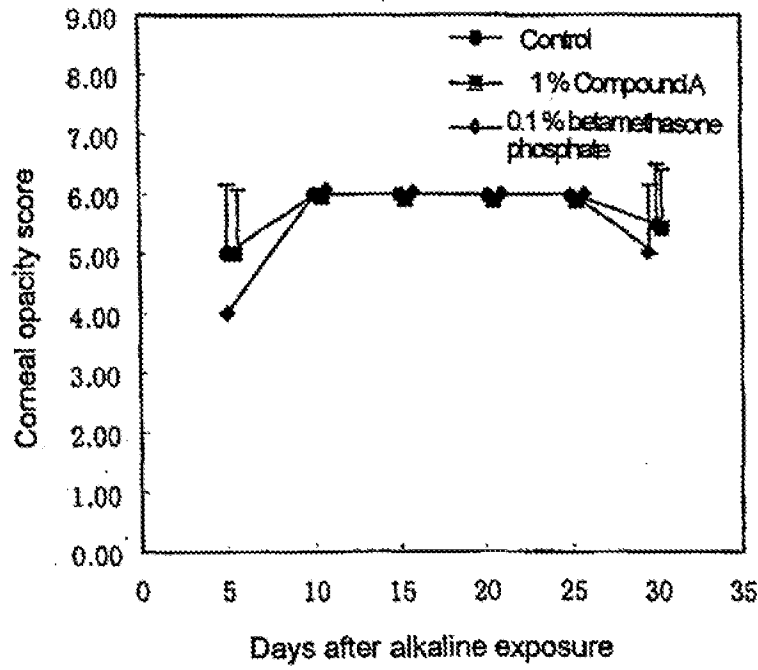
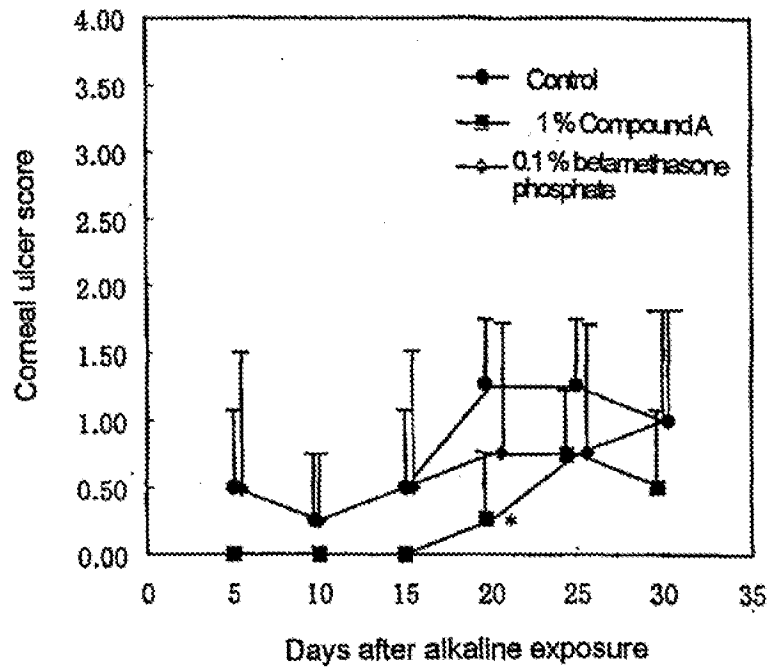


Fig. 6



7/9

Fig. 7

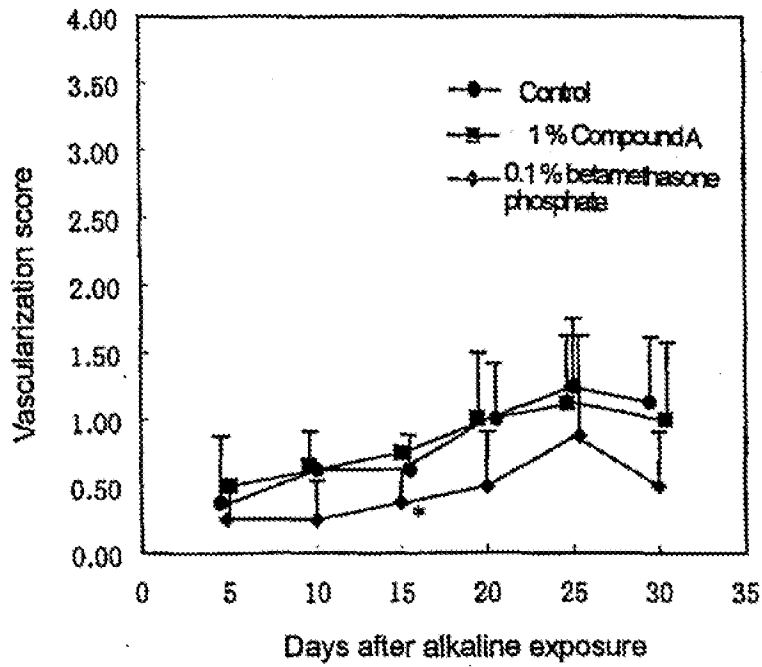


Fig. 8

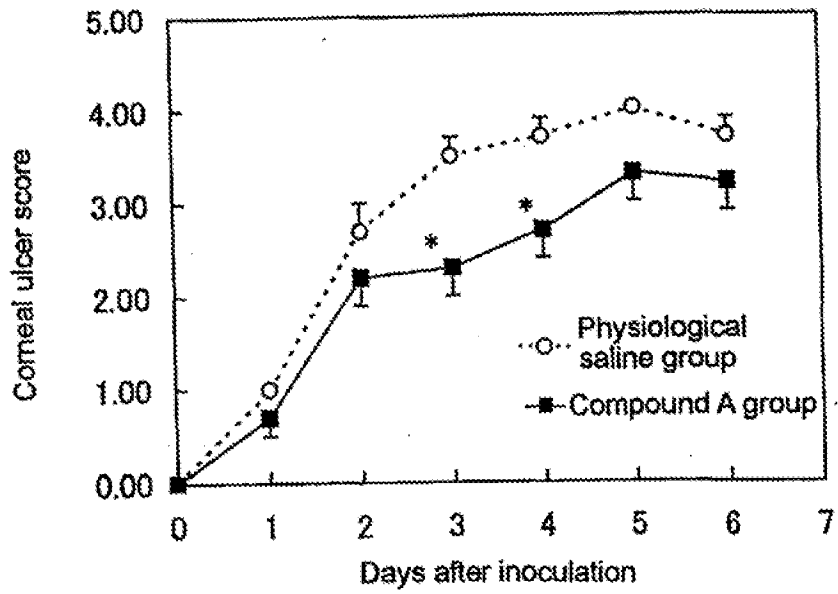
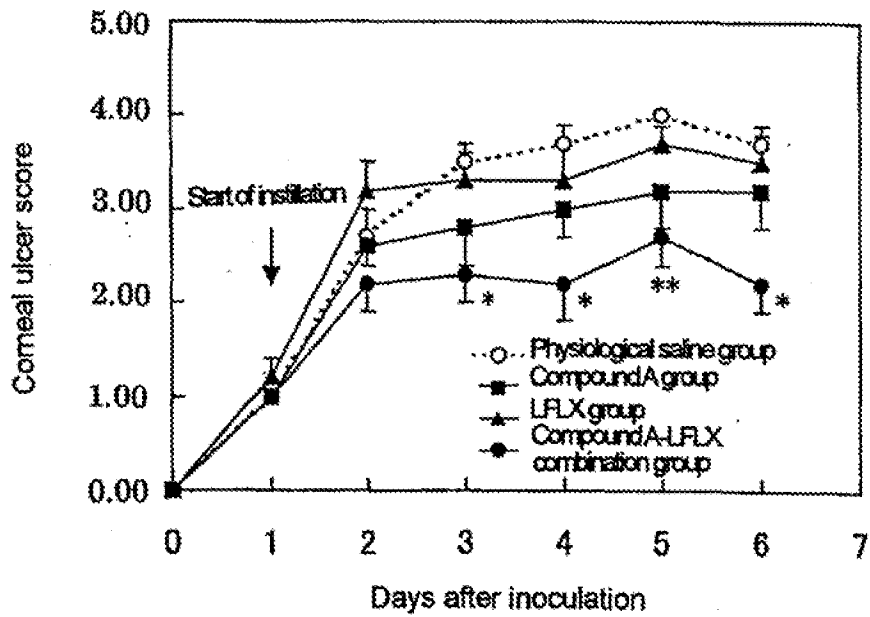


Fig. 9



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A. [US/US]; 5610 Hunterwood Lane, Arlington, TX 76017 (US). **GRAFF, Gustav** [US/US]; 6500 County Road 809, Cleburne, TX 76031 (US). **YANNI, John, M.** [US/US]; 2821 Donnybrook Drive, Burleson, TX 76028 (US).

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(74) Agents: **RYAN, Patrick, M.** et al.; R & D Counsel Q-148, 6201 South Freeway, Fort Worth, TX 76134-2099 (US).

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(71) Applicant (*for all designated States except US*): **ALCON UNIVERSAL LTD.** [CH/CH]; Bosch 59, P. O. Box 62, CH-6331 Hunenberg (CH).

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(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **KAPIN, Michael, A.** [US/US]; 3602 Silkwood Trail, Arlington, TX 76016 (US). **BINGAMAN, David, P.** [US/US]; 875 Kickapoo Falls Road, Lipan, TX 76462 (US). **GAMACHE, Daniel,**

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



WO 02/13804 A2

(54) Title: METHOD OF TREATING ANGIOGENESIS-RELATED DISORDERS

(57) Abstract: The use of 3-benzolphenylacetic acids and derivatives, including nepafenac, to treat angiogenesis-related disorders, including ophthalmic angiogenesis-related disorders such as diabetic retinopathy and exudative macular degeneration, is disclosed.



## METHOD OF TREATING ANGIOGENESIS-RELATED DISORDERS

FIELD OF THE INVENTION

5

This invention relates to the use of certain 3-benzoylphenylacetic acids and derivatives to treat or prevent angiogenic diseases.

BACKGROUND OF THE INVENTION

10

3-benzoylphenylacetic acid and certain of its derivatives are known to possess anti-inflammatory activity. U.S. Patent Nos. 4,254,146, 4,045,576, 4,126,635, and 4,503,073, and U.K. Patent Application Nos. 2,071,086A and 2,093,027A disclose various 3-benzoylphenylacetic acids, salts and esters, and hydrates thereof, having anti-inflammatory activity. U.S. Patent No. 4,568,695 discloses 2-amino-3-benzoylphenylethyl alcohols having anti-inflammatory activity. U.S. Patent No. 4,313,949 discloses 2-amino-3-benzoylphenylacetamides having anti-inflammatory activity.

20

Certain derivatives of 2-amino-3-benzoylbenzeneacetic acid (amfenac) and 2-amino-3-(4-chloro-benzoyl)benzeneacetic acid have also been evaluated by Walsh et al., J. Med Chem., 33:2296-2304 (1990), in an attempt to discover nonsteroidal anti-inflammatory prodrugs with minimal or no gastrointestinal side effects upon oral administration.

25

U.S. patent No. 4,683,242 teaches the transdermal administration of 2-amino-3-benzoylphenylacetic acids, salts, and esters, and hydrates and alcoholates thereof to control inflammation and alleviate pain.

30

U.S. Patent No. 4,910,225 teaches certain benzoylphenylacetic acids for local administration to control ophthalmic, nasal or otic inflammation. Only acetic acids are disclosed in the '225 patent; no esters or amides are

mentioned or taught as anti-inflammatory agents for local administration to the eyes, nose and ears.

U.S. Patent No. 5,475,034 discloses topically administrable compositions containing certain amide and ester derivatives of 3-benzoylphenylacetic acid, including nepafenac, useful for treating ophthalmic inflammatory disorders and ocular pain. According to the '035 patent at Col. 15, lines 35-39, "[s]uch disorders include, but are not limited to uveitis scleritis, episcleritis, keratitis, surgically-induced inflammation and endophthalmitis."

10

U.S. Patent No. 6,066,671 discloses the topical use of certain amide and ester derivatives of 3-benzoylphenylacetic acid, including nepafenac, for treating GLC1A glaucoma.

15

#### SUMMARY OF THE INVENTION

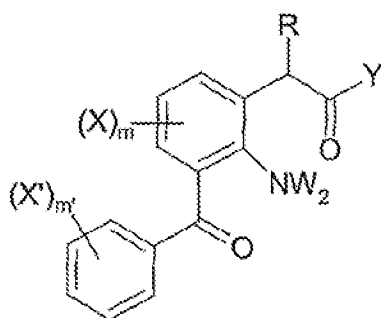
It has now been found that certain 3-benzoylphenylacetic acids and derivatives, including nepafenac (2-amino,3-benzoyl-phenylacetamide), are useful for the treatment of angiogenesis-related disorders.

20

#### DETAILED DESCRIPTION OF THE INVENTION

The 3-benzoylphenylacetic acids and derivatives useful in the methods of the present invention are those of formula (I) below.

25



(I)

R = H, C<sub>1-4</sub> (un)branched alkyl, CF<sub>3</sub>, SR<sup>4</sup>;

5 Y = OR', NR''R';

R' = H, C<sub>1-10</sub> (un)branched alkyl, (un)substituted (substitution as defined by X below), (un)substituted heterocycle (substitution as defined by X below),

-(CH<sub>2</sub>)<sub>n</sub>Z(CH<sub>2</sub>)<sub>n</sub>A;

n = 2-6;

10 n' = 1-6;

Z = nothing, O, C=O, OC(=O), C(=O)O, C(=O)NR<sup>3</sup>, NR<sup>3</sup>C(=O), S(O)<sub>n<sup>2</sup></sub>,  
CHOR<sup>3</sup>, NR<sup>3</sup>;

n<sup>2</sup> = 0-2;

15 R<sup>3</sup> = H, C<sub>1-6</sub> (un)branched alkyl, (un)substituted aryl (substitution as defined by X below), (un)substituted heterocycle (substitution as defined by X below);

A = H, OH, optionally (un)substituted aryl (substitution as defined by X below), (un)substituted heterocycle (substitution as defined by X below), -(CH<sub>2</sub>)<sub>n</sub>OR<sup>3</sup>;

R'' = H, OH, OR';

X and X' independently = H, F, Cl, Br, I, OR', CN, OH, S(O)<sub>n<sup>2</sup></sub>R<sup>4</sup>, CF<sub>3</sub>, R<sup>4</sup>, NO<sub>2</sub>;

20 R<sup>4</sup> = C<sub>1-6</sub> (un)branched alkyl;

m = 0-3;

m' = 0-5;

W = O, H.

25 As used herein, the acid (Y = OH) includes pharmaceutically acceptable salts as well.

Preferred compounds for use in the methods of the present invention are those of Formula I wherein:

- 5 R = H, C<sub>1-2</sub> alkyl;  
 Y = NR'R'';  
 R' = H, C<sub>1-6</sub> (un)branched alkyl,  $-(CH_2)_mZ(CH_2)_nA$ ;  
 Z = nothing, O, CHOR<sup>3</sup>, NR<sup>3</sup>;  
 R<sub>3</sub> = H;  
 10 A = H, OH, (un)substituted aryl (substitution as defined by X below);  
 X and X' independently = H, F, Cl, Br, CN, CF<sub>3</sub>, OR<sup>1</sup>, SR<sup>4</sup>, R<sup>4</sup>;  
 R'' = H;  
 R<sup>4</sup> = C<sub>1-4</sub> (un)branched alkyl;  
 m = 0-2;  
 15 m' = 0-2;  
 W = H;  
 n = 2-4;  
 n' = 0-3.

20 The most preferred compounds for use in the compositions or method of the present invention are 2-Amino-3-(4-fluorobenzoyl)-phenylacetamide; 2-Amino-3-benzoyl-phenylacetamide (nepafenac); and 2-Amino-3-(4-chlorobenzoyl)-phenylacetamide.

25 According to the present invention, a therapeutically effective amount of a compound of formula (I) is administered topically, locally or systemically to treat or prevent angiogenesis-related disorders. Such disorders include those that involve the proliferation of tumor cells, such as prostate cancer, lung cancer, breast cancer, bladder cancer, renal cancer, colon cancer, gastric  
 30 cancer, pancreatic cancer, ovarian cancer, melanoma, hepatoma, sarcoma and lymphoma. Ophthalmic angiogenesis-related disorders include, but are not limited to exudative macular degeneration; proliferative diabetic retinopathy; ischemic retinopathy (e.g., retinal vein or artery occlusion); retinopathy of

prematurity; neovascular glaucoma; iritis rubeosis; corneal neovascularization; cyclitis; sickle cell retinopathy; and pterygium. Certain disorders, such as sickle cell retinopathy and retinal vein or artery occlusion, can be characterized by both angiogenesis and neurodegenerative components. According to the present invention, a compound of formula (I) is administered to treat or prevent disorders characterized, at least in part, by angiogenesis.

The compounds of formula (I) can be administered in a variety of ways, including all forms of local delivery to the eye, such as subconjunctival injections or implants, intravitreal injections or implants, sub-Tenon's injections or implants, incorporation in surgical irrigating solutions, etc. Additionally, the compounds of formula (I) can be administered systemically, such as orally or intravenously. Suitable pharmaceutical vehicles or dosage forms for injectable compositions, implants, and systemic administration are known. The compounds of formula (I) and especially those wherein  $Y = NR'R''$ , however, are preferably administered topically to the eye and can be formulated into a variety of topically administrable ophthalmic compositions, such as solutions, suspensions, gels or ointment.

Pharmaceutical compositions comprising a compound of formula (I) in aqueous solution or suspension, optionally containing a preservative for multidose use and other conventionally employed ophthalmic adjuvants, can be topically administered to the eye. The most preferred form of delivery is by aqueous eye drops, but gels or ointments can also be used. Aqueous eye drops, gels and ointments can be formulated according to conventional technology and would include one or more excipients. For example, topically administrable compositions may contain tonicity-adjusting agents, such as mannitol or sodium chloride; preservatives such as chlorbutanol, benzalkonium chloride, polyquaternium-1, or chlorhexidine; buffering agents, such as phosphates, borates, carbonates and citrates; and thickening agents, such as high molecular weight carboxy vinyl polymers, including those known as carbomers, hydroxyethylcellulose, or polyvinyl alcohol.

The doses of the compounds of formula (I) used in the treatment or prevention of ophthalmic angiogenesis-related disorders will depend on the type of disorder to be prevented or treated, the age and body weight of the patient, and the form of preparation/route of administration. Compositions intended for topical ophthalmic administration will typically contain a compound of formula (I) in an amount of from about 0.001 to about 4.0% (w/v), preferably from about 0.01 to about 0.5% (w/v), with 1-2 drops once to several times a day. Likewise, representative doses for other forms of preparations are approximately 1 – 100 mg/day/adult for injections and approximately 10 – 1000 mg/adult for oral preparations, each administered once to several times a day.

Additional therapeutic agents may be added to supplement the compounds of formula (I).

The following examples are presented to illustrate various aspects of the present invention, but are not intended to limit the scope of the invention in any respect. The percentages are expressed on a weight/volume basis.

Example 1: The following formulations are representative of the topical compositions useful in the present invention.

#### Formulation 1

Compound of formula (I)	0.01 – 0.5%
Polysorbate 80	0.01%
Benzalkonium Chloride	0.01% + 10% excess
Disodium EDTA	0.1%
Monobasic Sodium Phosphate	0.03%
Dibasic Sodium Phosphate	0.1%
Sodium Chloride	q.s. 290-300 mOsm/Kg
pH adjustment with NaOH and/or HCl	pH 4.2 – 7.4
Water	q.s. 100%

## Formulation 2

	Compound of formula (I)	0.01 – 0.5%
	Hydroxypropyl Methylcellulose	0.5%
5	Polysorbate 80	0.01%
	Benzalkonium Chloride	0.01% + 5% excess
	Disodium EDTA	0.01%
	Dibasic Sodium Phosphate	0.2%
	Sodium Chloride	q.s. 290-300 mOsm/Kg
10	pH adjustment with NaOH and/or HCl	pH 4.2 – 7.4
	Water	q.s. 100%

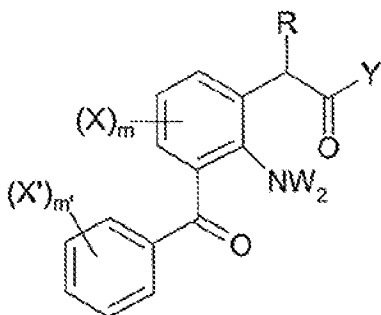
## Formulation 3

15	Nepafenac	0.1 + 6% excess
	Carbopol 974P	0.08%
	Tyloxapol	0.01%
	Glycerin	2.4%
	Disodium EDTA	0.01%
20	Benzalkonium Chloride	0.01%
	pH adjustment with NaOH and/or HCl	pH 7.5 ± 0.2
	Water	q.s. 100%

25 This invention has been described by reference to certain preferred embodiments; however, it should be understood that it may be embodied in other specific forms or variations thereof without departing from its special or essential characteristics. The embodiments described above are therefore considered to be illustrative in all respects and not restrictive, the scope of the invention being indicated by the appended claims rather than by the foregoing  
30 description.

We Claim:

1. A method of treating or preventing an angiogenesis-related disorder in a patient suffering from or predisposed to such a disorder which comprises administering to the patient a therapeutically effective amount of 3-benzoylphenylacetic acid or derivative of the formula:



wherein

- 10 R = H, C<sub>1-4</sub> (un)branched alkyl, CF<sub>3</sub>, SR<sup>4</sup>;  
 Y = OR', NR''R';  
 R' = H, C<sub>1-10</sub> (un)branched alkyl, (un)substituted (substitution as defined by X below), (un)substituted heterocycle (substitution as defined by X below),  
 -(CH<sub>2</sub>)<sub>n</sub>Z(CH<sub>2</sub>)<sub>n</sub>A;  
 15 n = 2-6;  
 n' = 1-6;  
 Z = nothing, O, C=O, OC(=O), C(=O)O, C(=O)NR<sup>3</sup>, NR<sup>3</sup>C(=O), S(O)<sub>n<sup>2</sup></sub>,  
 CHOR<sup>3</sup>, NR<sup>3</sup>;  
 n<sup>2</sup> = 0-2;  
 20 R<sup>3</sup> = H, C<sub>1-6</sub> (un)branched alkyl, (un)substituted aryl (substitution as defined by X below), (un)substituted heterocycle (substitution as defined by X below);  
 A = H, OH, optionally (un)substituted aryl (substitution as defined by X below), (un)substituted heterocycle (substitution as defined by X below), -(CH<sub>2</sub>)<sub>n</sub>OR<sup>3</sup>;  
 R'' = H, OH, OR';  
 25 X and X' independently = H, F, Cl, Br, I, OR', CN, OH, S(O)<sub>n<sup>2</sup></sub>R<sup>4</sup>, CF<sub>3</sub>, R<sup>4</sup>,  
 NO<sub>2</sub>;



$R^4 = C_{1-6}$  (un)branched alkyl;

$m = 0-3$ ;

$m' = 0-5$ ; and

$W = O, H$ .

5

2. The method of Claim 1 wherein

$R = H, C_{1-2}$  alkyl;

$Y = NR'R''$ ;

$R' = H, C_{1-6}$  (un)branched alkyl,  $-(CH_2)_m Z (CH_2)_{m'} A$ ;

10  $Z = \text{nothing}, O, CHOR^3, NR^3$ ;

$R_3 = H$ ;

$A = H, OH, (\text{un})\text{substituted aryl}$  (substitution as defined by X below);

X and X' independently = H, F, Cl, Br, CN,  $CF_3$ ,  $OR'$ ,  $SR^4$ ,  $R^4$ ;

$R'' = H$ ;

15  $R^4 = C_{1-4}$  (un)branched alkyl;

$m = 0-2$ ;

$m' = 0-2$ ;

$W = H$ ;

$n = 2-4$ ; and

20  $n' = 0-3$ .

3. The method of Claim 2 wherein the 3-benzoylphenylacetic acid or derivative is selected from the group consisting of 2-Amino-3-(4-fluorobenzoyl)-phenylacetamide; 2-Amino-3-benzoyl-phenylacetamide; and  
25 2-Amino-3-(4-chlorobenzoyl)-phenylacetamide.

4. The method of Claim 1 wherein the angiogenesis-related disorder is an ophthalmic angiogenesis-related disorder.

30 5. The method of Claim 4 wherein the 3-benzoylphenylacetic acid or derivative is topically administered to the eye.

6. The method of Claim 5 wherein the therapeutically effective amount of 3-benzoylphenylacetic acid or derivative is from about 0.001 to about 4.0% (w/v).

5 7. The method of Claim 4 wherein the angiogenesis-related disorder is selected from the group consisting of exudative macular degeneration; proliferative diabetic retinopathy; ischemic retinopathy; retinopathy of prematurity; neovascular glaucoma; iritis rubeosis; corneal neovascularization; cyclitis; sickle cell retinopathy; and pterygium.

10

8. The method of Claim 1 wherein the 3-benzoylphenylacetic acid or derivative is administered orally, intravenously, in a subconjunctival injection or implant, in a sub-Tenon's injection or implant, in an intravitreal injection or implant, or in a surgical irrigating solution.

15

9. The method of Claim 1 wherein the angiogenesis-related disorder is selected from the group consisting of prostate cancer; lung cancer; breast cancer; bladder cancer; renal cancer; colon cancer; gastric cancer; pancreatic cancer; ovarian cancer; melanoma; hepatoma; sarcoma; and lymphoma.

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④ Applicant: T.I.L. Medical Ltd.  
The Old Blue School Lower Square  
Isleworth Middlesex TW7 6RL(GB)

④ Inventor: Story, Michael John  
Elm Cottage Greaves Lane  
Threapwood Near Malpas Cheshire SY14  
6AS(GB)

Inventor: Flynn, Michael John  
Hunterscombe Dorking Road  
Leatherhead Surrey KT22 8JT(GB)

④ Representative: Sheard, Andrew Gregory et al  
Kilburn & Strode 30, John Street  
London WC1N 2DD(GB)

④ **Micelles containing a non-steroidal antiinflammatory compound.**

④ Non-steroidal anti-inflammatory drugs (NSAIDs) including diclofenac, flufenamic acid, flurbiprofen, ibuprofen, indomethacin, ketoprofen, naproxen, phenylbutazone, piroxicam and sulindac are administered in micelles to alleviate their adverse effects on the gastrointestinal tract. The drugs are formulated with surfactants such as polyethoxylated nonionics to give micelle-forming compositions.

EP 0 274 870 A2

Pharmaceutical Delivery Systems

This invention relates to pharmaceutical compositions for use in the treatment of inflammatory arthropathy.

Inflammatory arthropathy is the general name for a collection of debilitating and painful diseases which are extremely common in many countries of the world. Their classification is somewhat difficult, but inflammatory arthropathy or rheumatic disease seem to be the most common generic terms. In this specification, the term "inflammatory arthropathy" is used as the preferred generic term, but is to be understood to include forms of the disease known to some practitioners as rheumatic disease.

Of the various forms of inflammatory arthropathy, osteoarthritis (or osteoarthrosis) on the one hand and rheumatoid arthritis on the other hand are the commonest. Some workers in the field prefer the term osteoarthrosis to the term osteoarthritis, although it has been suggested that there is a place for both words. It has been suggested that osteoarthrosis is the most sensible way of labelling the presence of simple degenerative joint disease but osteoarthritis separates the acute episodes of an inflammatory nature which occur in degenerative joint disease.

Osteoarthrosis usually has an insidious onset of pain, stiffness and a reduced range of movement. It commonly effects one or only a small number of joints. Intermittent swelling due to an effusion or an inflammatory episode in the affected joint may appear and, later in the disease, a permanent increase in size or change of shape may result from bony enlargement. Joint laxity develops with locking and grating.

It is often the joints which have been used the most or previously effected by trauma or inflammatory processes that suffer greatest damage. Thus, the weight-bearing joints of the hips and knees, the lumbar spine and the thumb bases (first carpometacarpal joints) are common victims of the disease. The latter are particularly effected in those who have been manual workers or even keen knitters.

The essential features of rheumatoid arthritis are pain and swelling of several joints with morning stiffness continuing for at least a few weeks. Rheumatoid arthritis tends to affect the peripheral small joints symmetrically. Whereas the joints in osteoarthrosis may be described as dry, in rheumatoid arthritis they are "juicy", often swollen, hot, tender and red. There may also be accompanying systemic symptoms of a general malaise, weight loss, anorexia, mild fever and, on investigation, the finding of a normochromic (or hypochromic) normocytic anaemia.

Other common causes of inflammatory arthropathy include viral arthritis, ankylosing spondylitis, psoriatic arthropathy, Reiter's disease, gouty arthritis, septic arthritis (suppurative arthritis), erythema nodosum and Henoch-Schoenlein purpura. The most important in the present context are ankylosing spondylitis and gouty arthritis.

Ankylosing spondylitis is characterised by the gradual onset of low-back pain (sometimes bilateral buttock pain) with morning stiffness. Peripheral joints may become effected. There is a reduced range of spinal movement and chest expansion. Rigidity of the spine follows, often in a cranial direction (first lumbar, then dorsal then cervical) with a characteristic clinical picture of high dorsal kyphosis, obliteration of lumbar lordosis and flattening of the chest.

Gouty arthritis is due to the deposition of monosodium urate monohydrate crystals in the joint. Gouty arthritis is a very common disease: it is estimated that there are over 300,000 sufferers in the United Kingdom alone. The popularly held belief that gout is largely due to an over indulgence of port and pheasant is mainly fallacious, although provocative factors may often be related to its onset. Examples include trauma, surgery, unusual physical exercise, severe illness, dietary excess, alcohol and drugs. Any joint may be affected, and the onset may be polyarticular. Affected joints are painful, red, hot, swollen and exquisitely tender.

The treatment of inflammatory arthropathy has naturally received a fairly large amount of attention from pharmacologists and pharmaceutical manufacturers. A first class of drugs that have been used in the treatment of inflammatory arthropathy are steroids. Cortisol and its synthetic analogues have the capacity to prevent or suppress the development of the local heat, redness, swelling and tenderness by which inflammation is recognised. At the microscopic level they inhibit not only the early phenomena of the inflammatory process (oedema, fibrin deposition, capillary dilation, migration of leukocytes into the inflamed areas and phagocytic activity) but also the later manifestations (capillary proliferation, fibroblast proliferation, deposition of collagen and, still later, cicatrization).

In clinical terms, the administration of such corticosteroids for their anti-inflammatory effects is palliative therapy. The underlying cause of the disease remains: the inflammatory manifestations are merely suppressed. Nevertheless, they are effective in affording symptomatic relief, but prolonged administration of corticosteroids may be a very high price to pay for such relief: the adrenal cortex may become atrophied.

thereby limiting the body's own ability to survive and adapt in a constantly changing environment. The adrenal cortex is the organ of homeostasis: in the absence of the adrenal cortex, survival is possible, but only under the most rigidly prescribed conditions. In more general terms, it has long been recognised that corticosteroids are powerful drugs with slow cumulative toxic effects on many tissues, which may not be apparent until made manifest by a catastrophe.

In the treatment of inflammatory arthropathy, the focus of attention shifted from steroids to a structurally unrelated group of compounds known as slow acting anti-rheumatic drugs (SAARDs). SAARDs have empirically been categorised into three groups. Group I, including drugs of proven value which are widely used, encompasses azathioprine, chloroquine, D-penicillamine and gold salts. Group II relating to clinically active drugs under continuing investigation, includes cyclophosphamide, dapsone, levamisole, methotrexate, sulphasalazine, thiols and thymopoietin. The group III SAARDs are those of less practical or unproven treatment: this group includes methylprednisolone pulsing.

The range of SAARDs is considerable, as has been seen above, and despite much experimental work their modes of action are largely unknown. Logistical and toxicity factors prevent the use of SAARDs in all patients.

A third category of drugs for use in the treatment of inflammatory arthropathy consists of the non-steroidal anti-inflammatory drugs (NSAIDs). Aspirin is the prototype NSAID, and for this reason this group of drugs is also known as the "aspirin-like" drugs. This secondary nomenclature gives a key to a functional similarity of NSAIDs in the absence of any overall chemical similarity: they all appear to owe their anti-inflammatory action, at least in part, to the inhibition of prostaglandin synthesis. According to Goodman and Gilman in "The Pharmacological Basis of Therapeutics" MacMillan 7th Edition 1985, it has been established in recent years that:

1. All mammalian cell types studied (with the exception of the erythrocyte) have microsomal enzymes for the synthesis of prostaglandins;

2. Prostaglandins are always released when cells are damaged and have been detected in increased concentrations in inflammatory exudates - all available evidence indicates that cells do not store prostaglandins, and their release thus depends on biosynthesis de novo;

3. All aspirin-like drugs inhibit the biosynthesis and release of prostaglandins in all cells tested; and

4. With the exception of the anti-inflammatory glyccorticoids, other classes of drugs generally do not affect the biosynthesis of prostaglandins.

NSAIDs (or aspirin-like drugs - the two terms are used interchangeably in this specification) can be categorised conveniently into six structural groups. First, there are the salicylic acids and esters including aspirin, benorylate, aloxiprin, salsalate and choline magnesium trisalicylate.

Secondly, there are the propionic acid derivatives, including ibuprofen, naproxen, flurbiprofen, ketoprofen, fenoprofen, fenbuten, benoxaprofen and suprofen.

Thirdly, there is the class of oxicams, including piroxicam.

Fourthly, acetic acid derivatives can be split into two subclasses. Phenylacetic acids include diclofenac and fenclofenac; carbo- and heterocyclic acetic acids include indoles such as indomethacin and sulindac and pyrroles such as tolmetin.

Fifthly, there are the pyrazolones which include oxyphenbutazone, phenylbutazone, feprazone and azapropazone.

Sixthly, the fenamic acid derivatives include flufenamic acid and mefenamic acid.

NSAIDs have emerged as the drugs of choice in the treatment of inflammatory arthropathy. This is possibly more due to the disadvantages associated with other classes of drugs than in anything else. As indicated previously, the inflammatory diseases of the joints cause an extremely high level of discomfort and in many instances the results are crippling. The requirement for treatment is unquestioned and the treatment is in many cases chronic, that is to say it is continuous as the diseases are generally incurable. Unfortunately, the common element in the therapeutic properties of the NSAIDs is also the principle cause of side effects. As has been mentioned, the salicylates and other NSAIDs are thought to be effective in inflammatory joint disease, and their effectiveness is thought to be partly mediated through prostaglandin inhibition. Prostaglandins have been shown to have a protective effect on the gastrointestinal mucosa and, therefore, drugs which inhibit their activity are likely to cause gastrointestinal intolerance. Drugs with a potent inhibitory action on prostaglandin synthetase are marketed as having a potent anti-inflammatory action but have been shown to cause more faecal blood loss than those with weak anti-prostaglandin activity. Aspirin, for example, causes as much as an 8- to 10-fold increase in faecal blood loss and indomethacin a nearly 3-fold loss, compared with controls. However, when oral prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) at doses of 1mg three or four times daily is given with indomethacin or aspirin, the blood loss is reduced to control levels without reducing the effectiveness of the drugs.

Protection of the stomach from the drug has in some circumstances been shown to be effectively achieved by the use of enteric coating, as demonstrated by enteric coated aspirin preparations. However, the use of conventional enteric coating means that the drug is released in the neutral or slightly alkaline environment of the small or large intestine, which consequently experiences a considerably heightened local concentration from direct contact by the drug. Intestinal ulceration can occur with chronic administration of NSAIDs.

There is therefore a need for an improved and safer form of administration of NSAIDs to give protection both in the stomach and in the intestine. In addition, it would be advantageous to be able to provide a means of enhancing the absorption of the NSAIDs, which tend to be poorly water soluble, as well as providing an improved concentration of the drug at the cellular level at the site of its action. It is known that drugs with a low water solubility have a slow and variable dissolution pattern which can lead to reduced and erratic bioavailability. In short, what has been needed for some time is a delivery system for NSAIDs which protects the gastrointestinal tract from the drug, and which provides a means of alleviating the difficulties associated with very poor water solubility.

The present invention is based on the discovery that the use of micelles enables a particularly appropriate form of administration of NSAIDs to be achieved.

According to a first aspect of the present invention, there are provided micelles containing a non-steroidal anti-inflammatory drug.

Although NSAIDs themselves tend not to form micelles, amphipathic compounds, known more familiarly as surfactants, can form micelles. Surfactants have two distinct regions in their chemical structure, termed hydrophilic (water-liking) and hydrophobic (water-hating) regions. Micelles are aggregates in which the surfactant molecules are generally arranged in a spheroidal structure with the hydrophobic region at the core shielded, in an aqueous solution, from the water by a mantle of outer hydrophilic regions. According to a second aspect of the invention, therefore, there is provided a pharmaceutical composition comprising a non-steroidal anti-inflammatory drug and a surfactant, the composition being capable of forming micelles containing the non-steroidal anti-inflammatory drug when administered orally. It will generally be the case that the drug will be dissolved in the surfactant. In its simplest form, the pharmaceutical composition can be a solution of the drug in a surfactant, although other components may be present in the system if desired or necessary.

In a third aspect, the invention provides a process for the preparation of an anti-inflammatory composition capable of forming non-steroidal anti-inflammatory drug-containing micelles on oral administration to a human or non-human animal, the process comprising admixing a non-steroidal anti-inflammatory drug with a surfactant. The process may involve dissolving the drug in the surfactant.

According to a fourth aspect, the invention provides the use of a non-steroidal anti-inflammatory drug and a surfactant in the preparation of a composition for administering the drug in micellar form, insofar as the law allows, the invention also relates to a method for the treatment or prophylaxis of inflammatory arthropathy, the method comprising the administration of micelles containing a non-steroidal anti-inflammatory drug.

Micelles are to be contrasted in terms of their structure with vesicles and with liposomes. Vesicles are aggregates of amphipathic molecules arranged in a bilayer. Typically, a vesicle will have a hydrophilic interior and a hydrophilic exterior: hydrophilic regions of an internal layer of the molecules will be directed inwardly, and hydrophilic regions of an outer layer of the molecule will be directed outwardly. Hydrophobic regions of the two layers will be directed towards one another within the molecular wall of the vesicle.

Liposomes are nothing more than multilamellar vesicles, as is revealed by the fact that liposomes disintegrate to vesicles upon ultrasonication.

Surfactants can be variously classified, and often by reference to the nature of the hydrophilic region, which can be anionic, cationic, zwitterionic or non-ionic. In the present invention, nonionic surfactants are preferred. A particularly preferred subcategory of nonionic surfactants are polyoxyethylated surfactants, including polyoxyethylated glycol monoethers, polyoxyethylated fatty acids, polyoxyethylated sorbitan fatty esters, and polyoxyethylated castor oils. However, other nonionic surfactants are also particularly appropriate, including sorbitan fatty acid esters, poloxamers, polyethylene glycol fatty acid esters and polyethoxylated glyceryl fatty acid esters.

Whatever the precise chemical structure of the surfactant or surfactants used, it is generally preferred to use one or more of those that have been already cleared for human ingestion. Therefore, surfactants with a low toxicity are preferred. For example, surfactants having an LD<sub>50</sub> exceeding 10 g/kg and preferably 15 g/kg, are generally suitable. The absence of other side effects is of course also appropriate. Although surfactants which have already been approved for human ingestion are naturally preferred, the use of other

surfactants is not ruled out, not least because they may in time come to be approved for human ingestion.

The availability of nonionic surfactants is not perceived to be a cause of difficulty. For example, the following surfactants are known to be available.

5

Polyoxyethylene Alkylphenols POE(n) octylphenol n = 1-70  
 Triton X series (Rohm & Haas) Igepal CA series (GAF, USA) Antarox CA series (GAF, UK)  
 POE(n) nonylphenol n = 1.5-100  
 Triton N series (Rohm & Haas) Igepal CO series (GAF, USA) Antarox CO series (GAF, UK)

10

None of the polyoxyethylene alkylphenols are as yet approved for human ingestion.

15 Polyoxyethylated Glycol Monoethers POE(n) lauryl ether n = 4,23  
 Volpo L series (Croda)  
 Brij 30 series (Atlas ICI Specialties, UK)  
 POE(n) cetyl ether n = 2,10,20  
 Brij 50 series (Atlas ICI)  
 20 POE(n) stearyl ether n = 2,10,20  
 Brij 70 and 700 series (Atlas ICI)  
 POE(n) oleyl ether n = 2-20  
 Volpo N series (Croda)  
 Brij 90 series (Atlas ICI)  
 25 POE(n) ceto stearyl ether n = 3-20  
 Volpo CS series (Croda)

None of these have been approved for internal use, although Cetomacrogol 1000 (Brij 58, Volpo CS20)  
 30 has been extensively used in topical applications.

#### Polyoxyethylated Glyceryl Fatty Acid Esters

35 POE(n) glyceryl monolaurate n = 15,40 Glycerox L series (Croda)  
 These products have not been cleared for internal ingestion.

Polyoxyethylated Fatty Acids POE(n) monolaurate n = 4-100  
 40 Crodet L series (Croda)  
 POE(n) monooleate n = 4-100  
 Crodet O series (Croda)  
 POE(n) monostearate n = 4-100  
 Crodet S series (Croda)  
 45 Myrj series (Atlas ICI)

POE(8) monostearate and POE(40) monostearate appear to be approved for internal ingestion in the UK  
 and EEC, and the latter is also approved by the FDA in the US. The other POE(n) monostearates appear  
 50 valid contenders for approval, with the POE(n) monooleates and monolaurates also being likely candidates.

#### Sorbitan Fatty Acid Esters Sorbitan monolaurate

Crill 1 (Croda)  
 55 Span 20 (Atlas ICI)  
 Sorbitan monopalmitate  
 Crill 2 (Croda)  
 Span 40 (Atlas ICI)

Sorbitan monostearate  
 Crill 3 (Croda)  
 Span 60 (Atlas ICI)  
 Sorbitan tristearate  
 5 Crill 35 (Croda)  
 Span 65 (Atlas ICI)  
 Sorbitan monooleate  
 Crill 4 (Croda)  
 Span 80 (Atlas ICI)  
 10 Sorbitan sesquioleate  
 Crill 43 (Croda)  
 Sorbitan trioleate  
 Crill 45 (Croda)  
 Span 85 (Atlas ICI)  
 15 Sorbitan monoisostearate  
 Crill 6 (Croda)

20 The surfactants in this group have good approval rating in the UK, EEC and US, but not complete approval.

Polyoxyethylated Sorbitan Fatty Acid Esters POE(20) sorbitan monolaurate  
 Crillet 1 (Croda)  
 25 Tween 20 (Atlas ICI)  
 POE(4) sorbitan monolaurate  
 Crillet 11 (Croda)  
 Tween 21 (Atlas ICI)  
 POE(20) sorbitan monopalmitate  
 30 Crillet 2 (Croda)  
 Tween 40 (Atlas ICI)  
 POE(20) sorbitan monostearate  
 Crillet 3 (Croda)  
 Tween 60 (Atlas ICI)  
 35 POE(4) sorbitan monostearate  
 Crillet 31 (Croda)  
 Tween 61 (Atlas ICI)  
 POE(20) sorbitan tristearate  
 Crillet 35 (Croda)  
 40 Tween 65 (Atlas ICI)  
 POE(20) sorbitan monooleate  
 Crillet 4 (Croda)  
 Tween 80 (Atlas ICI)  
 POE(5) sorbitan monooleate  
 45 Crillet 41 (Croda)  
 Tween 81 (Atlas ICI)  
 POE(20) sorbitan trioleate  
 Crillet 45 (Croda)  
 Tween 85 (Atlas ICI)  
 50 POE(20) sorbitan monoisostearate  
 Crillet 6 (Croda)

55 These surfactants have a similar approval profile to the Sorbitan Fatty Acid Esters, above.



Polyoxyethylated Castor Oils POE(n) castor oil n = 10-100

Etocas Series (Croda)

Cremophor EL (BASF)

POE(n) hydrogenated castor oil n = 10-100

5 Croduret series (Croda)

Cremophor RH40 (BASF)

15 Cremophor EL and Cremophor RH40 are well established as orally ingestible surfactants. It is envisaged that there would be no problems in registering the Etocas or Croduret series provided BP Castor Oil was used in manufacture of the surfactant.

Polyoxamers POE(n)-POP(m)

15 Synperonic PE series (ICI Petrochem & Plastics Div) Pluronic series (Wyandotte Chem. Corp. USA)

Some of these have been used in orally ingested pharmaceuticals. They are of low toxicity.

20

Polyethylene Glycol Fatty Acid Esters PEG(400) distearate

Cithrol 4DS (Croda)

PEG(400) monolaurate

Cithrol 4ML (Croda)

25 PEG(n) monooleate n = 200,300,400

Cithrol MO series (Croda)

PEG(400) dioleate

Cithrol 4DO (Croda)

PEG(n) monostearate n = 400,600,1000

30 Cithrol MS series (Croda)

There are no toxicology data readily available for these surfactants.

35 One factor affecting the choice of surfactant or surfactants to be used is the hydrophilic-lipophilic balance (HLB), which gives a numerical indication of the relative affinity of the surfactant for aqueous and non aqueous systems. Surfactants having an HLB of about 10 or above, particularly about 12 or above, are preferred. However, there may be cases where a mixture of two or more surfactants provides an improved degree of solubilization over either surfactant used alone.

40 In addition to the HLB, the nature of the hydrophobic chain may be taken into account. For example, increasing the degree of unsaturation may improve the potential for solubilization, as may increasing the chain length and/or having branches. Further a reduction in the molecular weight may give improved solubilization on a weight for weight basis, even at the expense of a slight reduction in the HLB. It has been discovered that it is the provision of the solubilizing interior of the micelles which is important, and this may be related to the formation of a solution of the drug in the surfactant prior to the addition of the aqueous phase.

45 The physical nature of the surfactants will also be a factor to be taken into consideration when choosing surfactants for a particular formulation. The choice of surfactant will, among other things, depend on the type of formulation. For example, a formulation in the form of a solution may be in the form of a liquid, although a solid surfactant may be used in formulating a solution. Soft gelatin capsules may be formulated using a surfactant in the form of a liquid, a viscous liquid or melted waxy solid. Hard gelatin capsules may be formulated using a liquid, a paste (melted) or a solid (melted) surfactant. There follows below a list of potential nonionic surfactants, together with a description of their physical nature and an indication of their HLB and LD<sub>50</sub>.

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Chemical Identity	Description	HLB	LD50 g/kg
<u>Polyoxyethylated Glycol Monoethers</u>			
POE(4) lauryl ether	Water white liquid	9.5	9
POE(23) lauryl ether	Off-white soft solid	17.0	9
POE(2) cetyl ether	White solid	5.3	22
POE(15) cetostearyl ether	Off-white waxy solid	14.6	?
POE(20) cetostearyl ether	Off-white hard waxy solid	15.6	3.6
POE(15) oleyl ether	Pale straw paste	14.2	?
POE(20) oleyl ether	Pale straw soft solid	15.5	15.1
POE(2) stearyl ether	White solid	4.9	>25
POE(2) oleyl ether	Pale yellow liquid	4.9	25
<u>Polyoxyethylated Fatty Acids</u>			
POE(4) monolaurate	Pale straw liquid	9.3	?
POE(8) monolaurate	White soft solid	12.7	?
POE(12) monolaurate	White soft solid	14.5	?
POE(24) monolaurate	White waxy solid	16.8	?
POE(40) monolaurate	White hard solid	17.9	?
POE(100) monolaurate	White hard solid	19.1	?
POE(4) monooleate	Yellow/amber liquid	7.7	?
POE(8) monooleate	Yellow/amber liquid	10.4	?
POE(12) monooleate	Yellow/amber liquid	13.4	?
POE(24) monooleate	Yellow/amber paste/solid	15.8	?
POE(40) monooleate	Yellow soft solid	17.4	?

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Chemical Identity	Description	HLB	LD50 g/kg
POE(100) monooleate	Yellow waxy solid	18.8	?
POE(4) monostearate	White soft waxy solid	7.7	?
POE(8) monostearate	White waxy solid	11.1	64
POE(12) monostearate	White waxy solid	13.4	?
POE(20) monostearate	White waxy solid	15.0	10
POE(24) monostearate	White waxy solid	15.8	?
POE(30) monostearate	White hard solid	16.0	?
POE(40) monostearate	White hard solid	16.9	>30
POE(50) monostearate	White hard solid	17.9	>25
POE(100) monostearate	White hard solid	18.8	25
<u>Sorbitan Fatty Acid Esters</u>			
Sorbitan monolaurate	pale yellow viscous liquid	8.6	41
Sorbitan monopalmitate	pale tan waxy solid	6.7	>16
Sorbitan monostearate	pale tan waxy solid	4.7	31
Sorbitan tristearate	pale tan waxy solid	2.1	>16
Sorbitan monooleate	Amber viscous liquid	4.3	>40
Sorbitan sesquioleate	Amber viscous liquid	3.7	?
Sorbitan trioleate	Amber viscous liquid	1.8	>40
Sorbitan monoisostearate	Yellow viscous liquid	4.7	?

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Chemical Identity	Description	HLB	LD50 g/kg
<u>Polyoxyethylated Sorbitan Fatty Esters</u>			
POE(20) sorbitan monolaurate	Pale yellow liquid	16.7	>39
POE(4) sorbitan monolaurate	Yellow/amber liquid	13.3	>38
POE(20) sorbitan monopalmitate	Yellow pasty liquid	15.6	>38
POE(20) sorbitan monostearate	Yellow pasty liquid	14.9	>38
POE(4) sorbitan monostearate	Pale yellow waxy solid	9.6	>40
POE(20) sorbitan tristearate	Cream waxy solid	10.5	>40
POE(20) sorbitan monooleate	Yellow/amber liquid	15.0	>38
POE(5) sorbitan monooleate	Yellow/amber liquid	10.0	>37
POE(20) sorbitan trioleate	Yellow/amber liquid	11.0	>35
POE(20) sorbitan monoiscostearate	Yellow liquid	14.9	?
<u>Polyoxyethylated Castor Oils</u>			
POE(10) castor oil	Pale yellow liquid	6.3	?
POE(35) castor oil	Pale yellow liquid	12.5	>10
POE(40) castor oil	Pale yellow liquid	13.0	?
POE(60) castor oil	Pale yellow soft paste	14.7	?
POE(100) castor oil	Pale yellow waxy solid	16.5	?
POE(10) hydrogenated castor oil	Pale straw liquid	6.3	?
POE(30) hydrogenated castor oil	Pale straw liquid	11.6	?
POE(40) hydrogenated castor oil	White soft paste	13.0	?
POE(45) hydrogenated castor oil	White soft paste	14	>16

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Chemical Identity	Description	HLB	LD50 g/kg
POE(60)	hydrogenated castor oil	14.6	?
POE(100)	hydrogenated castor oil	16.4	?
<u>Poloxamers</u>			
POE(22) - POP (13)	Liquid (L35)	18.5	
POE(90) - POP (13)	Solid (F38)	30.5	
POE(7) - POP (17)	Liquid (L42)	8	
POE(20) - POP (17)	Liquid (L44)	16	
POE(4) - POP (23)	Liquid (L61)	3	
POE(10) - POP (23)	Liquid (L62)	7	
POE(27) - POP (23)	Liquid (L64)	7	
POE(159) - POP (23)	Solid (F68)	15	
POE(47) - POP (27)	Paste (P75)	16.5	
POE(6) - POP (30)	Liquid (L81)	2	
POE(51) - POP (30)	Paste (P85)	16	
POE(119) - POP (30)	Solid (F87)	24	
POE(205) - POP (30)	Solid (F88)	28	
POE(19) - POP (37)	Liquid (L92)	5.5	
POE(41) - POP (37)	Paste (P94)	13.5	
POE(8) - POP (43)	Liquid (L101)	1	
POE(32) - POP (43)	Paste (P103)	9	
POE(296) - POP (43)	Solid (F108)	27	
POE(10) - POP (53)	Liquid (L121)	0.5	
POE(193) - POP (53)	Solid (F127)	22	

Various non-steroidal anti-inflammatory drugs in common use today tend to have, as a common property, the property of being poorly soluble in water. The poor solubility does nothing to ameliorate the problems of their administration in conventional delivery systems, and the present invention provides a means of overcoming at least some of the difficulties associated with poor water solubility. Apart from anything else, particles of insoluble drug may tend to lie in folds of the intestinal mucosa, thereby giving rise to local irritancy.

There follows a brief discussion of each of the NSAIDs which are, in accordance with the present invention, particularly appropriate for being delivered in the form of micelles.

Diclofenac is sold as the free acid under the trade mark VOLTAROL by Geigy Pharmaceuticals. It is poorly soluble in water but soluble in some organic solvents. Gastrointestinal disturbances have been reported in about 7% of all cases. In general, it is fairly well absorbed, but more than 99% of the drug has been found to be bound to plasma proteins. The drug has been recommended for use in the treatment of rheumatoid arthritis and other rheumatic disorders at a dose of from 75 to 150 mg per day, depending upon the form of administration and its frequency. Diclofenac has been supplied as enteric coated tablets, slow release tablets, suppositories and in ampoules.

Flufenamic acid is sold under the trade mark MERALEN by Merrell Dow Pharmaceuticals. Its solubility is less than 1 part in 10,000 parts of water, although it is reasonably soluble in various organic solvents. Its most frequent adverse effects are gastrointestinal disturbances. The drug is well absorbed and is extensively bound to plasma proteins. It is prescribed for rheumatic disorders at doses of from 400 to 600 mg per day.

Flurbiprofen is sold under the trade mark FROBEN by the Boots Company plc. It is soluble in 100 to 1,000 parts of water only, but is readily soluble in most organic solvents. Gastrointestinal side effects have been reported in from 23 to 27% of cases. It is readily absorbed, approximately 99% of the drug being bound to plasma proteins. It is prescribed for rheumatoid arthritis and other rheumatic disorders and doses from 150 to 200 mg per day in a divided dose. The maximum dosage is stated to be 300 mg per day.

Another Boots Company drug is ibuprofen sold under the trade mark BRUFEN. Other trade marks in the UK for ibuprofen are FENBID and APSIFEN and in the US are RUFEN, ADVIL, MOTRIN and NUPRIN. It is poorly soluble in water: less than 1 part of drug will dissolve in 10,000 parts of water. However, it is fairly soluble in simple organic solvents. The most frequent adverse effects reported are, again, gastrointestinal. The drug is well absorbed and extensively bound to plasma proteins *in vivo*. It is prescribed for rheumatic arthritis and other musculoskeletal disorders, as well as acute gout. The dosage of the drug is from 600 to 1200 mg daily in divided doses, with 2,400 mg per day being the maximum.

Indomethacin is sold under the trade mark INDOCID by Thomas Morson Pharmaceuticals. It is also sold under the trade mark INBRILON in the UK and INDOCIN in the US. One part of drug is only soluble in more than 10,000 parts of water, but is more soluble in simple organic solvents. The most frequently reported adverse effects are gastrointestinal problems, headache and dizziness. The drug is readily absorbed, with more than 90% being bound to plasma proteins. It is prescribed for rheumatoid arthritis, ankylosing spondylitis, osteoarthritis and other rheumatic disorders, as well as acute gout. The recommended dosage is up to 150 to 200 mg daily in divided doses.

Ketoprofen is sold under the trade mark ORUDIS by May & Baker Limited, who also market controlled release pellets of the drug under the trade mark ORUVAIL. It is also sold in the UK under the trade mark ALRHEUMAT. Its solubility is less than 1 part in 10,000 parts of water, but it is freely soluble in various simple organic solvents. The most frequent side effects are gastrointestinal. The drug is readily absorbed and is extensively bound to plasma proteins. It is prescribed for rheumatoid arthritis and osteoarthritis at doses of from 50 to 100 mg twice daily.

Naproxen is sold under the trade mark NAPROSYN by Syntex Pharmaceuticals Limited. Naproxen sodium is sold as SYN-FLEX. The solubility of the free acid is less than 1 part in 10,000 parts water, but the drug is more soluble in simple organic solvents. The most frequent adverse effects reported are gastrointestinal. The drug is readily absorbed with more than 99% being bound to plasma proteins. Naproxen is prescribed for rheumatoid arthritis and other rheumatic or musculoskeletal disorders, dysmenorrhoea and acute gout. Its recommended dosage is from 500 to 1,000 mg daily in divided doses, with from 250 to 375 mg twice daily being preferred.

Phenylbutazone has been sold in the UK under the trade mark BUTAZOLIDIN by Geigy Pharmaceuticals; it is still available in the United States. Its solubility is less than 1 part in 10,000 parts of water, but it is more in common organic solvents. Its most adverse effects are nausea, vomiting and epigastric distress. It is readily absorbed, with 98% of the drug being bound to plasma proteins. It is generally only prescribed for the treatment of rheumatic disorders where other drugs have failed. The initial recommended

dosage ranges from 400 to 600 mg per day, but this should decrease to a maintenance dosage of from 200 to 300 mg per day. In both cases, the dosages should be divided through the day. The maximum daily dosage is 900 mg.

Piroxicam is marketed in the UK under the trade mark FELDENE by Pfizer Limited. It is known to be poorly soluble in water but soluble in some organic solvents. There is a high incidence of severe gastrointestinal side effects. The drug is well absorbed with 99% being bound to plasma proteins. It is prescribed for rheumatoid arthritis and other rheumatic disorders, as well as acute gout at dosages of from 10 to 30 mg per day, with 20 mg per day being preferred.

Sulindac is sold in the UK under the trade mark CLINORIL by Merck, Sharp & Dohme Limited. Its solubility is less than 1 part in 10,000 parts water, although it is slightly soluble in simple organic solvents. The most frequent side effects claimed of are gastrointestinal, headache and dizziness. It is incompletely absorbed from the gastrointestinal tract. It is prescribed for rheumatic and other musculoskeletal disorders at dosages of from 400 to 600 mg per day.

Specific paediatric preparations include:

Ibuprofen 200 ml x 100 mg/5 ml syrup;

Indomethacin 200 ml x 25 mg/5 ml suspension (UK, but not recommended in US for children under 14 years); and

Naproxen 500 ml x 25 mg/ml suspension.

Ketoprofen appears to be a possible further candidate for paediatric use.

Various surfactants and NSAIDs suitable for use in the present invention have now been described. However, the list is not to be taken as exhaustive. In addition, it should not be assumed that only these two ingredients have to be present as in some cases, including capsules, anti-oxidants will be required to ensure adequate stability. When preparing solutions, for example, for paediatric or geriatric use, additional excipients may be present such as preservatives, sweeteners and flavouring agents.

In certain cases it may be required to formulate an NSAID capsule which has sustained release properties. In such cases it is appropriate to include in the formulation ingredients which slow down the release of the surfactant NSAID combination from the total capsule mix. Such ingredients will generally be of a waxy nature, but this will not exclude the opportunity of using other techniques such as pellets with controlled release coatings.

The relative proportions of drug and surfactant used will, in the main, depend upon (a) the drug, (b) the surfactant and (c) the intended formulation, be it hard gelatin capsules, liquid solution or whatever. When preparing a micelle-forming drug:surfactant mix for use in capsules, it may be found appropriate to use the drug and surfactants in a weight ratio (drug:surfactant) of from 1:5.7 to 1:50, for example, from 1:8 to 1:20 or 1:25. When preparing solutions for, for example, paediatric or geriatric use, the drug:surfactant ratio may range from 1:8 to 1:30, with from 1:10 to 1:27.5 being preferred.

The following examples illustrate the invention.

#### EXAMPLE 1

##### Indomethacin Capsules - Size 2

Capsules of 25 mg active ingredient per capsule were prepared using the following proportions:

	<u>mg per capsule</u>
Indomethacin	25
POE(20) sorbitan monooleate (CRILLET 4)	310
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Total	335

The surfactant is heated to 50-60°C and the active ingredient is then added with stirring, the latter being sufficiently vigorous to ensure that the active ingredient dissolves completely in the surfactant.

When the mixture is homogeneous and it becomes a clear solution, it is stirred for at least a further 15 minutes before filling into capsules, the temperature being maintained at 50-60°C.

The filling of capsules requires equipment the same or similar to that used for filling Licaps of Capsugel. The capsule used in this example is the Licaps hard gelatin capsule, size 2. The capsule is filled to approximately 90% of its nominal capacity to ensure that there is no spillage, and the cap is sealed onto the body by the Licaps sealing process. This ensures no leakage of liquid contents, or of solid contents which may melt if raised to a moderately high temperature during transport, as well as providing security against tampering.

#### EXAMPLES 2 TO 11

The procedure of Example 1 was repeated except that 310 mg capsule of the surfactant indicated below was used.

In all cases the drug:surfactant weight ratio was 1:12.4.

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<u>Example No</u>	<u>Surfactant</u>
2	POE(20) sorbitan monoisostearate (CRILLET 6)
3	POE(40) monostearate (CRODET S24)
4	POE(24) monostearate (CRODET S40)
5	POE(40) monooleate (CRODET O40)
6	POE(20) cetostearyl ether (VOLPO CS20)
7	POE(15) cetostearyl ether (VOLPO CS15)
8	POE(20) oleyl ether (VOLPO N20)
9	POE(15) oleyl ether (VOLPO N15)
10	POE(40) hydrogenated castor oil (CREMOPHOR RH40)
11	POE(35) castor oil (ETOCAS 35)

#### EXAMPLE 12

##### Indomethacin Capsules - Size 1

Following the procedure of Example 1, but using Size 1 capsules, capsules of 25 mg active ingredient per capsule were prepared using the following proportions:

	<u>mg per capsule</u>
Indomethacin	25
POE(20) sorbitan monooleate (CRILLET 4)	425
Total	450



EXAMPLES 13 TO 23

The procedure of Example 12 was repeated except that 425 mg capsule of the surfactant indicated below was used. In all cases the drug:surfactant weight ratio was 1:17.

5

<u>Example No</u>	<u>Surfactant</u>
13	POE(20) sorbitan monoisostearate (CRILLET 6)
14	POE(40) monostearate (CRODET S40)
15	15 POE(24) monostearate (CRODET S24)
16	POE(40) monooleate (CRODET O40)
17	POE(20) cetostearyl ether (VOLPO CS20)
18	POE(15) cetostearyl ether (VOLPO CS15)
19	POE(20) oleyl ether (VOLPO N20)
20	POE(15) oleyl ether (VOLPO N15)
21	POE(45) hydrogenated castor oil (CRODURET 40 or CREMOPHOR RH40)
22	POE(35) castor oil (ETOCAS 35)
23	POE(15) glyceryl monolaurate (GLYCEROX L15)

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EXAMPLE 24

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Diclofenac Acid Capsules - Size 1

Capsules of 25 mg active ingredient per capsule are prepared, following generally the procedure of Example 1 but using Size 1 capsules, using the following proportions:

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	<u>mg per capsule</u>
Diclofenac acid	25
POE(15) cetostearyl ether (VOLPO CS15)	425
Total	<u>450</u>

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EXAMPLES 25 TO 27

The procedure of Example 24 was repeated except that 425 mg capsule of the surfactant shown below was used.

5

<u>Example No</u>	<u>Surfactant</u>
25	POE(20) oleyl ether (VOLPO N20)
26	POE(15) oleyl ether (VOLPO N15)
27	POE(24) monostearate (CRODET S24)

15

EXAMPLE 28Diclofenac Acid Capsules - Size 0

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Capsules of 25 mg active ingredient per capsule are prepared, following generally the procedure of Example 24 but using Size 0 capsules, using the following proportions:

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	<u>mg per capsule</u>
Diclofenac acid	25
POE(24) monostearate (CRODET S24)	585
Total	<u>610</u>

EXAMPLES 29 TO 35

The procedure of Example 28 was repeated except that 585 mg capsule of the surfactant shown below was used.

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	<u>Example No</u>	<u>Surfactant</u>
10	29	POE(40) monostearate (CRODET S40)
	30	POE(20) sorbitan monooleate (CRILLET 4)
15	31	POE(20) sorbitan monoisostearate (CRILLET 6)
	32	POE(40) hydrogenated castor oil (CRODURET 40 or CREMOPHOR RH40)
20	33	POE(35) castor oil (ETOCAS 35 or CREMOPHOR EL)
	34	POE(15) glyceryl monolaurate (GLYCEROX L15)
25	35	POE(20) cetostearyl ether (VOLPO CS20)

30 EXAMPLE 36Piroxicam capsules - Size 1

Following the general procedure of Example 1, except that Size 1 capsules were used, the following capsules were made up.

35

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	<u>mg per capsule</u>
45	Piroxicam 10
	POE(20) sorbitan monooleate (CRILLET 4) 440
50	Total <u>450</u>

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EXAMPLES 37 TO 44

The procedure of Example 36 was repeated, except that 440 mg. capsule of the surfactant shown below was used.

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<u>Example No</u>	<u>Surfactant</u>
10 37	POE(20) sorbitan monoisostearate (CRILLET 6)
38	POE(20) cetostearyl ether (VOLPO CS20)
15 39	POE(15) cetostearyl ether (VOLPO CS15)
40	POE(20) oleyl ether (VOLPO N20)
41	POE(15) oleyl ether (VOLPO N15)
20 42	POE(40) hydrogenated castor oil (CREMOPHOR RH40)
43	POE(35) castor oil (ETOCAS 35)
25 44	POE(15) glyceryl monolaurate (GLYCEROX L15)

EXAMPLE 45

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Ketoprofen Capsules - Size 1

Capsules of 50 mg active ingredient per capsule are prepared in Size 1 gelatin capsules following the general method of Example 1 and using the following proportions:

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	<u>mg per capsule</u>
45 Ketoprofen	50
POE(20) sorbitan monooleate (CRILLET 4)	400
50 Total	<hr/> 450

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EXAMPLES 46 TO 51

The procedure of Example 45 was repeated, except that 400 mg capsule of the surfactant shown below was used.

<u>Example No</u>	<u>Surfactant</u>
46	POE(20) sorbitan monoisostearate (CRILLET 6)
47	POE(40) monostearate (CRODET S40)
48	POE(24) monostearate (CRODET S24)
49	POE(45) hydrogenated castor oil (CRODURET 40)
50	POE(35) castor oil (ETOCAS 35 or CREMOPHOR EL)
51	POE(24) monolaurate (CRODET L24)

EXAMPLE 52Ketoprofen Capsules - Size 2

The procedure of Example 45 was repeated, except that Size 2 capsules were used and the ingredients were as follows:

	<u>mg per capsule</u>
Ketoprofen	50
POE(20) catostearyl ether (VOLPO CS20)	285
Total	<u>335</u>

EXAMPLES 53 TO 58

The procedure of Example 36 was repeated, except that 285 mg. capsule of the surfactant shown below was used:

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<u>Example No</u>	<u>Surfactant</u>
53	POE(15) cetostearyl ether (VOLPO CS15)
54	POE(20) oleyl ether (VOLPO N20)
55	POE(15) oleyl ether (VOLPO N15)
56	POE(40) glyceryl monolaurate (GLYCEROL L40)
57	POE(40) hydrogenated castor oil (CRODURET 40)
58	POE(35) castor oil (ETOCAS 35)

It should be noted that if Size 2 capsules formulate satisfactorily then it follows that Size 1 will too.

EXAMPLE 59Naproxen Capsules - Size 1

Capsules of 25 mg active ingredient per capsule are prepared in Size 1 gelatin capsules following the general method of Example 1 and using the following proportions:

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	<u>mg per capsule</u>
Naproxen	25
POE(15) cetostearyl ether (VOLPO CS15)	425
Total	<u>450</u>

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EXAMPLES 60 TO 62

The procedure of Example 59 was repeated, except that 425 mg. capsule of the surfactant shown below was used.

60 POE(20) cetostearyl ether (VOLPO CS20)

61 POE(15) oleyl ether (VOLPO N15)

62 POE(20) oleyl ether (VOLPO N20)

50

EXAMPLE 63

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Flufenamic Acid Capsules - Size 0

Capsules of 50 mg active ingredient per capsule are prepared in Size 0 gelatin capsules following the general method of Example 1 and using the following proportions:

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	<u>mg per capsule</u>
70 Flufenamic Acid	50
POE(24) monolaurate (CRODET L24)	560
15 Total	610

EXAMPLES 64 TO 73

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The procedure of Example 63 was repeated, except that 560 mg capsule of the surfactant shown below was used:

- 64 POE(24) monostearate (CRODET S24)
- 65 POE(40) monostearate (CRODET S40)
- 25 66 POE(20) sorbitan monooleate (CRILLET 4)
- 67 POE(20) sorbitan monoisostearate(CRILLET 6)
- 68 POE(4) hydrogenated castor oil (CREMOPHOR RH40)
- 69 POE(15) glyceryl monolaurate (GLYCEROX L15)
- 70 POE(15) cetostearyl ether (VOLPO CS15)
- 30 71 POE(20) cetostearyl ether (VOLPO CS20)
- 72 POE(15) oleyl ether (VOLPO N15)
- 73 POE(20) oleyl ether (VOLPO N20)

35

EXAMPLE 74Flufenamic Acid Capsules - Size 1

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Capsules of 50 mg active ingredient per capsule are prepared in Size 1 gelatin capsules following the general method of Example 1 and using the following proportions:

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	<u>mg per capsule</u>
Flufenamic Acid	50
50 POE(40) hydrogenated castor oil (CREMOPHOR RH40)	400
Total	450

55

EXAMPLES 75 TO 77

The procedure of Example 74 was repeated, except that 400 mg capsule of the surfactant shown below was used:

- 5  
 75 POE(15) cetostearyl ether (VOLPO CS15)  
 76 POE(20) cetostearyl ether (VOLPO CS20)  
 77 POE(15) oleyl ether (VOLPO N15)

EXAMPLE 78Ibuprofen Capsules - Size 0

15 Capsules of 50 mg active ingredient per capsule are prepared in Size 0 gelatin capsules following the general method of Example 1 and using the following proportions:

	<u>mg per capsule</u>
Ibuprofen	50
POE(24) monolaurate (CRODET L24)	560
	<hr/>
Total	610

EXAMPLES 79 TO 87

The procedure of Example 78 was repeated, except that 500 mg capsule of the surfactant shown below was used:

- 35  
 79 POE(24) monostearate (CRODET S24)  
 80 POE(20) sorbitan monooleate (CRILLET 4)  
 81 POE(20) sorbitan monoisostearate (CRILLET 6)  
 82 POE(40) hydrogenated castor oil (CREMOPHOR RH40)  
 83 POE(15) glyceryl monolaurate (GLYCEROX L15)  
 40 84 POE(15) cetostearyl ether (VOLPO CS15)  
 85 POE(20) cetostearyl ether (VOLPO CS20)  
 86 POE(15) oleyl ether (VOLPO N15)  
 87 POE(15) oleyl ether (VOLPO N20)

EXAMPLE 88



Ibuprofen Capsules - Size 1

Capsules of 50 mg active ingredient per capsule are prepared in Size 1 gelatin capsules following the general method of Example 1 and using the following proportions:

	<u>mg per capsule</u>
Ibuprofen	50
POE(24) monolaurate	400
	<hr/>
Total	450

EXAMPLES 88 TO 94

The procedure of Example 88 was repeated, except that 400 mg/capsule of the surfactant shown below was used:

- 88 POE(20) sorbitan monoisostearate (CRILLET 6)
- 90 POE(40) hydrogenated castor oil (CREMOPHOR RH40)
- 91 POE(15) cetostearyl ether (VOLPO CS15)
- 92 POE(20) cetostearyl ether (VOLPO CS20)
- 93 POE(15) oleyl ether (VOLPON15)
- 94 POE(20) oleyl ether (VOLPO N20)

EXAMPLE 95Indomethacin Solution

A solution of indomethacin for paediatric or geriatric use may be made according to the following proportions of principal ingredients, the potency being 25 mg per 5 ml, and the dispensed quantity 200 ml:

	<u>Quantity per 200 ml</u>
Indomethacin	1.00 g
Surfactant (POE(20) sorbitan monooleate)	20.0 g
Preservative (potassium sorbate)	0.40 g
Sweetener (sodium saccharin)	qs
Citric acid	qs
Flavouring	qs
Water, purified	to 200 ml

Approximately half the required water is placed in a suitable container, together with the potassium sorbate (or other suitable preservative), and the sodium saccharin (or other potent sweetener). The solution is stirred and heated continuously to 50-55°C. This forms the aqueous phase.

The surfactant (in this example POE (20) sorbitan monooleate eg CRILLET 4 or TWEEN 80) is heated to 50-55°C with continuous stirring in a separate suitable container. The indomethacin is then added and

stirring is continued until 15 minutes after all the active ingredient has dissolved, the temperature being maintained at 50-55°C. This comprises the non-aqueous phase.

The aqueous phase is then added to the non-aqueous phase with continuous stirring. The addition should be fairly rapid. A clear, slightly yellow solution is formed which is then stirred until cool, no further heating being applied after the start of the addition of the aqueous phase to the non-aqueous phase. The solution is then adjusted to give the correct potency by addition of purified water.

pH adjustment is by addition of citric acid until a pH of 3.0-3.5 is reached, the solution being continuously stirred and the citric acid being allowed to completely dissolve before a pH measurement is made. Flavouring is added according to requirements. The solution is then ready for bottling.

10

#### EXAMPLES 96 AND 97

Indomethacin solutions are prepared as in Example 95, except that 20g of the following surfactants were used:

15

96 POE(20) sorbitan monoisostearate (CRILLET 6)

97 POE(35) castor oil (CREMOPHOR EL)

20

#### EXAMPLE 98

##### Diclofenac Solution

A solution of diclofenac for paediatric or geriatric use may be made, following the general procedure of Example 95, according to the following proportions of principal ingredients, the potency being 25 mg per 5 ml, and the dispensed quantity 200 ml:

30

#### Quantity per 200ml

Diclofenac Acid	1.00 g
POE(40) hydrogenated castor oil (CREMOPHOR RH40)	27.5 g
Preservative (potassium sorbate)	0.40 g
Sweetener (sodium saccharin)	qs
Citric Acid	qs
Flavouring	qs
Water, purified	to 200 ml

45

#### EXAMPLE 99

A diclofenac solution is prepared as in Example 98, except that 27.5 g POE(35) castor oil (CREMOPHOR EL) is used.

50

#### EXAMPLE 100

##### Ketoprofen Solution

55

A solution of ketoprofen for paediatric or geriatric use may be made following the general procedure of Example 95, according to the following proportions of principal ingredients, the potency being 25 mg per 5 ml, and the dispensed quantity 200 ml:

	<u>Quantity per 200 ml</u>
5 Ketoprofen	1.00 g
Surfactant POE (20) sorbitan	
monoisostearate (CRILLET 6)	10.0 g
10 Preservative (potassium sorbate)	0.40 g
Sweetener (sodium saccharin)	qs
Citric acid	qs
15 Flavouring	qs
Water, purified	to 200 ml

EXAMPLE 101-103

20 A ketoprofen solution is prepared as in Example 100, except that 10g of the following surfactants were used:

25 101	POE(40) monostearate (CRODET S40)
102	POE(20) sorbitan monooleate (CRILLET 4 or TWEEN 80)
103	POE(40) hydrogenated castor oil (CREMOPHOR RH40)

EXAMPLE 104Flurbiprofen Capsules - Size 1

35 Capsules of 50mg active ingredient per capsule were prepared in Size 1 gelatin capsules following generally the procedure of Example-1 and using the following proportions:

	<u>mg per capsule</u>
45 Flurbiprofen	50
POE(40) hydrogenated castor oil	
(CRODURET 40)	400
50 Total:	450

55

EXAMPLES 105 TO 109

The procedure of Example 104 was repeated, except that 400mg capsule of the surfactant shown below was used.

5

	<u>Example No.</u>	<u>Surfactant</u>
10	105	POE(35) castor oil (ETOCAS 35)
	106	POE(20) cetostearyl ether (VOLPO CS20)
	107	POE(15) cetostearyl ether (VOLPO CS15)
15	108	POE(20) oleyl ether (VOLPO N20)
	109	POE(15) oleyl ether (VOLPO N15)

20 EXAMPLE 110Flurbiprofen Capsules - Size 0

Following the procedure of Example 104, but using Size 0 capsules, capsules of 50mg active ingredient per capsule were prepared using the following proportions:

25

30

35

40

45

50

55

mg per capsule

Flurbiprofen	50
POE(20) sorbitan monooleate (CRILLET 4)	560
	<hr/>
Total:	610

EXAMPLE 111 TO 121

The procedure of Example 110 was repeated, except that 560mg capsule of the surfactant shown below was used.

5

<u>Example No.</u>	<u>Surfactant</u>
111	POE(40) hydrogenated castor oil (CREMOPHOR RH40 or CRODURET 40)
112	POE(35) castor oil (ETOCAS 35 or CREMOPHOR EL)
113	POE(24) monolaurate (CRODET L24)
114	POE(24) monostearate (CRODET S24)
115	POE(20) sorbitan monoisostearate (CRILLET 6)
116	POE(60) hydrogenated castor oil (CREMOPHOR RH60)
117	POE(15) glyceryl monolaurate (GLYCEROX L15)
118	POE(15) cetostearyl ether (VOLPO CS15)
119	POE(20) cetostearyl ether (VOLPO CS20)
120	POE(15) oleyl ether (VOLPO N15)
121	POE(20) oleyl ether (VOLPO N20)

35

EXAMPLE 122Slow Release Indomethacin Capsules

40

Capsules of 75mg active ingredient per capsule were prepared using the following proportions:

	<u>mg per capsule</u>
Indomethacin	75
GELUCIRE 46/07	214
POE(24) monostearate [CRODET S24]	321
	<hr/>
Total:	610

50

GELUCIRE 46.07 (by Gattefosse) is a mixture of glycerol and PEG fatty acid esters, with melting point of 43-49°C, HLB of 7, and oral toxicity of LDO > 20g/kg.

55

The GELUCIRE 46.07 and the POE(24) monostearate were heated, melted and mixed together to 55-60°C and the indomethacin was then added with stirring, the latter being sufficiently vigorous to ensure that the active ingredient was dissolved completely in the mix. The mixture was then filled into hard gelatin

capsules, Size 0.

EXAMPLE 123

The procedure of Example 122 was repeated except that the following ingredients were used in the formulation:

	<u>mg per capsule</u>
Indomethacin	75
GELUCIRE 50/02	214
POE(24) monostearate [CRODET S24]	321
	<hr/>
Total:	610

GELUCIRE 50/02 (by Gattefosse) is a mixture of glycerol and PEG fatty acid esters, with melting point of 48-52°C, HLB of 2, and oral toxicity of LD50 > 18g/kg.

EXAMPLE 124

The procedure of Example 122 was repeated except that the following ingredients were used in this formulation:

	<u>mg per capsule</u>
Indomethacin	75
GELUCIRE 53/10	161
POE(24) monostearate [CRODET S24]	374
	<hr/>
Total:	610

GELUCIRE 53/10 (by Gattefosse) is a mixture of glycerol and fatty acid esters, with melting point of 51-56°C, HLB of 10, and oral toxicity of LD0 > 20g/kg.

EXAMPLE 125

The procedure of Example 122 was repeated except that the following ingredients were used in the formulation:

8

	<u>mg per capsule</u>
Indomethacin	75
GELUCIRE 53/10	214
POE(24) monostearate [CRODET S24]	321
	<hr/>
Total:	610

EXAMPLE 126

The procedure of Example 122 was repeated except that the following ingredients were used in the formulation:

25

	<u>mg per capsule</u>
Indomethacin	75
GELUCIRE 53/10	267
POE(24) monostearate [CRODET S24]	268
	<hr/>
Total:	610

EXAMPLE 127

The procedure of Example 122 was repeated except that the following ingredients were used in the formulation:

45

	<u>mg per capsule</u>
Indomethacin	75
GELUCIRE 53/10	321
POE(24) monostearate [CRODET S24]	214
	<hr/>
Total:	610

55

EXAMPLE 128

Capsules from Examples 122 to 127 were assessed for their dissolution rate using USP Apparatus No. 2 (USPXXI) with a paddle speed of 100 rpm, the dissolution medium being 0.2M phosphate buffer pH 7.2 maintained at 37°C.

Aliquots were taken at hourly intervals and the amount of indomethacin dissolved was determined by UV spectrophotometric absorption at 318nm. The results which are the average of three capsules are as follows:

Percentage of Indomethacin dissolved

Time(h)	Example 122	Example 123	Example 124	Example 125	Example 126	Example 127
1	36.0	26.1	31.2	26.4	25.9	19.0
2	59.3	42.6	44.2	37.7	37.4	27.5
3	78.0	54.1	55.2	46.8	44.9	33.7
4	84.5	64.0	66.0	55.1	51.5	39.0
5	90.2	71.9	75.7	63.1	57.5	44.1
6	94.0	78.6	85.1	70.1	63.4	48.7
7	97.0	84.0	91.4	76.4	69.6	52.9
8	98.7	88.6	95.7	81.9	74.7	57.2
9	99.7	90.6	97.7	86.0	79.2	61.8
10	100.0	92.3	98.9	89.8	83.2	66.2
11	100.0	92.8	98.8	92.4	86.3	70.2
12	100.0	92.8	98.4	93.8	88.3	73.6

**Claims**

1. Micelles containing a non-steroidal anti-inflammatory drug.
2. Micelles as claimed in claim 1, wherein the non-steroidal anti-inflammatory drug is diclofenac, flufenamic acid, flurbiprofen, ibuprofen, indomethacin, ketoprofen, naproxen, phenylbutazone, piroxicam and/or sulindac.
3. A pharmaceutical composition comprising a non-steroidal anti-inflammatory drug and a surfactant, the composition being capable of forming micelles containing the non-steroidal anti-inflammatory drug when administered orally.
4. A composition as claimed in claim 3, wherein the non-steroidal anti-inflammatory drug is diclofenac, flufenamic acid, flurbiprofen, ibuprofen, indomethacin, ketoprofen, naproxen, phenylbutazone, piroxicam and/or sulindac.
5. A composition as claimed in claim 3 or 4, wherein the surfactant is a nonionic surfactant.
6. A composition as claimed in claim 5, wherein the nonionic surfactant is a polyoxyethylated surfactant.
7. A composition as claimed in any one of claims 3 to 6, wherein the surfactant is a polyoxyethylated glycol monoether, a polyoxyethylated fatty acid, a polyoxyethylated sorbitan fatty ester or a polyoxyethylated castor oil.



8. A composition as claimed in any one of claims 3 to 7, wherein the surfactant has an HLB of 10 or above.

9. A composition as claimed in any one of claims 3 to 8, wherein the drug:surfactant weight ratio is in a range of from 1:5.7 to 1:50.

5 10. A process for the preparation of an anti-inflammatory composition capable of forming non-steroidal anti-inflammatory drug-containing micelles on oral administration to a human or non-human animal, the process comprising admixing a non-steroidal anti-inflammatory drug with a surfactant.

11. The use of a non-steroidal anti-inflammatory drug and a surfactant in the preparation of a composition for administering the drug in micellar form.

10

Claims for the following Contracting States: ES and GR

1. A process for the preparation of an anti-inflammatory composition capable of forming non-steroidal anti-inflammatory drug-containing micelles on oral administration to a human or non-human animal, the process comprising admixing a non-steroidal anti-inflammatory drug with a surfactant.

15

2. A process as claimed in claim 1, wherein the non-steroidal anti-inflammatory drug is diclofenac, flufenamic acid, flurbiprofen, ibuprofen, indomethacin, ketoprofen, naproxen, phenylbutazone, piroxicam and/or sulindac.

3. A process as claimed in claim 1 or 2, wherein the surfactant is a nonionic surfactant.

20

4. A process as claimed in claim 3, wherein the nonionic surfactant is a polyoxyethylated surfactant.

5. A process as claimed in any one of claims 1 to 4, wherein the surfactant is a polyoxyethylated glycol monoether, a polyoxyethylated fatty acid, a polyoxyethylated sorbitan fatty ester or a polyoxyethylated castor oil.

6. A process as claimed in any one of claims 1 to 5, wherein the surfactant has an HLB of 10 or above.

25

7. A process as claimed in any one of claims 1 to 6, wherein the drug:surfactant weight ratio is in a range of from 1:5.7 to 1:50.

8. The use of a non-steroidal anti-inflammatory drug and a surfactant in the preparation of a composition for administering the drug in micellar form.

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

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<p>(54) Title: SUBMICRON EMULSIONS AS OCULAR DRUG DELIVERY VEHICLES</p>		
<p>(57) Abstract</p> <p>An ocular drug delivery vehicle of an oil-in-water submicron emulsion comprising about 0.5 to 50 % of a first component of an oil, about 0.1 to 10 % of a second component of an emulsifier, about 0.05 to 5 % of a non-ionic surfactant and an aqueous component, with the mean droplet size being in the submicron range, i.e., below about 0.5 <math>\mu\text{m}</math> and preferably between about 0.1 and 0.3 <math>\mu\text{m}</math>. Also, topical pharmaceutical compositions containing a drug such as an anti-glaucoma drug, beta adrenergic blocker or other autonomic system drug, a local anesthetic, a steroid, a non-steroidal anti-inflammatory drug, an antibiotic drug, an anti-fungal drug, an antiviral drug or combinations thereof and the vehicle described above. Methods of administering such vehicles or compositions to the eye of a patient while reducing irritation thereof and providing increased bioavailability of the drug.</p>		

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- 1 -

**SUBMICRON EMULSIONS AS  
OCULAR DRUG DELIVERY VEHICLES**

5 **FIELD OF THE INVENTION**

The present invention relates to the field of drug delivery and, particularly, to the administration of various pharmaceutical agents to a patient through the eye by application of the innovative compositions of these agents in a non-irritating submicron  
10 emulsion.

**BACKGROUND OF THE PRESENT INVENTION**

The primary problem associated with topical applications of drugs to the eye is that the human eye  
15 is a very sensitive organ and any substance which is not compatible with it causes irritation and pain. This evokes blinking and reflex-tearing, which is a physiological reaction intended for removal of the irritating substance from the ocular surface.  
20 Irritation is a major cause of poor patient compliance with many ophthalmic drugs. This phenomenon is aggravated by the need to include relatively high concentrations of a drug in such ophthalmic compositions in order to obtain a therapeutic effect,  
25 since bioavailability of topically applied ophthalmic drugs is generally very poor. Thus, there is no doubt that a reduction in the irritating effect of a drug will enable increased ocular drug bioavailability, increased patient compliance with the drug, and  
30 enhanced therapeutic efficacy of the drug.

Currently, aqueous solutions are by far the most common vehicles for ophthalmic drugs. Such vehicles have a serious drawback, however, in that the ocular  
35 bioavailability of drugs administered thereby is generally very poor due to rapid drainage and tear turnover. See Fitzgerald et al. (1987) J. Pharm.

Pharmacol. 39:487-490. A typical dose of ophthalmic solution is in the range of about 50-100  $\mu$ l, which far exceeds the normal lachrymal volume of about 7-10  $\mu$ l. Thus, the portion of the dose that is not  
5 eliminated by spillage from the pulberal fissure is quickly drained. Furthermore, lachrymation and physiological tear turnover, which in humans is about 16% per minute under normal conditions, increases after the introduction of the solution, resulting in  
10 rapid dilution of the remaining amount of drug that has not been spilled or drained. As a consequence, the contact time with the absorbing surfaces of the eye (i.e., the cornea and sclera) of drugs which are applied to the eye via liquid aqueous compositions is  
15 less than about two minutes.

Another drawback of aqueous vehicles is that many drugs which may potentially be used in eye therapy are hydrophobic and their delivery into the eye by such aqueous vehicles is not possible. While such  
20 hydrophobic drugs may potentially be administered to the eye in conjunction with various organic solvents, the use of such solvents usually causes irritation and inflammatory reactions. See Harmia et al. (1987) Pharm. Acta Helv. 62:322-332.

25 Attempts have been made to develop various delivery vehicles in which the drug residence time in the eye is increased. The most direct approach for achieving this goal is by an increase in the viscosity of the vehicle. Thus, various viscous vehicles, such  
30 as hydrogels or ointments, have been attempted, some of which also enable delivery of hydrophobic drugs into the eye. Additionally, many attempts to use various non-conventional carriers, such as liposomes, micellar solutions and nanoparticles, as vehicles of  
35 ophthalmic drugs have also been made. While the use of such delivery systems may provide limited success in prolonging the residence time of drugs in the eye

and hence some enhancement of the ocular bio-availability, such carriers also produce various deleterious side effects. See Harmia et al., *supra.*, Saettone et al. (1988) *J. Pharm.* 43:67-70 and Meisner  
5 et al. (1989) *Int. J. Pharm.* 55:105-113.

Emulsions have also been suggested as vehicles for delivery of drugs to the eye in references such as EP 391,369, Ellis et al. (1987) *J. Ocular Pharmacol.* (U.S.) 3:121-128, and Shell (1984) *Surv. Ophthalmol.*  
10 29:177-178. Nevertheless, the practical inability to realize the potential of emulsion systems for ocular drug delivery stems predominantly from two problems. First, ocular drug formulations must be comfortable to the patient as well as safe, due to the sensitivity of  
15 the delicate eye tissues involved. Second, emulsions are generally metastable dispersions of immiscible fluids and these instability problems must be overcome.

An emulsion is a dispersion of oil in water  
20 ("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  $\mu\text{m}$  and is generally thermodynamically unstable. In comparison, a microemulsion is a translucent to  
25 transparent composition having a droplet size of 0.005 to 0.5  $\mu\text{m}$ , 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  
30 proportion of surfactants to oil required to generate microemulsions is generally much higher than in macroemulsions.

Emulsions developed specifically for ophthalmic use have attempted to solve the problem of inherent  
35 instability through the use of microemulsions or the addition of stabilizing polymers to classical emulsions. In several instances, specific drugs have

been formulated successfully in microemulsions. Examples of this approach include ophthalmic microemulsions of tepoxalin, as disclosed in EP 480,690, or flurbiprofen, as disclosed in  
5 EP 253,472.

An alternative approach to solve the problem of emulsion instability utilizes lightly crosslinked polymers, as exemplified by the autoclavable emulsions for ophthalmic use which are disclosed in EP 028,110.

10 In addition, the use of emulsions in ophthalmic preparations has been limited to a large extent by the inclusion of surfactants in the emulsions which surfactants are highly irritating to the eye. For example, the use of the emulsion preparations of  
15 EP 391,369 are limited considerably by the irritating effect of the ionic surfactants which are used in those emulsions. Thus, to date no commercially successful ophthalmic compositions in the form of oil-in-water emulsions are available.

20 The present invention solves the problem of emulsion instability without resorting to either of the prior art suggestions by instead converting classical emulsions to submicron emulsions with the input of energy by shear forces and homogenization to  
25 provide submicron emulsions possessing substantially reduced eye irritation properties. Also, the irritation of the eye is further reduced through the use of non-irritating non-ionic surfactants in such emulsions. Thus, when drugs are included with these  
30 submicron emulsions, the present invention provides ophthalmic compositions which are improved over those which are currently available in the art. In accordance with the present invention, effective means for reducing irritation of the eye, particularly such  
35 irritation which is drug-induced, is provided for the first time and thereby a long felt need has been fulfilled.

SUMMARY OF THE INVENTION

The present invention provides an ocular drug delivery vehicle of an oil-in-water submicron emulsion comprising about 0.5 to 50% of a first component of an oil, about 0.1 to 10% of a second component of an emulsifier, about 0.05 to 5% of a non-ionic surfactant and an aqueous component, with the mean droplet size being in the submicron range, i.e., below about 0.5  $\mu\text{m}$  and preferably between about 0.1 and 0.3  $\mu\text{m}$ .

10 The first component may be a medium chain triglyceride oil, a vegetable oil, a mineral oil or mixtures thereof, and is usually present in an amount of about 1 to 20%. For viscous compositions or creams, the oil may be present in an amount of about 15 30 to 50%.

The emulsifier is preferably a phospholipid compound or a mixture of phospholipids, such as lecithin, phosphatidylcholine, phosphatidyl-ethanolamine or mixtures thereof, and is preferably 20 present in an amount of about 0.2 to 1%.

The surfactant is preferably 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, and is preferably present 25 in an amount of about 0.2 to 1%.

This vehicle may be used to prepare topical ophthalmic compositions which include an effective amount of an ophthalmic drug. In these compositions, the drug can be an anti-glaucoma drug, such as a beta 30 adrenergic blocker or other autonomic system drugs, a local anesthetic, a steroid, a non-steroidal anti-inflammatory drug, an antibiotic drug, an antifungal drug, an antiviral drug or combinations thereof. Moreover, the drug may be hydrophilic or amphiphilic, 35 such as pilocarpine or timolol, or hydrophobic, such as indomethacin, betaxolol or adaprolol. The drug is typically present in an amount of about 0.05 to 5% by



weight depending upon the specific drug to be used. If desired, these compositions may also include a preservative, an antioxidant or an osmotic agent such as an osmotic pressure regulator.

5           The present invention also provides a method for reducing eye irritation which comprises topically administering to the eye the oil-in-water submicron emulsion described above. A particular aspect of this embodiment of the present invention is the combined  
10 topical administration to the eye of the submicron emulsion defined above and an effective amount of a drug, in order to reduce irritation which may otherwise be induced by the drug. This enables increased amounts of the drug to be administered  
15 without irritation.

#### BRIEF DESCRIPTION OF THE DRAWINGS

In the following detailed description of the invention, reference will be made to the annexed  
20 drawings, in which:

Fig. 1 shows the baseline intraocular pressure ("IOP") in eyes of rabbits and the IOP following administration of a pilocarpine containing emulsion which includes the non-ionic surfactant TYLOXAPOL;

25           Fig. 2 shows the IOP results from the contralateral eyes of the rabbits which received the pilocarpine emulsion as per Fig. 1;

Fig. 3 shows miosis in an eye of human subjects following treatment with a 2% pilocarpine emulsion  
30 composition compared to the same emulsion without pilocarpine;

Fig. 4 shows miosis in the contralateral eye of human subjects following treatment with a 2% pilocarpine emulsion composition compared to the same  
35 emulsion without pilocarpine, as per Fig. 3;

Fig. 5 shows the IOP in human subjects following administration of a 2% pilocarpine containing emulsion

versus baseline in both treated and contralateral eyes with a comparison to the administration of the same emulsion without pilocarpine; and

Fig. 6 shows the change in IOP versus baseline level in human subjects following administration of a 2% pilocarpine containing emulsion versus for both treated and contralateral eyes with a comparison to the administration of the same emulsion without pilocarpine.

10

#### DETAILED DESCRIPTION OF THE INVENTION

The present invention has for the first time achieved emulsions effective as a general drug delivery vehicle for ophthalmological use. The present invention provides stable pharmaceutical preparations which are oil-in-water emulsions having droplets or colloidal particles of a submicron size and utilizing surfactants that are non-ionic.

The ingredients in the composition of the present invention are preferably those which are compatible physiologically with the eye, i.e., those which do not cause irritation to the eye by themselves. The judicious optimization of such ingredients enables reduced irritation of commonly used ophthalmic drugs, while simultaneously providing enhanced bioavailability of certain drugs. In parallel, the intrinsic problems of instability of drug containing emulsions have been solved by providing the droplet size of the oil phase in the submicron range.

The term "submicron" is used herein to mean a size of about 0.05 to 0.5  $\mu\text{m}$ , and preferably about 0.1 to 0.3  $\mu\text{m}$ . Thus, a submicron emulsion having droplets of these sizes would be smaller than those of a classical macroemulsion, which has droplet sizes of above 0.5  $\mu\text{m}$ , but generally larger than those of a classical microemulsion, which, for practical purposes, has droplet sizes of less than 0.1  $\mu\text{m}$ .

These submicron emulsion can easily be sterilized by filtration, for example, in 0.45 $\mu$ m and/or 0.22 $\mu$ m filters, are more stable in long-term storage and can better withstand sterilization in an autoclave.

5 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  
10 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;

15 "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.

20 These colloidal particles have a soothing effect on the eye by a physiological mechanism which has not yet been elucidated. Owing to this soothing effect, the topical ophthalmic compositions of the invention having a certain drug concentration will have a  
25 smaller irritating effect than a prior art composition having the same drug concentration. This is surprisingly the case both with respect to hydrophilic and hydrophobic drugs. The surprising fact that the soothing and irritation reducing effect occurs also  
30 where the drug is hydrophilic, i.e. water soluble, shows that the reduced irritation does not result merely by containment of the drug in the colloid particles but rather by some other mechanism.

The present invention is useful for reducing  
35 drug-induced irritation of various anti-glaucoma drugs, such as beta-adrenergic blockers or other autonomic system drugs, anesthetics, steroids, non-

steroidal anti-inflammatory drugs, antibiotic drugs, anti-fungal drugs, antiviral drugs or combinations thereof. The term "effective amount" is used herein to denote an amount of a drug which is effective in exerting a pharmaceutical affect on the eye.

A number of exemplary drugs which are known to induce irritation were tested in accordance with the invention, and in all cases the drug-induced irritation was considerably reduced when the drugs were administered together with the above colloid particles. These drugs include the water soluble drugs timolol and pilocarpine. Pilocarpine, 3-ethylidihydro-4-[(1-methyl-1H-imidazole-5-yl)methyl]-2(3H)-furanon, is a drug which is soluble in water and sparingly soluble in oil, which is used in the treatment of glaucoma. Also, water insoluble drugs, such as indomethacin, betaxolol and adaprolol (adaprolol being an experimental soft beta blocker disclosed in U.S. Patent No. 4,289,080), can be used. Owing to the reduced irritability, compositions of the present invention may contain higher concentrations of drugs than prior art compositions.

The oily phase comprises an oil which 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 emulsions. 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 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  
5 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.

10 The amphiphilic phase comprises the emulsifiers and surfactants. Preferred emulsifiers include a phospholipid compound or a mixture of phospholipids. Suitable components include lecithin; EPICURON 120 (Lucas Meyer, Germany) which is a mixture of about 70%  
15 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  
20 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  
25 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 be non-ionic and one  
30 skilled in the art can conduct tests to routinely select specific surfactants which induce minimal (and preferably no) irritation of the eye. Generally, the surfactant is a non-ionic alkylene oxide condensate of an organic compound which contains one or more  
35 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; POLYSORBATE 80, and POLYSORBATE 20, as well as various compounds  
5 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). The TYLOXAPOL and TWEEN surfactants are preferred because they are  
10 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.

15 In addition, the compositions of the invention may also comprise conventional additives such as preservatives, osmotic agents or pressure regulators and antioxidants. Typical preservatives include Thimerosal, chlorbutanol, and methyl, ethyl, propyl or  
20 butyl parabens. Typical osmotic pressure regulators include glycerol and mannitol, with glycerol being preferred. The preferred oil phase antioxidant is  $\alpha$ -tocopherol or  $\alpha$ -tocopherol succinate. The aqueous phase may also include an antioxidant of a polyamine  
25 carboxylic acid such as ethylene diamino tetraacetic acid, or a pharmaceutically acceptable salt thereof.

If desired, the compositions of the present invention may also include additional drugs which are effective in decreasing the intraocular pressure of  
30 the eye. Such drugs may for example be  $\beta$ -adrenergic blockers, cannabinoids, cholinesterase inhibitors, sympathomimetic agents or carbonic anhydrase inhibitors.

In the following description, concentrations will  
35 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  
5 concentrations of the oil will generally require higher concentrations of the emulsifier and surfactant.

The emulsion used in the ophthalmic compositions of the present invention may comprise about 0.5 to 50%  
10 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  
15 obtain a non-viscous composition, the concentration of the non-aqueous phase should generally not exceed about 25%.

Preferred concentrations of the components are as follows: about 1 to 20% oil, most preferably about 1  
20 to 10% for a composition intended to be fluid, or about 30 to 50% for a viscous composition which may be useful as a cream or ointment; 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,  
25 with about 0.2 to 1% being particularly preferred.

The drug 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 drug is  
30 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 drug, but as close to neutral as possible for compatibility with the eye.

35 The present invention is also based on the surprising finding that the colloidal particles of the oil-in-water emulsions disclosed herein have a

soothing and irritation reducing effect on the eye. Thus, where a drug which otherwise causes an irritating effect on the eye is administered together with such colloidal particles, the irritation which would have otherwise occurred, is reduced considerably. The soothing effect of the composition of the present invention also occurs where an emulsion without a drug is administered to an already irritated eye. Thus, the submicron emulsions of the present invention are useful for reducing drug-induced irritation of a number of pharmaceuticals.

#### EXAMPLES

The present invention will now be illustrated with reference to several non-limiting embodiments described in the following examples, which utilize the following ingredients:

MCT oil: TCR - Societe Industrielle des Oleagineux, St. Laurent, Blangy, France.

LIPOID E-75 or E-80: Lipoid, Ludwigshafen, Germany.

$\alpha$ -tocopherol,  $\alpha$ -tocopherol succinate and glycerol: Sigma, St. Louis, MO, U.S.A., in conformity with U.S.P. specifications.

Pilocarpine base: Merck, Darmstadt, Germany, in conformity with U.S.P. and B.P.

EDTA: ethylene diamine tetraacetate disodium dihydrate).

Example 1: A blank oil-in-water type emulsion (without a drug) was prepared from the following ingredients:

MCT (medium chain triglyceride) oil	4.25%
LIPOID E-75	0.75%
TYLOXAPOL (a non-ionic surfactant)	1.0 %
$\alpha$ -tocopherol (an oil phase antioxidant)	0.02%
EDTA (an aqueous phase antioxidant)	0.1 %



Preservatives (antibacterial)		
	Chlorbutanol	0.2 %
	Thimerosal	0.01%
	Glycerol (an osmotic agent)	2.25%
5	Distilled water	balance to 100.00%

The emulsion was prepared as follows:

The aqueous and oily phases were separately prepared. The aqueous phase consisted of water, tyloxapol,  
 10 chlorbutanol, thimerosal and glycerol; and the oily phase consisted of the MCT oil, lecithin and  $\alpha$ -tocopherol. The pH of the aqueous phase was adjusted to pH 6.8 and the two phases were filtered (TE and BA filter types, Schleicher & Schull, Dassel, Germany, having a pore size of 0.22  $\mu$ m).  
 15 Next, the two phases were heated separately to over 50°C and then were combined and stirred with a magnetic stirrer to produce a coarse emulsion. The mixture was further heated to a temperature of 80-85°C. The coarse emulsion was further mixed by a high-shear mixer, POLYTRON (Kinematics,  
 20 Switzerland), for 3 minutes, and then was rapidly cooled to below 40°C. After cooling, the emulsion was homogenized by a 2-stage homogenizer (APV Montin Gaulin, Germany) at 8000 psi and then cooled again to storage (i.e., room) temperature. After adjusting the pH to 6.8-7, the emulsion  
 25 was filtered through a membrane filter (TE, Schleicher & Schull, having a pore size of 0.45  $\mu$ m) and transferred to plastic bottles that were sealed under nitrogen atmosphere. The emulsions were then sterilized either by a steam autoclave at 121°C or by a double stage membrane filtration,  
 30 through a 0.45  $\mu$ m filter followed by a 0.22  $\mu$ m filter (i.e., TE filters manufactured by Schleicher & Schull). The final preparation had an osmolarity of 298 mOsmol/l and an initial pH of 6.47.

### 35 Examples 2-5: Pilocarpine Compositions

This composition had the same constituents as the composition of Example 1 above, except with the addition of

1.7% pilocarpine base (2% as Pilo-HCl). In the preparation process, pilocarpine was added to the aqueous phase and the solutions were mixed at about 50°C due to the heat sensitivity of the drug. The resulting composition had an initial pH of 5 and an osmolarity of 278 mOsmol/l.

Three additional pilocarpine compositions were prepared as above except that they contained 1.5% TYLOXAPOL, 1% TWEEN-80 and 1% TWEEN-20, respectively.

10 Examples 6-8: Adaprolol Maleate Compositions

This composition had the following constituents:

	Adaprolol maleate	0.4 %
	MCT oil	4.25%
	LIPOID E-80	0.75%
15	TWEEN-80	1.0 %
	α-tocopherol	0.02%
	EDTA	0.1 %
	Glycerol	2.2 %
	Distilled water	balance to 100.00%

20

The composition was prepared in a similar manner to that described above in Example 1 except that adaprolol was added during preparation to the oil phase. The resultant composition had an initial pH of 6.5 and an osmolarity of 338 mOsmol/l.

25

Two additional adaprolol compositions were prepared as above except that they contained 1 TYLOXAPOL and 1% TWEEN-20, respectively.

30 Example 9: Betaxolol Composition

This composition had the following constituents:

	MCT oil	4.25%
	LIPOID E-80	0.75%
	TWEEN-80	0.5 %
35	α-tocopherol succinate	0.02%
	Betaxolol	0.5 %

Glycerol	2.2 %
Distilled water	balance to 100.00%

The manner of preparation was the same as that of  
 5 the adaprolol compositions of Examples 6-8 above.

Examples 10-11: Indomethacin Compositions

This composition had the following constituents:

	Indomethacin	0.4 %
10	MCT oil	17 %
	LIPOID E-80	3 %
	TWEEN-80	1 %
	$\alpha$ -tocopherol succinate	0.02%
	Methyl paraben	0.1 %
15	Propyl paraben	0.02%
	Glycerol	2.25%
	EDTA	0.1 %
	Distilled water	balance to 100.0 %

20 A second composition (Example 11) was made similar to that of Example 10, except that it contained 0.2% of indomethacin. The manner of preparation was the same as that of the adaprolol composition of Example 6 above. The initial pH of these compositions was about 5.

25

Examples 12-13: Ocular Irritation Tests

Acute irritative response and long term irritative response of animal eyes to various ophthalmic preparations were tested as follows:

30

Example 12: Acute Irritative Response Tests

The acute response was quantified using the guinea pig blinking test. In this test, the number of blinks during a 5 minute period was counted in 0.5 minute increments  
 35 following application of a 25  $\mu$ l drop of test solution. Each eye was first tested with normal saline (0.9% NaCl) and then with the test formulation, with at least a 30-minute

interval between the two tests. The number of blinks of both eyes of each animal was averaged and entered as a single value. Two parameters were calculated from the data thus obtained:

- 5        Maximal Blinking Ratio (MBR): The highest number of blinks, counted during an 0.5 minute period, following drug application, divided by the highest number of blinks, in an 0.5 minute period, following saline treatment.

$$\text{MBR} = \frac{\text{maximum blinks} - \text{drug}}{\text{maximum blinks} - \text{saline}}$$

- 10        MBR represents the maximal measured response to the drug and is thought to be equivalent to the burning or stinging response described by human subjects.

- 15        Blinking Index (BI): The number of blinks, counted during the entire 5 minute observation period, following drug treatment, divided by the number of blinks counted during the 5 minute period following saline treatment.

$$\text{BI} = \frac{\text{number of blinks} - \text{drug}}{\text{number of blinks} - \text{saline}}$$

- 20        BI incorporates both the maximal response and its duration and is thought to be indicative of the drug induced irritation. Results are shown in Table 1.

TABLE 1 Acute Irritative Response

25	Test compound	Aqueous solution		SME formulation	
		MBR	BI	MBR	BI
	Blank (saline)	-	1.0±0.3	-	0.7±0.4*
	Pilocarpine HCl 2% (Mi-Pilo Fischer)	-	2.1±0.7	1.1±0.7	1.4±0.5*
30	Adaprolol 0.4%	4.9±2.4	3.5±0.9	0.9±0.3*	1.6±0.4*
	Timolol Maleate 0.5% (Tiloptic)	3.7±2.5	2.2±0.7	1.8±0.7*	1.8±0.8
	Betaxolol 0.5% (Betoptic)	1.5±0.4	1.6±0.4	1.6±1.2	1.5±0.3

35        Means ± S.D. (n = 10 animals)

\* Submicron emulsion significantly differs from aqueous solution at P < 0.05.

Example 13: Long Term Irritative Response Tests

These effects were quantified in albino NZW rabbits by the Draize Test (c.f., Draize (1944) J. Pharmacol. Exp. Ther. 83:377-390) using slit-lamp biomicroscopy. The  
 5 irritative responses of the ocular surface, i.e., conjunctiva erythema (on a scale of 0-3), discharge (on a scale of 0-3), and corneal fluorescein staining (on a scale of 0-4), were graded following topical treatment using  
 10 standardized scales. The effects were studied during a 5 day period with 4 drops/day being administered. Assessment of irritation was done after 2, 6, 9, 13 and 18 drops. The scores obtained in each category (i.e., conjunctiva, cornea, etc.) were combined to form one irritative index, with the maximum score being 10. The results which were obtained are  
 15 shown in Table 2.

TABLE 2 Long Term Irritative Response

Treatment	Irritative index No. of treatment (drops)				
	2	6	9	13	18
Emulsion alone	1.0±0.8	0.2±0.2	0.4±0.3	0.2±0.2	0.9±0.5
Adaprolol 0.4% (aqueous sol.)	3.0±0.9	3.9±0.6	3.1±0.8	3.2±0.8	3.6±0.7
25 Adaprolol 0.4% Emulsion	1.5±1.0*	2.0±1.0	1.7±0.6*	1.8±0.7*	2.7±1.5*
Timoptic 0.5% Timolol Maleate	1.4±0.9	2.3±0.8	0.9±0.2	2.3±0.9	1.1±0.7
30 Timolol Maleate 0.5% Emulsion	0.6±0.4*	1.1±0.7*	1.0±1.0	1.4±1.2*	0.7±0.8*

Means ± S.D. n=12 eyes

\* Submicron emulsion formulations significantly differ at P < 0.05 from buffer/aqueous formulation

These results clearly show that drugs administered with  
 35 the microemulsion formulations of the present invention were much less irritating than drugs administered in standard formulations, whether the drug is hydrophilic such as

pilocarpine or timolol and whether the drug is hydrophobic such as betaxolol or adaprolol. It should be noted that surprisingly, this reduced irritation was observed even with preparations which did not contain any drug.

5

Examples 14-15: Increased Bioavailability

The bioavailability of compositions formulated in accordance with the invention was compared to that of aqueous ophthalmic drug formulations in two systems.

10

Example 14: Miotic Activity of Pilocarpine

Changes in pupil diameter were measured at 30 min intervals in 10 rabbits following treatment with one 50  $\mu$ l drop of different pilocarpine formulations.

15 The maximum Reduction in Pupil Diameter (max. RPD) and the Area Under the Curve (AUC) of the RPD/time curve were used to quantify the miotic activity. Results are shown below in Table 3.

Table 3

20

Formulation	max. RPD (mm)	AUC (mm x hr)
2% pilocarpine nitrate (Lab. H. Faure, France)	-1.7 $\pm$ 0.5	2.9 $\pm$ 1.2
25 2% pilocarpine HCl (Example 2)	-2.1 $\pm$ 0.6	4.3 $\pm$ 1.5

Mean  $\pm$  SD, n=10

30 The pilocarpine composition of Example 2 of the invention showed a significantly higher ( $P < 0.05$ ) miotic activity as compared commercially available pilocarpine formulation.

Example 15: Ocular Permeability of Indomethacin

35 Indomethacin is a synthetic non-steroid anti-inflammatory drug. It is practically insoluble in water and although soluble in alkaline solutions, it is unstable under these

conditions. Interest in the use of indomethacin in ophthalmology has fluctuated through the years. It is currently available as 1% suspension (INDOPTIC, Merck, Sharp & Dohme) used in conjunction with cataract surgery.

- 5 Anterior aqueous humor drug levels (Ca) of indomethacin were measured in albino rabbits, following topical treatment with 1 drop (50  $\mu$ l) of: a) INDOPTIC (1% suspension); b) 0.2% Indomethacin (Example 11); and c) 0.4% Indomethacin (Example 10). The results are presented below in Table 4.

10

Table 4  
Anterior Chamber Concentration ( $\mu$ M)

15 Time (hrs)	1% INDOPTIC Solution	0.2% Indomethacin (Example 11)	0.4% Indomethacin (Example 10)
0.5	2.2 $\pm$ 1.7 (7)	1.1 $\pm$ 0.1 (7)	1.4 $\pm$ 0.9 (5)
1	1.0 $\pm$ 0.5 (6)	0.9 $\pm$ 0.3 (7)	2.5 $\pm$ 0.9 (6)
3	0.6 $\pm$ 0.3 (6)	0.3 $\pm$ 0.1 (4)	1.1 $\pm$ 0.4 (6)

20 Mean  $\pm$  SD. Number of eyes in parenthesis.

Aqueous humor indomethacin levels in the INDOPTIC solution treated eyes were up to two-fold higher than those measured in the 0.2% indomethacin (Example 11) treated eyes. 25 This difference between these treatments was not statistically significant, and is smaller than the 5-fold difference between the concentration of indomethacin in the two formulations (0.2% vs. 1%). The 0.4% indomethacin (Example 10) treatment yielded Ca levels even higher than 30 the 1% INDOPTIC solution at 1 hr.

The area under the curve for 0.2% Indomethacin (Example 11) was 2.2 times larger than that of the 1% INDOPTIC solution despite the higher concentration of indomethacin in the latter. Maximum irritation following one drop, four 35 times a day for five days of 0.4% Indomethacin (Example 10) was significantly lower than INDOPTIC (0.4  $\pm$  0.1 vs.

1.1 ± 0.2, respectively, p<0.05). Thus, a higher bioavailability of the drug is obtained for the compositions of the invention while at the same time greatly reduced irritation is achieved.

5

Examples 16-17:

The physical and chemical stability of the compositions of the invention were tested on a range of formulations including various active drugs, surfactant types and concentrations, and other excipients such as preservatives and antioxidants.

Example 16: The pilocarpine composition of Example 2 was studied for 6 months at four different temperatures: 4°C, 15 28°C, 37°C and 45°C. There was no change in the drug content even at the higher test temperatures. It is worth noting that 6 months at 45°C is equivalent to 2-3 years at room temperature. The droplet size measured after 3 months at 45°C was 122 ± 30 nm, as compared to 102 ± 31 nm at the 20 time of production. Visual observations are made to assess color, creaming and oil separation, and these were found to be acceptable. The phospholipid oxidation was less than 0.3% measured by the tetrabarbituric acid method described in Liposome Technology, 2nd edition (1992) Gregoriadis, ed., 25 CRS Press Inc., Boca Raton, FL pp 501-527.

Example 17: The adaprolol compositions of Examples 6-8 were subjected to accelerated stability measurements after two months at 45°C. For each composition, the drug content 30 after two months dropped to 96% of the label content. There was no pronounced change in the droplet size which stayed at 120 ± 38 nm. In the composition of Example 7, the pH dropped from 6 to 5.4 which is reasonable under these conditions. Visual observations of the emulsion properties 35 were acceptable, and there was only minor phospholipid oxidation.



Example 18: A dose response following a single administration of the composition was carried out on adult male albino rabbits weighing about 3.0-3.5 kg. Two groups of rabbits were used for comparing the effect of pilocarpine administered in either a generic composition (comprising pilocarpine hydrochloride in aqueous buffer at about pH 5) or with the TYLOXOPOL emulsion of Example 2. The compositions were administered to the right eye of the rabbits following three days' measurement of baseline IOP which was performed in order to observe the health of the eye as well as to establish a baseline IOP for each animal.

The intraocular pressure in the eye was measured using a Langum pneumatic tonometer with a floating tip sensor. The sensor pressure was measured with a Sanborn recorder. The tonometer was standardized every day against a pressurized Silastic membrane. For IOP measurement, one drop of the local anesthetic Benoximate HCl (Fisher Laboratories, Israel) diluted three-fold in a sterile saline solution, was instilled into each eye.

In this study, the baseline IOP was measured on the day preceding the administration of pilocarpine at specific times: 8:00, 9:00, 11:00, 13:00, 15:00, 18:00 hours. The tested preparation was then applied to the right eye and the left eye was left untreated. IOP was then measured in the treated and the contralateral eyes, which measurements were taken on the same day and during the next day at the same time at which the baseline IOP curve was taken.

As can be seen in Fig. 1, a single dose of the TYLOXAPOL emulsion of Example 2 caused a decrease in IOP levels which persisted throughout the entire tested period. The maximal change in IOP reduction obtained by a single dose of this emulsion was 16% and was noted at 24 and 34 hours after administration.

The results from the contralateral eye are shown in Fig. 2, and as can be seen there was also some reduction in IOP, although less statistically significant ( $p > 0.05$ ). The maximal reducing effect did not exceed 1.9 mmHg (a

decrease of about 10%) which occurred at 31 and 34 hours after administration.

Example 19 A study on the clinical affects of the 2% pilocarpine emulsion of Example 2 was made. The study was performed on 20 young healthy volunteers, each receiving a single topical dose in the right eye of either the 2% pilocarpine microemulsion or of a placebo containing the microemulsion alone. The parameters that were measured in each case were IOP and a decrease of the pupil diameter (miosis).

Miosis was observed in the treated eyes upon addition of the drug although measurements were made only 1 hr following administration. The results, presented in Fig. 3 show that the pilocarpine effect is dramatic both as compared to the placebo application and to the effect in the contralateral eye. As can be seen, the diameter of the pupil prior to administration which was measured to be about 3.5 mm (standard error of mean (SE) = 0.2, n = 38), decreased within 1 hr to about 1.3 mm (SE = 0.1, n = 10). After about 12 hrs the normal size of the pupil was regained. This data is presented as the change in IOP vs. time in Fig. 4.

Intraocular pressure was measured after 1 hr in all 40 eyes (of the 20 volunteers). As can be seen in Figs. 5 and 6, the IOP decreased from 12.1 mmHg (SE = 0.4, n = 20) prior to administration of the drug, to 8.2 (SE = 0.6, n = 10) 1 hr after administration and to 7.4 (SE = 0.5, n = 10) after 6 hrs. IOP was maintained at about 8.3 mmHg (SE = 0.6) for up to 12 hrs. The IOP returned to normal level after about 24 hrs.

As can further be seen in Figs. 5 and 6, the IOP dropped also in the untreated (left eye) which likely occurs as a result of a systemic reaction. As a control, the emulsion of Example 1 was administered in a similar manner, and no significant change in IOP was measured.

THE CLAIMS

What is claimed is:

1. An ocular drug delivery vehicle of an oil-in-water submicron emulsion comprising about 0.5 to 50% of a first component of an oil, about 0.1 to 10% of a second component of an emulsifier, about 0.05 to 5% of a non-ionic surfactant and an aqueous component, said submicron emulsion having a mean droplet size in the range of 0.05 to 0.5  $\mu\text{m}$ .
2. The vehicle of claim 1 wherein the mean droplet size is between about 0.1 and 0.3  $\mu\text{m}$ .
3. The vehicle of claim 1 wherein the first component is a medium chain triglyceride oil, a vegetable oil, a mineral oil or mixtures thereof.
4. The vehicle of claim 3 wherein the first component is present in an amount of about 1 to 20%.
5. The vehicle of claim 3 wherein the first component is present in an amount of about 30 to 50% to form a viscous composition.
6. The vehicle of claim 1 wherein the emulsifier is a phospholipid compound or a mixture of phospholipids.
7. The vehicle of claim 6 wherein the phospholipid is lecithin, phosphatidylcholine, phosphatidylethanolamine or mixtures thereof.
8. The vehicle of claim 7 wherein the emulsifier is present in an amount of about 0.2 to 5%.
9. The vehicle of claim 1 wherein the surfactant is a non-ionic alkylene oxide condensate of an organic compound which contains one or more hydroxyl groups.
10. The vehicle of claim 9 wherein the surfactant is an ethoxylated alcohol or ester compound.
11. The vehicle of claim 10 wherein the non-ionic surfactant is present in an amount of about 0.2 to 5%.
12. The vehicle of claim 1 wherein the first component is present in an amount of about 1 to 20%, and the second component and the non-ionic surfactant are each present in an amount of about 0.2 to 1%.

13. A topical ophthalmic composition comprising an effective amount of an ophthalmic drug and the ocular drug delivery vehicle of claim 1.

14. The composition of claim 13 wherein the drug is an  
5 anti-glaucoma drug, beta adrenergic blocker or other autonomic system drug, a local anesthetic, a steroid, a non-steroidal anti-inflammatory drug, an antibiotic drug, an antifungal drug, an antiviral drug or combinations thereof.

15. The composition of claim 13 wherein the drug is  
10 hydrophilic or amphiphilic.

16. The composition of claim 14 wherein the drug is pilocarpine or timolol.

17. The composition of claim 13 wherein the drug is hydrophobic.

18. The composition of claim 17 wherein the drug is  
15 indomethacin, betaxolol or adaprolol.

19. The composition of claim 13 wherein the drug is present in an amount of about 0.05 to 5% by weight.

20. The composition of claim 13 further comprising a  
20 preservative, an antioxidant or an osmotic agent.

21. The composition of claim 13 further comprising an effective amount of an additional drug.

22. The composition of claim 21 wherein the additional drug is a  $\beta$ -adrenergic blocker, a cannabinoid, a  
25 cholinesterase inhibitor, a sympathomimetic or a carbonic anhydrase inhibitor.

23. The composition of claim 16 further comprising an effective amount of an additional drug which decreases intraocular pressure when administered to the eye of a  
30 patient.

24. A method for reducing eye irritation induced by the administration of a drug, which comprises administering said drug to the eye together with the ocular drug delivery vehicle of claim 1.

25. The method of claim 24 which further comprises  
35 selecting the emulsion to have droplets of a mean diameter of between about 0.1 and 0.3  $\mu\text{m}$ .

26. A method for reducing eye irritation which comprises administering to an irritated eye an effective amount of the ocular drug delivery vehicle of claim 1.

27. The method of claim 26 which further comprises  
5 selecting the emulsion to have droplets of a mean diameter of between about 0.1 and 0.3  $\mu\text{m}$ .

28. A method for administering a topical ophthalmic composition of a drug having a therapeutic effect on the eye, which comprises formulating the topical ophthalmic  
10 composition of claim 13 and administering an effective amount of such composition to the eye of a patient.

29. The method of claim 28 which further comprises selecting the emulsion to have droplets of a mean diameter of between about 0.1 and 0.3  $\mu\text{m}$ .

15 30. A method for administering increased amount of a drug to the eye without causing irritation thereof, which comprises administering said increased amount of said drug to the eye with the ocular drug delivery vehicle of claim 1.

31. The method of claim 30 which further comprises  
20 selecting the emulsion to have droplets of a mean diameter of between about 0.1 and 0.3  $\mu\text{m}$ .

32. A method for administering increased amount of a drug to the eye without causing irritation thereof, which comprises administering said increased amount of said drug  
25 to the eye in the composition of claim 13.

33. The method of claim 32 which further comprises selecting the emulsion to have droplets of a mean diameter of between about 0.1 and 0.3  $\mu\text{m}$ .

34. A method for providing increased bioavailability  
30 of an ophthalmic drug which comprises administering said drug to the eye in the composition of claim 13.

35. The method of claim 34 which further comprises selecting the emulsion to have droplets of a mean diameter of between about 0.1 and 0.3  $\mu\text{m}$ .

35 36. A method for providing increased bioavailability of an ophthalmic drug which comprises administering said

drug to the eye with the ocular drug delivery vehicle of claim 1.

37. The method of claim 36 which further comprises selecting the emulsion to have droplets of a mean diameter of between about 0.1 and 0.3  $\mu\text{m}$ .

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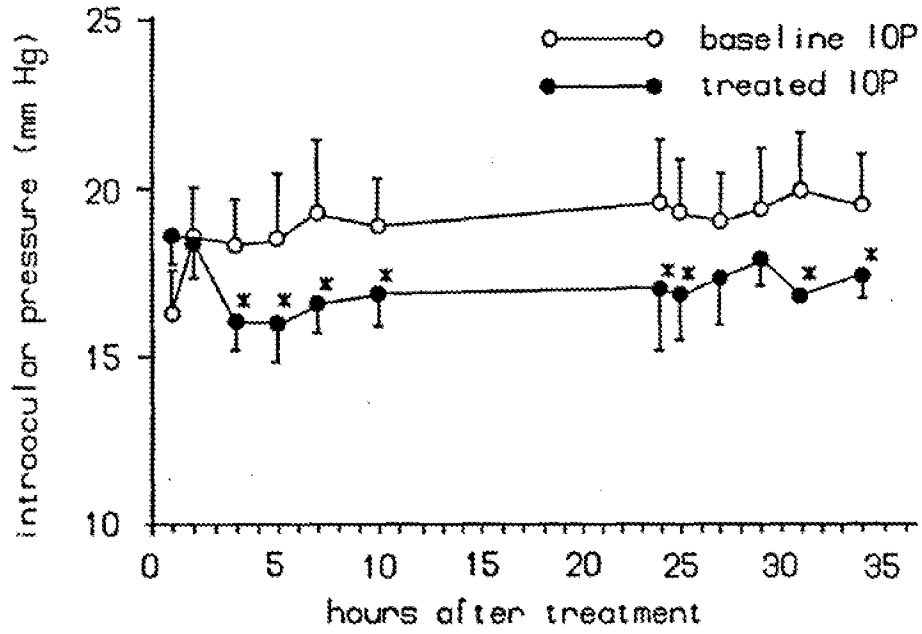


FIG. 1

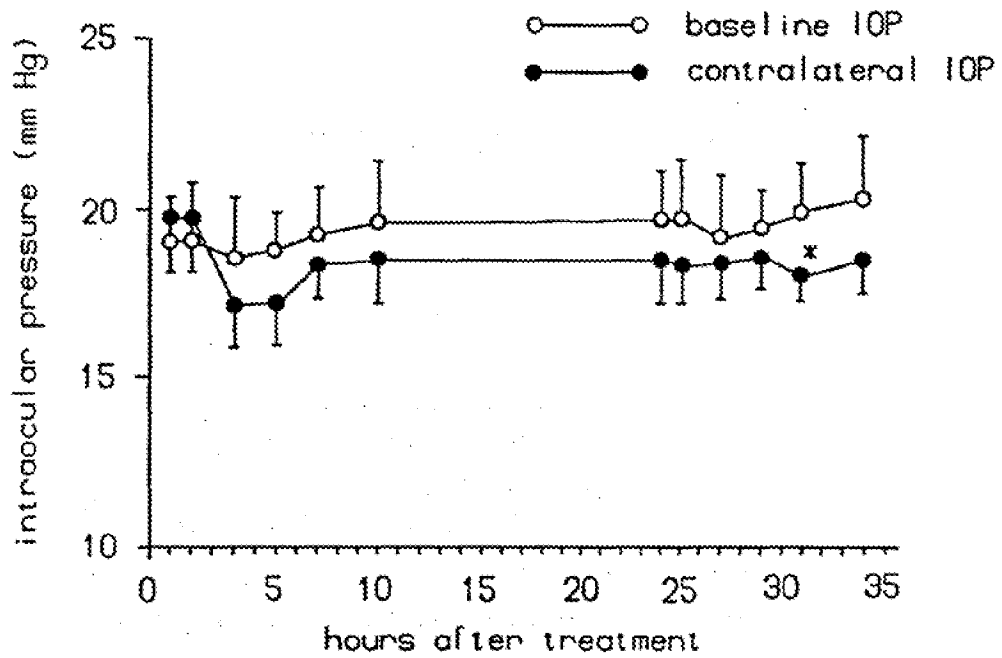


FIG. 2

2/3

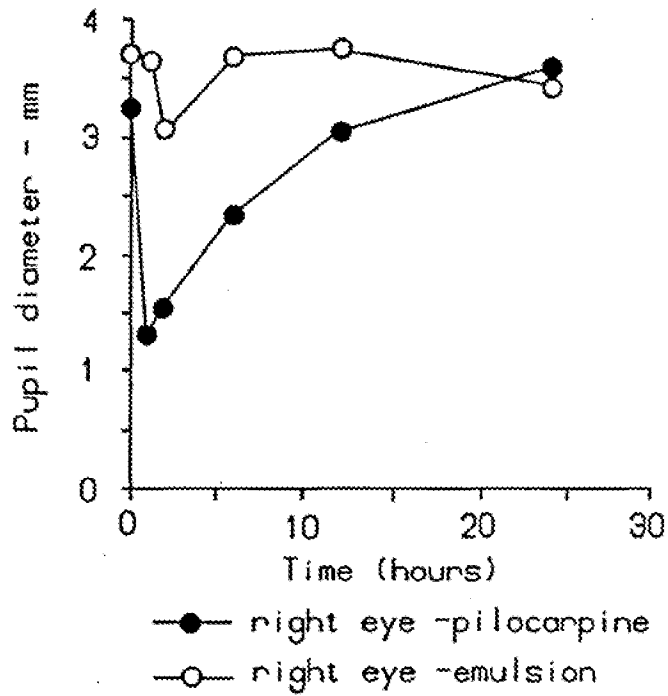


FIG. 3

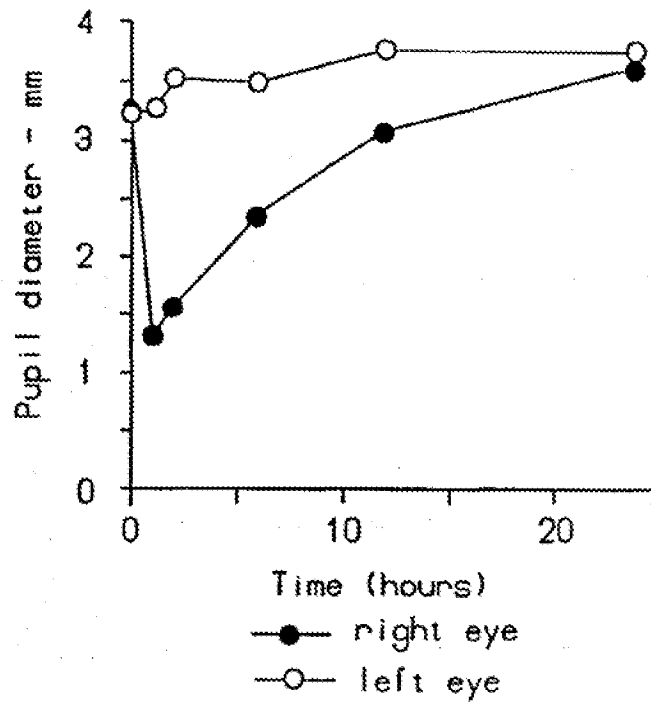


FIG. 4

SUBSTITUTE SHEET



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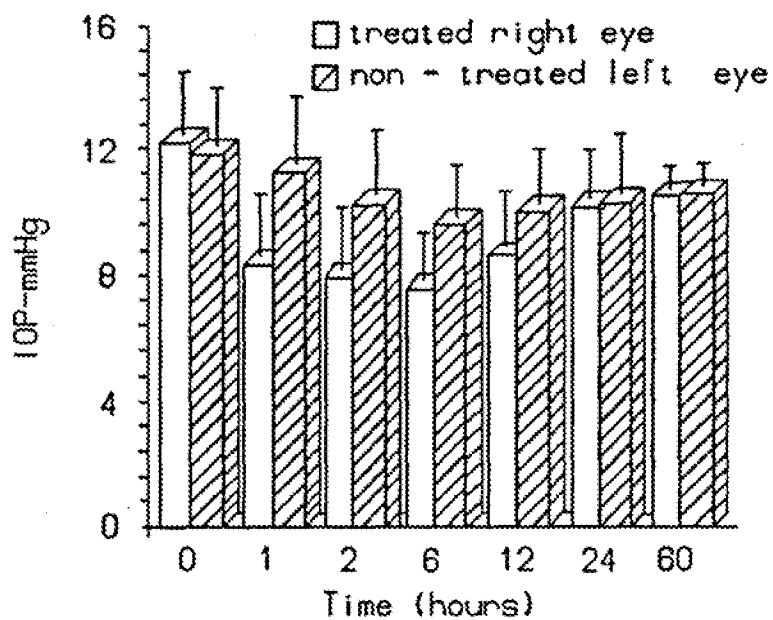


FIG. 5

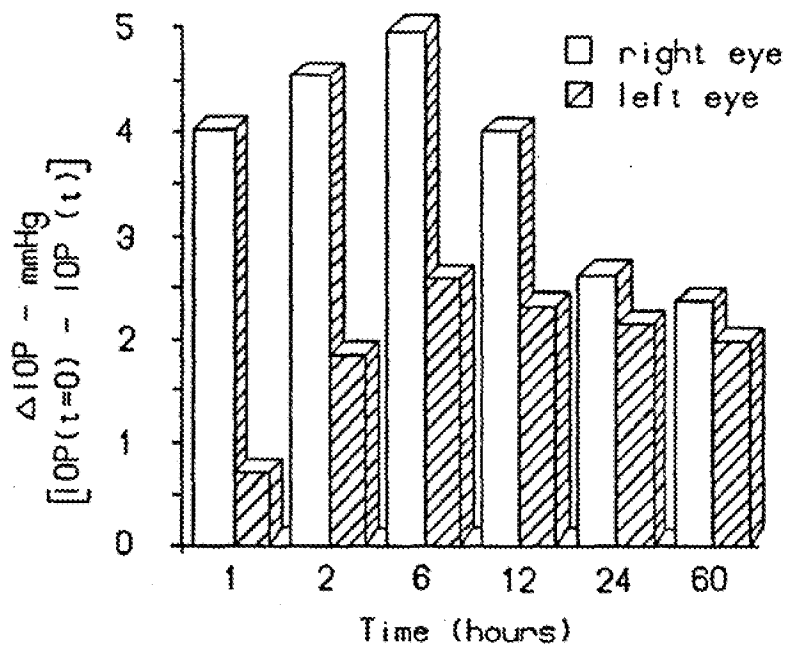


FIG. 6

SUBSTITUTE SHEET

INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US93/00044

<b>A. CLASSIFICATION OF SUBJECT MATTER</b> IPC(5) :A61K 31/66, 31/685, 31/20 US CL :514/75, 76, 78, 558 According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b> Minimum documentation searched (classification system followed by classification symbols) U.S. : 514/75, 76, 78, 558 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)		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A, 4,914,088 (GONEK ET AL.) 03 April 1990. See the entire document. Archives of Ophthalmology, vol. 93.	1-22
Y	January 1975, Hardberger et al., Effect of Drug Vehicle on Ocular Contact Time. pp. 42-45. See the entire document.	1-22
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.		
* Special categories of cited documents: *A* document defining the general state of the art which is not considered to be part of particular relevance *E* earlier document published on or after the international filing date *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) *O* document referring to an oral disclosure, use, exhibition or other means *P* document published prior to the international filing date but later than the priority date claimed *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art *Z* document member of the same patent family		
Date of the actual completion of the international search 17 MARCH 1993		Date of mailing of the international search report 26 APR 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 M. ZOHREH FAY Telephone No. (703) 308-1235 <i>M. Zohreh Fay</i> INTERNATIONAL PATENT CLASSIFICATION

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

## Electronic Acknowledgement Receipt

<b>EFS ID:</b>	20432699
<b>Application Number:</b>	14493903
<b>International Application Number:</b>	
<b>Confirmation Number:</b>	7395
<b>Title of Invention:</b>	AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID
<b>First Named Inventor/Applicant Name:</b>	Shirou SAWA
<b>Customer Number:</b>	513
<b>Filer:</b>	Warren M. Cheek Jr./maurice linder
<b>Filer Authorized By:</b>	Warren M. Cheek Jr.
<b>Attorney Docket Number:</b>	2014-1250
<b>Receipt Date:</b>	16-OCT-2014
<b>Filing Date:</b>	23-SEP-2014
<b>Time Stamp:</b>	14:48:43
<b>Application Type:</b>	Utility under 35 USC 111(a)

### Payment information:

Submitted with Payment	no
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### File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Information Disclosure Statement (IDS) Form (SB08)	AttachZ1_ids.pdf	186413 <small>598f4c07188474c88f8663769ab0315cfe6f441c</small>	no	3

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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**

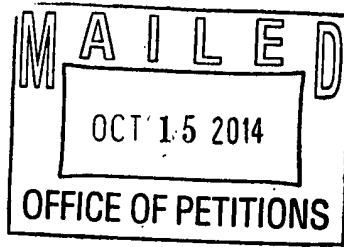
**If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.**

**New International Application Filed with the USPTO as a Receiving Office**

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WENDEROTH LIND & PONACK LLP  
1030 15<sup>TH</sup> STREET, N.W.  
SUITE 400 EAST  
WASHINGTON DC 20005-1503



Doc Code: TRACK1.GRANT

<b>Decision Granting Request for Prioritized Examination (Track I or After RCE)</b>	Application No.: 14/493,903
<p>1. THE REQUEST FILED <u>September 23, 2014</u> IS <b>GRANTED</b>.</p> <p>The above-identified application has met the requirements for prioritized examination</p> <p>A. <input checked="" type="checkbox"/> for an original nonprovisional application (Track I).</p> <p>B. <input type="checkbox"/> for an application undergoing continued examination (RCE).</p> <p>2. <b>The above-identified application will undergo prioritized examination.</b> The application will be accorded special status throughout its entire course of prosecution until one of the following occurs:</p> <p>A. filing a <b><u>petition for extension of time</u></b> to extend the time period for filing a reply;</p> <p>B. filing an <b><u>amendment to amend the application to contain more than four independent claims, more than thirty total claims</u></b>, or a multiple dependent claim;</p> <p>C. filing a <b><u>request for continued examination</u></b>;</p> <p>D. filing a notice of appeal;</p> <p>E. filing a request for suspension of action;</p> <p>F. mailing of a notice of allowance;</p> <p>G. mailing of a final Office action;</p> <p>H. completion of examination as defined in 37 CFR 41.102; or</p> <p>I. abandonment of the application.</p> <p>Telephone inquiries with regard to this decision should be directed to Irvin Dingle at (571)272-3210, Office of Petitions.</p> <p>Irvin Dingle <u>/Irvin Dingle/</u> [Signature]</p> <p><u>Paralegal Specialist</u> (Title)</p>	

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This is to certify that the annexed is a true copy of the following application as filed with this Office.

出 願 年 月 日                    2 0 0 3 年   1 月 2 1 日  
Date of Application:

出 願 番 号                    特 願 2 0 0 3 - 0 1 2 4 2 7  
Application Number:

パリ条約による外国への出願  
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番号  
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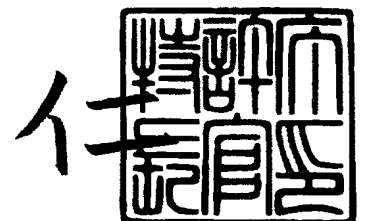
J P 2 0 0 3 - 0 1 2 4 2 7

出 願 人                    千 寿 製 薬 株 式 有 限 公 司  
Applicant(s):

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特 許 庁 長 官  
Commissioner,  
Japan Patent Office

伊 藤 伸



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【整理番号】 598-03

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【あて先】 特許庁長官 殿

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A61K 9/08

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A61K 47/18

A61K 47/32

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A61P 27/16

【発明者】

【住所又は居所】 兵庫県神戸市西区南別府4-366-1 105号

【氏名】 澤 嗣郎

【発明者】

【住所又は居所】 兵庫県神戸市西区王塚台3-93ルックハイツ2-105

【氏名】 藤田 修平

【特許出願人】

【識別番号】 000199175

【氏名又は名称】 千寿製薬株式会社

【代理人】

【識別番号】 100118360

【弁理士】

【氏名又は名称】 松田 玲子

【電話番号】 06-6201-9627

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【予納台帳番号】 004167

【納付金額】 21,000

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【物件名】 明細書 1

【物件名】 要約書 1

【包括委任状番号】 0104918

【プルーフの要否】 要

【書類名】 明細書

【発明の名称】 2-アミノ-3-(4-ブロモベンゾイル)フェニル酢酸  
含有水性液剤

【特許請求の範囲】

【請求項1】 2-アミノ-3-(4-ブロモベンゾイル)フェニル酢酸もしくはその薬理学的に許容できる塩またはそれらの水和物と、アルキルアリアルポリエーテルアルコール型ポリマーまたはポリエチレングリコール脂肪酸エステルを含有する水性液剤。

【請求項2】 アルキルアリアルポリエーテルアルコール型ポリマーはその重合度が3～10であり、アルキルの炭素数が1～18であり、アリアルがフェノール残基であり、かつポリエーテルアルコールが式  $(\text{CH}_2\text{CH}_2\text{O})_x\text{H}$  で表され、式中のXは5～100の整数を示すものである請求項1記載の水性液剤。

【請求項3】 アルキルアリアルポリエーテルアルコール型ポリマーがチロキサポールである請求項1または2に記載の水性液剤。

【請求項4】 ポリエチレングリコール脂肪酸エステル中の脂肪酸の炭素数が12～18である請求項1記載の水性液剤。

【請求項5】 ポリエチレングリコール脂肪酸エステルがモノステアリン酸ポリエチレングリコールである請求項1または4に記載の水性液剤。

【請求項6】 アルキルアリアルポリエーテルアルコール型ポリマーの濃度は下限濃度が0.01 w/v%で、上限濃度が0.5 w/v%の範囲から選択される請求項1～3のいずれかに記載の水性液剤。

【請求項7】 ポリエチレングリコール脂肪酸エステルの濃度は下限濃度が0.02 w/v%で、上限濃度が0.1 w/v%の範囲から選択される請求項1、2または4のいずれかに記載の水性液剤。

【請求項8】 2-アミノ-3-(4-ブロモベンゾイル)フェニル酢酸もしくはその薬理学的に許容できる塩またはそれらの水和物の濃度は0.01～0.5 w/v%である請求項1～7のいずれかに記載の水性液剤。

【請求項9】 保存剤として塩化ベンザルコニウムを含有する請求項1～8のいずれかに記載の水性液剤。

【請求項 1 0】 2-アミノ-3-(4-ブロモベンゾイル)フェニル酢酸の薬理的に許容できる塩がナトリウム塩である請求項 1～9 のいずれかに記載の水性液剤。

【請求項 1 1】 水性液剤の pH が 7～9 の範囲内である請求項 1～1 0 のいずれかに記載の水性液剤。

【請求項 1 2】 水性液剤の pH が 7.5～8.5 の範囲内である請求項 1 1 に記載の水性液剤。

【請求項 1 3】 点眼液である請求項 1～1 2 のいずれかに記載の水性液剤。

【請求項 1 4】 点鼻液である請求項 1～1 2 のいずれかに記載の水性液剤。

【請求項 1 5】 2-アミノ-3-(4-ブロモベンゾイル)フェニル酢酸ナトリウム・水和物およびチロキサポール 0.01 w/v %～0.5 w/v % を含有する点眼液。

【請求項 1 6】 2-アミノ-3-(4-ブロモベンゾイル)フェニル酢酸ナトリウム・水和物およびモノステアリン酸ポリエチレングリコール 0.02 w/v %～0.1 w/v % を含有する点眼液。

【請求項 1 7】 2-アミノ-3-(4-ブロモベンゾイル)フェニル酢酸もしくはその薬理的に許容できる塩またはそれらの水和物を含有する水性液剤にチロキサポールまたはモノステアリン酸ポリエチレングリコールを配合することを特徴とする、水性液剤中の 2-アミノ-3-(4-ブロモベンゾイル)フェニル酢酸、その薬理的に許容できる塩およびそれらの水和物を安定化する方法。

【請求項 1 8】 2-アミノ-3-(4-ブロモベンゾイル)フェニル酢酸もしくはその薬理的に許容できる塩またはそれらの水和物および保存剤を含有する水性液剤にチロキサポールまたはモノステアリン酸ポリエチレングリコールを配合することを特徴とする、該水性液剤中の保存剤の防腐効力の低下を抑制する方法。

【発明の詳細な説明】

【0001】

【発明の属する技術分野】

本発明は、2-アミノ-3-(4-ブロモベンゾイル)フェニル酢酸もしくは

その薬理的に許容できる塩またはそれらの水和物を含有する水性液剤に関する。さらに詳しくは、本発明は、2-アミノ-3-(4-ブロモベンゾイル)フェニル酢酸もしくはその薬理的に許容できる塩またはそれらの水和物とアルキルアリアルポリエーテルアルコール型ポリマーまたはポリエチレングリコール脂肪酸エステルを含有する水性液剤に関する。

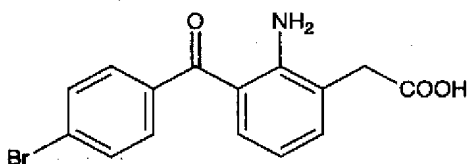
【0002】

【従来の技術】

次の式(I)：

【0003】

【化1】



【0004】

で表され、化学名が2-アミノ-3-(4-ブロモベンゾイル)フェニル酢酸(一般名：ブロムフェナク)である化合物を包含するベンゾイルフェニル酢酸誘導体が知られている(特許文献1参照。)。2-アミノ-3-(4-ブロモベンゾイル)フェニル酢酸、その薬理的に許容できる塩およびそれらの水和物は、非ステロイド性抗炎症剤として知られ、眼科領域においては外眼部および前眼部の炎症性疾患(眼瞼炎、結膜炎、強膜炎、術後炎症)に対して有効であり、そのナトリウム塩として点眼液の形態で実用に供されている(非特許文献1参照)。

【0005】

上記点眼液は、2-アミノ-3-(4-ブロモベンゾイル)フェニル酢酸に、水溶性高分子(ポリビニルピロリドン、ポリビニルアルコールなど)および亜硫酸塩(亜硫酸ナトリウム塩、亜硫酸カリウム塩など)を添加することにより、2-アミノ-3-(4-ブロモベンゾイル)フェニル酢酸の安定化が図られている(特許文献3参照。)

【0006】



また上記以外の点眼剤として、酸性眼科用試剤に抗菌性高分子4級アンモニウム化合物およびホウ酸を配合させてなる安定な眼科用組成物が報告され、酸性眼科用試剤の例示として2-アミノ-3-(4-ブロモベンゾイル)フェニル酢酸が挙げられている(特許文献4参照。)

【特許文献1】

特開昭52-23052号公開公報

【特許文献2】

特開昭62-126124号公開公報

【特許文献3】

特許第2683676号公報

【特許文献4】

特許第2954356号公報, 6欄, 26-27行, 45行

【非特許文献1】

「最近の新薬2001」、2001年版、株式会社薬事日報社、2001年5月11日、p. 27-29

【0007】

【発明が解決しようとする課題】

本発明は、2-アミノ-3-(4-ブロモベンゾイル)フェニル酢酸もしくはその薬理的に許容できる塩またはそれらの水和物を含有する、眼に刺激のないpH領域で安定で、かつ十分な防腐効力を有する水性液剤を提供することにある。

【0008】

また、本発明の他の目的は、水溶液における2-アミノ-3-(4-ブロモベンゾイル)フェニル酢酸もしくはその薬理的に許容できる塩またはそれらの水和物の安定化方法を提供することにある。

【0009】

さらに本発明の他の目的は、2-アミノ-3-(4-ブロモベンゾイル)フェニル酢酸もしくはその薬理的に許容できる塩またはそれらの水和物および防腐剤を含有する水性液剤中の防腐剤の防腐効力の低下を抑制する方法を提供するこ

とにある。

【0010】

【課題を解決するための手段】

本発明者らは種々検討を重ねた結果、2-アミノ-3-(4-ブロモベンゾイル)フェニル酢酸、その薬理的に許容される塩およびそれらの水和物がチロキサポールなどのアルキルアリアルポリエーテル型ポリマーまたはモノステアリン酸ポリエチレングリコールなどのポリエチレングリコール脂肪酸エステルを添加することにより、眼刺激のないpH領域において安定で、かつ十分な防腐効力を有することを見出し、さらに研究を進めて本発明を完成させた。

【0011】

すなわち、本発明は、

(1) 2-アミノ-3-(4-ブロモベンゾイル)フェニル酢酸もしくはその薬理的に許容できる塩またはそれらの水和物と、アルキルアリアルポリエーテルアルコール型ポリマーまたはポリエチレングリコール脂肪酸エステルを含有する水性液剤。

(2) アルキルアリアルポリエーテルアルコール型ポリマーはその重合度が3~10であり、アルキルの炭素数が1~18であり、アリアルがフェノール残基であり、かつポリエーテルアルコールが式 $(CH_2CH_2O)_xH$ で表され、式中のXは5~100の整数を示すものである上記(1)記載の水性液剤。

(3) アルキルアリアルポリエーテルアルコール型ポリマーがチロキサポールである上記(1)または(2)に記載の水性液剤。

(4) ポリエチレングリコール脂肪酸エステル中の脂肪酸の炭素数が12~18である上記(1)記載の水性液剤。

(5) ポリエチレングリコール脂肪酸エステルがモノステアリン酸ポリエチレングリコールである上記(1)または(4)に記載の水性液剤。

(6) アルキルアリアルポリエーテルアルコール型ポリマーの濃度は下限濃度が0.01w/v%で、上限濃度が0.5w/v%の範囲から選択される上記(1)~(3)のいずれかに記載の水性液剤。

(7) ポリエチレングリコール脂肪酸エステルの濃度は下限濃度が0.02w/v%

v%で、上限濃度が0.1 w/v%の範囲から選択される上記(1)、(2)または(4)のいずれかに記載の水性液剤。

(8) 2-アミノ-3-(4-プロモベンゾイル)フェニル酢酸もしくはその薬理的に許容できる塩またはそれらの水和物の濃度は0.01~0.5 w/v%である上記(1)~(7)のいずれかに記載の水性液剤。

(9) 保存剤として塩化ベンザルコニウムを含有する上記(1)~(8)のいずれかに記載の水性液剤。

(10) 2-アミノ-3-(4-プロモベンゾイル)フェニル酢酸の薬理的に許容できる塩がナトリウム塩である上記(1)~(9)のいずれかに記載の水性液剤。

(11) 水性液剤のpHが7~9の範囲内である上記(1)~(10)のいずれかに記載の水性液剤。

(12) 水性液剤のpHが7.5~8.5の範囲内である上記(11)に記載の水性液剤。

(13) 点眼液である上記(1)~(12)のいずれかに記載の水性液剤。

(14) 点鼻液である上記(1)~(12)のいずれかに記載の水性液剤。

(15) 2-アミノ-3-(4-プロモベンゾイル)フェニル酢酸ナトリウム・水和物およびチロキサポール0.01 w/v%~0.5 w/v%を含有する点眼液。

(16) 2-アミノ-3-(4-プロモベンゾイル)フェニル酢酸ナトリウム・水和物およびモノステアリン酸ポリエチレングリコール0.02 w/v%~0.1 w/v%を含有する点眼液。

(17) 2-アミノ-3-(4-プロモベンゾイル)フェニル酢酸もしくはその薬理的に許容できる塩またはそれらの水和物を含有する水性液剤にチロキサポールまたはモノステアリン酸ポリエチレングリコールを配合することを特徴とする、水性液剤中の2-アミノ-3-(4-プロモベンゾイル)フェニル酢酸、その薬理的に許容できる塩およびそれらの水和物を安定化する方法。

(18) 2-アミノ-3-(4-プロモベンゾイル)フェニル酢酸もしくはその薬理的に許容できる塩またはそれらの水和物および保存剤を含有する水性液剤

にチロキサポールまたはモノステアリン酸ポリエチレングリコールを配合することを特徴とする、該水性液剤中の保存剤の防腐効力の低下を抑制する方法に関する。

#### 【0012】

本発明において、2-アミノ-3-(4-ブロモベンゾイル)フェニル酢酸の薬理学的に許容できる塩としては、例えば、ナトリウム塩、カリウム塩などのアルカリ金属塩やカルシウム塩、マグネシウム塩などのアルカリ土類金属塩などが挙げられる。これらの塩のうち、特にナトリウム塩が好ましい。

#### 【0013】

2-アミノ-3-(4-ブロモベンゾイル)フェニル酢酸およびその薬理学的に許容できる塩は、例えば、特許文献1記載の方法またはそれに準じた方法により適宜製造することができる。これら化合物は、合成の条件、再結晶の条件などによりそれらの水和物として得られる。水和物としては例えば3/2水和物が例示される。

#### 【0014】

本発明の水性液剤において、2-アミノ-3-(4-ブロモベンゾイル)フェニル酢酸もしくはその薬理学的に許容できる塩またはそれらの水和物の含有量は、通常、0.01 w/v%~0.5 w/v%程度、好ましくは0.05 w/v%~0.2 w/v%程度、特に好ましくは0.1 w/v%程度とし、使用目的、適応症状の程度に応じて適宜増減する。

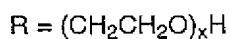
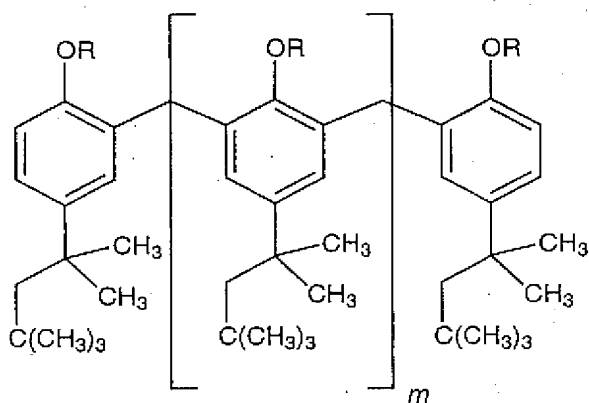
#### 【0015】

本発明において2-アミノ-3-(4-ブロモベンゾイル)フェニル酢酸もしくはその薬理学的に許容できる塩またはそれらの水和物の安定化剤として用いられる、非イオン性界面活性剤のアルキルアリアルポリエーテルアルコール型ポリマー（重合度：3~10）は、アルキルの炭素数は1~18程度である。具体的には、たとえばメチル基、エチル基、プロピル基、イソプロピル基、シクロプロピル基、ブチル基、イソブチル基、sec-ブチル基、tert-ブチル基、シクロブチル基、ペンチル基、イソペンチル基、ネオペンチル基、tert-ペンチル基、1-エチルプロピル基、4-メチルペンチル基、1,1ジメチルブチル

基、2, 2-ジメチルブチル基、1, 2-ジメチルブチル基、2-エチルブチル基、シクロペンチル基、ヘキシル基、シクロヘキシル基、ヘプチル基、イソヘプチル基、オクチル基、イソオクチル基、ノニル基、イソノニル基、デシル基、イソデシル基、ウンデシル基、イソウンデシル基、ドデシル基、イソドデシル基、トリデシル基、イソトリデシル基、テトラデシル基、イソテトラデシル基、ペンタデシル基、イソペンタデシル基、ヘキサデシル基、イソヘキサデシル基、ヘプタデシル基、イソヘプタデシル基、オクタデシル基、イソオクタデシル基およびそれらの異性体などが挙げられるが、これらのうちオクチル基の異性体である1, 1, 3, 3-テトラメチルブチル基が特に好ましい。上記アリアルとしてはフェノール残基が好ましい。上記ポリエーテルアルコールとしては、式  $(\text{CH}_2\text{C}(\text{H}_2\text{O}))_x\text{H}$  (式中のXは5~100の整数を示す。) で表されるポリエーテルアルコール、好ましくはXは5~30の整数であるポリエーテルアルコール、さらに好ましくはXは8~10の整数であるポリエーテルアルコールである。上記アルキルアリアルポリエーテルアルコール型ポリマーのうち、下記構造を有するチロキサポール (Tyloxapol) が特に好ましい。

【0016】

【化2】



$$x = 8 - 10$$

$$m < 6$$

【0017】

本発明において2-アミノ-3-(4-ブロモベンゾイル)フェニル酢酸もしくはその薬理的に許容できる塩またはそれらの水和物の安定化剤として用いられる、非イオン性界面活性剤のポリエチレングリコール脂肪酸エステルの脂肪酸は炭素数12~18の脂肪酸が好ましい。具体的化合物としては、モノステアリン酸ポリエチレングリコール、モノラウリン酸ポリエチレングリコール、モノオレイン酸ポリエチレングリコール、ジイソステアリン酸ポリエチレングリコール、ジラウリル酸ポリエチレングリコール、ジオレイン酸ポリエチレングリコールなどが挙げられる。これらのうちモノステアリン酸ポリエチレングリコールが好ましく、ステアリン酸ポリオキシ40 (Polyoxy 40 stearate) が特に好ましい。ステアリン酸ポリオキシ40は、酸化エチレンの縮重合体のモノステアリン酸エステルで、 $C_{17}H_{35}COO(CH_2CH_2O)_nH$ で表され、nは約40の非イオン性界面活性剤である。

#### 【0018】

本発明の水性液剤において、アルキルアリアルポリエーテルアルコール型ポリマーの含有量は使用する化合物の種類などによって異なるが、下限0.01w/v%程度、上限0.5w/v%程度である。たとえば、チロキサポールの含有量は、下限0.01、0.02、0.03w/v%程度、上限0.05、0.1、0.3、0.5w/v%程度、好ましくは下限0.02w/v%程度、上限0.05w/v%程度である。

#### 【0019】

本発明の水性液剤において、ポリエチレングリコール脂肪酸エステルの含有量は使用する化合物の種類などによって異なるが、下限0.02w/v%程度、上限0.1w/v%程度である。たとえば、モノステアリン酸ポリエチレングリコールの含有量は、下限0.02w/v%程度、上限0.1w/v%程度、好ましくは下限0.02w/v%程度、上限0.05w/v%程度である。

#### 【0020】

本発明の水性液剤において、たとえばチロキサポールの配合比は、2-アミノ-3-(4-ブロモベンゾイル)フェニル酢酸もしくはその薬理的に許容できる塩またはそれらの水和物1重量部に対し、下限0.1、0.2重量部程度、上

限0.5、1、3、5重量部程度である。

#### 【0021】

本発明の水性液剤において、たとえばモノステアリン酸ポリエチレングリコールの配合比は、2-アミノ-3-(4-ブロモベンゾイル)フェニル酢酸もしくはその薬理的に許容できる塩またはそれらの水和物1重量部に対し、下限0.2重量部程度、上限0.5、1重量部程度である。

#### 【0022】

本発明の水性液剤に用いられる防腐剤としては、例えば、塩化ベンザルコニウムや塩化ベンゼトニウムなどの第4級アンモニウム塩類、グルコン酸クロルヘキシジンなどが挙げられるが、特に塩化ベンザルコニウムが好ましい。

#### 【0023】

さらに、本発明の水性液剤には、本発明の目的に反しない限り、通常用いられる等張化剤、緩衝剤、粘稠化剤、安定化剤、キレート剤、pH調整剤、芳香剤等の各種添加剤を適宜添加してもよい。等張化剤としては、塩化ナトリウム、塩化カリウム、グリセリン、マンニトール、ソルビトール、ホウ酸、ブドウ糖、プロピレングリコールなどが挙げられる。緩衝剤としては、例えば、リン酸緩衝剤、ホウ酸緩衝剤、クエン酸緩衝剤、酒石酸緩衝剤、酢酸緩衝剤、ホウ酸、ホウ砂、アミノ酸などが挙げられる。粘稠化剤としては、ポリビニルピロリドン、カルボキシメチルセルロース、カルボキシプロピルセルロース、ヒドロキシエチルセルロース、ヒドロキシプロピルセルロース、ヒドロキシプロピルメチルセルロース、ポリビニルアルコール、ポリアクリル酸ナトリウムなどが挙げられる。安定化剤としては、亜硫酸ナトリウムなどの亜硫酸塩などが挙げられる。キレート剤としては、エデト酸ナトリウム、クエン酸ナトリウム、縮合燐酸ナトリウムなどが挙げられる。pH調整剤としては、塩酸、水酸化ナトリウム、リン酸、酢酸などが挙げられる。芳香剤としては、1-メントール、ボルネオール、カンフル、ユーカリ油などが挙げられる。

#### 【0024】

本発明の水性液剤に配合される上記各添加剤の濃度は、例えば等張化剤は浸透圧比が0.8~1.2程度になる濃度に配合し、緩衝剤は0.01~2w/v%

程度、粘稠化剤は0.1～10w/v%程度である。

#### 【0025】

本発明の水溶性液剤のpHは、約7～9程度、好ましくは約7.5～8.5程度に調整される。

#### 【0026】

本発明の水溶性液剤においては、本発明の目的に反しない限り、その他の同種または別種の薬効成分を適宜含有させてもよい。

#### 【0027】

本発明の水溶性液剤は、自体公知の調製法、例えば、第14改正日本薬局方、製剤総則の液剤あるいは点眼剤に記載された方法で製造することができる。

#### 【0028】

本発明の水溶性液剤は、温血動物（例えば、ヒト、ラット、マウス、ウサギ、ウシ、ブタ、イヌ、ネコなど）に使用することができる。

#### 【0029】

本発明の水溶性液剤を、例えば、点眼剤として使用する場合は、外眼部および前眼部の炎症性疾患、具体的には例えば眼瞼炎、結膜炎、強膜炎、術後炎症などに用いることができる。その投与量は、例えば2-アミノ-3-(4-ブロモベンゾイル)フェニル酢酸ナトリウム・水和物0.1w/v%含有する本発明の点眼剤を成人に点眼する場合は、1回1～2滴を1日3～6回点眼すればよい。なお、適応症状の程度などにより、適宜投与回数を増減する。

#### 【0030】

##### 【実施例】

以下に、実験例、実施例を挙げて、本発明をさらに詳細に説明するが、本発明はこれらによって限定されるものではない。

#### 【0031】

実験例1 2-アミノ-3-(4-ブロモベンゾイル)フェニル酢酸ナトリウムの安定性試験

(実験方法)

表1に示す4処方2-アミノ-3-(4-ブロモベンゾイル)フェニル酢酸



ナトリウム配合の点眼液を調製し、ポリプロピレン容器に充填後、60℃における安定性について試験した。

【0032】

【表1】

処方	比較例 1	A-01	A-02	A-03
2-アミノ-3-(4-ブロモベンゾイル)フェニル酢酸ナトリウム	0.1 g	0.1 g	0.1 g	0.1 g
柿酸	1.5 g	1.5 g	1.5 g	1.5 g
塩化ベンザルコニウム	0.005g	0.005g	0.005g	0.005g
ポリソルベート 80	0.15g	—	—	—
ステアリン酸ポリオキシル 40	—	0.15g	—	—
チロキサポール	—	—	0.15g	0.02g
滅菌精製水	適量	適量	適量	適量
全量	100 mL	100 mL	100 mL	100 mL
pH	7.0	7.0	7.0	7.0
60℃-4W	51.3	63.7	73.8	89.6

【0033】

表1の残存率(%)は、2-アミノ-3-(4-ブロモベンゾイル)フェニル酢酸ナトリウムの含量に対し、容器からの水分の飛散を補正した値である。表1から明らかなように、pH7.0、60℃、4週において、ポリソルベート80、ステアリン酸ポリオキシル40、チロキサポール配合点眼液の順で2-アミノ-3-(4-ブロモベンゾイル)フェニル酢酸ナトリウムは安定であった。

また、チロキサポール配合点眼液において、チロキサポール0.02w/vの方が0.15w/v配合したものよりも2-アミノ-3-(4-ブロモベンゾイル)フェニル酢酸ナトリウムは安定であった。

【0034】

実験例2 2-アミノ-3-(4-ブロモベンゾイル)フェニル酢酸ナトリウムの安定性試験

(実験方法)

表2に示す5処方の2-アミノ-3-(4-ブロモベンゾイル)フェニル酢酸配合の点眼液を調製し、ポリプロピレン容器に充填した。60℃、4週間保存後、点眼液中の2-アミノ-3-(4-ブロモベンゾイル)フェニル酢酸量および

点眼液のpHを測定した。調整時の2-アミノ-3-(4-ブロモベンゾイル)フェニル酢酸を100%としたときの残存量およびpHを表2に示した。なお残存量は容器からの水分の飛散を補正した値である。

【0035】

【表2】

処方	A-04	A-05	A-06	A-07	A-08	
2-アミノ-3-(4-ブロモベンゾイル)フェニル酢酸ナトリウム	0.1 g	0.1 g	0.1 g	0.1 g	0.1 g	
紗酸	1.1 g	1.1 g	1.1 g	1.1 g	1.1 g	
紗砂	1.1 g	1.1 g	1.1 g	1.1 g	1.1 g	
塩化ベンザルコニウム	0.005g	0.005g	0.005g	0.005g	0.005g	
ポリリルベ-ト80	—	—	—	—	—	
チロキサール	0.02 g	0.05 g	0.03 g	—	—	
ステアリン酸ポリオキシル40	—	—	—	0.02 g	0.05 g	
ポリビニルピロリドン(K-30)	2.0 g	2.0 g	2.0 g	2.0 g	1.0 g	
エドト酸ナトリウム	0.02 g	0.02 g	0.02 g	0.02 g	0.02 g	
水酸化ナトリウム	適量	適量	適量	適量	適量	
滅菌精製水	適量	適量	適量	適量	適量	
全量	100 mL	100 mL	100 mL	100 mL	100 mL	
pH	8.17	8.16	8.15	8.19	8.19	
60℃-4W	残存量	92.6	90.9	92.0	93.4	93.1
	pH	8.15	8.16	8.15	8.13	8.14

【0036】

表2から明らかなように、0.02、0.03および0.05 w/v%チロキサールまたは0.02、0.05 w/v%ステアリン酸ポリオキシル40を配合した処方では60℃、4週で残存率が90%以上であり、点眼液剤として十分な安定性を示した。

【0037】

実験例3 2-アミノ-3-(4-ブロモベンゾイル)フェニル酢酸ナトリウム含有水性液剤の防腐効力試験

実験例2のA-04、A-05およびA-07の処方の防腐効力につき試験した。

その結果を表3に示す。

【0038】

【表3】

表3-1

A-04	接種菌数	6 <sup>th</sup>	24 <sup>th</sup>	1W	2W	3W	4W
<i>S. aureus</i>	$2.1 \times 10^6$	$3.0 \times 10^1$	0	0	0	0	0
<i>E. coli</i>	$6.5 \times 10^6$	0	0	0	0	0	0
<i>P. aeruginosa</i>	$5.8 \times 10^6$	0	0	0	0	0	0
<i>C. albicans</i>	$3.2 \times 10^5$	—	—	0	0	0	0
<i>A. niger</i>	$1.8 \times 10^5$	—	—	0	0	0	0

Unit : CFU/mL

表3-2

A-05	接種菌数	6 <sup>th</sup>	24 <sup>th</sup>	1W	2W	3W	4W
<i>S. aureus</i>	$2.1 \times 10^6$	$1.7 \times 10^5$	$2.0 \times 10^1$	0	0	0	0
<i>E. coli</i>	$6.5 \times 10^6$	0	0	0	0	0	0
<i>P. aeruginosa</i>	$5.8 \times 10^6$	0	0	0	0	0	0
<i>C. albicans</i>	$3.2 \times 10^5$	—	—	0	0	0	0
<i>A. niger</i>	$1.8 \times 10^5$	—	—	0	0	0	0

Unit : CFU/mL

表3-3

A-07	接種菌数	6 <sup>th</sup>	24 <sup>th</sup>	1W	2W	3W	4W
<i>S. aureus</i>	$2.7 \times 10^6$	$3.1 \times 10^4$	0	0	0	0	0
<i>E. coli</i>	$7.4 \times 10^6$	0	0	0	0	0	0
<i>P. aeruginosa</i>	$8.8 \times 10^6$	0	0	0	0	0	0
<i>C. albicans</i>	$4.6 \times 10^5$	—	—	0	0	0	0
<i>A. niger</i>	$1.0 \times 10^5$	—	—	0	0	0	0

Unit : CFU/mL

【0039】

表3-1、表3-2および表3-3から明らかなように、処方A-04の防腐効力はE P-Aの基準1)、処方A-05およびA-07の防腐効力はE P-Bの基準2)に適合することがわかった。

【0040】

1) EP (European Pharmacopoeia) —Aの基準

細菌 (*S. aureus*, *P. aeruginosa*) の生菌数が、接種6時間後に1/100以下、24時間後に1/1000以下となり、28日後に生菌が検出されないこと。

真菌 (*C. Albicans*, *A. niger*) の生菌数が、接種7日後に1/100以下、以降は7日後と同レベルかそれ以下となること。

2) EP—Bの基準

細菌 (*S. aureus*, *P. aeruginosa*) の生菌数が、接種24時間後に1/10以下、7日後に1/1000以下となり、以降は7日後と同レベルかそれ以下となること。

真菌 (*C. Albicans*, *A. niger*) の生菌数が、接種14日後に1/10以下、以降は7日後と同レベルかそれ以下となること。

【0041】

実施例1 点眼液

2-アミノ-3-(4-ブロモベンゾイル) フェニル酢酸ナトリウム・3/2水和物

	0.1 g
ホウ酸	1.1 g
ホウ砂	1.1 g
塩化ベンザルコニウム	0.005 g
チロキサポール	0.02 g
ポリビニルピロリドン (K-30)	2.0 g
エデト酸ナトリウム	0.02 g
水酸化ナトリウム	適量
滅菌精製水	全量100 mL
	pH8.17

以上の成分を用いて、常法により点眼液とする。

【0042】

実施例2 点眼液

2-アミノ-3-(4-ブロモベンゾイル) フェニル酢酸ナトリウム・3/2水和物

	0.1 g
ホウ酸	1.1 g
ホウ砂	1.1 g
塩化ベンザルコニウム	0.005 g
チロキサポール	0.05 g
ポリビニルピロリドン (K-30)	2.0 g
エデト酸ナトリウム	0.02 g
水酸化ナトリウム	適量
滅菌精製水	全量100 mL
	pH8.16

以上の成分を用いて、常法により点眼液とする。

【0043】

実施例3 点眼液

2-アミノ-3-(4-ブロモベンゾイル)フェニル酢酸ナトリウム・3/2水和物

	0.1 g
ホウ酸	1.1 g
ホウ砂	1.1 g
塩化ベンザルコニウム	0.005 g
ステアリン酸ポリオキシシル40	0.02 g
ポリビニルピロリドン (K-30)	2.0 g
エデト酸ナトリウム	0.02 g
水酸化ナトリウム	適量
滅菌精製水	全量100 mL
	pH8.19

以上の成分を用いて、常法により点眼液とする。

【0044】

【発明の効果】

本発明によれば、2-アミノ-3-(4-ブロモベンゾイル)フェニル酢酸も

しくはその薬理学的に許容できる塩またはそれらの水和物を含有する水性液剤に、チロキサポールなどのアルキルアリアルポリエーテルアルコール型ポリマーまたはモノステアリン酸ポリエチレングリコールなどのポリエチレングリコール脂肪酸エステルを配合することにより、2-アミノ-3-(4-ブロモベンゾイル)フェニル酢酸もしくはその薬理学的に許容できる塩またはそれらの水和物を含有する安定な水性液剤を調製できる。また、本発明の水性液剤は十分な防腐効力も有している。

したがって、本発明の水性液剤は、例えば点眼液として、眼瞼炎、結膜炎、強膜炎、術後炎症などの治療に有利に用いられる。

【書類名】 要約書

【要約】

【課題】 安定化された2-アミノ-3-(4-ブロモベンゾイル)フェニル酢酸もしくはその薬理学的に許容できる塩またはそれらの水和物を含有する安定かつ十分な防腐効力を有する水性液剤を提供する。

【解決手段】 2-アミノ-3-(4-ブロモベンゾイル)フェニル酢酸もしくはその薬理学的に許容できる塩またはそれらの水和物とチロキサポールなどのアルキルアリアルポリエーテルアルコール型ポリマーまたはモノステアリン酸グリコールなどのポリエチレングリコール脂肪酸エステルとを含有する水性液剤。

【選択図】 なし

出願人履歴

000199175

19900822

新規登録

大阪府大阪市中央区平野町2丁目5番8号

千寿製薬株式会社







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Table with 7 columns: APPLICATION NUMBER, FILING or 371(c) DATE, GRP ART UNIT, FIL FEE REC'D, ATTY. DOCKET NO, TOT CLAIMS, IND CLAIMS. Row 1: 14/493,903, 09/23/2014, 1629, 2400, 2014-1250, 30, 3

CONFIRMATION NO. 7395

513
WENDEROTH, LIND & PONACK, L.L.P.
1030 15th Street, N.W.,
Suite 400 East
Washington, DC 20005-1503

FILING RECEIPT



Date Mailed: 10/01/2014

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)

Shirou SAWA, Hyogo, JAPAN;
Shuhei FUJITA, Hyogo, JAPAN;

Applicant(s)

SENJU PHARMACEUTICAL CO., LTD., Osaka, JAPAN

Power of Attorney: The patent practitioners associated with Customer Number 00513

Domestic Priority data as claimed by applicant

This application is a DIV of 14/261,720 04/25/2014
which is a DIV of 14/165,976 01/28/2014 PAT 8754131
which is a DIV of 13/687,242 11/28/2012 PAT 8669290
which is a DIV of 13/353,653 01/19/2012 PAT 8497304
which is a DIV of 10/525,006 03/28/2005 PAT 8129431
which is a 371 of PCT/JP2004/000350 01/16/2004

Foreign Applications (You may be eligible to benefit from the Patent Prosecution Highway program at the USPTO. Please see http://www.uspto.gov for more information.)
JAPAN 2003-012427 01/21/2003

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**If Required, Foreign Filing License Granted:** 09/29/2014

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 14/493,903**

**Projected Publication Date:** 01/08/2015

**Non-Publication Request:** No

**Early Publication Request:** No  
**Title**

AQUEOUS LIQUID PREPARATION CONTAINING  
2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID

**Preliminary Class**

514

**Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications:** No

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor :  
Shirou SAWA :  
Serial No. NEW :  
Filed September 23, 2014 : Attorney Docket No. 2014-1250  
AQUEOUS LIQUID PREPARATION  
CONTAINING 2-AMINO-3-(4-  
BROMOBENZOYL)PHENYLACETIC ACID  
**(Rule 1.53(b) Divisional  
of Serial No. 14/261,720,  
Filed April 25, 2014)**

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**INFORMATION DISCLOSURE STATEMENT**

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

Sir/Madam:

Pursuant to the provisions of 37 CFR § 1.56, 1.97 and 1.98, Applicant requests consideration of the information listed on attached Form PTO/SB/08.

It is requested that the Examiner consider all the information of record in the prior parent application(s) (Serial No. 14/261,720), relied on by the present application under 35 U.S.C. § 120. A copy of any listed reference that was previously cited by or submitted to the PTO in the prior parent application(s) is not required or provided herein (see 37 C.F.R. 1.98(d)).

- 1a.  This Information Disclosure Statement is submitted:  
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before the mailing of a first Office Action on the merits or the mailing of a first Office Action after the filing of an RCE,

**and thus no certification and/or fee is required.**

1b.  This Information Disclosure Statement is submitted

after the events of above paragraph 1a and prior to the mailing date of a final Office Action or a Notice of Allowance or an action which otherwise closes prosecution in the application, and thus:

(1)  the certification of paragraph 2 below is provided, or

(2)  the fee of \$180.00 (\$90.00 for small entity) specified in 37 CFR 1.17(p) is enclosed.

1c.  This Information Disclosure Statement is submitted:

after the mailing date of a final Office Action or Notice of Allowance or action which otherwise closes prosecution in the application, and prior to payment of the issue fee, and thus:

**the certification of paragraph 2 below is provided, and  
the fee of \$180.00 (\$90.00 for small entity) specified in 37 CFR 1.17(p) is enclosed.**

2. It is hereby certified

a.  that each item of information contained in this 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 Statement (37 C.F.R. § 1.97(e)(1)), or

b.  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, was known to any individual designated in §1.56(c) more than three months prior to the filing of the Statement (37 C.F.R. § 1.97(e)(2)).

3. For each non-English language reference listed on the attached Form PTO/SB/08, reference is made to one or more of the following:
- a.  a full or partial English language translation submitted herewith,
  - b.  an International Search Report submitted herewith,
  - c.  a foreign patent office search report or office action (in the English language) submitted herewith,
  - d.  the concise explanation contained in the specification of the present application at page,
  - e.  the concise explanation set forth in the attached English language abstract,
  - f.  the concise explanation set forth below or on a separate sheet attached to the reference:
4.  A foreign patent office search report citing one or more of the references is enclosed.

Respectfully submitted,

**/Warren M.  
Cheek, Jr./**

Digitally signed by /Warren M. Cheek, Jr./  
DN: cn=/Warren M. Cheek, Jr./, o, ou,  
email=wcheek@wenderoth.com, c=US  
Date: 2014.09.23 13:20:07 -04'00'

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Warren M. Cheek  
Registration No. 33,367  
Attorney for Applicant

WMC/dlk  
Washington, D.C. 20005-1503  
Telephone (202) 721-8200  
Facsimile (202) 721-8250  
September 23, 2014



## INFORMATION DISCLOSURE STATEMENT

FORM PTO/SB/08 A&amp;B (modified)

ATTY DOCKET NO.  
2014-1250SERIAL NO.  
NEWU.S. DEPARTMENT OF COMMERCE  
PATENT AND TRADEMARK OFFICEFIRST NAMED INVENTOR  
Shirou SAWALIST OF REFERENCES CITED BY APPLICANT(S)  
(Use several sheets if necessary)FILING DATE  
September 23, 2014

GROUP

Date Submitted to PTO: September 23, 2014

## U.S. PATENT DOCUMENTS

*EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
	AA	5,603,929	2/1997	Desai et al.			
	AB	5,653,972	8/1997	Desai et al.			
	AC	4,910,225	3/1990	Ogawa et al.			
	AD	5,110,493	5/1992	Cheng-Chyi et al.			
	AE	6,383,471	5/2002	Chen et al.			
	AF	4,045,576	8/1977	Welstead, Jr. et al.			
	AG	4,683,242	7/1987	Poser			
	AH	6,319,513	11/2001	Dobrozsi			
	AI	2007/0082857	4/2007	Sawa			
	AJ	6,369,112	4/2002	Xia			
	AK	5,998,465	12/1999	Hellberg et al.			
	AL	5,597,560	1/1997	Bergamini et al.			
	AM	6,395,746	5/2002	Cagle et al.			
	AN	5,475,034	12/1995	Yanni et al.			
	AO	5,540,930	7/1996	Guy			
	AP	5,942,508	8/1999	Sawa			
	AQ	6,274,592	8/2001	Sawa			
	AR	2001/0056098	12/2001	Sawa			
	AS	6,274,609	8/2001	Yasueda et al.			
	AT	5,558,876	9/1996	Desai et al.			
	AU	6,162,393	12/2000	De Bruiju et al.			
	AV	8,129,431	3/2012	Sawa et al.			
	AW	6,107,343	8/2000	Sallmann et al.			
	AX	2,880,130	3/1959	Johnson			

## INFORMATION DISCLOSURE STATEMENT

FORM PTO/SB/08 A&B ( <i>modified</i> )				ATTY DOCKET NO. 2014-1250			SERIAL NO. NEW	
U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE  LIST OF REFERENCES CITED BY APPLICANT(S) (Use several sheets if necessary)  Date Submitted to PTO: September 23, 2014				FIRST NAMED INVENTOR Shirou SAWA				
				FILING DATE September 23, 2014			GROUP	
	AY	2,880,138	3/1959	Johnson				
	AZ	6,071,904	6/2000	Ali et al.				
FOREIGN PATENT DOCUMENTS								
		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION/ADDITIONAL INFORMATION YES NO	
	BA	9-503791	4/1997	JP				
	BB	2-124819	5/1990	JP				
	BC	1-104023	4/1989	JP				
	BD	00/59475	10/2000	WO				
	BE	11-228404	8/1999	JP			Yes	
	BF	5-223052	8/1993	JP			Abstract	
	BG	62-126124	6/1987	JP				No
	BH	96/14829	5/1996	WO				
	BI	01/15677	3/2001	WO				
	BJ	2 013 188	9/1990	CA				
	BK	02/13804	2/2002	WO				
	BL	707 119	9/1995	AU				
	BM	02083323	3/1990	JP				
	BN	2002-308764	10/2002	JP				
	BO	0 306 984	3/1989	EP				
	BP	22042/88	3/1989	AU				
	BQ	94/15597	7/1994	WO				
	BR	2 383 971	3/2001	CA				
	BS	0 274 870	7/1988	EP				
	BT	94/05298	3/1994	WO				
OTHER DOCUMENT(S) ( <i>Including Author, Title, Date, Pertinent Pages, Etc.</i> )								
	CA	New Drugs in Japan, 2001, 2001 Edition, Published by Yakuji Nippo Ltd., May 11, 2001, pp. 27-29, and its English translation of the material portions.						

Sheet 3 of 5		INFORMATION DISCLOSURE STATEMENT	
FORM PTO/SB/08 A&B ( <i>modified</i> )  U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE  LIST OF REFERENCES CITED BY APPLICANT(S) ( <i>Use several sheets if necessary</i> )  Date Submitted to PTO: September 23, 2014		<b>ATTY DOCKET NO.</b> 2014-1250	<b>SERIAL NO.</b> NEW
		<b>FIRST NAMED INVENTOR</b> Shirou SAWA	
		<b>FILING DATE</b> September 23, 2014	<b>GROUP</b>
	CB	ISTA Pharmaceuticals, "New Drug Applications: Xibrom", <a href="http://www.drugs.com/nda/xibrom_040525.html">http://www.drugs.com/nda/xibrom_040525.html</a> , accessed online 9/19/2007.	
	CC	Nolan et al., "The Topical Anti-Inflammatory and Analgesic Properties of Bromfenic in Rodents", <i>Agents and Actions</i> , Vol. 25, No. 1-2, pp. 77-85, August 1988.	
	CD	Corrected partial English translation of New Drugs in Japan, 2001, 2001 Edition, Published by Yakuji Nippo Ltd., May 11, 2001, pp. 27-29, previously submitted on April 11, 2005.	
	CE	Complete English translation of New Drugs in Japan, 2001, 2001 Edition, Published by Yakuji Nippo Ltd., May 11, 2001, pp. 27-29.	
	CF	Notice of Opposition dated February 19, 2009 issued by EPO in connection with the corresponding European patent application and Opposition.	
	CG	<a href="http://medical-dictionary.thefreedictionary.com/prophylactic">http://medical-dictionary.thefreedictionary.com/prophylactic</a> accessed 12/15/2009.	
	CH	Y. Hara, "Evaluation of New Drugs by Clinicians", <i>Clinics &amp; Drug Therapy</i> , Vol. 19, No. 10, October 2000, pp. 1-2.	
	CI	G. Smolin, M.D., "New Drugs in Ophthalmology", <i>International Ophthalmology Clinics</i> , Vol. 36, No. 2, 1996, pp. 1-9.	
	CJ	ISTA News Release, XIBROM™, Bromfenac Ophthalmic Solution, 2007, p.1.	
	CK	S. Prince et al., "Analysis of Benzalkonium Chloride and its Homologs: HPLC Versus HPCE <sup>1</sup> ", <i>Journal of Pharmaceutical and Biomedical Analysis</i> , Vol. 19, pp. 877-882, 1999.	
	CL	M. Doughty, "Therapeutics: Medicines Update <i>p18</i> Side-Effects of Anti-Epilepsy Drugs", <i>Optician</i> , Vol. 223, No. 5853, May 31, 2002, pp. 16-22.	
	CM	I. Reddy, Ph.D., "Ocular Therapeutics and Drug Delivery", Technomics Publishing Co., Basel, pp. 42-43, 390, 1996.	
	CN	H. Schott, "Comparing the Surface Chemical Properties and the Effect of Salts on the Cloud Point of a Conventional Nonionic Surfactant, Octoxynol 9 (Triton X-100), and of its Oligomer, Tyloxapol (Triton WR-1339)", <i>Journal of Colloid and Interface Science</i> , Vol. 205, pp. 496-502, 1998.	
	CO	O. Regev, "Aggregation Behavior of Tyloxapol, a Nonionic Surfactant Oligomer, in Aqueous Solution", <i>Journal of Colloid and Interface Science</i> , Vol. 210, pp. 8-17, 1999.	
	CP	PDR 50th Edition 1996, <i>Physicians' Desk Reference</i> , p. 469.	
	CQ	PDR 54th Edition 2000, <i>Physicians' Desk Reference</i> , pp. 486-487, 491-492.	
	CR	V. A. Ostrovskii et al., "Acid-Base Properties of 5-Substituted Tetrazoles", <i>Khimiya Get. Soc.</i> , pp. 412-416, 1981.	
	CS	LOTEMAX™ product brochure, Loteprednol Etabonate Ophthalmic Suspension, 0.5%, pp. 1-16, March 6, 1998.	

Sheet 4 of 5		INFORMATION DISCLOSURE STATEMENT	
FORM PTO/SB/08 A&B (modified)  U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE  LIST OF REFERENCES CITED BY APPLICANT(S) (Use several sheets if necessary)  Date Submitted to PTO: September 23, 2014		<b>ATTY DOCKET NO.</b> 2014-1250	<b>SERIAL NO.</b> NEW
		<b>FIRST NAMED INVENTOR</b> Shirou SAWA	
		<b>FILING DATE</b> September 23, 2014	<b>GROUP</b>
	CT	Webster's New World Dictionary of the American Language, Second College Edition, "monohydrate", Simon & Schuster, NY, p. 920, 1982.	
	CU	Pharmacopeia, R. S. Cook et al., "Edetic Acid", pp. 177-179, JT Steward, "Sodium Metabisulfide", pp. 451-453, 2000.	
	CV	Yakuji Nippo Limited, "Recent New Drugs 2001", Japanese Pharmacopoeia 2001 Edition, pp. 27-29, May 2001 (English translation).	
	CW	Sigma-Aldrich catalog, Biochemicals and Reagents for Life Science Research, p. 175, 2000.	
	CX	G. Patani et al., "Bioisosterism: A Rational Approach in Drug Design", Chemical Reviews, Vol. 96, No. 8, pp. 3147-3176, 1996.	
	CY	P. Deluca et al., "Interaction of Preservatives with Macromolecules IV, Binding of Quaternary Ammonium Compounds by Nonionic Agents", Journal of the American Pharmaceutical Association, Vol. 49, No. 7, pp. 430-437, July 1960.	
	CZ	D. Guttman et al., "Solubilization of Anti-Inflammatory Steroids by Aqueous Solutions of Triton WR-1339", Journal of Pharmaceutical Sciences, Vol. 50, No. 4, pp. 305-307, April 1961.	
	CCA	T. Fan et al., "Determination of Benzalkonium Chloride in Ophthalmic Solutions Containing Tyloxapol by Solid-Phase Extraction and Reversed-Phase High-Performance Liquid Chromatography", Journal of Pharmaceutical Sciences, Vol. 82, No. 11, pp. 1172-1174, November 1993.	
	CCB	FDA Website search of Orange Book (Patent and Exclusivity Search Results): Approved Drug Products with Therapeutic Equivalence Evaluations; Search Results for N203168, 2014.	
	CCC	FDA website search of Orange Book (Detail Record Search): Approved Drug Products with Therapeutic Equivalence Evaluations, Search Results for N203168, 2014.	
	CCD	Remington: The Science and Practice of Pharmacy, 20 <sup>th</sup> Edition, "Boric Acid", Lippincott, Williams, Baltimore MD, p. 1041, 2000.	
	CCE	PDR 52nd Edition 1998, Physicians' Desk Reference, "Duract", Method Economics Co., Monroville, NJ, pp. 3035-3037.	
	CCF	ALREX <sup>TM</sup> product package, Loteprednol Etabonate, Ophthalmic Suspension, 0.2%, pp. 1-13, 1998.	
	CCG	XIBROM <sup>TM</sup> product package, Bromfenac Ophthalmic Solution, 0.09%, pp. 3-6, 2000.	
	CCH	BROMDAY product package, Bromfenac Ophthalmic Solution, 0.09%, pp. 4-8, 1997.	
	CCI	PROLENSA <sup>TM</sup> product package, Bromfenac Ophthalmic Solution, 0.07%, pp. 4-9, 2013.	
	CCJ	PDR 54 Edition 2000, Physicians' Desk Reference, pp. 489-491, TOBRADEX®, Tobramycin and Dexamethasone Ophthalmic Suspension and Ointment.	
	CCK	FDA website description of VOLTAREN, Diclofenac Sodium, Ophthalmic Solution, 0.1%, pp. 1-2, 1991.	

## INFORMATION DISCLOSURE STATEMENT

FORM PTO/SB/08 A&B ( <i>modified</i> )		<b>ATTY DOCKET NO.</b> 2014-1250	<b>SERIAL NO.</b> NEW
U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE  LIST OF REFERENCES CITED BY APPLICANT(S) ( <i>Use several sheets if necessary</i> )  Date Submitted to PTO: September 23, 2014		<b>FIRST NAMED INVENTOR</b> Shirou SAWA	
		<b>FILING DATE</b> September 23, 2014	<b>GROUP</b>
	CCL	ALREX™ product package, Loteprednol Etabonate, Ophthalmic Suspension, 0.2%, pp. 1-13, 1998.	
	CCM	The United States Pharmacopeia, The National Formulary, USP 24, NF 19, pp. 1809-1813, 1864-1866, 2000.	
	CCN	Dorset & Baber, Webster's New Twentieth Century Dictionary, Second Edition, "Ophthalmic" and "Ophthalmic" p. 1254, 1979.	
	CCO	BRONUCK® news release, Bromfenac Sodium Hydrate Ophthalmic Solution, p.1, 2005.	
EXAMINER		DATE CONSIDERED	

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor : Attorney Docket No. 2014-1250  
Shirou SAWA :  
Serial No. NEW :  
Filed September 23, 2014 :

AQUEOUS LIQUID PREPARATION  
CONTAINING 2-AMINO-3-(4-  
BROMOBENZOYL)PHENYLACETIC ACID  
**(Rule 1.53(b) Divisional  
of Serial No. 14/261,720,  
Filed September 23, 2014)**

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**PRELIMINARY AMENDMENT**

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

Sir/Madam:

Prior to examination, please amend the above-identified application as follows:

## AMENDMENTS TO THE CLAIMS

### **1-18. (Cancelled)**

**19. (New)** A method for treating an inflammatory disease of an eye, the method comprising administering to said eye a stable aqueous liquid preparation that comprises: (a) a first component; and (b) a second component; wherein the first component is 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, wherein the hydrate is at least one selected from a 1/2 hydrate, 1 hydrate, and 3/2 hydrate; the first component is the sole pharmaceutical active ingredient contained in the preparation; the second component is tyloxapol and is present in said liquid preparation in an amount sufficient to stabilize said first component; wherein said stable liquid preparation is formulated for ophthalmic administration; and wherein said liquid preparation is administered to said eye at a dose and a frequency effective to treat said inflammatory disease.

**20. (New)** The method according to claim 19, wherein said inflammatory disease is a disease of an anterior or posterior segment of said eye.

**21. (New)** The method according to claim 20, wherein said disease is postoperative inflammation.

**22. (New)** The method according to claim 19, wherein the first component is a 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt.

**23. (New)** The method according to claim 19, wherein the concentration of tyloxapol is from about 0.01 w/v % to about 0.05 w/v %; and wherein the first component is a 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.01 to about 0.2 w/v %.

**24. (New)** The method according to claim 23, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.02 w/v% to about 0.1 w/v %.

**25. (New)** The method according to claim 23, wherein the aqueous liquid preparation further comprises a quaternary ammonium salt.

**26. (New)** The method according to claim 23, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is about 0.1 w/v %.

**27. (New)** The method according to claim 19, wherein the stable aqueous liquid preparation consists essentially of: (a) 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt, (d) sodium tetraborate, (e) EDTA sodium salt, (f) benzalkonium chloride, (g) polyvinylpyrrolidone, and (h) sodium sulfite, wherein said liquid preparation is formulated for ophthalmic administration, and wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.02 w/v% to about 0.1 w/v %.

**28. (New)** The method according to claim 19, wherein said dose comprises one or two drops.

**29. (New)** A method for treating an inflammatory disease of an eye, the method comprising administering to said eye a stable aqueous liquid preparation that comprises: (a) a first component; and (b) a second component; wherein the first component is 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, wherein the hydrate is at least one selected from a 1/2 hydrate, 1 hydrate, and 3/2 hydrate; the first component is the sole pharmaceutical active ingredient contained in the preparation; the second component is tyloxapol; wherein said stable liquid preparation is formulated for ophthalmic administration; wherein the stable aqueous liquid preparation is characterized in that greater than about 90% of the original amount of the first component remains in the preparation after storage at about 60 °C for 4 weeks; and wherein said liquid preparation is administered to said eye at a dose and a frequency effective to treat said inflammatory disease.

**30. (New)** The method according to claim 29, wherein the stable aqueous liquid preparation is characterized in that greater than about 92% of the original amount of the first component remains in the preparation after storage at about 60 °C for 4 weeks.



**31. (New)** The method according to claim 29, wherein said inflammatory disease is a disease of an anterior or posterior segment of said eye.

**32. (New)** The method according to claim 31, wherein said disease is postoperative inflammation.

**33. (New)** The method according to claim 29, wherein the concentration of tyloxapol is from about 0.01 w/v % to about 0.05 w/v %; and wherein the first component is a 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.01 to about 0.2 w/v %.

**34. (New)** The method according to claim 33, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.02 w/v% to about 0.1 w/v %.

**35. (New)** The method according to claim 29, further comprising a quaternary ammonium salt

**36. (New)** The method according to claim 29, wherein the stable aqueous liquid preparation consists essentially of: (a) 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, wherein the hydrate is at least one selected from a 1/2 hydrate, 1 hydrate, and 3/2 hydrate; (b) tyloxapol; (c) boric acid; (d) sodium tetraborate; (e) EDTA sodium salt; (f) benzalkonium chloride; (g) polyvinylpyrrolidone; and (h) sodium sulfite; and wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.02 w/v% to about 0.1 w/v %.

**37. (New)** A method for treating an inflammatory disease of an eye, the method comprising administering to said eye a stable aqueous liquid preparation that comprises: (a) a first component; and (b) a second component; wherein the first component is 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, wherein the hydrate is at least one selected from a 1/2 hydrate, 1 hydrate, and 3/2 hydrate; the first component is the sole pharmaceutical active ingredient contained in the preparation; the second component is tyloxapol; wherein said stable liquid preparation is formulated for ophthalmic administration; provided that the liquid preparation does not include

mannitol; and wherein said liquid preparation is administered to said eye at a dose and a frequency effective to treat said inflammatory disease.

**38. (New)** The method according to claim 37, wherein said inflammatory disease is a disease of an anterior or posterior segment of said eye.

**39. (New)** The method according to claim 38, wherein said disease is postoperative inflammation.

**40. (New)** The method according to claim 37, wherein the first component is a 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt.

**41. (New)** The method according to claim 40, wherein the concentration of tyloxapol is from about 0.01 w/v % to about 0.05 w/v % and the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.05 to about 0.2 w/v %.

**42. (New)** The method according to claim 40, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.02 w/v% to about 0.1 w/v %.

**43. (New)** The method according to claim 38; wherein the stable aqueous liquid preparation consists essentially of: (a) 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, wherein the hydrate is at least one selected from a 1/2 hydrate, 1 hydrate, and 3/2 hydrate; (b) tyloxapol; (c) boric acid; (d) sodium tetraborate; (e) EDTA sodium salt; (f) benzalkonium chloride; (g) polyvinylpyrrolidone; and (h) sodium sulfite; wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.02 w/v% to about 0.1 w/v %.

**44. (New)** The method according to claim 38, wherein the stable aqueous liquid preparation is characterized in that greater than about 90% of the original amount of the first component remains in the preparation after storage at about 60 °C for 4 weeks.

**45. (New)** The method according to claim 38, wherein the concentration of tyloxapol is from about 0.01 w/v % to about 0.05 w/v %; and wherein the first component is a 2-amino-3-(4-

bromobenzoyl)phenylacetic acid sodium salt, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.02 to about 0.1 w/v %.

**46. (New)** The method according to claim 19, wherein the aqueous liquid preparation further satisfies the preservative efficacy standard of EP-criteria B of the European Pharmacopoeia as follows: viable cell counts of bacteria (*S. aureus*, *P. aeruginosa*) 24 hours and 7 days after inoculation decrease to not more than 1/10 and not more than 1/1000, respectively, and thereafter, the cell count levels off or decreases; and viable cell count of fungi (*C. albicans*, *A. niger*) 14 days after inoculation decreases to not more than 1/10, and thereafter, the cell count keeps the same level as that of 14 days after inoculation.

**47. (New)** The method according to claim 29, wherein the aqueous liquid preparation further satisfies the preservative efficacy standard of EP-criteria B of the European Pharmacopoeia as follows: viable cell counts of bacteria (*S. aureus*, *P. aeruginosa*) 24 hours and 7 days after inoculation decrease to not more than 1/10 and not more than 1/1000, respectively, and thereafter, the cell count levels off or decreases; and viable cell count of fungi (*C. albicans*, *A. niger*) 14 days after inoculation decreases to not more than 1/10, and thereafter, the cell count keeps the same level as that of 14 days after inoculation.

**48. (New)** The method according to claim 37, wherein the aqueous liquid preparation further satisfies the preservative efficacy standard of EP-criteria B of the European Pharmacopoeia as follows: viable cell counts of bacteria (*S. aureus*, *P. aeruginosa*) 24 hours and 7 days after inoculation decrease to not more than 1/10 and not more than 1/1000, respectively, and thereafter, the cell count levels off or decreases; and viable cell count of fungi (*C. albicans*, *A. niger*) 14 days after inoculation decreases to not more than 1/10, and thereafter, the cell count keeps the same level as that of 14 days after inoculation.

**REMARKS**

The present application is a divisional of Serial No. 14/261,720. The present Preliminary Amendment is submitted to cancel original claims 1-18, and add new claims 19-48.

No new matter has been added.

Respectfully submitted,

**/Warren M.  
Cheek, Jr./**

Digitally signed by /Warren M. Cheek,  
Jr./  
DN: cn=/Warren M. Cheek, Jr./, o, ou,  
email=wcheek@wenderoth.com,  
c=US  
Date: 2014.09.23 13:20:52 -04'00'

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Warren M. Cheek  
Registration No. 33,367  
Attorney for Applicant

WMC/dlk  
Washington, D.C. 20005-1503  
Telephone (202) 721-8200  
Facsimile (202) 721-8250  
September 23, 2014

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor :  
Shirou SAWA :  
Serial No. NEW :  
Filed September 23, 2014 : Attorney Docket No. 2014-1250

AQUEOUS LIQUID PREPARATION  
CONTAINING 2-AMINO-3-(4-  
BROMOBENZOYL)PHENYLACETIC  
ACID

**(Rule 1.53(b) Divisional  
of Serial No. 14/261,720,  
Filed April 25, 2014)**

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**CLAIM OF PRIORITY UNDER 35 USC 119**

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

Sir/Madam:

Applicant, in the above-identified application hereby claims the date of priority under the International Convention of Japanese Patent Application No. 2003-012427, filed January 21, 2003, as acknowledged in the Application Data Sheet of this application.

A certified copy of said Japanese Patent Application is of record in a parent application.

Respectfully submitted,

/Warren M.  
Cheek, Jr./

Digitally signed by /Warren M. Cheek, Jr./  
DN: cn=/Warren M. Cheek, Jr./, o, ou,  
email=wcheek@wenderoth.com,  
c=US  
Date: 2014.09.23 13:21:08 -04'00'

Warren M. Cheek  
Registration No. 33,367  
Attorney for Applicant

WMC/dlk  
Washington, D.C. 20005-1503  
Telephone (202) 721-8200  
Facsimile (202) 721-8250  
September 23, 2014

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

First Named Inventor:	Shirou SAWA	Nonprovisional Application Number (if known):	
Title of Invention:	AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID		

**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).

**Warren M.**

Digitally signed by /Warren M. Cheek, Jr./  
 DN: cn=/Warren M. Cheek, Jr./, o, ou,  
 email=wcheek@wenderoth.com, c=US  
 Date: 2014.09.23 13:21:29 -04'00'

Signature	<b>Cheek, Jr./</b>	Date	<b>September 23, 2014</b>
Name (Print/Typed)	<b>Warren M. Cheek</b>	Practitioner Registration Number	<b>33,367</b>

**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.

## Electronic Patent Application Fee Transmittal

<b>Application Number:</b>				
<b>Filing Date:</b>				
<b>Title of Invention:</b>	AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID			
<b>First Named Inventor/Applicant Name:</b>	Shirou SAWA			
<b>Filer:</b>	Warren M. Cheek Jr./Donna King			
<b>Attorney Docket Number:</b>	2014-1250			
Filed as Large Entity				
<b>Track I Prioritized Examination - Nonprovisional Application under 35 USC 111(a) Filing Fees</b>				
<b>Description</b>	<b>Fee Code</b>	<b>Quantity</b>	<b>Amount</b>	<b>Sub-Total in USD(\$)</b>
<b>Basic Filing:</b>				
Utility application filing	1011	1	280	280
Utility Search Fee	1111	1	600	600
Utility Examination Fee	1311	1	720	720
Request for Prioritized Examination	1817	1	4000	4000
<b>Pages:</b>				
<b>Claims:</b>				
Claims in Excess of 20	1202	10	80	800
<b>Miscellaneous-Filing:</b>				

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
PROCESSING FEE, EXCEPT PROV. APPLS.	1830	1	140	140
<b>Petition:</b>				
<b>Patent-Appeals-and-Interference:</b>				
<b>Post-Allowance-and-Post-Issuance:</b>				
<b>Extension-of-Time:</b>				
<b>Miscellaneous:</b>				
<b>Total in USD (\$)</b>				<b>6540</b>



## Electronic Acknowledgement Receipt

<b>EFS ID:</b>	20217594
<b>Application Number:</b>	14493903
<b>International Application Number:</b>	
<b>Confirmation Number:</b>	7395
<b>Title of Invention:</b>	AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID
<b>First Named Inventor/Applicant Name:</b>	Shirou SAWA
<b>Customer Number:</b>	513
<b>Filer:</b>	Warren M. Cheek Jr./pam veazey
<b>Filer Authorized By:</b>	Warren M. Cheek Jr.
<b>Attorney Docket Number:</b>	2014-1250
<b>Receipt Date:</b>	23-SEP-2014
<b>Filing Date:</b>	
<b>Time Stamp:</b>	15:16:34
<b>Application Type:</b>	Utility under 35 USC 111(a)

### Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	\$6540
RAM confirmation Number	1704
Deposit Account	230975
Authorized User	CHEEK JR., WARREN M.

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	Transmittal of New Application	AttachA1_Trans.pdf	208673 5f80295ab1263e92a00bd18fd4a672bf8377	no	1

### Warnings:

The PDF file has been signed with a digital signature and the legal effect of the document will be based on the contents of the file not the digital signature.

### Information:

2	Application Data Sheet	AttachA2_Ads.pdf	1561663 8eba3864e12fdaa11e7c976e491ffc9694da3	no	7
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### Warnings:

### Information:

3		AttachB_Spec.pdf	977738 a1a7d181017ab6549e70b9c7d62f32395b06ab	yes	29
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### Multipart Description/PDF files in .zip description

Document Description	Start	End
Specification	1	24
Claims	25	28
Abstract	29	29

### Warnings:

The PDF file has been signed with a digital signature and the legal effect of the document will be based on the contents of the file not the digital signature.

### Information:

4	Oath or Declaration filed	AttachC1_Decl.pdf	111532 e240517d0d541bc4b864898115fa38c8896c5a8b	no	2
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### Warnings:

The PDF file has been signed with a digital signature and the legal effect of the document will be based on the contents of the file not the digital signature.

### Information:

5	Power of Attorney	AttachC2_Poa.pdf	436477 fba4694300b19c1b0946efb80d97e476cd5e0239	no	2
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### Warnings:

The PDF file has been signed with a digital signature and the legal effect of the document will be based on the contents of the file not the digital signature.

**Information:**

6	Information Disclosure Statement (IDS) Form (SB08)	AttachD1_Ids.pdf	185726	no	3
			ec6b733593bb26aae8874bea86607509b889b24e		

**Warnings:**

**Information:**

This is not an USPTO supplied IDS fillable form

The PDF file has been signed with a digital signature and the legal effect of the document will be based on the contents of the file not the digital signature.

7	Information Disclosure Statement (IDS) Form (SB08)	AttachD2_SB08.pdf	167944	no	5
			736d4aa0d1d695dbf19e4bcd3fc286af59523246		

**Warnings:**

**Information:**

This is not an USPTO supplied IDS fillable form

The PDF file has been signed with a digital signature and the legal effect of the document will be based on the contents of the file not the digital signature.

8		AttachE_Pa.pdf	248473	yes	7
			4df1310f4104ce83e3f2cbea8c2fda4ea84da26		

**Multipart Description/PDF files in .zip description**

Document Description	Start	End
Preliminary Amendment	1	1
Claims	2	6
Applicant Arguments/Remarks Made in an Amendment	7	7

**Warnings:**

The PDF file has been signed with a digital signature and the legal effect of the document will be based on the contents of the file not the digital signature.

**Information:**

9	Miscellaneous Incoming Letter	AttachF_Cop.pdf	174438	no	1
			ea0ff74e0674321f3881a5fb03b4c5672e8d13		

**Warnings:**

The PDF file has been signed with a digital signature and the legal effect of the document will be based on the contents of the file not the digital signature.

**Information:**

10	TrackOne Request	AttachG.pdf	170141	no	1
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**Warnings:**

The PDF file has been signed with a digital signature and the legal effect of the document will be based on the contents of the file not the digital signature.

**Information:**

11	Fee Worksheet (SB06)	fee-info.pdf	40697	no	2
			ef29523de14e52e574b6bbf8b6342a16b3626b21		

**Warnings:****Information:**

<b>Total Files Size (in bytes):</b>	4283502
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**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.**

<p><b>UTILITY PATENT APPLICATION TRANSMITTAL</b></p> <p><i>(Only for new nonprovisional applications under 37 CFR 1.53(b))</i></p>	<p><i>Attorney Docket No.:</i> 2014-1250</p> <hr/> <p><i>First Named Inventor:</i> Shirou SAWA</p> <hr/> <p><i>Title:</i> AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID</p> <hr/> <p><i>Express Mail Label No.:</i></p>
<p>APPLICATION ELEMENTS</p> <p><i>See MPEP chapter 600 concerning utility patent application contents.</i></p>	<p><i>ADDRESS TO:</i> Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450</p>
<p>1. <input type="checkbox"/> Small Entity Status is hereby asserted.</p> <p>2. <input checked="" type="checkbox"/> Specification <span style="float: right;"><i>[Total Pages: 29]</i></span> Both the claims and abstract must start on a new page <i>(For information on the preferred arrangement, see MPEP 608.01(a))</i></p> <p>3. <input type="checkbox"/> Drawing(s) <i>(35 USC 113)</i> <span style="float: right;"><i>[Total Sheets: ]</i></span></p> <p>4. <input checked="" type="checkbox"/> Declaration(s) <span style="float: right;"><i>[Total Pages: 2]</i></span> a. <input type="checkbox"/> Copy from a prior application (37 CFR 1.63(d)(1)) <i>(for continuation/divisional with (37 CFR 1.63(d)(1)) completed)</i></p> <p>5. <input checked="" type="checkbox"/> Application Data Sheet (see 37 CFR 1.76)</p> <p>6. <input type="checkbox"/> CD-ROM or CD-R in duplicate, large table or computer program <i>(Appendix)</i></p> <p>7. <input type="checkbox"/> Nucleotide and/or Amino Acid Sequence Submission <i>(if applicable, all necessary)</i> a. <input type="checkbox"/> Computer Readable Form b. Specification Sequence Listing on: i. <input type="checkbox"/> CD-ROM or CD-R (2 copies); or ii. <input type="checkbox"/> Paper c. <input type="checkbox"/> The paper and computer readable copies are identical</p>	<p><b>ACCOMPANYING APPLICATION PARTS</b></p> <p>8. <input checked="" type="checkbox"/> Power of Attorney with cover letter</p> <p>9. <input checked="" type="checkbox"/> Information Disclosure Statement (IDS)/PTO/SB/08 <input type="checkbox"/> Copies of IDS Citations</p> <p>10. <input checked="" type="checkbox"/> Preliminary Amendment</p> <p>11. <input type="checkbox"/> Non-Publication Request and Certification under 35 U.S.C. 122 (b)(2)(B)(i). Applicant must attach form PTO/SB/35 or its equivalent.</p> <p>12. <input checked="" type="checkbox"/> Other - Claim of Priority; Certification and Request for Prioritized Examination</p>
<p>18. If a CONTINUING APPLICATION, check appropriate box, and supply the requisite information below, and in a preliminary amendment, or in an Application Data Sheet :</p> <p><input type="checkbox"/> Continuation      <input checked="" type="checkbox"/> Divisional      <input type="checkbox"/> Continuation-in-part (CIP)      of prior application No. 14/261,720</p> <p><i>Prior Application Information:</i> Examiner: Layla Soroush      Group Art Unit: 1627</p>	
<p>19. CORRESPONDENCE ADDRESS</p> <p style="text-align: center;">CUSTOMER NO. <b>00513</b></p>	<p style="text-align: center;"><b>Warren M. Cheek, Jr./</b></p> <p style="text-align: center;">Warren M. Cheek Registration No. 33,367</p> <p style="text-align: center;">WENDEROTH, LIND &amp; PONACK, L.L.P. 1030 15<sup>th</sup> Street, N.W., Suite 400 East Washington, D.C. 20005-1503 Phone:(202) 721-8200 Fax:(202) 721-8250</p> <p style="text-align: center;">September 23, 2014</p>

Digitally signed by /Warren M. Cheek, Jr./  
DN: cn=/Warren M. Cheek, Jr./, o, ou,  
email=wcheek@wenderoth.com, c=US  
Date: 2014.09.23 13:17:27 -04'00'

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.

<b>Application Data Sheet 37 CFR 1.76</b>		Attorney Docket Number	2014-1250
		Application Number	
Title of Invention	AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID		
<p>The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.</p> <p>This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.</p>			

**Secrecy Order 37 CFR 5.2**

<input type="checkbox"/>	Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)
--------------------------	---

**Inventor Information:**

<b>Inventor 1</b>					<input type="button" value="Remove"/>
<b>Legal Name</b>					
<b>Prefix</b>	<b>Given Name</b>	<b>Middle Name</b>	<b>Family Name</b>	<b>Suffix</b>	
	Shirou		SAWA		
<b>Residence Information (Select One)</b> <input type="radio"/> US Residency <input checked="" type="radio"/> Non US Residency <input type="radio"/> Active US Military Service					
<b>City</b>	Hyogo	<b>Country of Residence i</b>	JP		

**Mailing Address of Inventor:**

<b>Address 1</b>	c/o SENJU PHARM. CO., LTD., Kobe Creative Center				
<b>Address 2</b>	5-4, Murotani 1-chome, Nishi-ku, Kobe-shi				
<b>City</b>	Hyogo	<b>State/Province</b>			
<b>Postal Code</b>	651-2241	<b>Country i</b>	JP		

<b>Inventor 2</b>					<input type="button" value="Remove"/>
<b>Legal Name</b>					
<b>Prefix</b>	<b>Given Name</b>	<b>Middle Name</b>	<b>Family Name</b>	<b>Suffix</b>	
	Shuhei		FUJITA		
<b>Residence Information (Select One)</b> <input type="radio"/> US Residency <input checked="" type="radio"/> Non US Residency <input type="radio"/> Active US Military Service					
<b>City</b>	Hyogo	<b>Country of Residence i</b>	JP		

**Mailing Address of Inventor:**

<b>Address 1</b>	c/o SENJU PHARM., CO., LTD., Kobe Creative Center				
<b>Address 2</b>	5-4, Murotani 1-chome, Nishi-ku, Kobe-shi				
<b>City</b>	Hyogo	<b>State/Province</b>			
<b>Postal Code</b>	651-2241	<b>Country i</b>	JP		

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button.

**Correspondence Information:**

<b>Application Data Sheet 37 CFR 1.76</b>		Attorney Docket Number	2014-1250
		Application Number	
Title of Invention	AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID		

Enter either Customer Number or complete the Correspondence Information section below.  
For further information see 37 CFR 1.33(a).

An Address is being provided for the correspondence information of this application.

Customer Number	00513		
Email Address	wlp@wenderoth.com	<input type="button" value="Add Email"/>	<input type="button" value="Remove Email"/>

### Application Information:

Title of the Invention	AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID		
Attorney Docket Number	2014-1250	Small Entity Status Claimed	<input type="checkbox"/>
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	0	Suggested Figure for Publication (if any)	

### Filing By Reference :

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

### Publication Information:

Request Early Publication (Fee required at time of Request 37 CFR 1.219)

**Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not be** the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

### Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32). Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer number will be used for the Representative Information during processing.

Please Select One:	<input checked="" type="radio"/> Customer Number	<input type="radio"/> US Patent Practitioner	<input type="radio"/> Limited Recognition (37 CFR 11.9)
Customer Number	00513		

<b>Application Data Sheet 37 CFR 1.76</b>		Attorney Docket Number	2014-1250
		Application Number	
Title of Invention	AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID		

### Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, or 365(c) or indicate National Stage entry from a PCT application. Providing this information in the application data sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.

When referring to the current application, please leave the application number blank.

Prior Application Status	Pending	<input type="button" value="Remove"/>			
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)		
	Division of	14/261720	2014-04-25		
Prior Application Status	Patented	<input type="button" value="Remove"/>			
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
14/261720	Division of	14/165976	2012-01-28	8754131	2014-06-17
Prior Application Status	Patented	<input type="button" value="Remove"/>			
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
14/165976	Division of	13/687242	2012-11-28	8669290	2014-03-11
Prior Application Status	Patented	<input type="button" value="Remove"/>			
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
13/687242	Division of	13/353653	2012-01-19	8497304	2013-07-30
Prior Application Status	Patented	<input type="button" value="Remove"/>			
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
13/353653	Division of	10/525006	2005-03-28	8129431	2012-03-06
Prior Application Status	Expired	<input type="button" value="Remove"/>			
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)		
10/525006	a 371 of international	PCT/JP2004/000350	2004-01-16		
Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the <b>Add</b> button.					<input type="button" value="Add"/>

### Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55(d). When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX) the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(h)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

<input type="button" value="Remove"/>			
Application Number Page 328 of 366	Country <sup>i</sup>	Filing Date (YYYY-MM-DD)	Access Code <sup>j</sup> (if applicable)



<b>Application Data Sheet 37 CFR 1.76</b>		Attorney Docket Number	2014-1250
		Application Number	
Title of Invention	AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID		
2003-012427	JP	2003-01-21	
Additional Foreign Priority Data may be generated within this form by selecting the <b>Add</b> button.			<input type="button" value="Add"/>

## Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

- This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
- NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

## Authorization to Permit Access:

<input checked="" type="checkbox"/> Authorization to Permit Access to the Instant Application by the Participating Offices
<p>If checked, the undersigned hereby grants the USPTO authority to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the World Intellectual Property Office (WIPO), and any other intellectual property offices in which a foreign application claiming priority to the instant patent application is filed access to the instant patent application. See 37 CFR 1.14(c) and (h). This box should not be checked if the applicant does not wish the EPO, JPO, KIPO, WIPO, or other intellectual property office in which a foreign application claiming priority to the instant patent application is filed to have access to the instant patent application.</p> <p>In accordance with 37 CFR 1.14(h)(3), access will be provided to a copy of the instant patent application with respect to: 1) the instant patent application-as-filed; 2) any foreign application to which the instant patent application claims priority under 35 U.S.C. 119(a)-(d) if a copy of the foreign application that satisfies the certified copy requirement of 37 CFR 1.55 has been filed in the instant patent application; and 3) any U.S. application-as-filed from which benefit is sought in the instant patent application.</p> <p>In accordance with 37 CFR 1.14(c), access may be provided to information concerning the date of filing this Authorization.</p>

## Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

<b>Application Data Sheet 37 CFR 1.76</b>	Attorney Docket Number	2014-1250
	Application Number	
Title of Invention	AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID	

<b>Applicant 1</b>		<input type="button" value="Remove"/>	
<p>If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.</p>			
<input type="button" value="Clear"/>			
<input checked="" type="radio"/> Assignee	<input type="radio"/> Legal Representative under 35 U.S.C. 117	<input type="radio"/> Joint Inventor	
<input type="radio"/> Person to whom the inventor is obligated to assign.	<input type="radio"/> Person who shows sufficient proprietary interest		
If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:			
Name of the Deceased or Legally Incapacitated Inventor : <input type="text"/>			
If the Applicant is an Organization check here. <input checked="" type="checkbox"/>			
Organization Name	SENJU PHARMACEUTICAL CO., LTD.		
<b>Mailing Address Information:</b>			
Address 1	5-8, Hiranomachi 2-chome, Chuo-ku, Osaka-shi		
Address 2			
City	Osaka	State/Province	
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<b>Application Data Sheet 37 CFR 1.76</b>		Attorney Docket Number	2014-1250
		Application Number	
Title of Invention	AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID		

Prefix	Given Name	Middle Name	Family Name	Suffix

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## DESCRIPTION

AQUEOUS LIQUID PREPARATION CONTAINING  
2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID

5

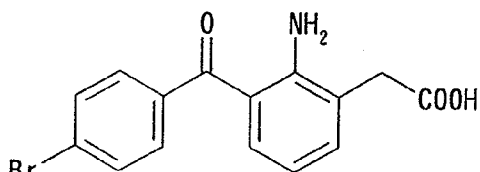
## TECHNICAL FIELD

The present invention relates to an aqueous liquid preparation containing 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof. More particularly, the present invention relates to an aqueous liquid preparation containing 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof and an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester.

15

## BACKGROUND ART

Benzoylphenylacetic acid derivatives including bromfenac (generic name) of formula (I):



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of which chemical name is 2-amino-3-(4-bromobenzoyl)phenylacetic acid are known as disclosed in JP-A-23052/1977 and its corresponding US patent No. 4,045,576. 2-Amino-3-(4-bromobenzoyl)phenylacetic acid, its pharmacologically acceptable salt and a hydrate thereof are

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known as a non-steroidal anti-inflammatory agent, and they are effective against inflammatory diseases of anterior or posterior segment of the eye, such as blepharitis, conjunctivitis, scleritis, and postoperative inflammation in the field of ophthalmology, and its sodium salt has been practically used in the form of eye drops ("New Drugs in Japan, 2001", 2001 Edition, Published by Yakuji Nippo Ltd., May 11, 2001, p.27-29).

The eye drop as mentioned above is designed to stabilize 2-amino-3-(4-bromobenzoyl)phenylacetic acid by means of addition of a water-soluble polymer (e.g. polyvinylpyrrolidone, polyvinyl alcohol, etc.) and a sulfite (e.g. sodium sulfite, potassium sulfite, etc.)(Japanese patent No. 2,683,676 and its corresponding US patent No.4,910,225).

In addition, as an eye drop other than the above-mentioned one, Japanese patent No. 2,954,356 (corresponding to US patents Nos. 5,603,929 and 5,653,972) discloses a stable ophthalmic composition which comprises incorporating an antibacterial quaternary ammonium polymer and boric acid into an acidic ophthalmic agent. The acidic agent described therein includes, for example, 2-amino-3-(4-bromobenzoyl)phenylacetic acid.

Further, in Japanese patent No. 2,954,356, there is the following description-"Benzalkonium chloride is a widely used preservative in ophthalmic solutions. However, benzalkonium chloride and other quaternary ammonium compounds are generally considered to be incompatible with ophthalmic compositions of drugs with acidic groups, such as nonsteroidal anti-inflammatory drugs. These preservatives lose their

ability to function as they form complexes with the charged drug compounds".

In these prior art references, there is no disclosure that alkyl aryl polyether alcohol type polymers or polyethylene glycol fatty acid esters are able to stabilize an aqueous liquid preparation of 2-amino-3-(4-bromobenzoyl)phenylacetic acid or its pharmacologically acceptable salt, and inhibit decrease in preservative effect of benzalkonium chloride and other quaternary ammonium compounds.

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#### DISCLOSURE OF THE INVENTION

It is an object of the present invention to provide an aqueous liquid preparation comprising 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, which is stable within a pH range giving no irritation to eyes and in which, when a preservative such as benzalkonium chloride is incorporated therein, preservative effect of the preservative does not substantially deteriorate.

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Another object of the invention is to provide a method for stabilizing an aqueous liquid preparation of 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof.

25

Further object of the invention is to provide an aqueous liquid preparation comprising 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof and a preservative, wherein, when specifically a quaternary ammonium salt such as

benzalkonium chloride is incorporated as a preservative, decrease in preservative effect of said preservative is inhibited.

As a result of various studies, the inventors of the present invention have found that, by adding, for example, an alkyl aryl polyether alcohol type polymer such as tyloxapol, or a polyethylene glycol fatty acid ester such as polyethylene glycol monostearate to an aqueous liquid preparation of 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, the aqueous solution becomes stable within a pH range giving no irritation to eyes, and change of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid over time can be inhibited, and furthermore, when the aqueous solution contains a preservative, deterioration in the preservative effect of said preservative can be inhibited for a long period of time. The inventors of the present invention have further studied extensively and completed the present invention.

Namely, the present invention relates to:

- (1) An aqueous liquid preparation comprising 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, and an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester,
- (2) The aqueous liquid preparation according to the above (1), wherein the alkyl aryl polyether alcohol type polymer has a polymerization degree of 3 to 10, the alkyl contains 1 to 18 carbon atoms, the aryl is a phenyl residue, and the polyether



alcohol is represented by the formula  $O(CH_2CH_2O)_xH$  in which X is an integer of 5 to 100,

(3) The aqueous liquid preparation according to the above (1) or (2), wherein the alkyl aryl polyether alcohol type polymer is tyloxapol,

(4) The aqueous liquid preparation according to the above (1), wherein the carbon number of the fatty acid in the polyethylene glycol fatty acid ester is 12 to 18,

(5) The aqueous liquid preparation according to the above (1) or (4), wherein the polyethylene glycol fatty acid ester is polyethylene glycol monostearate,

(6) The aqueous liquid preparation according to any one of the above (1) to (3), wherein the concentration of the alkyl aryl polyether alcohol type polymer is selected from a range of minimum concentration of 0.01 w/v % to maximum concentration of 0.5 w/v %,

(7) The aqueous liquid preparation according to any one of the above (1), (2) or (4), wherein the concentration of the polyethylene glycol fatty acid ester is selected from a range of minimum concentration of 0.02 w/v % to maximum concentration of 0.1 w/v %,

(8) The aqueous liquid preparation according to any one of the above (1) to (7), wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof is 0.01 to 0.5 w/v %,

(9) The aqueous liquid preparation according to any one of the above (1) to (8), wherein benzalkonium chloride is contained as a preservative,

(10) The aqueous liquid preparation according to anyone of the above (1) to (9), wherein the pharmacologically acceptable salt of 2-amino-3-(4-bromobenzoyl)phenylacetic acid is a sodium salt,

5 (11) The aqueous liquid preparation according to any one of the above (1) to (10), wherein the pH of the aqueous liquid preparation is within a range of 7 to 9,

(12) The aqueous liquid preparation according to the above (11), wherein the pH of the aqueous liquid preparation is within a  
10 range of 7.5 to 8.5,

(13) The aqueous liquid preparation according to any one of the above (1) to (12), wherein the aqueous liquid preparation is an eye drop,

(14) The aqueous liquid preparation according to any one of the  
15 above (1) to (12), wherein the aqueous liquid preparation is a nasal drop,

(15) An eye drop comprising sodium 2-amino-3-(4-bromobenzoyl)phenylacetate hydrate and 0.01 to 0.5 w/v % of tyloxapol,

20 (16) An eye drop comprising sodium 2-amino-3-(4-bromobenzoyl)phenylacetate hydrate and 0.02 to 0.1 w/v % of polyethylene glycol monostearate,

(17) A method for stabilizing 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically  
25 acceptable salt thereof or a hydrate thereof in an aqueous liquid preparation, which comprises incorporating tyloxapol or polyethylene glycol monostearate into an aqueous liquid preparation containing

2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, and

(18) A method for inhibiting decrease in preservative effect of a preservative in an aqueous liquid preparation of 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, which comprises incorporating tyloxapol or polyethylene glycol monostearate into an aqueous liquid preparation containing 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof and a preservative.

According to the present invention, a stable aqueous liquid preparation containing 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof can be prepared by incorporating an alkyl aryl polyether alcohol type polymer such as tyloxapol, or a polyethylene glycol fatty acid ester such as polyethylene glycol monostearate into an aqueous liquid preparation containing 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof. Also, an aqueous liquid preparation of the present invention, wherein a preservative is incorporated, has a sufficient preservative effect.

Therefore, the aqueous liquid preparation of the present invention is advantageously used as an eye drop for the treatment of, for example, blepharitis, conjunctivitis,

scleritis, and postoperative inflammation. In addition, such aqueous liquid preparation can be used as a nasal drop for the treatment of, for example, allergic rhinitis and inflammatory rhinitis (e.g. chronic rhinitis, hypertrophic rhinitis, nasal polyp, etc.).

The pharmacologically acceptable salt of 2-amino-3-(4-bromobenzoyl)phenylacetic acid includes, for example, an alkali metal salt such as sodium salt and potassium salt, and an alkaline earth metal salt such as calcium salt and magnesium salt, among which sodium salt is especially preferable.

2-Amino-3-(4-bromobenzoyl)phenylacetic acid and its pharmacologically acceptable salt can be prepared according to the method as described in JP-A-23052/1977 (corresponding to US patent No. 4,045,576) or by a similar method thereof. These compounds can be obtained as their hydrate depending on synthetic conditions and recrystallization conditions. The hydrate includes 1/2 hydrate, 1 hydrate, and 3/2 hydrate, among which 3/2 hydrate is preferable.

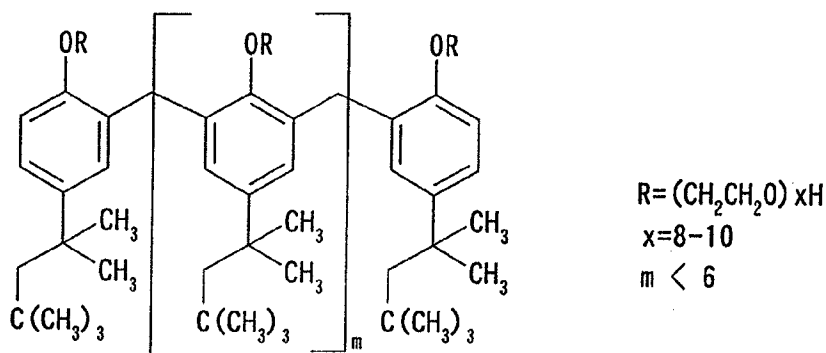
In the aqueous liquid preparation of the present invention, the content (concentration range) of 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof is usually about 0.01 to 0.5 w/v %, preferably about 0.05 to 0.2 w/v %, especially about 0.1 w/v %, and it is preferable to appropriately vary the content depending on the purpose of use and the degree of disease to be treated.

The carbon number of the alkyl in the an alkyl aryl polyether alcohol type polymer which is a non-ionic surfactant

used as a stabilizer for 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof is approximately 1 to 18. Specifically, the alkyl group includes, for example, methyl, ethyl, propyl, isopropyl, cyclopropyl, butyl, isobutyl, 5 sec-butyl, tert-butyl, cyclobutyl, pentyl, isopentyl, neopentyl, tert-pentyl, 1-ethylpropyl, 4-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 1,2-dimethylbutyl, 2-ethylbutyl, cyclopentyl, hexyl, cyclohexyl, heptyl, isoheptyl, octyl, isooctyl, nonyl, isononyl, decyl, isodecyl, 10 undecyl, isoundecyl, dodecyl, isododecyl, tridecyl, isotridecyl, tetradecyl, isotetradecyl, pentadecyl, isopentadecyl, hexadecyl, isohexadecyl, heptadecyl, isoheptadecyl, octadecyl, isooctadecyl, and isomers thereof, among which octyl and its isomer (e.g. isooctyl, sec-octyl, 15 1-methylheptyl, 1-ethylhexyl, 2-ethylhexyl, 1-propylpentyl, 1,5-dimethylhexyl, 1,1,3,3-tetramethylbutyl, etc.) are preferable, and 1,1,3,3-tetramethylbutyl which is an isomer of octyl groups is especially preferable.

20 The aryl in the alkyl aryl polyether alcohol type polymer can be preferably a phenyl residue. The polyether alcohol can be represented by the formula  $O(CH_2CH_2O)_xH$  in which X is an integer of 5 to 100, preferably 5 to 30, more preferably 8 to 10. The average polymerization degree is preferably about 3 25 to 10.

Among the above-mentioned alkyl aryl polyether alcohol type polymers, tyloxapol having the following formula is especially preferable.



The fatty acid of the polyethylene glycol fatty acid ester which is a non-ionic surfactant used as a stabilizer for 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof can be preferably a fatty acid having the carbon number of 12 to 18. Specific examples of such polyethylene glycol fatty acid esters are polyethylene glycol monostearate (e.g. polyoxyl 8 stearate, polyoxyl 40 stearate, etc.), polyethylene glycol monolaurate, polyethylene glycol monooleate, polyethylene glycol diisostearate, polyethylene glycol dilaurate, polyethylene glycol dioleate, and the like. Among these compounds, polyethylene glycol monostearate is preferable, and polyoxyl 40 stearate is especially preferable. The polyoxyl 40 stearate is a monostearic acid ester of an ethylene oxide condensed polymer, and can be represented by the formula  $\text{C}_{17}\text{H}_{35}\text{COO}(\text{CH}_2\text{CH}_2\text{O})_n\text{H}$  which is a non-ionic surfactant and n is about 40.

Although the content (concentration range) of the alkyl aryl polyether alcohol type polymer in the aqueous liquid preparation of the present invention depends on the kind of compounds used, the minimum concentration is about 0.01 w/v %

and the maximum concentration is about 0.5 w/v %. With respect to the tyloxapol content (concentration range), for example, the minimum content is about 0.01 w/v %, 0.02 w/v % or 0.03 w/v %, and the maximum content is about 0.05 w/v %, 0.1 w/v %, 0.3 w/v % or 0.5 % w/v, and preferably the minimum content is about 0.02 w/v % and the maximum content is about 0.05 w/v %.

Although the content (concentration range) of the polyethylene glycol fatty acid ester in the aqueous liquid preparation of the present invention depends on the kind of compounds used, it is within a range of about 0.02 w/v % of minimum concentration to about 0.1 w/v % of maximum concentration. For example, the content (concentration range) of polyethylene glycol monostearate is within a range of about 0.02 w/v % of minimum content to about 0.1 w/v of maximum content, and preferably within a range of about 0.02 w/v % of the minimum content to about 0.05 w/v % of the maximum content.

The incorporation ratio of tyloxapol in the aqueous liquid preparation of the invention is within a range of the minimum content of about 0.1 or 0.2 part by weight to the maximum content of about 0.5, 1, 3 or 5 parts by weight, relative to 1 part by weight of 2-amino-3-(4-bromobenzoyl)phenylacetic acid or its pharmacologically acceptable salt or a hydrate thereof.

The incorporation ratio of polyethylene glycol monostearate in the aqueous liquid preparation of the present invention is within a range of the minimum content of about 0.2 part by weight to the maximum content of about 0.5 or 1 part by weight, relative to 1 part by weight of

2-amino-3-(4-bromobenzoyl)phenylacetic acid or its pharmacologically acceptable salt or a hydrate thereof.

The preservative used in the present invention includes, for example, quaternary ammonium salts (e.g. benzalkonium chloride, benzethonium chloride, etc.), chlorhexidine gluconate, and the like, among which benzalkonium chloride is especially preferable.

Further, so long as the purpose of the present invention is achieved, conventional various additives such as isotonics, buffers, thickeners, stabilizers, chelating agents, pH controlling agents, perfumes and the like may be appropriately added to the aqueous liquid preparation of the present invention. The isotonics include sodium chloride, potassium chloride, glycerine, mannitol, sorbitol, boric acid, glucose, propylene glycol and the like. The buffers include, for example, phosphate buffer, borate buffer, citrate buffer, tartarate buffer, acetate buffer, boric acid, borax, amino acids, and the like. The thickeners include polyvinylpyrrolidone, carboxymethylcellulose, carboxypropylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, polyvinyl alcohol, sodium polyacrylate, and the like. The stabilizers include sulfites such as sodium sulfite and the like. The chelating agents include sodium edetate, sodium citrate, condensed sodium phosphate and the like. The pH controlling agents include hydrochloric acid, sodium hydroxide, phosphoric acid, acetic acid and the like. The perfumes include 1-menthol, borneol, camphor, Eucalyptus oil, and the like.



With respect to the concentrations of the above various additives in the aqueous liquid preparation of the present invention,

the isotonic is incorporated into an osmotic pressure ratio of about 0.8 to 1.2, and the concentrations of the buffer and the thickner to be added are about 0.01 to 2 w/v % and 0.1 to 10 w/v %, respectively.

The pH of the aqueous liquid preparation of the present invention is adjusted to about 6 to 9, preferably about 7 to 9, especially about 7.5 to 8.5.

So long as the purpose of the present invention is achieved, other same or different kind of active ingredients may be appropriately added.

The aqueous liquid preparation of the present invention can be prepared by per se known method or according to the method as described in the Japanese Pharmacopoeia, 14<sup>th</sup> Edition, General Rules for Preparations, Solutions or Ophthalmic solutions.

The aqueous liquid preparation of the present invention can be applied to warm-blooded animals such as human, rat, mouse, rabbit, cow, pig, dog, cat, and the like.

The aqueous liquid preparation of the present invention can be prepared easily by dissolving the above-mentioned components in, for example, distilled water or sterile purified water. For example, the aqueous liquid preparation in the form of an eye drop can be used for the treatment of inflammatory diseases in anterior or posterior segment of the eye such as blepharitis, conjunctivitis, scleritis, postoperative

inflammation, and the like. The dose of the aqueous liquid preparation containing 0.1 w/v % of sodium 2-amino-3-(4-bromobenzoyl)phenylacetate hydrate is, for example, administered to an adult 3 to 6 times daily in an amount of 1 to 2 drops per one time. Depending on the degree of diseases, frequency of dosing is appropriately controlled.

#### BEST MODE FOR CARRYING OUT THE INVENTION

The present invention is illustrated by way of the following Experimental Examples and Working Examples, but it is not restricted by these Examples.

#### Experimental Example 1: Stability test of sodium 2-amino-3-(4-bromobenzoyl)phenylacetate

Four eye drops of sodium 2-amino-3-(4-bromobenzoyl)phenylacetate comprising the components as shown in Table 1 were prepared, filled respectively into a polypropylene container and subjected to stability test at 60°C.

Table 1

Component	Comparison Example 1	A-01	A-02	A-03
Sodium 2-amino-3-(4-bromobenzoyl)phenylacetate	0.1 g	0.1 g	0.1 g	0.1 g
Boric acid	1.5 g	1.5 g	1.5 g	1.5 g
Benzalkonium chloride	0.005 g	0.005 g	0.005 g	0.005 g
Polysorbate 80	0.15 g	-	-	-
Polyoxyl 40 stearate	-	0.15 g	-	-
Tyloxapol	-	-	0.15 g	0.02 g
Sterile purified water	q.s.	q.s.	q.s.	q.s.
Total volume	100 mL	100 mL	100 mL	100 mL
pH	7.0	7.0	7.0	7.0
Remaining rate (%) at 60 °C after 4 weeks	51.3	63.7	73.8	89.6

The remaining rate (%) in the above Table 1 indicates values obtained by correcting moisture vaporization from the container. As is apparent from the Table 1, stability test was carried out under the conditions of pH 7.0 at 60°C for 4 weeks, and sodium 2-amino-3-(4-bromobenzoyl)phenylacetate in each eye drop was stable in the order of tyloxapol-containing preparation > polyoxyl 40 stearate-containing preparation > polysorbate 80-containing preparation.

Further, with respect to eye drops containing tyloxapol (compositions A-02 and A-03), sodium 2-amino-3-(4-bromobenzoyl)phenylacetate in composition A-03 containing 0.02 w/v % of tyloxapol is more stable than that in composition

A-02 containing 0.15 w/v % of tyloxapol.

Experimental Example 2: Stability test of sodium 2-amino-3-(4-bromobenzoyl)phenylacetate

5           Five eye drops of sodium 2-amino-3-(4-bromobenzoyl)phenylacetate comprising the components as shown in Table 2 were prepared, filled respectively into a polypropylene container and preserved at 60°C for 4 weeks, and then the content of 2-amino-3-(4-bromobenzoyl)phenylacetic  
10 acid and the pH in each eye drop were measured.

Table 2

Components		A-04	A-05	A-06	A-07	A-08
Sodium 2-amino-3-(4-bromobenzoyl)phenylacetate		0.1 g	0.1 g	0.1 g	0.1 g	0.1 g
Boric acid		1.1 g	1.1 g	1.1 g	1.1 g	1.1 g
Borax		1.1 g	1.1 g	1.1 g	1.1 g	1.1 g
Benzalkonium chloride		0.005g	0.005g	0.005g	0.005g	0.005g
Polysorbate 80		—	—	—	—	—
Tyloxapol		0.02 g	0.05 g	0.03 g	—	—
Polyoxyl 40 stearate		—	—	—	0.02 g	0.05 g
Polyvinylpyrrolidone (K-30)		2.0 g	2.0 g	2.0 g	2.0 g	1.0 g
Sodium edetate		0.02 g	0.02 g	0.02 g	0.02 g	0.02 g
Sodium hydroxide		q.s.	q.s.	q.s.	q.s.	q.s.
Sterile purified water		q.s.	q.s.	q.s.	q.s.	q.s.
Total volume		100 mL	100 mL	100 mL	100 mL	100 mL
pH		8.17	8.16	8.15	8.19	8.19
60°C, 4 weeks	Remaining rate (%)	92.6	90.9	92.0	93.4	93.1
	pH	8.15	8.16	8.15	8.13	8.14

Table 2 shows the remaining rate and the pH of sodium 2-amino-3-(4-bromobenzoyl)phenylacetate after storage at 60°C for 4 weeks, when the remaining rate of sodium 2-amino-3-(4-bromobenzoyl)phenylacetate at the time of production of eye drops is set to 100%. The remaining rate is a value obtained by correcting moisture vaporization from the container. As is

apparent from Table 2, the remaining rate of sodium 2-amino-3-(4-bromobenzoyl)phenylacetate in the compositions A-04, A-05, A-06, A-07 and A-08 containing 0.02 w/v %, 0.03 w/v % and 0.05 w/v % of tyloxapol or 0.02 w/v % and 0.05 w/v % of polyoxyl 40 stearate is not less than 90 % after storage at 60°C for 4 weeks, which indicates that those compositions have sufficient stability for eye drops.

Experimental Example 3: Preservative effect test of aqueous liquid preparation containing sodium 2-amino-3-(4-bromobenzoyl)phenylacetate

Preservative effect test of compositions A-04, A-05 and A-07 of Experimental Example 2 was carried out against *Staphylococcus aureus* (hereinafter referred to as *S. aureus*), *Escherichia Coli* (hereinafter referred to as *E. coli*), *Pseudomonas aeruginosa* (hereinafter referred to as *P. aeruginosa*), *Candida albicans* (hereinafter referred to as *C. albicans*) and *Aspergillus niger* (hereinafter referred to as *A. niger*).

The results are shown in Tables 3-1, 3-2 and 3-3.

Table 3-1

A-04	Cell count (CFU/mL)						
	Inoculum count	6 hours after inocula- tion	24 hours after inocula- tion	7 days after inocula- tion	14 days after inocula- tion	21 days after inocula- tion	28 days after inocula- tion
<i>S. aureus</i>	$2.1 \times 10^6$	$3.0 \times 10^1$	0	0	0	0	0
<i>E. coli</i>	$6.5 \times 10^6$	0	0	0	0	0	0
<i>P. aeruginosa</i>	$5.8 \times 10^6$	0	0	0	0	0	0
<i>C. albicans</i>	$3.2 \times 10^5$	—	—	0	0	0	0
<i>A. niger</i>	$1.8 \times 10^5$	—	—	0	0	0	0

Table 3-2

A-05	Cell count (CFU/mL)						
	Inoculum count	6 hours after inocula- tion	24 hours after inocula- tion	7 days after inocula- tion	14 days after inocula- tion	21 days after inocula- tion	28 days after inocula- tion
<i>S. aureus</i>	$2.1 \times 10^6$	$1.7 \times 10^5$	$2.0 \times 10^1$	0	0	0	0
<i>E. coli</i>	$6.5 \times 10^6$	0	0	0	0	0	0
<i>P. aeruginosa</i>	$5.8 \times 10^6$	0	0	0	0	0	0
<i>C. albicans</i>	$3.2 \times 10^5$	—	—	0	0	0	0
<i>A. niger</i>	$1.8 \times 10^5$	—	—	0	0	0	0

Table 3-3

A-07	Cell count (CFU/mL)						
	Inoculum	6 hours	24 hours	7 days	14 days	21 days	28 days
	count	after	after	after	after	after	after
		inocula-	inocula-	inocula-	inocula-	inocula-	inocula-
		tion	tion	tion	tion	tion	tion
<i>S. aureus</i>	$2.7 \times 10^6$	$3.1 \times 10^4$	0	0	0	0	0
<i>E. coli</i>	$7.4 \times 10^6$	0	0	0	0	0	0
<i>P. aeruginosa</i>	$8.8 \times 10^6$	0	0	0	0	0	0
<i>C. albicans</i>	$4.6 \times 10^5$	—	—	0	0	0	0
<i>A. niger</i>	$1.0 \times 10^5$	—	—	0	0	0	0

As is apparent from Tables 3-1, 3-2 and 3-3, the preservative effect of composition A-04 was found to be compatible with EP-criteria A in European Pharmacopoeia (EP), and those of compositions A-05 and A-07 were found to be compatible with EP-criteria B.

The EP-criteria A and EP-criteria B are given in the following.

10 EP-criteria A:

Viable cell counts of bacteria (*S. aureus*, *P. aeruginosa*) 6 hours, 24 hours, and 28 days after inoculation decrease to not more than 1/100, not more than 1/1000, and undetectable, respectively.

15 Viable cell count of fungi (*C. albicans*, *A. niger*) 7 hours after inoculation decreases to not more than 1/100, and thereafter, the cell count levels off or decreases.

EP-criteria B



Viable cell counts of bacteria (*S. aureus*, *P. aeruginosa*) 24 hours and 7 days after inoculation decrease to not more than 1/10 and not more than 1/1000, respectively, and thereafter, the cell count levels off or decreases.

- 5 Viable cell count of fungi (*C. albicans*, *A. niger*) 14 days after inoculation decreases to not more than 1/10, and thereafter, the cell count keeps the same level as that of 14 days after inoculation.

10 Example 1: Eye Drop

Sodium 2-amino-3-(4-bromobenzoyl)phenylacetate 3/2 hydrate	0.1 g
Boric acid	1.1 g
Borax	1.1 g
Benzalkonium chloride	0.005 g
Tyloxapol	0.02 g
Polyvinylpyrrolidone (K-30)	2.0 g
Sodium edetate	0.02 g
Sodium hydroxide	q.s.
Sterile purified water	to make total volume of 100 mL
	pH 8.17

An eye drop is prepared using the above components in a conventional manner.

## Example 2: Eye Drop

Sodium 2-amino-3-(4-bromobenzoyl)phenylacetate 3/2 hydrate	0.1 g
Boric acid	1.1 g
Borax	1.1 g
Benzalkonium chloride	0.005 g
Tyloxapol	0.05 g
Polyvinylpyrrolidone (K-30)	2.0 g
Sodium edetate	0.02 g
Sodium hydroxide	q.s.
Sterile purified water	to make total volume of 100 mL
	pH 8.16

An eye drop is prepared using the above components in a conventional manner.

## Example 3: Eye Drop

Sodium 2-amino-3-(4-bromobenzoyl)phenylacetate 3/2 hydrate	0.1 g
Boric acid	1.1 g
Borax	1.1 g
Benzalkonium chloride	0.005 g
Polyoxyl 40 stearate	0.02 g
Polyvinylpyrrolidone (K-30)	2.0 g
Sodium edetate	0.02 g
Sodium hydroxide	q.s.
Sterile purified water	to make total volume of 100 mL
	pH 8.19

An eye drop is prepared using the above components in a conventional manner.

## 5 INDUSTRIAL APPLICABILITY

The aqueous liquid preparation of the present invention in the form of eye drops is useful for the treatment of blepharitis, conjunctivitis, scleritis, and postoperative inflammation. Such preparation is also useful for the treatment of nasal drop for treatment of, for example, allergic rhinitis and inflammatory rhinitis (e.g. chronic rhinitis, hypertrophic rhinitis, nasal polyp, etc.)

The present application is based on application No. 12427/2003 filed in Japan, and includes the entire contents thereof. By reference, the references including patents and patent applications cited herein are incorporated in the

present application at the same level as when the entire contents thereof are disclosed. Furthermore, since it is obvious that the present invention can be carried out beyond the description of the above explanation and Working Examples, in light of the foregoing description, various other modifications and changes can be made to the present invention, and thus these modifications and changes should be considered to be within the scope of the claims appended hereto.

## CLAIMS

1. An aqueous liquid preparation comprising 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, and an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester.  
5
2. The aqueous liquid preparation according to claim 1, wherein the  
10 alkyl aryl polyether alcohol type polymer has a polymerization degree of 3 to 10, the alkyl contains 1 to 18 carbon atoms, the aryl is a phenyl residue, and the polyether alcohol is represented by the formula  $O(CH_2CH_2O)_xH$  in which X is an integer  
15 of 5 to 100.
3. The aqueous liquid preparation according to claim 1 or 2, wherein the alkyl aryl polyether alcohol type polymer is tyloxapol.  
20
4. The aqueous liquid preparation according to claim 1, wherein the carbon number of the fatty acid in the polyethylene glycol fatty acid ester is 12 to 18.
- 25 5. The aqueous liquid preparation according to claim 1 or 4, wherein the polyethylene glycol fatty acid ester is polyethylene glycol monostearate.

6. The aqueous liquid preparation according to any one of claims 1 to 3, wherein the concentration of the alkyl aryl polyether alcohol type polymer is selected from a range of minimum concentration of 0.01 w/v % to maximum concentration  
5 of 0.5 w/v %.
7. The aqueous liquid preparation according to any one of claims 1, 2 or 4, wherein the concentration of the polyethylene glycol fatty acid ester is selected from a range of minimum  
10 concentration of 0.02 w/v % to maximum concentration of 0.1 w/v %.
8. The aqueous liquid preparation according to any one of claims 1 to 7, wherein the concentration of the 2-amino-3-(4-  
15 bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof is 0.01 to 0.5 w/v %.
9. The aqueous liquid preparation according to any one of claims 1 to 8, wherein benzalkonium chloride is contained as  
20 a preservative.
10. The aqueous liquid preparation according to any one of 1 to 9, wherein the pharmacologically acceptable salt of 2-amino-3-(4-bromobenzoyl)phenylacetic acid is a sodium salt.  
25
11. The aqueous liquid preparation according to any one of claims 1 to 10, wherein the pH of the aqueous liquid preparation is within a range of 7 to 9.

12. The aqueous liquid preparation according to claim 11, wherein the pH of the aqueous liquid preparation is within a range of 7.5 to 8.5.

5

13. The aqueous liquid preparation according to any one of claims 1 to 12, wherein the aqueous liquid preparation is an eye drop.

10 14. The aqueous liquid preparation according to any one of claims 1 to 12, wherein the aqueous liquid preparation is a nasal drop.

15 15. An eye drop comprising sodium 2-amino-3-(4-bromobenzoyl)phenylacetate hydrate and 0.01 to 0.5 w/v % of tyloxapol.

20 16. An eye drop comprising sodium 2-amino-3-(4-bromobenzoyl)phenylacetate hydrate and 0.02 to 0.1 w/v % of polyethylene glycol monostearate.

25 17. A method for stabilizing 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof in an aqueous liquid preparation, which comprises incorporating tyloxapol or polyethylene glycol monostearate into an aqueous liquid preparation containing 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate

thereof.

18. A method for inhibiting decrease in preservative effect  
of a preservative in an aqueous liquid preparation of  
5 2-amino-3-(4- bromobenzoyl)phenylacetic acid or a  
pharmacologically acceptable salt thereof or a hydrate thereof,  
which comprises incorporating tyloxapol or polyethylene glycol  
monostearate into an aqueous liquid preparation containing  
2-amino-3-(4- bromobenzoyl)phenylacetic acid or a  
10 pharmacologically acceptable salt thereof or a hydrate thereof  
and a preservative.



## Abstract

An aqueous liquid preparation of the present invention containing 2-amino-3-(4-bromobenzoyl)phenylacetic acid or its pharmacologically acceptable salt or a hydrate thereof, an alkyl aryl polyether alcohol type polymer such as tyloxapol, or a polyethylene glycol fatty acid ester such as polyethylene glycol monostearate is stable. Since even in the case where a preservative is incorporated into said aqueous liquid preparation, the preservative exhibits a sufficient preservative effect for a long time, said aqueous liquid preparation in the form of an eye drop is useful for the treatment of blepharitis, conjunctivitis, scleritis, and postoperative inflammation. Also, the aqueous liquid preparation of the present invention in the form of a nasal drop is useful for the treatment of allergic rhinitis and inflammatory rhinitis (e.g. chronic rhinitis, hypertrophic rhinitis, nasal polyp, etc.).

### DECLARATION FOR UTILITY OR DESIGN APPLICATION

Title of  
Invention

AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID

As the below named inventor, I hereby declare that:

This declaration  
is directed to:

The attached application, or

United States application or PCT international application  
number filed on .

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

Note to Inventor: 37 C.F.R. § 1.63(c) states: "A person may not execute an oath or declaration for an application unless that person has reviewed and understands the contents of the application, including the claims, and is aware of the duty to disclose to the Office all information known to the person to be material to patentability as defined in § 1.56."

Inventor (Legal Name): Shirou SAWA

Signature: Shirou Sawa

Date: Nov. 16. 2012

Note: Use an additional form for each additional inventor.

DECLARATION FOR UTILITY OR DESIGN APPLICATION	
Title of Invention	<u>AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID</u>
As the below named inventor, I hereby declare that:	
This declaration is directed to:	<input checked="" type="checkbox"/> The attached application, or <input type="checkbox"/> United States application or PCT international application number filed on .
The above-identified application was made or authorized to be made by me.	
I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.	
I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.	
Note to Inventor: 37 C.F.R. § 1.63(c) states: "A person may not execute an oath or declaration for an application unless that person has reviewed and understands the contents of the application, including the claims, and is aware of the duty to disclose to the Office all information known to the person to be material to patentability as defined in § 1.56."	
Inventor (Legal Name):	<u>Shuhei FUJITA</u>
Signature:	<u>Shuhei Fujita</u> Date: <u>2012.11.19</u>
Note: Use an additional form for each additional inventor.	

**TRANSMITTAL FOR POWER OF ATTORNEY TO ONE OR MORE REGISTERED PRACTITIONERS**

NOTE: This form is to be submitted with the Power of Attorney by Applicant form (PTO/AIA/82B or equivalent) to identify the application to which the Power of Attorney is directed, in accordance with 37 CFR 1.5. If the Power of Attorney by Applicant form is not accompanied by this transmittal form or an equivalent, the Power of Attorney will not be recognized in the application.

Application Number	<b>NEW</b>
Filing Date	<b>September 23, 2014</b>
First Named Inventor	<b>Shirou SAWA</b>
Title	<b>AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID</b>
Art Unit	
Examiner Name	
Attorney Docket Number	<b>2014-1250</b>
Applicant's or Agent's Reference No.	

**Signature of Applicant or Patent Practitioner**

Signature	<b>Cheek, Jr./</b> <small>Digitally signed by /Warren M. Cheek, Jr./, ou=, email=wcheek@wenderoth.com, c=US Date: 2014.09.23 13:19:44 -04'00'</small>	Date	September 23, 2014
Name	<b>Warren M. Cheek</b>	Telephone	(202) 721-8200
Registration Number	33,367		

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

Total of 1 form are submitted.

**GENERAL POWER OF ATTORNEY BY APPLICANT  
FOR UNITED STATES PATENT**

I hereby revoke all previous powers of attorney given in the application referenced in the attached transmittal letter (form PTO/AIA/82A or equivalent).

I hereby appoint the practitioners associated with the following Customer Number for **Wenderoth, Lind & Ponack, L.L.P.:**

**00513**

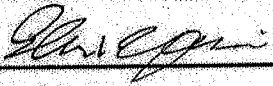
as my/our attorneys or agents, and to transact all business in the United States Patent and Trademark Office in connection with the application referenced in the attached transmittal letter (form PTO/AIA/82A or equivalent).

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- Person Who Otherwise Shows Sufficient Proprietary Interest (e.g., a petition under 37 CFR 1.46(b)(2) was granted in the application or is currently being filed in this document)

**SIGNATURE of Applicant for Patent**

Signature		Date	2012, 11, 19
Name	Shuhei YOSHIDA		
Title	Executive Vice President		
Company	SENJU PHARMACEUTICAL CO., LTD.		

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<b>PATENT APPLICATION FEE DETERMINATION RECORD</b> Substitute for Form PTO-875	Application or Docket Number <b>14/493,903</b>	Filing Date <b>09/23/2014</b>	<input type="checkbox"/> To be Mailed
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ENTITY:  LARGE  SMALL  MICRO

**APPLICATION AS FILED – PART I**

FOR	NUMBER FILED	NUMBER EXTRA	RATE (\$)	FEE (\$)
<input type="checkbox"/> BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
<input type="checkbox"/> SEARCH FEE (37 CFR 1.16(k), (l), or (m))	N/A	N/A	N/A	
<input type="checkbox"/> EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X \$ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X \$ =	
<input type="checkbox"/> 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).			
<input type="checkbox"/> MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

**APPLICATION AS AMENDED – PART II**

	(Column 1)	(Column 2)	(Column 3)	PRESENT EXTRA	RATE (\$)	ADDITIONAL FEE (\$)
<b>AMENDMENT</b>	<b>09/23/2014</b>	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR		
	Total (37 CFR 1.16(i))	* 30	Minus	** 30	= 0	X \$80 = 0
	Independent (37 CFR 1.16(h))	* 3	Minus	***3	= 0	X \$420 = 0
	<input type="checkbox"/> Application Size Fee (37 CFR 1.16(s))					
<input type="checkbox"/> FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	<b>0</b>

	(Column 1)	(Column 2)	(Column 3)	PRESENT EXTRA	RATE (\$)	ADDITIONAL FEE (\$)
<b>AMENDMENT</b>		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR		
	Total (37 CFR 1.16(i))	*	Minus	**	=	X \$ =
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X \$ =
	<input type="checkbox"/> Application Size Fee (37 CFR 1.16(s))					
<input type="checkbox"/> FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	

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

LIE  
 /YUVANNA CHAPHIV/

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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