AO 120 (Rev. 08/10)

TO: **Mail Stop 8** **Director of the U.S. Patent and Trademark Office** **P.O. Box 1450** **Alexandria, VA 22313-1450**	**REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK**

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court for the District of Delaware on the following ☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	1/26/2015	for the District of Delaware

PLAINTIFF	DEFENDANT
SENJU PHARMACEUTICAL CO., LTD., et al.	PADDOCK LABORATORIES, LLC, et al.

PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1 8,129,431 B2	3/6/2012	Senju Pharmaceutical Co., Ltd.
2 8,669,290 B2	3/11/2014	Senju Pharmaceutical Co., Ltd.
3 8,754,131 B2	6/17/2014	Senju Pharmaceutical Co., Ltd.
4 8,871,813 B2	10/28/2014	Senju Pharmaceutical Co., Ltd.
5 8,917,606 B1	1/6/2015	Senju Pharmaceutical Co., Ltd.

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading

PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1		
2		
3		
4		
5		

In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE

Copy 1—Upon initiation of action, mail this copy to Director Copy 3—Upon termination of action, mail this copy to Director
Copy 2—Upon filing document adding patent(s), mail this copy to Director Copy 4—Case file copy

AO 120 (Rev. 08/10)

TO:	**Mail Stop 8** **Director of the U.S. Patent and Trademark Office** **P.O. Box 1450** **Alexandria, VA 22313–1450**	**REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK**

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the **U.S. District Court for the District of New Jersey** on the following:
____ Trademarks or **X** Patents. (____ the patent action involves 35 U.S.C. § 292.)

DOCKET NO. 1:14–cv–06893–JBS–KMW	DATE FILED 11/3/2014	U.S. DISTRICT COURT CAMDEN, NJ
PLAINTIFF SENJU PHARMACEUTICAL CO., LTD.		DEFENDANT INNOPHARMA LICENSING, INC.

PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1 8,129,431	3/6/2012	SENJU
2 8,669,290	3/11/2014	SENJU
3 8,754,131	6/17/2014	SENJU
4 8,871,813	10/28/2014	SENJU
5		

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ___ Amendment ___ Answer ___ Cross Bill ___ Other Pleading

PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1		
2		
3		
4		
5		

In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE
William T. Walsh	s/ Nicholas Zotti	11/3/2014

Copy 1—Upon initiation of action, mail this copy to Director Copy 3—Upon termination of action, mail this copy to Director
Copy 2—Upon filing document adding patent(s), mail this copy to Director Copy 4—Case file copy

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/261,720	10/28/2014	8871813	2014-0545	1021

513 7590 10/08/2014

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;

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)

513 7590 09/05/2014
WENDEROTH, LIND & PONACK, L.L.P.
1030 15th Street, N.W.,
Suite 400 East
Washington, DC 20005-1503

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

Certificate of Mailing or Transmission

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

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

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/261,720	04/25/2014	Shirou SAWA	2014-0545	1021

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	12/05/2014

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

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

☐ Applicant asserting small entity status. See 37 CFR 1.27

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

☐ Applicant changing to regular undiscounted fee status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

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

Authorized Signature /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 14:26:35 -04'00'

Date September 23, 2014

Typed or printed name Warren M. Cheek

Registration No. 33,367

Electronic Patent Application Fee Transmittal

Application Number:	14261720
Filing Date:	25-Apr-2014
Title of Invention:	AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID
First Named Inventor/Applicant Name:	Shirou SAWA
Filer:	Warren M. Cheek Jr./Donna King
Attorney Docket Number:	2014-0545

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

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

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

Electronic Acknowledgement Receipt

EFS ID:	20218778
Application Number:	14261720
International Application Number:	
Confirmation Number:	1021
Title of Invention:	AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID
First Named Inventor/Applicant Name:	Shirou SAWA
Customer Number:	513
Filer:	Warren M. Cheek Jr./maurice linder
Filer Authorized By:	Warren M. Cheek Jr.
Attorney Docket Number:	2014-0545
Receipt Date:	23-SEP-2014
Filing Date:	25-APR-2014
Time Stamp:	15:36:03
Application Type:	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	2044
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	421174 701eb6392280ddaff6f0fe49939941191597fd18	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:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
2	Fee Worksheet (SB06)	fee-info.pdf	30692 3b69ac6ea8727aeb5a42a86c7cd38afeea330d7d	no	2

Warnings:

Information:

Total Files Size (in bytes):	451866

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

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

NOTICE OF ALLOWANCE AND FEE(S) DUE

513 7590 09/05/2014
WENDEROTH, LIND & PONACK, L.L.P.
1030 15th Street, N.W.,
Suite 400 East
Washington, DC 20005-1503

EXAMINER	
SOROUSH, LAYLA	
ART UNIT	**PAPER NUMBER**
1627	

DATE MAILED: 09/05/2014

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/261,720	04/25/2014	Shirou SAWA	2014-0545	1021

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	12/05/2014

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)

513 7590 09/05/2014
WENDEROTH, LIND & PONACK, L.L.P.
1030 15th Street, N.W.,
Suite 400 East
Washington, DC 20005-1503

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

Certificate of Mailing or Transmission

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

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

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/261,720	04/25/2014	Shirou SAWA	2014-0545	1021

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	12/05/2014

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 ____________________

2 ____________________

3 ____________________

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

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

(A) NAME OF ASSIGNEE

(B) RESIDENCE: (CITY and STATE OR COUNTRY)

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

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

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

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

☐ Applicant certifying micro entity status. See 37 CFR 1.29	<u>NOTE:</u> Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
☐ Applicant asserting small entity status. See 37 CFR 1.27	<u>NOTE:</u> If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
☐ Applicant changing to regular undiscounted fee status.	<u>NOTE:</u> 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 DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/261,720	04/25/2014	Shirou SAWA	2014-0545	1021

513 7590 09/05/2014

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

EXAMINER	
SOROUSH, LAYLA	
ART UNIT	**PAPER NUMBER**
1627	

DATE MAILED: 09/05/2014

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.** 14/261,720	**Applicant(s)** SAWA ET AL.	
	Examiner LAYLA SOROUSH	**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 7/31/14 and approved on 8/1/14*.

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 *19-45*.

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 Draftperson's Patent Drawing Review (PTO-948)
3. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 7/18/14
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 _____ .
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 07/31/2014 to the Office Action mailed on 07/24/2014 is acknowledged.

Claim Status

Claims 19-45 are pending.

Claims 19-45 are allowed.

Withdrawn Rejections

The Double Patenting rejections over U.S. Patent No. 8129431, 8497304, 8669290, 8754131 is withdrawn in view of the TD's filed on 7/31/14 and approved on 8/1/2014.

Reasons for Allowance

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

The composition as claimed are found to be patentable over the prior art because the prior art does not teach or fairly suggest a stable aqueous liquid preparation consisting essentially of: (a) a first component; (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; (c) boric acid; (d) sodium tetraborate; and (e) water; 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 and is present in the preparation at a concentration from about 0.05 w/v % to about 0.2 w/v %; the second component is tyloxapol and is present in said liquid preparation in an amount sufficient to stabilize said first component; and wherein said stable liquid preparation is formulated for ophthalmic administration.

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)phenalyacetic 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;

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 preconcentrate; 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 shown in Table 1 were prepared, filled respectively into a polypropylene container and subjected to a stability test at 60℃ for 4 weeks. As is apparent from Table 1, the stability test was carried out under the conditions of pH 7.0 at 60℃ 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℃ 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 composition as claimed are found to be patentable over the prior art because the prior art does not teach or fairly suggest a stable aqueous liquid preparation consisting essentially of: (a) a first component; (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; (c) boric acid; (d) sodium tetraborate; and (e) water; 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 and is present in the preparation at a concentration from about 0.05 w/v % to about 0.2 w/v %; the second component is tyloxapol and is present in said liquid preparation in an amount sufficient to stabilize said first component; and wherein said stable liquid preparation is formulated for ophthalmic administration.

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 SOROUSH 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

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BIB DATA SHEET

CONFIRMATION NO. 1021

SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
14/261,720	04/25/2014 **RULE**	514	1627	2014-0545

APPLICANTS
SENJU PHARMACEUTICAL CO., LTD., Osaka, JAPAN, Assignee (with 37 CFR 1.172 Interest);

INVENTORS
Shirou SAWA, Hyogo, JAPAN;
Shuhei FUJITA, Hyogo, JAPAN;

** **CONTINUING DATA** *************************
This application 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** *************************
JAPAN 2003-012427 01/21/2003

** **IF REQUIRED, FOREIGN FILING LICENSE GRANTED** **
05/09/2014

Foreign Priority claimed ☑ Yes ☐ No
35 USC 119(a-d) conditions met ☐ Yes ☐ No ☑ Met after Allowance
Verified and Acknowledged /LAYLA SOROUSH/ Examiner's Signature LS Initials

STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
JAPAN	0	27	3

ADDRESS

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

TITLE

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

FILING FEE RECEIVED
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FEES: Authority has been given in Paper
No.____________ to charge/credit DEPOSIT ACCOUNT
No.____________ for following:

- ☐ All Fees
- ☐ 1.16 Fees (Filing)
- ☐ 1.17 Fees (Processing Ext. of time)
- ☐ 1.18 Fees (Issue)
- ☐ Other ________________
- ☐ Credit

Sheet 1 of 3

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: July 18, 2014	**ATTY DOCKET NO.** 2014-0545	**SERIAL NO.** 14/261,720
	FIRST NAMED INVENTOR Shirou SAWA	
	FILING DATE April 25, 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.

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

Sheet 2 of 3

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: July 18, 2014

ATTY DOCKET NO.
2014-0545

SERIAL NO.
14/261,720

FIRST NAMED INVENTOR
Shirou SAWA

FILING DATE
April 25, 2014

GROUP

/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[1]”, 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	Webester’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.

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

Sheet 3 of 3	**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: July 18, 2014	**ATTY DOCKET NO.** 2014-0545	**SERIAL NO.** 14/261,720
	FIRST NAMED INVENTOR Shirou SAWA	
	FILING DATE April 25, 2014	**GROUP**

/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, 20th 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™ product package, Loteprednol Etabonate, Ophthalmic Suspension, 0.2%, pp. 1-13, 1998.
	CZ	XIBROM™ 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™ 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	ALREX™ product package, Loteprednol Etabonate, Ophthalmic Suspension, 0.2%, pp. 1-13, 1998.
	CAF	The United States Pharmacopeia, The National Formulary, USP 24, NF 19, pp. 1809-1813, 1864-1866, 2000.
	CAG	Dorset & Baber, Webster's New Twentieth Century Dictionary, Second Edition, "Ophthalmic" and "Ophthalmitic" p. 1254, 1979.
	CAH	BRONUCK® news release, Bromfenac Sodium Hydrate Ophthalmic Solution, p.1, 2005.

EXAMINER /Layla Soroush/	DATE CONSIDERED

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

Issue Classification	**Application/Control No.** 14/261,720	**Applicant(s)/Patent under Reexamination** SAWA ET AL.
	Examiner LAYLA SOROUSH	**Art Unit** 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/ 8/28/14 (Primary Examiner) (Date)	**Total Claims Allowed: 27**
(Legal Instruments Examiner) (Date)		O.G. Print Claim(s): 1 — O.G. Print Fig.: NONE

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

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
	1	13	31		61		91		121		151		181
	2	14	32		62		92		122		152		182
	3	15	33		63		93		123		153		183
	4	16	34		64		94		124		154		184
	5	17	35		65		95		125		155		185
	6	18	36		66		96		126		156		186
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10	28		58		88		118		148		178		208
11	29		59		89		119		149		179		209
12	30		60		90		120		150		180		210

Search Notes	**Application/Control No.** 14/261,720	**Applicant(s)/Patent under Reexamination** SAWA ET AL.
	Examiner LAYLA SOROUSH	**Art Unit** 1627

SEARCHED

Class	Subclass	Date	Examiner
514	619	8/28/14	LS
514	535	8/28/14	LS
514	570	8/28/14	LS

SEARCH NOTES (INCLUDING SEARCH STRATEGY)

	DATE	EXMR
STIC (see also 13535653); and updated npl and EAST	8/28/14	LS
odp:SAWA, SHIROU and FUJITA, SHUHEI	8/28/14	LS

INTERFERENCE SEARCHED

Class	Subclass	Date	Examiner
514	**618**	**8/28/14**	**LS**

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
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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
14/261,720	04/25/2014	Shirou SAWA	2014-0545

CONFIRMATION NO. 1021

PUBLICATION NOTICE

OC000000070320770

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-2014-0235721-A1
Publication Date:08/21/2014

NOTICE OF PUBLICATION OF APPLICATION

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

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

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

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

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

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

Application Number	**Application/Control No.** 14/261,720	**Applicant(s)/Patent under Reexamination** SAWA ET AL.

Document Code - DISQ	**Internal Document – DO NOT MAIL**

TERMINAL DISCLAIMER	☒ APPROVED	☐ DISAPPROVED
Date Filed : 7/31/14	**This patent is subject to a Terminal Disclaimer**	

Approved/Disapproved by:

Janice Ford

4 tds approved

U.S. Patent and Trademark Office

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor	:	Attorney Docket No. 2014-0545
Shirou SAWA	:	**Confirmation No. 1021**
Serial No. 14/261,720	:	Group Art Unit 1627
Filed April 25, 2014	:	Examiner Layla Soroush
AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID	:	**Mail Stop: AMENDMENT**

RESPONSE

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

Sir/Madam:

This is responsive to the Official Action dated July 24, 2014.

The USPTO is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16, 1.17, and 1.492, which may be required by this paper to Deposit Account No. 23-0975.

REMARKS

Favorable reconsideration is respectfully requested in view of the following remarks.

1. DOUBLE PATENTING REJECTIONS

All claims are rejected on the ground of nonstatutory double patenting as being unpatentable over claims of U.S. Patent No. 8,129,431, U.S. Patent No. 8,497,304, U.S. Patent No. 8,669,290 and U.S. Patent No. 8,754,131.

Without acquiescing to the grounds of rejection, there is submitted herewith a Terminal Disclaimer over each cited U.S. patent.

Accordingly, these grounds of rejection are deemed to be overcome.

II. CONCLUSION

In view of the foregoing, it is believed that each ground of rejection has been overcome, and that the application is now in condition for allowance.

Applicant respectfully submits that claims 19-48 are patentable over the prior art. A favorable action on the merits is solicited.

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: 2014.07.31 10:49:01 -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
July 31, 2014

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor	:	Attorney Docket No. 2014-0545
Shirou SAWA	:	**Confirmation No. 1021**
Serial No. 14/261,720	:	Group Art Unit 1627
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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

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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.

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

[X] The undersigned is an attorney of record.

July 31, 2014

/Warren M. Cheek, Jr./

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Date: 2014.07.31 10:49:17 -04'00'

Warren M. Cheek
Reg. No. 33,367

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

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Shirou SAWA	:	**Confirmation No. 1021**
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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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Date: 2014.07.31 10:50:01 -04'00'

July 31, 2014

Warren M. Cheek
Reg. No. 33,367

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

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Shirou SAWA	:	**Confirmation No. 1021**
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Commissioner for Patents
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Alexandria, VA 22313-1450

Sir/Madam:

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July 31, 2014

/Warren M. Cheek, Jr./

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Date: 2014.07.31 10:50:17 -04'00'

Warren M. Cheek
Reg. No. 33,367

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

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Electronic Patent Application Fee Transmittal

Application Number:	14261720
Filing Date:	25-Apr-2014
Title of Invention:	AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID
First Named Inventor/Applicant Name:	Shirou SAWA
Filer:	Warren M. Cheek Jr./Donna King
Attorney Docket Number:	2014-0545

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

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

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

Electronic Acknowledgement Receipt

EFS ID:	19739097
Application Number:	14261720
International Application Number:	
Confirmation Number:	1021
Title of Invention:	AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID
First Named Inventor/Applicant Name:	Shirou SAWA
Customer Number:	513
Filer:	Warren M. Cheek Jr./maurice linder
Filer Authorized By:	Warren M. Cheek Jr.
Attorney Docket Number:	2014-0545
Receipt Date:	31-JUL-2014
Filing Date:	25-APR-2014
Time Stamp:	13:58:47
Application Type:	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	191
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	Amendment/Req. Reconsideration-After Non-Final Reject	AttachA_Response.pdf	174771 b7a52633d37d1ce1a89b88a4b9bd188d3070ac47	no	2

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	177566 95e66bb2889d89e5e7088cf8f6fdfaaceb099c66	no	2

Warnings:

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Information:

3	Terminal Disclaimer Filed	AttachC.pdf	177571 9d09162a1f5fc9ef04c3c2c51892e3a090295d5a	no	2

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4	Terminal Disclaimer Filed	AttachD.pdf	177579 2c36d43168472ed4985bf5dcb485084a42c3c0c7	no	2

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Information:

5	Terminal Disclaimer Filed	AttachE.pdf	177223 e0a62793c1a3341e43f3f9a88e52ab771eba8507	no	2

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Information:

6	Fee Worksheet (SB06)	fee-info.pdf	30755 9017345560baf0b117ea55e12d37cd99af27608a	no	2

Warnings:

Information:	
Total Files Size (in bytes):	915465

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. 2014-0545
Shirou SAWA	:	**Confirmation No. 1021**
Serial No. 14/261,720	:	Group Art Unit 1627
Filed April 25, 2014	:	Examiner Layla Soroush
AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID	:	**Mail Stop: AMENDMENT**

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.

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The USPTO is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16, 1.17, and 1.492, which may be required by this paper to Deposit Account No. 23-0975.

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.

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

[X] The undersigned is an attorney of record.

/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: 2014.07.31 10:49:45 -04'00'

July 31, 2014

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
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Facsimile (202) 721-8250

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/261,720	04/25/2014	Shirou SAWA	2014-0545	1021

513 7590 07/24/2014
WENDEROTH, LIND & PONACK, L.L.P.
1030 15th Street, N.W.,
Suite 400 East
Washington, DC 20005-1503

EXAMINER	
SOROUSH, LAYLA	
ART UNIT	PAPER NUMBER
1627	
NOTIFICATION DATE	DELIVERY MODE
07/24/2014	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ddalecki@wenderoth.com
eoa@wenderoth.com

Office Action Summary	Application No.	Applicant(s)	
	14/261,720	SAWA ET AL.	
	Examiner	**Art Unit**	**AIA (First Inventor to File) Status**
	LAYLA SOROUSH	1627	No

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

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *4/25/14*.
  ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.
2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.
3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *19-48* is/are pending in the application.
  5a) Of the above claim(s) _____ is/are withdrawn from consideration.
6)☐ Claim(s) _____ is/are allowed.
7)☒ Claim(s) *19-48* is/are rejected.
8)☐ Claim(s) _____ is/are objected to.
9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

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

Application Papers

10)☐ The specification is objected to by the Examiner.
11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.
  Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
  Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☒ All b)☐ Some** c)☐ None of the:
  1.☐ Certified copies of the priority documents have been received.
  2.☒ Certified copies of the priority documents have been received in Application No. 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)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b)
  Paper No(s)/Mail Date *4/25/14*.
3) ☐ Interview Summary (PTO-413)
  Paper No(s)/Mail Date. _____ .
4) ☐ Other: _____.

DETAILED ACTION

The following is in response to the Preliminary amendments filed on 4/25/2014.

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

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper time wise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the claims at issue are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the reference application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO internet Web site contains terminal disclaimer forms which may be used. Please visit http://www.uspto.gov/forms/. The filing date of the application will determine what form should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to http://www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

Claims 19-48 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-22 of U.S. Patent No. 8129431. Although the claims at issue are not identical, they are not patentably distinct from each other because the claims in the patent are drawn to an aqueous liquid preparation consisting essentially of the following two components, wherein the first component is 2-amino-3-(4-bromobenzoyl)phenylaceticacid 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 and the second component is tyloxapol wherein said liquid preparation is formulated for ophthalmic administration, and wherein when a quaternary ammonium compound is included in said liquid preparation, the quaternary ammonium compound is benzalkonium chloride whereas the claims herein are drawn to a stable aqueous liquid preparation consisting essentially of: (a) a first component; (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; (c) boric acid; (d) sodium tetraborate; and (e) water; 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 and is present in the preparation at a concentration from about 0.05 w/v % to about 0.2 w/v %; the second component is tyloxapol and is present in said liquid preparation in an amount sufficient to stabilize said first component; and wherein said stable liquid preparation is formulated for ophthalmic administration.

Claims 19-48 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-17 of U.S. Patent No. 8497304. Although the claims at issue are not identical, they are not patentably distinct from each other because the claims in the copending application are drawn to an aqueous liquid preparation comprising 2-amino-3-(4- bromobenzoyl)phenylacetic acid sodium salt thereof or a hydrate thereof, and polyoxyl 40 stearate, wherein the concentration of the polyoxyl 40 stearate is selected from a range of a minimum concentration of 0.02 w/v % to a maximum concentration of O. 1 w/v% whereas the claims herein are drawn to a stable aqueous liquid preparation consisting essentially of: (a) a first component; (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; (c) boric acid; (d) sodium tetraborate; and (e) water; 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 and is present in the preparation at a concentration from about 0.05 w/v % to about 0.2 w/v %; the second component is tyloxapol and is present in said liquid preparation in an amount sufficient to stabilize said first component; and wherein said stable liquid preparation is formulated for ophthalmic administration.

Claims 19-48 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-30 of U.S. Patent No. 8669290. Although the claims at issue are not identical, they are not patentably distinct from each other because the claims in the copending application are drawn to a stable aqueous liquid preparation comprising: (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; and wherein said stable liquid preparation is formulated for ophthalmic administration whereas the claims herein are drawn to a stable aqueous liquid preparation consisting essentially of: (a) a first component; (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; (c) boric acid; (d) sodium tetraborate; and (e) water; 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 and is present in the preparation at a concentration from about 0.05 w/v % to about 0.2 w/v %; the second component is tyloxapol and is present in said liquid preparation in an amount sufficient to stabilize said first component; and wherein said stable liquid preparation is formulated for ophthalmic administration.

Claims 19-48 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-30 of U.S. Patent No. 8754131. Although the claims at issue are not identical, they are not patentably distinct from each other because the claims in the patent are drawn to a stable aqueous liquid preparation comprising: (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 and is present in the preparation at a concentration from about 0.05 w/v % to about 0.2 w/v %; the second component is tyloxapol and is present in said liquid preparation in an amount sufficient to stabilize said first component; and wherein said stable liquid preparation is formulated for ophthalmic administration whereas the claims herein are drawn to a stable aqueous liquid preparation consisting essentially of: (a) a first component; (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; (c) boric acid; (d) sodium tetraborate; and (e) water; 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 and is present in the preparation at a concentration from about 0.05 w/v % to about 0.2 w/v %; the second component is tyloxapol and is present in said liquid preparation in an amount sufficient to stabilize said first component; and wherein said stable liquid preparation is formulated for ophthalmic administration.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Layla Soroush whose telephone number is (571)272-5008. The examiner can normally be reached on Monday through Friday from 8:30 a.m. to 5:00 p.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).

/Layla Soroush/

Examiner, Art Unit 1627

Sheet 1 of 2

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: April 25, 2014	**ATTY DOCKET NO.** 2014-0545	**SERIAL NO.** NEW
	FIRST NAMED INVENTOR Shirou SAWA	
	FILING DATE April 25, 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	Cherng-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.			

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION/ADDITIONAL INFORMATION YES	NO
/L.S./	BA	9-503791	4/1997	JP				
/L.S./	BB	2-124819	5/1990	JP				

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

Sheet 2 of 2

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: April 25, 2014

ATTY DOCKET NO.
2014-0545

SERIAL NO.
NEW

FIRST NAMED INVENTOR
Shirou SAWA

FILING DATE
April 25, 2014

GROUP

/L.S./	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				

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.
	CB	ISTA Pharmaceuticals, "New Drug Applications: Xibrom", http://www.drugs.com/nda/xibrom_040525.htmt, 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	http://medical-dictionary.thefreedictionary.com/prophylactic accessed 12/15/2009.
	CH	H. Scott et al., "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.

EXAMINER /Layla Soroush/

DATE CONSIDERED

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

Search Notes	**Application/Control No.** 14/261,720	**Applicant(s)/Patent under Reexamination** SAWA ET AL.	
	Examiner LAYLA SOROUSH	**Art Unit** 1627	

SEARCHED

Class	Subclass	Date	Examiner

INTERFERENCE SEARCHED

Class	Subclass	Date	Examiner

SEARCH NOTES (INCLUDING SEARCH STRATEGY)

	DATE	EXMR
2-amino-3-(4-bromobenzoyl)phenylaceticacid	7/18/2014	LS
SAWA, Shirou FUJITA, Shuhei	7/18/2014	LS

U.S. Patent and Trademark Office

Part of Paper No. 20140718

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor	:	Attorney Docket No. 2014-0545
Shirou SAWA	:	**Confirmation No. 1021**
Serial No. 14/261,720	:	Group Art Unit 1629
Filed April 25, 2014	:	Examiner Not Yet Assigned
AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID	:	**Mail Stop: AMENDMENT**

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. [X] 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:

The USPTO is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16, 1.17, and 1.492, which may be required by this paper to Deposit Account No. 23-0975.

(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. [X] the concise explanation set forth below on the attached PTO/SB/08 Form.

4. [] A foreign patent office search report citing one or more of the references is enclosed.

5. [] <u>Statement Under 37 CFR 1.704(d)</u> 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.

Respectfully submitted,

/Warren M. Cheek/

Digitally signed by /Warren M. Cheek/
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email=wcheek@wenderoth.com,
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July 18, 2014

Sheet 1 of 3

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: July 18, 2014	**ATTY DOCKET NO.** 2014-0545	**SERIAL NO.** 14/261,720
	FIRST NAMED INVENTOR Shirou SAWA	
	FILING DATE April 25, 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.

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

Sheet 2 of 3	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: July 18, 2014	**ATTY DOCKET NO.** 2014-0545	**SERIAL NO.** 14/261,720
	FIRST NAMED INVENTOR Shirou SAWA	
	FILING DATE April 25, 2014	**GROUP**

	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[1]", 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	Webester'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.

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

Sheet 3 of 3

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: July 18, 2014

ATTY DOCKET NO. 2014-0545	**SERIAL NO.** 14/261,720
FIRST NAMED INVENTOR Shirou SAWA	
FILING DATE April 25, 2014	**GROUP**

	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, 20th 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™ product package, Loteprednol Etabonate, Ophthalmic Suspension, 0.2%, pp. 1-13, 1998.
	CZ	XIBROM™ 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™ 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	ALREX™ product package, Loteprednol Etabonate, Ophthalmic Suspension, 0.2%, pp. 1-13, 1998.
	CAF	The United States Pharmacopeia, The National Formulary, USP 24, NF 19, pp. 1809-1813, 1864-1866, 2000.
	CAG	Dorset & Baber, Webster’s New Twentieth Century Dictionary, Second Edition, “Ophthalmic” and “Ophthalmitic” p. 1254, 1979.
	CAH	BRONUCK® news release, Bromfenac Sodium Hydrate Ophthalmic Solution, p.1, 2005.

EXAMINER	DATE CONSIDERED

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

(19) **Canadian Intellectual Property Office**

An Agency of
Industry Canada

Office de la Propriété Intellectuelle du Canada

Un organisme
d'Industrie Canada

(11) **CA 2 013 188** (13) **C**

(40) **14.03.2000**
(43) **28.09.1990**
(45) **14.03.2000**

(12)

(21) **2 013 188**

(22) **27.03.1990**

(51) Int. Cl.^{5}: **A61K 031/71**, A61K 031/19, A61K 031/405

(30) **07/329,451 US 28.03.1989**

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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 ophthamologically 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.

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(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 ophthamologically 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.

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ABSTRACT OF THE DISCLOSURE

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 ophthamologically 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.

PRESERVATIVE SYSTEM FOR OPHTHALMIC FORMULATIONS

FIELD OF THE INVENTION

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 formulations of carboxyl ("-COOH") group-containing non-steroidal anti-inflammatory drugs ("NSAIDs") and contain an opthalmologically acceptable antibiotic, preferably tobramycin. The invention also relates to methods of using these formulations 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. In addition, the formulation can be used to treat bacterial infection.

BACKGROUND OF THE INVENTION

To be ophthalmologically acceptable, a formulation must possess a number of characteristics to comply with 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. 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 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 $NaH_2PO_4 \cdot H_2O$, $Na_2HPO_4 \cdot H_2O$, NaCl, benzalkonium chloride ("BAC") and sterilized water. While the formulations described 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 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 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 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 (pranoprofen) in an aqueous based formula with a known 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 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. 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 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 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 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 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 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 quarternary 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 inpreventing or eliminating infection.

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 -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 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.

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

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 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 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 forth below. Reference being made to the accompanying general structural formulae forming a part hereof wherein like symbols refer to like molecular moieties throughout.

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.

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 mammal, including:

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

(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.

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.

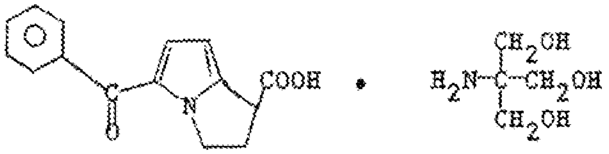
As used herein, the term "antimicrobially effective" refers to the stability of the formulation prior to administration and means ability to withstand the U.S. Pharmacopia antimicrobial challenge put by a panel of microbes.

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

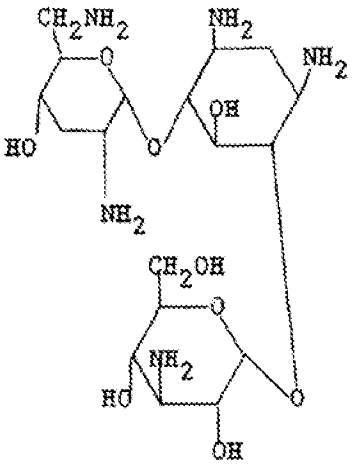
As used herein, the term "quarternary ammonium preservative" means a quarternary ammonium compound as described below.

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.

"Ketorolac tromethamine" shall mean the compound (±)-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)



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



Tobramycin is a water soluble aminoglycosidic antibiotic having a broad spectrum of action against both gram negative and gram positive bacteria. Such aminoglycosidic antibiotics are useful in treating ocular infections and are used prophylactically before and after ocular surgery.

Formulations

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 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.

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

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., 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.

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 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:

Ingredient	Amount
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.;
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 antiobiotic.

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

Ingredient	Amount
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.

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

Ingredient	Amount
NSAID	0.50% wt/vol.;
Antibiotic	0.30% wt/vol.;
BAC (50% aq. soln.)	0.02% wt/vol.;
Octoxynol 40 (70% aq. soln.)	0.01% wt/vol.;
EDTA Na_2	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; and
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.

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

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 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 CA897 (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.

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.

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.

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. The inclusion of an antibiotic in the formulation does not effect the rate of diffusion of the NSAID.

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 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.

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.
antibiotic	0.30% wt/vol.
BAC (50% aq. soln.)	0.02% wt/vol.
Octoxynol 40 (70% aq. soln.)	0.01% wt/vol.
EDTA Na_2	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
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.

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 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 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 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 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 formulations, their preparation and administration, see *Remington's Pharmaceutical Sciences*, 15th Ed., pages 1489-1504, (1975).

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(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 is made as to whether a given microbe survives in it.

EXAMPLES

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

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

Tromethamine and the antibiotic tobramycin.

Ingredient	Amount
ketorolac tromethamine	0.50% wt/vol.
tobramycin	0.30% wt/vol.
BAC (50% aq. soln.)	0.02% wt/vol.
Octoxynol 40 (70% aq. soln.)	0.01% wt/vol.
EDTA Na_2	0.10% wt/vol.
NaCl	0.18% wt/vol.
Boric Acid	0.9% wt/vol.
Na Borate	0.45% 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, such as those described above, can be used as the active compound in the preparation of the formulation of this example.

EXAMPLE 2

This example illustrates the preparation of a general pharmaceutical formulation for ophthalmic administration containing an NSAID and an antibiotic.

Ingredient	Amount
NSAID	0.50% wt/vol.
antibiotic	0.3% wt/vol.
BAC (50% aq. soln.)	0.01% wt/vol.
Octoxynol 40 (70% aq. soln.)	0.02% wt/vol.
EDTA Na_2	0.20% wt/vol.
NaCl	0.18% wt/vol.
Boric Acid	0.9% wt/vol.
Na Borate	0.45% wt/vol.

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
BAC (50% aq. soln.)	0.01% wt/vol.
Octoxynol 40 (70% aq. soln.)	0.01% wt/vol.
EDTA Na_2	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 formulation of any of these examples.

EXAMPLE 4

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

Ingredient	Amount
Flurbiprofen Sodium	0.03% wt/vol.
BAC (50% aq. soln.)	0.02% wt/vol.
Octoxynol 40 (70% aq. soln.)	0.01% wt/vol.
EDTA Na_2	0.10% wt/vol.
NaCl	0.18% wt/vol.
Boric Acid	0.9% wt/vol.
Na Borate	0.45% 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 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

Physical stability of the formulations of the 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 considered stable in this procedure.

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 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.

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 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 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.

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 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 experiments. A side arm allowed sampling of the receptor 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 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 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 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% 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 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.

^{14}C-glycerol Penetration - To monitor corneal integrity throughout the course of the permeability studies, ^{14}C-glycerol penetration was evaluated (^{14}C-glycerol 15.76 mCi/mmole was obtained from NEN with a radiochemical purity of 98%). Nonionized ^{14}C-glycerol was incorporated into selected test 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 ^{14}C-glycerol was added. At 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 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 column. The mobile phase flow rate was 1.0 ml/min; the sample injection volume was 50 µl; and the absorbance wavelength was 254 nm. A 100 µl aliquot of each sample was diluted with 150 µl of mobile phase.

2. Quantitation of tobramycin was performed using 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 µg/ml. The assay is based on competition for antibody sites between free drug in 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 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 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. Since these were control cornea, each is from a different 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}C-glycerol. Changes in the permeability profile of ^{14}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}C-glycerol penetration would indicate substantial corneal alteration. Table I shows that ^{14}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.

TABLE I

	Percent of Initial Counts per Minute	
<u>Preparation</u>	<u>at 60 min</u>	<u>at 120 min</u>
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
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 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.

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 formulation demonstrated that after 60 minutes, there occurs a two to three fold increas in ketorolac diffusion, that is, enhanced penetration.

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 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 modifications are intended to be within the scope of the claims appended hereto.

WHAT IS CLAIMED IS:

1. An ophthalmologically acceptable non-steroidal anti-inflammatory drug formulation, comprising:

an ophthalmologically acceptable non-steroidal anti-inflammatory carboxyl group-containing drug in an effective amount for ophthalmic treatment;

an ophtalmologically acceptable 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.

2. The ophthalmologically acceptable non-steroidal anti-inflammatory drug formulation of Claim 1 wherein said quaternary ammonium preservative is benzalkonium chloride.

3. The ophtalmologically acceptable non-steroidal anti-inflammatory drug formulation of Claim 1 wherein said nonionic polyoxyethylated octylphenol surfactant is Octoxynol 40 and the antibiotic is tobramycin.

4. The ophthalmologically acceptable non-steroidal anti-inflammatory drug formulation of Claim 1 including disodium edetate.

5. The ophthalmologically acceptable 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.

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:

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
Purified Water	q.s. to 100%.

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

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
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 ophtalmologically acceptable non-steroidal anti-inflammatory drug formulation of

Claim 8, further comprising:

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 ophtalmologically acceptable non-steroidal anti-inflammatory drug formulation of Claim 9 comprising:

ketorolac tromethamine	0.50% wt/vol.;
Tobramycin	0.30% wt/vol.;
BAC (50% aq. soln.)	0.02% wt/vol.;
Octoxynol 40 (70% aq. soln.)	0.01% wt/vol.;
EDTA Na_2	0.10% wt/vol.;
NaCl	0.18% wt/vol.;
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%.

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.;
BAC (50% aq. soln.)	0.01% wt/vol.;
Octoxynol 40 (70% aq. soln.)	0.01% wt/vol.;
EDTA Na_2	0.10% wt/vol.;
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
Purified Water	q.s. to 100%.

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(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.

Form 10

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952-69

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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 us

PRESERVATIVE SYSTEM FOR OPHTHALMIC FORMULATIONS

BACKGROUND OF THE INVENTION

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").

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.

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 $NaH_2PO_4 \cdot H_2O$, $Na_2HPO_4 \cdot H_2O$, NaCl, benzalkonium chloride ("BAC") and sterilized water. While the formulations described 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 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 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 solutions of NSAIDs for occular 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 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 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 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 preservative.

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 preservate 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.

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 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.

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

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 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 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 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 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:

Ingredient	Amount
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.;
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:

Ingredient	Amount
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.

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

Ingredient	Amount
NSAID	0.002% to 5.0% wt/vol.;
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_2	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:

Ingredient	Amount
NSAID	0.005% to 1.0% wt/vol.;
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_2	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:

Ingredient	Amount
NSAID	0.50% wt/vol.;
BAC (50% aq. soln.)	0.02% wt/vol.;
Octoxynol 40 (70% aq. soln.)	0.01% wt/vol.;
EDTA Na_2	0.10% 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%.

The invention relates primarily to formulations having as the active agent ophthalmologically acceptable drugs (including the isomers (as either the (d)- or (1)-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.

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.

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.

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.

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:

Ingredient	Amount
NSAID	0.002% to 5.0% wt/vol.;
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_2	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%.

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

Ingredient	Amount
NSAID	0.005% to 1.0% wt/vol.;
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_2	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%.

A preferred ophthalmic NSAID solution has the following formulation:

Ingredient	Amount
NSAID	0.50% wt/vol.
BAC (50% aq. soln.)	0.02% wt/vol.
Octoxynol 40 (70% aq. soln.)	0.01% wt/vol.
EDTA Na_2	0.10% 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
Purified Water	q.s. to 100%

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

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 supresses already developed inflammatory processes.

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).

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

EXAMPLES

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

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

Ingredient	Amount
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_2	0.10% wt/vol.
NaCl	0.79% 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 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.

EXAMPLE 2

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

Ingredient	Amount
Ketorolac Tromethamine	0.50% wt/vol.
BAC (50% aq. soln.)	0.02% wt/vol.
Octoxynol 40 (70% aq. soln.)	0.02% wt/vol.
EDTA Na_2	0.20% wt/vol.
NaCl	0.79% 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 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.

EXAMPLE 3

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

Ingredient	Amount
Ketorolac Tromethamine	0.10% wt/vol.
BAC (50% aq. soln.)	0.004% wt/vol.
Octoxynol 40 (70% aq. soln.)	0.004% wt/vol.
EDTA Na_2	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.

Ingredient	Amount
Flurbiprofen Sodium	0.03% wt/vol.
BAC (50% aq. soln.)	0.02% wt/vol.
Octoxynol 40 (70% aq. soln.)	0.01% wt/vol.
EDTA Na_2	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.

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

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 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 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 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 various temperatures for future visual observations.

	Octoxynol 40		Tween 80		Myrj 52	
	0.004%	0.02%	0.0035%	0.01%	0.0015%	0.01%
1 month						
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
5 month						
60°C	clear	clear	clear	clear	clear	clear
40°C	clear	clear	turbid	turbid	turbid	turbid
RT	clear	clear	turbid	turbid	turbid	turbid

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.

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.

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.

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

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 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 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 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 (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 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 the blood-aqueous barrier becomes permeable to 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 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 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 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 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 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 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 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 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 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 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.

EXAMPLE 8

This was a double-blind, parallel comparison with vehicle to evaluate the efficacy of ketorolac 0.5% 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 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 each of these visits, patients received ophthalmic 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 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 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 days produces a decrease in eosinophilic granules as compared to vehicle in the treatment of allergic conjunctivitis.

EXAMPLE 9

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 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, photophobia) or signs (tearing, ocular discharge, conjunctival vasodilation, chemosis, keratitis, fluorescein staining, Rose Bengal staining) was found between ketorolac and vehicle.

EXAMPLE 10

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.

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.

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 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 modifications are intended to be within the scope of the claims appended hereto.

~~WHAT IS CLAIMED IS:~~

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

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.

2. The ophthalmic NSAID formulation of Claim 1 wherein said quaternary ammonium preservative is benzalkonium chloride.

3. The ophthalmic NSAID formulation of Claim 1 wherein said nonionic ethoxylated octylphenol surfactant 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 wherein said nonionic ethoxylated octylphenol surfactant is Octoxynol 40.

5. The ophthalmic NSAID formulation of Claim 4 including disodium edetate.

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 esters.

7. The ophthalmic NSAID formulation of Claim 6 wherein said NSAID is Ketorolac Tromethamine.

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

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.; and
Purified Water	q.s. to 100%.

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

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

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

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.

14. The ophthalmic NSAID formulation of Claim 13 comprising:

NSAID	0.50% wt/vol.;
BAC (50% aq. soln.)	0.02% wt/vol.;
Octoxynol 40 (70% aq. soln.)	0.01% wt/vol.;
EDTA Na_2	0.10% wt/vol.;
NaCl	0.79% wt/vol.;
1N NaOH or 1N HCl	q.s. to adjust pH to 7.4 ±0.4; and
Purified Water	q.s. to 100%.

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

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

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

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

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 (50% aq. soln.)	0.02% wt/vol.;
Octoxynol 40 (70% aq. soln.)	0.01% wt/vol.;
EDTA Na_2	0.10% wt/vol.;
NaCl	0.79% wt/vol.;
1N NaOH or 1N HCl	to adjust pH to 7.4 ± 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.
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(54) Title: OPHTHALMIC COMPOSITIONS COMPRISING BENZYLLAURYLDIMETHYLAMMONIUM CHLORIDE

(57) Abstract

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_{12} 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.

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OPHTHALMIC COMPOSITIONS COMPRISING BENZYLLAURYLDIMETHYLAMMONIUM CHLORIDE

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®).

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.

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

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.

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 alkyldimethylbenzyl-ammonium 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.

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.

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. 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, known as benzalkonium chloride, which includes a mixture of the alkyls from C_8H_{17} to $C_{18}H_{37}$.

SUMMARY OF THE INVENTION

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.

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.

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.

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 insoluable ion-pairs are produced when the drug is in combination with lauralkonium chloride, taken itself.

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 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 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 compounding of flurbiprofen formulations as follows.

Compounding occurs in two parts:

Part 1: Disperse polyvinyl alcohol in rapidly stirring purified water 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 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.

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 (0.22μ) and aseptically fill units into pre-sterilized containers.

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 Perkasie, PA, respectively.

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.

TABLE 1

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

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
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 Pharmacopeia while Example B passes the British Pharmacopieia 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

370	48.2

TABLE 3

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

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

INTERNATIONAL SEARCH REPORT

Inten. al Application No
PCT/US 94/00188

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 A61K31/19 A61K9/00 A61K47/18

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 A61K

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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

☐ Further documents are listed in the continuation of box C.

☐ Patent family members are listed in annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

"&" document member of the same patent family

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Date of mailing of the international search report
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INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter. nal Application No
PCT/US 94/00188

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
JP-A-01246227	21-05-75	JP-A- 50058310 JP-B- 59016038 US-A- 4091167	21-05-75 12-04-84 23-05-78
JP-A-57102817	26-06-82	NONE	

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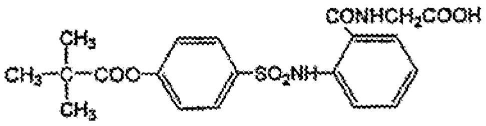
(54) MEDICAMENTS THERAPEUTIQUE ET PROPHYLACTIQUE POUR TRAITER LES MALADIES OPHTALMIQUES

(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.



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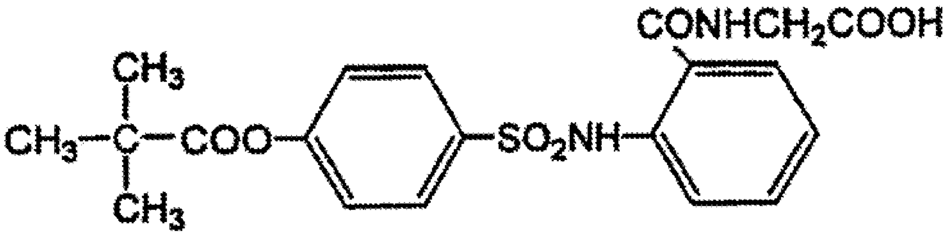
(54) **Titre :** MEDICAMENTS THERAPEUTIQUE ET PROPHYLACTIQUE POUR TRAITER LES MALADIES OPHTALMIQUES
(54) **Title:** PROPHYLACTIC AND THERAPEUTIC MEDICAMENTS FOR OPHTHALMIC DISEASES



(I)

(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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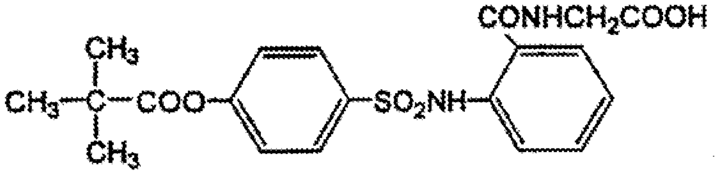
Abstract of the disclosure:

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):



(I)

or a pharmacologically acceptable salt or hydrate thereof.

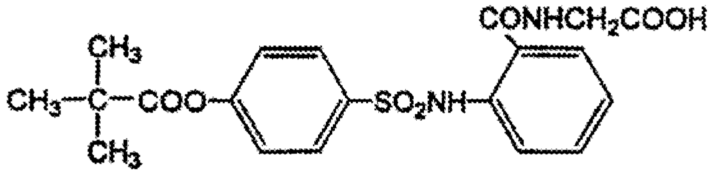
PROPHYLACTIC AND THERAPEUTIC MEDICAMENTS FOR OPHTHALMIC DISEASES

TECHNICAL FIELD

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

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):



(I)

(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 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 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 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 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 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-pivaloyloxybenzenesulfonylamino)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 ± standard deviation (n=4). A statistically significant 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 represents a mean ± 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 keratitis (effect on a vascularization). Each symbol represents a mean ± 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 mean ± 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 (effect on a corneal opacity). Each symbol represents a mean ± 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 ± 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 ± 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 ± 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 ± 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.

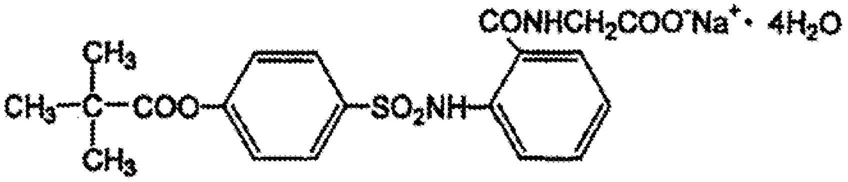
DETAILED DESCRIPTION OF THE INVENTION

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 keratophathy, 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 insufficiency-induced keratomalacia, necrotic keratitis, neuroparalytic keratitis, diabetic keratophathy, keratoconjunctiva sicca, contact lens-induced keratoconjunctivitis, vernal conjunctivitis, allergic conjunctivitis and the like). It is useful also for 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 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 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 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):



(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 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), 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 keratophathy, 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 insufficiency-induced keratomalacia, necrotic keratitis, neuroparalytic keratitis, diabetic keratophathy, keratoconjunctiva sicca, contact lens-induced keratoconjunctivitis, vernal conjunctivitis, allergic conjunctivitis and the like). It is useful also for preventing and treating corneal ulcer (including 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 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 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 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, 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., 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 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 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 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 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 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 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 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 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.

EXPERIMENT 1

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

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.

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 temperature of 24 ± 4°C and a humidity of 55 ± 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 % NaH_2PO_4, 0.1 % polysorbate 80 and 0.9 % 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

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 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 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 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

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 µl every 2 hours.

Table 1

Rabbit keratitis scoring criteria

* Corneal opacity$^{\text{remarks 1)}}$

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

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 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

4: Perforation in cornea

* Vascularization[remarks 1)]

A) Length

0: No vascularization into cornea

1: Less than 1/3 from corneal limbus through center

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 circumference

2: 2/3 or more of corneal circumference

Remarks 1) Each as score A x score B

RESULTS AND DISCUSSION

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

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 ± 3°C and a humidity of 55 ± 10 %.

(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 % sodium acetate, 0.1 % polysorbate 80 and 0.9 % NaCl, pH 5.0). A 0.3 % lomefloxacin (LFLX) hydrochloride was used as an antibacterial agent, and physiological saline was used as a control.

(3) Methods

1) Excision of nictitating membrane

After instilling 0.4 % oxybuprocaine hydrochloride 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 rabbit was anesthetized systemically with 5 % ketamine hydrochloride and 2 % xylazine hydrochloride (equal volume mixture), and then inoculated by an infusion of 30 µl of a 3.9 x 10^4 CFU/ml cell suspension (1.17 x 10^3 CFU/cornea) using a 100 µl 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 µl 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

* 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

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

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 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.

Component	Quantity
Compound A	0.1 g
Sodium chloride	0.9 g
Sodium acetate	0.1 g
Benzalkonium chloride	0.005 g
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.

EXAMPLE 2

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

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
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 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 obtaining an eye drop formulation as an aqueous suspension.

EXAMPLE 3

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

Component	Quantity
Compound A	0.5 g
Concentrated glycerin	2.6 g
Sodium acetate	0.1 g
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
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 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. Sterilized purified water was added to make the entire volume 100 mL, whereby obtaining an eye drop formulation as an aqueous suspension.

Example 4

The following composition was used to make an ophthalmic ointment

Component	Quantity
Compound A	2.0 g
Liquid paraffin	2.0 g
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.

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
Propylene glycol	1.0 g
Polyvinyl pyrrolidone (K-25)	0.5 g
Sodium alginate	0.2 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, 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 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-dispersion performance without any aggregation.

EXAMPLE 6

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
Propylene glycol	1.0 g
Polyvinyl pyrrolidone (K-25)	0.5 g
Sodium alginate	0.2 g
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, 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 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
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. 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 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.

EXAMPLE 8

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

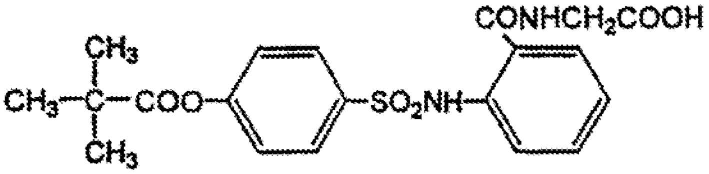
In about 80 ml of purified water, sodium citrate, concentrated glycerin and polyvinyl pyrrolidone were dissolved. In this solution, Compound A was dissolved and the solution was filtered through a 0.22 µm membrane filter, adjusted at pH 5.0 with hydrochloric acid, whereby precipitating a fine crystal (2 to 3 µm) of Compound A. Sodium alginate 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.

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):



(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 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 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, 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 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 ophthalmic disease is an ophthalmic inflammatory

disease.

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

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.

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.

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.

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 32 wherein the surfactant is tyloxapol or polysorbate 80.

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Fig. 1

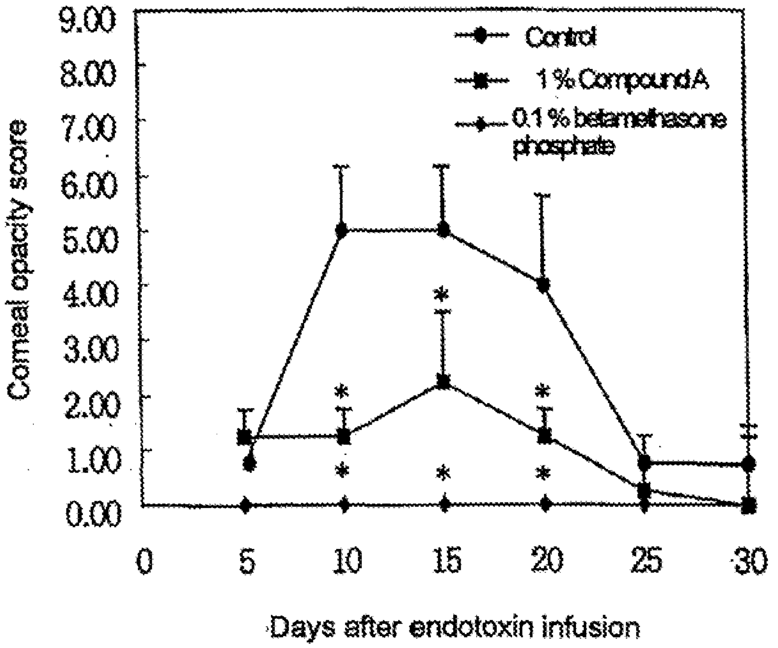

9.00
8.00
7.00
6.00
5.00
4.00
3.00
2.00
1.00
0.00
Corneal opacity score
Control
1 % Compound A
0.1 % betamethasone phosphate
*
0
5
10
15
20
25
30
Days after endotoxin infusion

Fig. 2

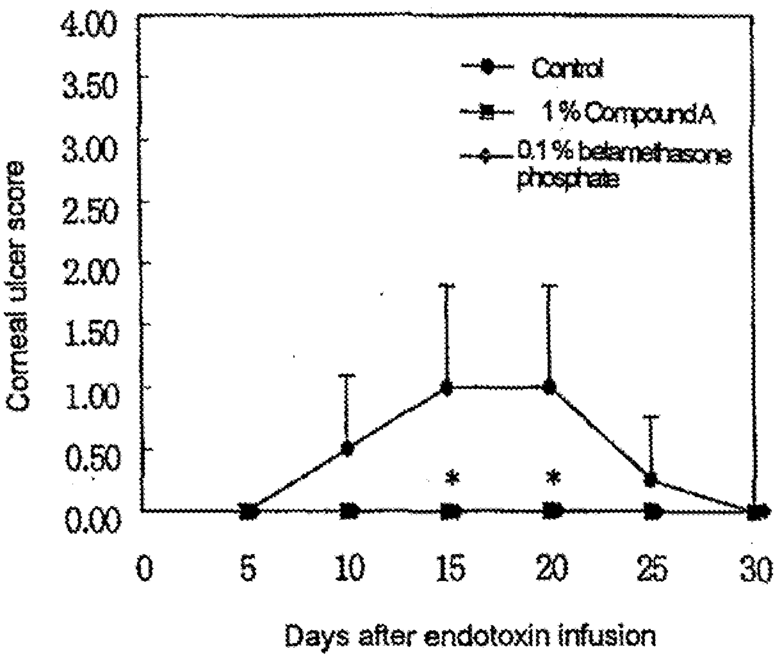

4.00
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00
Corneal ulcer score
Control
1 % Compound A
0.1 % betamethasone phosphate
*
*
0
5
10
15
20
25
30
Days after endotoxin infusion

Fig. 3

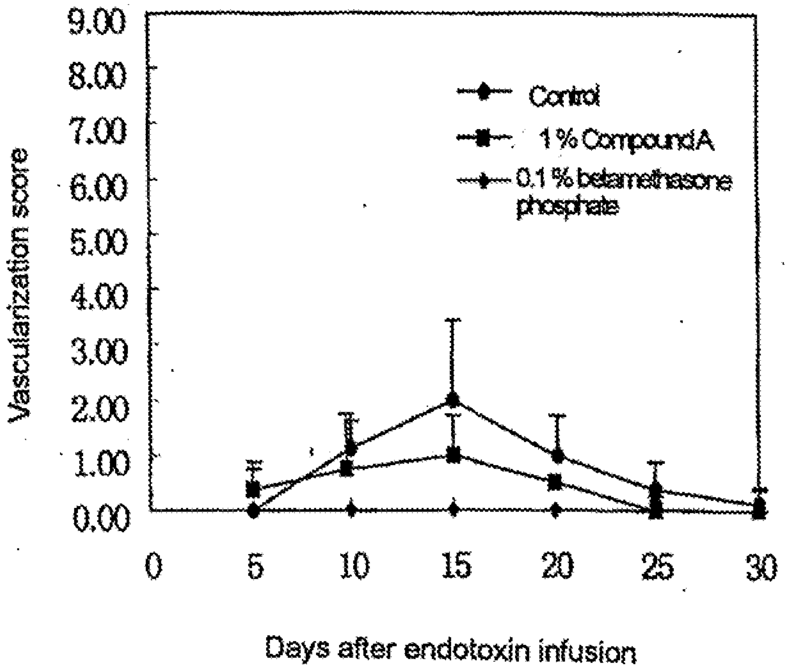

9.00
8.00
7.00
6.00
5.00
4.00
3.00
2.00
1.00
0.00
Vascularization score
0
5
10
15
20
25
30
Days after endotoxin infusion
Control
1 % Compound A
0.1 % betamethasone phosphate

Fig. 4

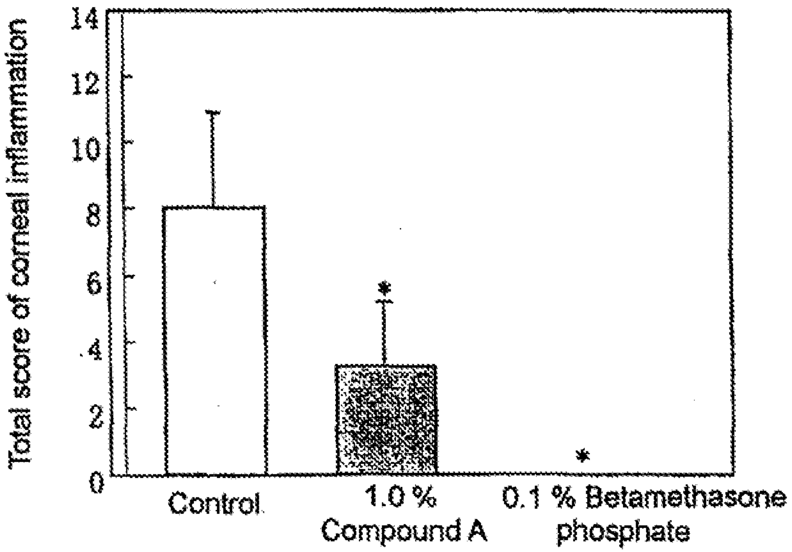

Total score of corneal inflammation
14
12
10
8
6
4
2
0
*
*
Control
1.0 %
Compound A
0.1 % Betamethasone
phosphate

Fig. 5

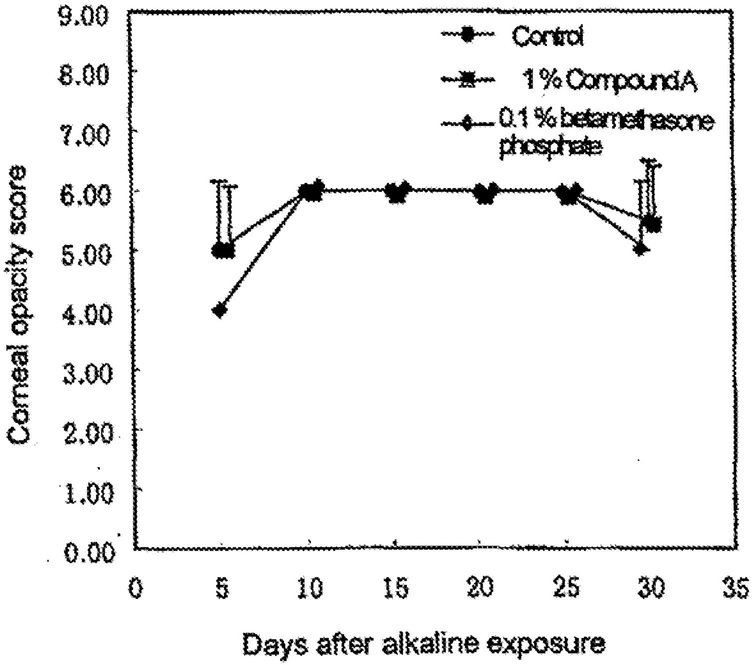

9.00
8.00
7.00
6.00
5.00
4.00
3.00
2.00
1.00
0.00
Corneal opacity score
0
5
10
15
20
25
30
35
Days after alkaline exposure
Control
1% Compound A
0.1% betamethasone phosphate

Fig. 6

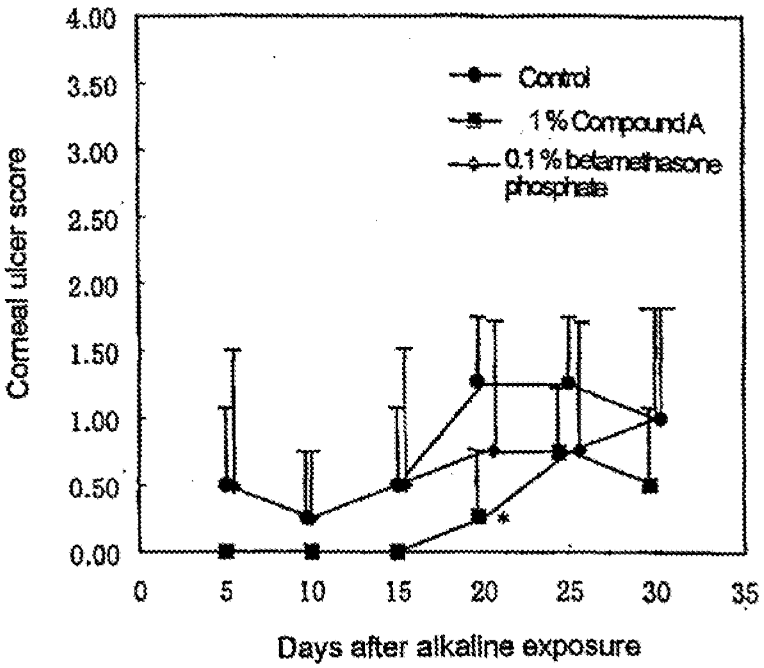

Corneal ulcer score
4.00
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00
0
5
10
15
20
25
30
35
Days after alkaline exposure
Control
1 % Compound A
0.1 % betamethasone phosphate
*

Fig. 7

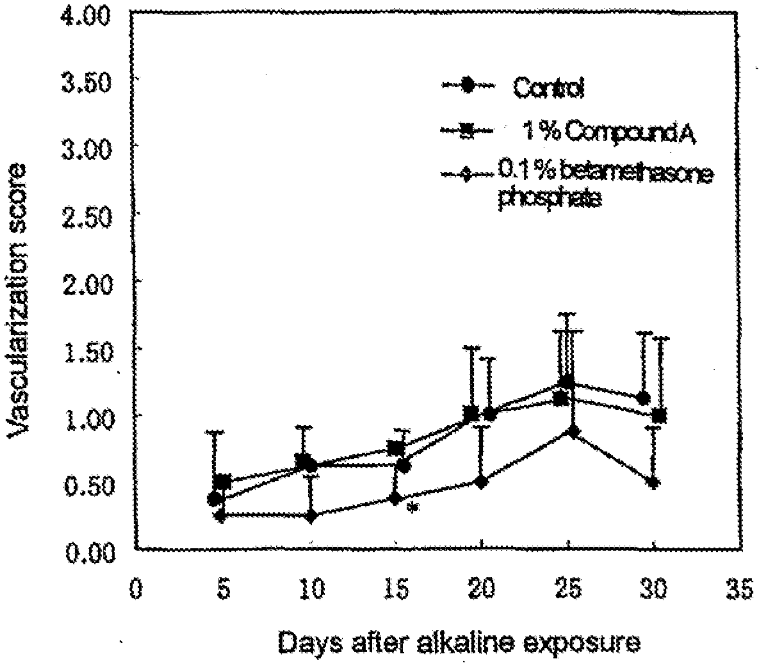

4.00
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00
Vascularization score
Control
1 % Compound A
0.1 % betamethasone phosphate
*
0
5
10
15
20
25
30
35
Days after alkaline exposure

Fig. 8

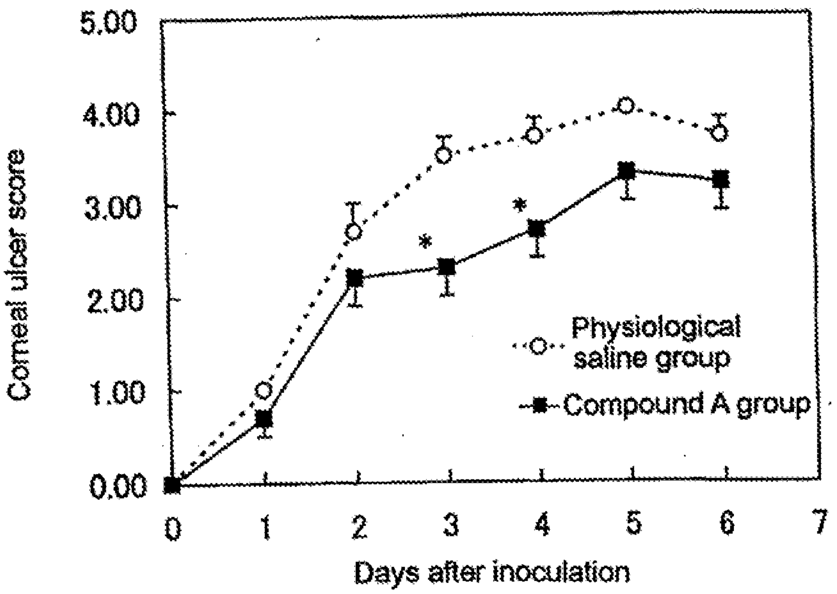
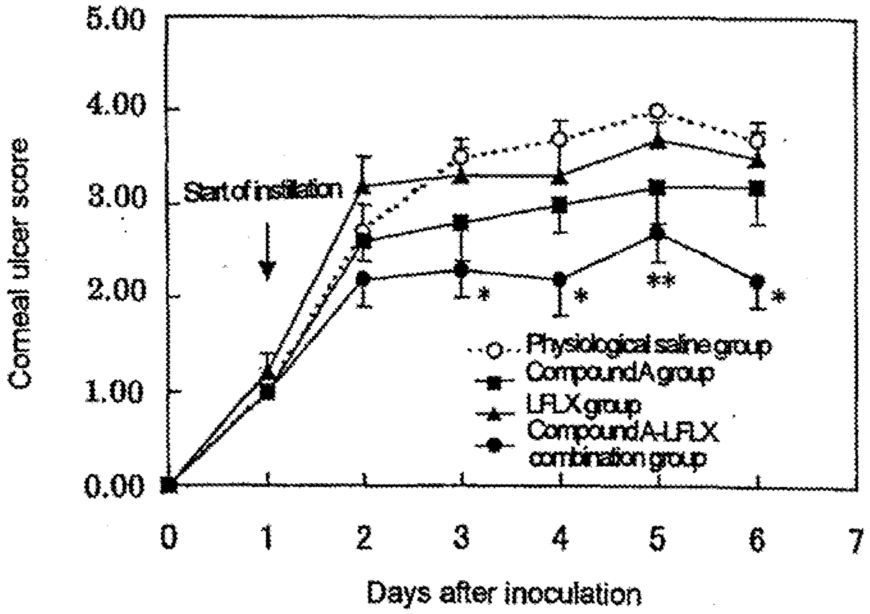

5.00
4.00
3.00
2.00
1.00
0.00
Corneal ulcer score
0
1
2
3
4
5
6
7
Days after inoculation
*
*
Physiological saline group
Compound A group

Fig. 9



5.00
4.00
3.00
2.00
1.00
0.00
Corneal ulcer score
Start of instillation
*
*
**
*
Physiological saline group
Compound A group
LFLX group
Compound A-LFLX combination group
0
1
2
3
4
5
6
7
Days after inoculation

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(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

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

BACKGROUND OF THE INVENTION

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-benzoyl-phenylacetamides having anti-inflammatory activity.

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.

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.

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-benzyolphenylacetic 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.*"

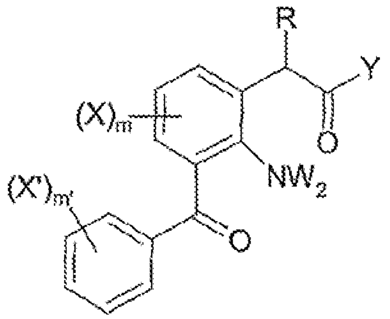
U.S. Patent No. 6,066,671 discloses the topical use of certain amide and ester derivatives of 3-benzoylphenylacetic acid, including nepafenac, for treating GLC1A glaucoma.

SUMMARY OF THE INVENTION

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

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.



(I)

R = H, C_{1-4} (un)branched alkyl, CF_3, SR^4;

Y = OR', NR"R';

R' = H, C_{1-10} (un)branched alkyl, (un)substituted (substitution as defined by X below), (un)substituted heterocycle (substitution as defined by X below), $-(CH_2)_nZ(CH_2)_{n'}A$;

n = 2-6;

n'= 1-6;

Z = nothing, O, C=O, OC(=O), C(=O)O, C(=O)NR^3, NR^3C(=O), $S(O)_{n2}$, $CHOR^3$, NR^3;

n^2 = 0-2;

R^3 = H, C_{1-6} (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), $—(CH_2)_nOR^3$;

R" = H, OH, OR';

X and X' independently = H, F, Cl, Br, I, OR', CN, OH, $S(O)_{n2}R^4$, CF_3, R^4, NO_2;

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

m = 0-3;

m' = 0-5;

W = O, H.

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:

R = H, C_{1-2} alkyl;
$Y = NR'R''$;
R' = H, C_{1-6} (un)branched alkyl, $-(CH_2)_nZ(CH_2)_{n'}A$;
Z = nothing, O, $CHOR^3$, NR^3;
R_3 = H;
A = H, OH, (un)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;
R^4 = C_{1-4} (un)branched alkyl;
m = 0-2;
m' = 0-2;
W = H;
n = 2-4;
n' = 0-3.

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.

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 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 chlorobutanol, 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%
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
pH adjustment with NaOH and/or HCl	pH 4.2 – 7.4
Water	q.s. 100%

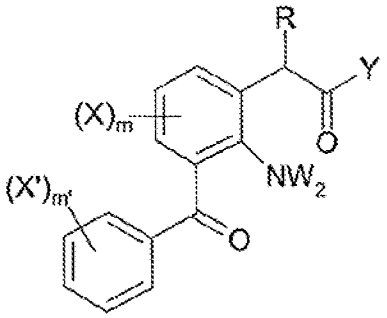
Formulation 3

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

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 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

R = H, $C_{1\text{-}4}$ (un)branched alkyl, CF_3, SR^4;

Y = OR', NR"R';

R' = H, $C_{1\text{-}10}$ (un)branched alkyl, (un)substituted (substitution as defined by X below), (un)substituted heterocycle (substitution as defined by X below), $-(CH_2)_nZ(CH_2)_{n'}A$;

n = 2-6;

n'= 1-6;

Z = nothing, O, C=O, OC(=O), C(=O)O, C(=O)NR^3, NR^3C(=O), $S(O)_{n2}$, $CHOR^3$, NR^3;

n^2 = 0-2;

R^3 = H, $C_{1\text{-}6}$ (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), $-(CH_2)_{n}OR^3$;

R" = H, OH, OR';

X and X' independently = H, F, Cl, Br, I, OR', CN, OH, $S(O)_{n2}R^4$, CF_3, R^4, NO_2;

R^4 = C_{1-6} (un)branched alkyl;
m = 0-3;
m' = 0-5; and
W = O, H.

2. The method of Claim 1 wherein
R = H, C_{1-2} alkyl;
Y = NR'R";
R' = H, C_{1-6} (un)branched alkyl, $—(CH_2)_nZ(CH_2)_{n'}A$;
Z = nothing, O, $CHOR^3$, NR^3;
R_3 = H;
A = H, OH, (un)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;
R^4 = C_{1-4} (un)branched alkyl;
m = 0-2;
m' = 0-2;
W = H;
n = 2-4; and
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 2-Amino-3-(4-chlorobenzoyl)-phenylacetamide.

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

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).

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.

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.

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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(54) Micelles containing a non-steroidal antiinflammatory compound.

(57) 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.

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, osteoarthrosis (or osteoarthritis) 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 is 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 capometacarpal 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 suffers 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 glycocorticoids, 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, fenbufen, 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 E2 (PGE2) 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 a 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$_{50}$ 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.

Polyoxyethylene AlkylphenolsPOE(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 (Rhom & Haas) Igepal CO series (GAF, USA) Antarox CO series (GAF, UK)

None of the polyoxyethylene alkylphenols are as yet approved for human ingestion.

Polyoxyethylated Glycol MonoethersPOE(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)
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)
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) has been extensively used in topical applications.

Polyoxyethylated Glyceryl Fatty Acid Esters

POE(n) glyceryl monolaurate n = 15,40 Glycerox L series (Croda)
These products have not been cleared for internal ingestion.

Polyoxyethylated Fatty AcidsPOE(n) monolaurate n = 4-100
Crodet L series (Croda)
POE(n) monooleate n = 4-100
Crodet O series (Croda)
POE(n) monostearate n = 4-100
Crodet S series (Croda)
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 valid contenders for approval, with the POE(n) monooleates and monolaurates also being likely candidates.

Sorbitan Fatty Acid EstersSorbitan monolaurate
Crill 1 (Croda)
Span 20 (Atlas ICI)
Sorbitan monopalmitate
Crill 2 (Croda)
Span 40 (Atlas ICI)

Sorbitan monostearate
Crill 3 (Croda)
Span 60 (Atlas ICI)
Sorbitan tristearate
Crill 35 (Croda)
Span 65 (Atlas ICI)
Sorbitan monooleate
Crill 4 (Croda)
Span 80 (Atlas ICI)
Sorbitan sesquioleate
Crill 43 (Croda)
Sorbitan trioleate
Crill 45 (Croda)
Span 85 (Atlas ICI)
Sorbitan monoisostearate
Crill 6 (Croda)

The surfactants in this group have good approval rating in the UK, EEC and US, but not complete approval.

<u>Polyoxyethylated Sorbitan Fatty Acid Esters</u>POE(20) sorbitan monolaurate
Crillet 1 (Croda)
Tween 20 (Atlas ICI)
POE(4) sorbitan monolaurate
Crillet 11 (Croda)
Tween 21 (Atlas ICI)
POE(20) sorbitan monopalmitate
Crillet 2 (Croda)
Tween 40 (Atlas ICI)
POE(20) sorbitan monostearate
Crillet 3 (Croda)
Tween 60 (Atlas ICI)
POE(4) sorbitan monostearate
Crillet 31 (Croda)
Tween 61 (Atlas/ICI)
POE(20) sorbitan tristearate
Crillet 35 (Croda)
Tween 65 (Atlas ICI)
POE(20) sorbitan monooleate
Crillet 4 (Croda)
Tween 80 (Atlas/ICI)
POE(5) sorbitan monooleate
Crillet 41 (Croda)
Tween 81 (Atlas/ICI)
POE(20) sorbitan trioleate
Crillet 45 (Croda)
Tween 85 (Atlas/ICI)
POE(20) sorbitan monoisostearate
Crillet 6 (Croda)

These surfactants have a similar approval profile to the Sorbitan Fatty Acid Esters, above.

Polyoxyethylated Castor OilsPOE(n) castor oil n = 10-100
Etocas Series (Croda)
Cremophor EL (BASF)
POE(n) hydrogenated castor oil n = 10-100
Crodurat series (Croda)
Cremophor RH40 (BASF)

Cremophor EL and Cremophor RH40 are well established as orally ingestable surfactants. It is envisaged that there would be no problems in registering the Etocas or Corduret series provided BP Castor Oil was used in manufacture of the surfactant.

PoloxamersPOE(n)-POP(m)
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.

Polyethylene Glycol Fatty Acid EstersPEG(400) distearate
Cithrol 4DS (Croda)
PEG(400) monolaurate
Cithrol 4ML (Croda)
PEG(n) monooleate n = 200,300,400
Cithrol MO series (Croda)
PEG(400) dioleate
Cithrol 4DO (Croda)
PEG(n) monostearate n = 400,600 1000
Cithrol MS series (Croda)

There are no toxicology data readily available for these surfactants.

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.

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.

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_{50}.

Chemical Identity	Description	HLB	LD50 g/kg
Polyoxyethylated Glycol Monoethers			
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
Polyoxyethylated Fatty Acids			
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	?

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	?

Chemical Identity	Description	HLB	LD50 g/kg
Polyoxyethylated Sorbitan Fatty Esters			
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	>36
POE(20) sorbitan monoisostearate	Yellow liquid	14.9	?
Polyoxyethylated Castor Oils			
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

Chemical Identity	Description	HLB	LD50 g/kg
POE(60) hydrogenated castor oil	White soft paste	14.6	?
POE(100) hydrogenated castor oil	White waxy solid	16.4	?
Poloxamers			
POE(22) - POP (13) (L35)	Liquid	18.5	
POE(90) - POP (13) (F38)	Solid	30.5	
POE(7) - POP (17) (L42)	Liquid	8	
POE(20) - POP (17) (L44)	Liquid	16	
POE(4) - POP (23) (L61)	Liquid	3	
POE(10) - POP (23) (L62)	Liquid	7	
POE(27) - POP (23) (L64)	Liquid	7	
POE(159)- POP (23) (F68)	Solid	15	
POE(47) - POP (27) (P75)	Paste	16.5	
POE(6) - POP (30) (L81)	Liquid	2	
POE(51) - POP (30) (P85)	Paste	16	
POE(119)- POP (30) (F87)	Solid	24	
POE(205)- POP (30) (F88)	Solid	28	
POE(19) - POP (37) (L92)	Liquid	5.5	
POE(41) - POP (37) (P94)	Paste	13.5	
POE(8) - POP (43) (L101)	Liquid	1	
POE(32) - POP (43) (P103)	Paste	9	
POE(296)- POP (43) (F108)	Solid	27	
POE(10) - POP (53) (L121)	Liquid	0.5	
POE(193)- POP (53) (F127)	Solid	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 SYNFLEX. 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 800 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 × 100 mg/5 ml syrup;

Indomethacin 200 ml × 25 mg/5 ml suspension (UK, but nor recommended in US for children under 14 years); and

Naproxen 500 ml × 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 1:6 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:

	mg per capsule
Indomethacin	25
POE(20) sorbitan monooleate (CRILLET 4)	310
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 thee 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.

Example No	Surfactant
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:

	mg per capsule
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.

Example No	Surfactant
13	POE(20) sorbitan monoisostearate (CRILLET 6)
14	POE(40) monostearate (CRODET S40)
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)

EXAMPLE 24

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:

	mg per capsule
Diclofenac acid	25
POE(15) cetostearyl ether (VOLPO CS15)	425
Total	450

EXAMPLES 25 TO 27

The procedure of Example 24 was repeated except that 425 mg capsule of the surfactant shown below was used:

Example No	Surfactant
25	POE(20) oleyl ether (VOLPO N20)
26	POE(15) oleyl ether (VOLPO N15)
27	POE(24) monostearate (CRODET S24)

EXAMPLE 28

Diclofenac Acid Capsules - Size 0

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:

	mg per capsule
Diclofenac acid	25
POE(24) monostearate (CRODET S24)	585
Total	610

EXAMPLES 29 TO 35

The procedure of Example 28 was repeated except that 585 mg/capsule of the surfactant shown below was used.

Example No	Surfactant
29	POE(40) monostearate (CRODET S40)
30	POE(20) sorbitan monooleate (CRILLET 4)
31	POE(20) sorbitan monoisostearate (CRILLET 6)
32	POE(40) hydrogenated castor oil (CRODURET 40 or CREMOPHOR RH40)
33	POE(35) castor oil (ETOCAS 35 or CREMOPHOR EL)
34	POE(15) glyceryl monolaurate (GLYCEROX L15)
35	POE(20) cetostearyl ether (VOLPO CS20)

EXAMPLE 36

Piroxicam capsules - Size 1

Following the general procedure of Example 1, except that Size 1 capsules were used, the following capsules were made up.

	mg per capsule
Piroxicam	10
POE(20) sorbitan monooleate (CRILLET 4)	440
Total	450

EXAMPLES 37 TO 44

The procedure of Example 36 was repeated, except that 440 mg capsule of the surfactant shown below was used.

Example No	Surfactant
37	POE(20) sorbitan monoisostearate (CRILLET 6)
38	POE(20) cetostearyl ether (VOLPO CS20)
39	POE(15) cetostearyl ether (VOLPO CS15)
40	POE(20) oleyl ether (VOLPO N20)
41	POE(15) oleyl ether (VOLPO N15)
42	POE(40) hydrogenated castor oil (CREMOPHOR RH40)
43	POE(35) castor oil (ETOCAS 35)
44	POE(15) glyceryl monolaurate (GLYCEROX L15)

EXAMPLE 45

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:

	mg per capsule
Ketoprofen	50
POE(20) sorbitan monooleate (CRILLET 4)	400
Total	450

EXAMPLES 46 TO 51

The procedure of Example 45 was repeated, except that 400 mg capsule of the surfactant shown below was used.

Example No	Surfactant
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 52

Ketoprofen Capsules - Size 2

The procedure of Example 45 was repeated, except that Size 2 capsules were used and the ingredients were as follows:

	mg per capsule
Ketoprofen	50
POE(20) cetostearyl ether (VOLPO CS20)	285
Total	335

EXAMPLES 53 TO 58

The procedure of Example 36 was repeated, except that 285 mg/capsule of the surfactant shown below was used:

Example No	Surfactant
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 (GLYCEROX 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 59

Naproxen 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:

	mg per capsule
Naproxen	25
POE(15) cetostearyl ether (VOLPO CS15)	425
Total	450

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 (VOLPON15)
62	POE(20) oleyl ether (VOLPO N20)

EXAMPLE 63

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:

	mg per capsule
Flufenamic Acid	50
POE(24) monolaurate (CRODET L24)	560
Total	610

EXAMPLES 64 TO 73

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)
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)
71	POE(20) cetostearyl ether (VOLPO CS20)
72	POE(15) oleylether (VOLPO N15)
73	POE(20) oleylether (VOLPO N20)

EXAMPLE 74

Flufenamic Acid 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:

	mg per capsule
Flufenamic Acid	50
POE(40) hydrogenated castor oil (CREMOPHOR RH40)	400
Total	450

EXAMPLES 75 TO 77

The procedure of Example 74 was repeated, except that 400 mg.capsule of the surfactant shown below was used:

75 POE(15) cetostearyl ether (VOLPO CS15)
76 POE(20) cetostearyl ether (VOLPO CS20)
77 POE(15) oleyl ether (VOLPO N15)

EXAMPLE 78

Ibuprofen 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:

	mg per capsule
Ibuprofen	50
POE(24) monolaurate (CRODET L24)	560
Total	610

EXAMPLES 79 TO 87

The procedure of Example 78 was repeated, except that 560 mg.capsule of the surfactant shown below was used:

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)
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:

		mg per capsule
Ibuprofen		50
POE(24) monolaurate		400
	Total	450

EXAMPLES 89 TO 94

The procedure of Example 88 was repeated, except that 400 mg/capsule of the surfactant shown below was used:

89	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 95

Indomethacin 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:

	Quantity per 200 ml
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.

EXAMPLES 96 AND 97

Indomethacin solutions are prepared as in Example 95, except that 20g of the following surfactants were used:

96	POE(20) sorbitan monoisostearate (CRILLET 6)
97	POE(35) castor oil (CREMOPHOR EL)

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:

	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

EXAMPLE 99

A diclofenac solution is prepared as in Example 98, except that 27.5 g POE(35) castor oil (CREMOPHOR EL) is used.

EXAMPLE 100

Ketoprofen Solution

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:

	Quantity per 200 ml
Ketoprofen	1.00 g
Surfactant POE (20) sorbitan monoisostearate (CRILLET 6)	10.0 g
Preservative (potassium sorbate)	0.40 g
Sweetener (sodium saccharin)	qs
Citric acid	qs
Flavouring	qs
Water, purified	to 200 ml

EXAMPLE 101-103

A ketoprofen solution is prepared as in Example 100, except that 10g of the following surfactants were used:

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 104

Flurbiprofen Capsules - Size 1

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:

	mg per capsule
Flurbiprofen	50
POE(40) hydrogenated castor oil (CRODURET 40)	400
Total:	450

EXAMPLES 105 TO 109

The procedure of Example 104 was repeated, except that 400mg capsule of the surfactant shown below was used.

Example No.	Surfactant
105	POE(35) castor oil (ETOCAS 35)
106	POE(20) cetostearyl ether (VOLPO CS20)
107	POE(15) cetostearyl ether (VOLPO CS15)
108	POE(20) oleyl ether (VOLPO N20)
109	POE(15) oleyl ether (VOLPO N15)

EXAMPLE 110

Flurbiprofen 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:

	mg per capsule
Flurbiprofen	50
POE(20) sorbitan monooleate (CRILLET 4)	560
Total:	610

EXAMPLE 111 TO 121

The procedure of Example 110 was repeated, except that 560mg capsule of the surfactant shown below was used.

Example No.	Surfactant
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)

EXAMPLE 122

Slow Release Indomethacin Capsules

Capsules of 75mg active ingredient per capsule were prepared using the following proportions:

	mg per capsule
Indomethacin	75
GELUCIRE 46/07	214
POE(24) monostearate [CRODET S24]	321
Total:	610

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.

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 proceudre of Example 122 was repeated except that the following ingredients were used in the formulation:

	mg per capsule
Indomethacin	75
GELUCIRE 50/02	214
POE(24) monostearate [CRODET S24]	321
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:

	mg per capsule
Indomethacin	75
GELUCIRE 53/10	161
POE(24) monostearate [CRODET S24]	374
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 LDO > 20g kg.

EXAMPLE 125

The procedure of Example 122 was repeated except that the following ingredients were used in the formulation:

	mg per capsule
Indomethacin	75
GELUCIRE 53/10	214
POE(24) monostearate [CRODET S24]	321
Total:	610

EXAMPLE 126

The procedure of Example 122 was repeated except that the following ingredients were used in the formulation:

	mg per capsule
Indomethacin	75
GELUCIRE 53/10	267
POE(24) monostearate [CRODET S24]	268
Total:	610

EXAMPLE 127

The procedure of Example 122 was repeated except that the following ingredients were used in the formulation:

	mg per capsule
Indomethacin	75
GELUCIRE 53/10	321
POE(24) monostearate [CRODET S24]	214
Total:	610

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, flurbibuprofen, 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.

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 antiinflammatory 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.

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.

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.

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.

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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(57) Abstract

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 µm and preferably between about 0.1 and 0.3 µm. 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.

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SUBMICRON EMULSIONS AS OCULAR DRUG DELIVERY VEHICLES

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 emulsion.

BACKGROUND OF THE PRESENT INVENTION

The primary problem associated with topical applications of drugs to the eye is that the human eye 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. 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, 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 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 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 μl, which far exceeds the normal lachrymal volume of about 7-10 μl. Thus, the portion of the dose that is not 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 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 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 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.

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 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 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 bioavailability, such carriers also produce various deleterious side effects. See Harmia et al., supra., Saettone et al. (1988) J. Pharm. 43:67-70 and Meisner 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 Pharmcol. (U.S.) 3:121-128, and Shell (1984) Surv. Ophthalmol. 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 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 ("o/w"), and can be defined as either a macroemulsion or a microemulsion. A macroemulsion is a cloudy turbid composition having an oil-droplet size of 0.5 to 100 µm and is generally thermodynamically unstable. In comparison, a microemulsion is a translucent to transparent composition having a droplet size of 0.005 to 0.5 µm, is thermodynamically stable and is generally self emulsifying. See, e.g., Friberg et al. (1987) Microemulsions Structure and Dynamics, CRC Press Inc., Boca Raton, FL, pp. 154. Also, the proportion of surfactants to oil required to generate microemulsions is generally much higher than in macroemulsions.

Emulsions developed specifically for ophthalmic use have attempted to solve the problem of inherent 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 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.

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 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.

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 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 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 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 μm and preferably between about 0.1 and 0.3 μm.

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 30 to 50%.

The emulsifier is preferably a phospholipid compound or a mixture of phospholipids, such as lecithin, phosphatidylcholine, phosphatidylethanolamine or mixtures thereof, and is preferably 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 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 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, 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.

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 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 without irritation.

BRIEF DESCRIPTION OF THE DRAWINGS

In the following detailed description of the invention, reference will be made to the annexed 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;

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 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 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.

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 μm, and preferably about 0.1 to 0.3 μm. 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 μm, but generally larger than those of a classical microemulsion, which, for practical purposes, has droplet sizes of less than 0.1 μm.

These submicron emulsion can easily be sterilized by filtration, for example, in 0.45μm and/or 0.22μm filters, are more stable in long-term storage and can better withstand sterilization in an autoclave.

An oil-in-water emulsion is a dispersion of droplets or colloidal particles in an aqueous medium, with the colloid particles having an oily core surrounded by an interfacial film of the emulsifiers and surface acting agents or surfactants. For clarity in understanding the present invention, the following terms will be used:

"aqueous phase" - to denote the aqueous solution in which the droplets or colloid particles are dispersed;

"oily phase" - to denote the oily cores of the droplets or colloidal particles; and

"amphiphilic phase" - to denote the interfacial films of emulsifier and surfactant surrounding the oily phase of the droplets or colloidal particles.

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 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 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 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-ethyldihydro-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 oleic acid and linoleic acid, fatty alcohols, such as oleyl alcohol, and fatty esters, such as sorbitan monooleate and sucrose mono- di- or tri-palmitate, can be used as the oil component, although these are not as preferred as the other oils mentioned above.

The 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% of phophatidylcholine, 12% phosphatidylethanolamine and about 15% other phospholipids; OVOTHIN 160 (Lucas Meyer, Germany) which is a mixture comprising about 60% phosphatidylcholine, 18% phosphatidylethanolamine and 12% other phospholipids; a purified phospholipid mixture; LIPOID E-75 or LIPOID E-80 (Lipoid, Germany) which is a phospholipid mixture comprising about 80% phosphatidylcholine, 8% phosphatidylethanolamine, 3.6% non-polar lipids and about 2% sphingomyelin. Purified egg yolk phospholipids, soybean oil phospholipids or other purified phospholipid mixtures are useful as this component. This listing is representative and not limiting, as other phospholipid materials which are known to those skilled in the art can be used.

The surfactant chosen should be non-ionic and one 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 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 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 FDA approved for human use.

The aqueous component will be the continuous phase of the emulsion and may be water, saline or any other suitable aqueous solution which can yield an isotonic and pH controlled preparation.

In addition, the compositions of the invention may also comprise conventional additives such as preservatives, osmotic agents or pressure regulators and antioxidants. Typical preservatives include Thimerosal, chlorbutanol, and methyl, ethyl, propyl or butyl parabens. Typical osmotic pressure regulators include glycerol and mannitol, with glycerol being preferred. The preferred oil phase antioxidant is α-tocopherol or α-tocopherol succinate. The aqueous phase may also include an antioxidant of a polyamine 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 the eye. Such drugs may for example be β-adrenergic blockers, cannabinoids, cholinesterase inhibitors, sympathomimetic agents or carbonic anhydrase inhibitors.

In the following description, concentrations will be indicated by % which denotes the concentration by weight of the component per 100 units volume of entire composition. All indicated concentrations should be understood as standing each by itself, and not cumulative. It should be appreciated by the artisan, however, that there is some dependency between the concentrations of the components, e.g., higher concentrations of the oil will generally require higher concentrations of the emulsifier and surfactant.

The emulsion used in the ophthalmic compositions of the present invention may comprise about 0.5 to 50% oil, about 0.1 to 10% emulsifier and about 0.05 to 5% surfactants. Generally, increasing the concentration of the non-aqueous phase, i.e., the combined concentration of the oily and the amphiphilic phase, increases viscosity of the composition. In order to obtain a 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 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, 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 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.

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 Oleagnieux, St. Laurent, Blangy, France.

LIPOID E-75 or E-80: Lipoid, Ludwigshafen, Germany.

α-tocopherol, α-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 %
α-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%
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, chlorbutanol, thimerosal and glycerol; and the oily phase consisted of the MCT oil, lecithin and α-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 μm). 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, 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 was filtered through a membrane filter (TE, Schleicher & Schull, having a pore size of 0.45 μm) 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, through a 0.45 μm filter followed by a 0.22 μm 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.

<u>Examples 2-5</u>: 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.

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%
TWEEN-80	1.0 %
α-tocopherol	0.02%
EDTA	0.1 %
Glycerol	2.2 %
Distilled water	balance to 100.00%

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.

Two additional adaprolol compositions were prepared as above except that they contained 1 TYLOXAPOL and 1% TWEEN-20, respectively.

Example 9: Betaxolol Composition

This composition had the following constituents:

MCT oil	4.25%
LIPOID E-80	0.75%
TWEEN-80	0.5 %
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 the adaprolol compositions of Examples 6-8 above.

Examples 10-11: Indomethacin Compositions

This composition had the following constituents:

Indomethacin	0.4 %
MCT oil	17 %
LIPOID E-80	3 %
TWEEN-80	1 %
α-tocopherol succinate	0.02%
Methyl paraben	0.1 %
Propyl paraben	0.02%
Glycerol	2.25%
EDTA	0.1 %
Distilled water	balance to 100.0 %

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.

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:

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 following application of a 25 μl 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:

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.

$$\text{MBR} = \frac{\text{maximum blinks - drug}}{\text{maximum blinks - saline}}$$

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.

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.

$$\text{BI} = \frac{\text{number of blinks - drug}}{\text{number of blinks - saline}}$$

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

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*
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

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 Draise Test (c.f., Draise (1944) J. Pharmacol. Exp. Ther. 83:377-390) using slit-lamp biomicroscopy. The 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 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 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
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
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 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.

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.

Example 14: Miotic Activity of Pilocarpine

Changes in pupil diameter were measured at 30 min intervals in 10 rabbits following treatment with one 50 µl drop of different pilocarpine formulations.

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

Formulation	max. RPD (mm)	AUC (mm x hr)
2% pilocarpine nitrate (Lab. H. Faure, France)	-1.7 ± 0.5	2.9 ± 1.2
2% pilocarpine HCl (Example 2)	-2.1 ± 0.6	4.3 ± 1.5

Mean ± SD, n=10

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

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.

Anterior aqueous humor drug levels (Ca) of indomethacin were measured in albino rabbits, following topical treatment with 1 drop (50 µl) 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.

Table 4

Anterior Chamber Concentration (µM)

Time (hrs)	1% INDOPTIC Solution	0.2% Indomethacin (Example 11)	0.4% Indomethacin (Example 10)
0.5	2.2 ± 1.7 (7)	1.1 ± 0.1 (7)	1.4 ± 0.9 (6)
1	1.0 ± 0.5 (6)	0.9 ± 0.3 (7)	2.5 ± 0.9 (6)
3	0.6 ± 0.3 (6)	0.3 ± 0.1 (4)	1.1 ± 0.4 (6)

Mean ± 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. 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 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 times a day for five days of 0.4% Indomethacin (Example 10) was significantly lower than INDOPTIC (0.4 ± 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.

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, 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 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., 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 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 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 μm.

2. The vehicle of claim 1 wherein the mean droplet size is between about 0.1 and 0.3 μm.

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 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 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 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 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 β-adrenergic blocker, a cannabinoid, a 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 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 selecting the emulsion to have droplets of a mean diameter of between about 0.1 and 0.3 μm.

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 selecting the emulsion to have droplets of a mean diameter of between about 0.1 and 0.3 μm.

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 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 μm.

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 selecting the emulsion to have droplets of a mean diameter of between about 0.1 and 0.3 μm.

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 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 μm.

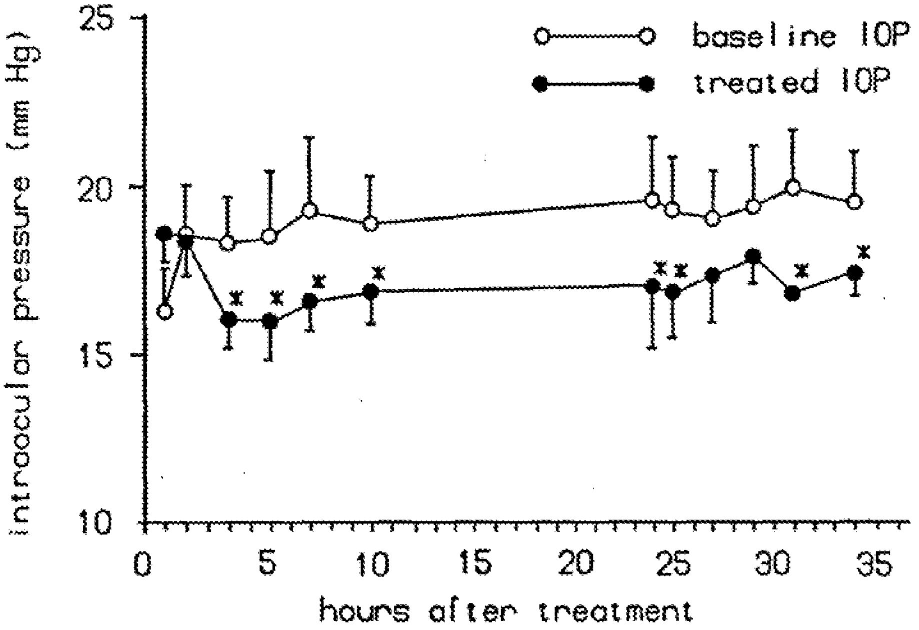
34. A method for providing increased bioavailability of an ophthalmic drug which comprises administering said drug to the eye in the composition of claim 13.

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 μm.

36. A method for providing increased bioavailability of an ophthalmic drug which comprises administering said

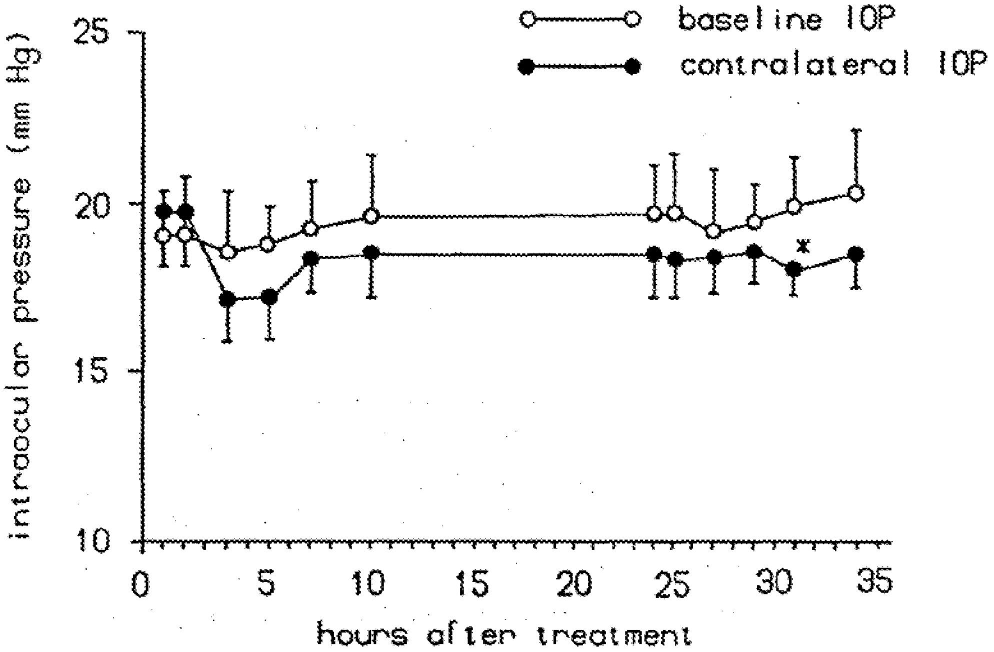
drug to the eye with the ocular drug delivery vehicle of claim 1.

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 μm.



25
20
15
10
intraocular pressure (mm Hg)
0
5
10
15
20
25
30
35
hours after treatment
baseline IOP
treated IOP
*

FIG. 1



25
20
15
10
intraocular pressure (mm Hg)
0
5
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15
20
25
30
35
hours after treatment
baseline IOP
contralateral IOP
*

FIG. 2

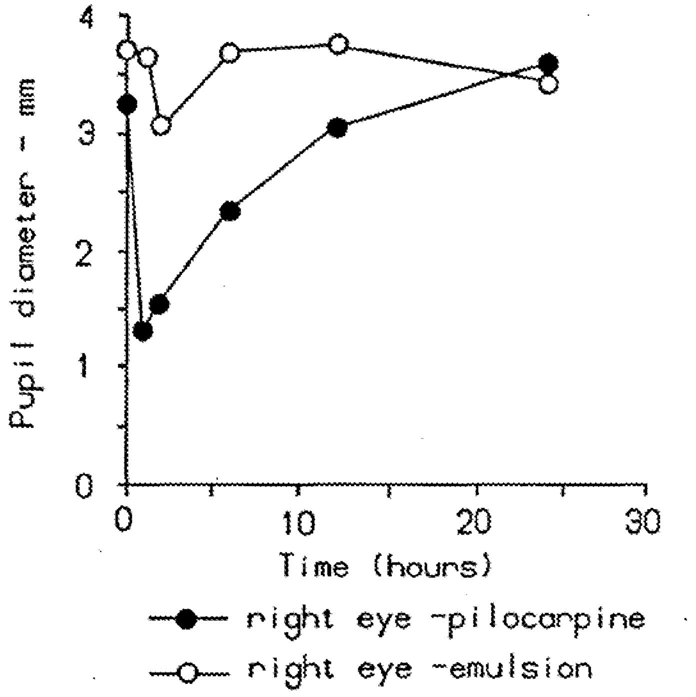

FIG. 3

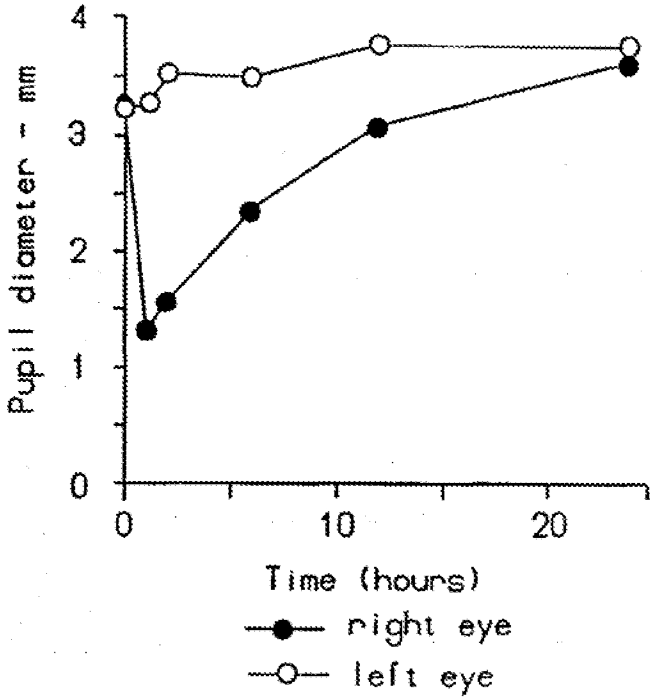

FIG. 4

SUBSTITUTE SHEET

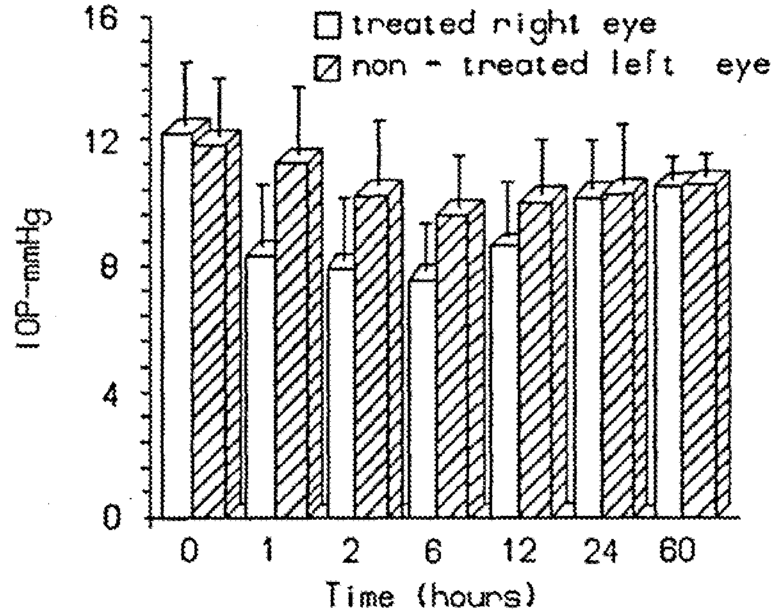

FIG. 5

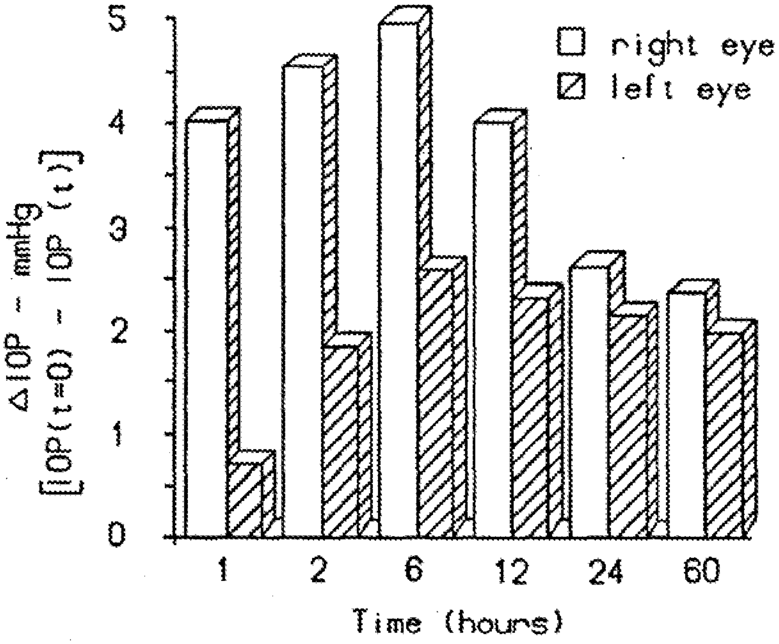

FIG. 6

SUBSTITUTE SHEET

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/00044

A. CLASSIFICATION OF SUBJECT MATTER

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. FIELDS SEARCHED

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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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. Archieves of Ophthamology, 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

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"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
"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	"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
"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)	"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
"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	"&"	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
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Washington, D.C. 20231

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Authorized officer
fn ZOHREH FAY Ngutto Nguyen
[illegible]

Telephone No. (703) 308-1235

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Electronic Acknowledgement Receipt

EFS ID:	19619650
Application Number:	14261720
International Application Number:	
Confirmation Number:	1021
Title of Invention:	AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID
First Named Inventor/Applicant Name:	Shirou SAWA
Customer Number:	513
Filer:	Warren M. Cheek Jr./ann leveille
Filer Authorized By:	Warren M. Cheek Jr.
Attorney Docket Number:	2014-0545
Receipt Date:	18-JUL-2014
Filing Date:	25-APR-2014
Time Stamp:	15:55:36
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Information Disclosure Statement (IDS) Form (SB08)	AttachZ1_Ids.pdf	185909 f76485da4db4ef1c0bb090668e2e898d4424b464	no	3

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If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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1030 15th Street, N.W.,
Suite 400 East
Washington DC 20005-1503

Decision Granting Request for Prioritized Examination (Track I or After RCE)	Application No.:14/261,720

1. THE REQUEST FILED April 25, 2014 IS **GRANTED**.

The above-identified application has met the requirements for prioritized examination
A. ☒ for an original nonprovisional application (Track I).
B. ☐ for an application undergoing continued examination (RCE).

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

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

Telephone inquiries with regard to this decision should be directed to Kimberly Inabinet at 571-272-4618.

/ Kimberly Inabinet/ Paralegal Specialist, Office of Petitions

日本国特許庁
JAPAN PATENT OFFICE

別紙添付の書類に記載されている事項は下記の出願書類に記載されている事項と同一であることを証明する。

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 Date of Application:	２００３年　１月２１日
出願番号 Application Number:	特願２００３－０１２４２７
パリ条約による外国への出願に用いる優先権の主張の基礎となる出願の国コードと出願番号 The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is	ＪＰ２００３－０１２４２７
出願人 Applicant(s):	千寿製薬株式会社

２０１４年　５月１４日

特許庁長官
Commissioner,
Japan Patent Office
羽藤秀雄

【書類名】特許願
【整理番号】598-03
【提出日】平成15年 1月21日
【あて先】特許庁長官　殿
【国際特許分類】
A61K　9/08
A61K 31/195
A61K 47/18
A61K 47/32
A61P 27/02
A61P 27/16
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　【氏名】澤　嗣郎
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　【電話番号】06-6201-9627
【手数料の表示】
　【予納台帳番号】004167
　【納付金額】21,000
【提出物件の目録】

【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、アルキルアリー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】アルキルアリー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、アリー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$(\mathrm{CH_2CH_2O})_X\mathrm{H}$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】アルキルアリー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】アルキルアリー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０．０２ｗ／ｖ％で、上限濃度が０．１ｗ／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０．０１～０．５ｗ／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１０】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１１】水性液剤のｐＨが７～９の範囲内である請求項１～１０のいずれかに記載の水性液剤。

【請求項１２】水性液剤のｐＨが７．５～８．５の範囲内である請求項１１に記載の水性液剤。

【請求項１３】点眼液である請求項１～１２のいずれかに記載の水性液剤。

【請求項１４】点鼻液である請求項１～１２のいずれかに記載の水性液剤。

【請求項１５】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０．０１ｗ／ｖ％～０．５ｗ／ｖ％を含有する点眼液。

【請求項１６】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０．０２ｗ／ｖ％～０．１ｗ／ｖ％を含有する点眼液。

【請求項１７】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、その薬理学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１８】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ー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。

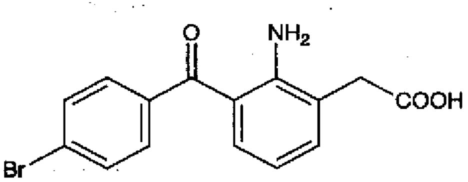
【０００２】

【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、その薬理学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学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、かつ充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学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学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、その薬理学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ー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、かつ充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、アルキルアリー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）アルキルアリー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、アリー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）アルキルアリー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）アルキルアリー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％で、上限濃度が０．１ｗ／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－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０．０１～０．５ｗ／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－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－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０．０１ｗ／ｖ％～０．５ｗ／ｖ％を含有する点眼液。

（１６）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０．０２ｗ／ｖ％～０．１ｗ／ｖ％を含有する点眼液。

（１７）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、その薬理学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－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、０．０１ｗ/ｖ％～０．５ｗ/ｖ％程度、好ましくは０．０５ｗ/ｖ％～０．２ｗ/ｖ％程度、特に好ましくは０．１ｗ/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。

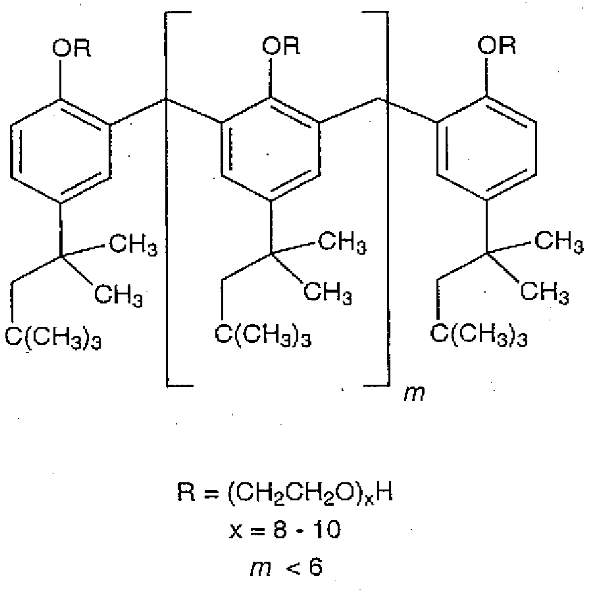
【００１５】

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ー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。上記アリー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（$\mathrm{CH_2CH_2O}$）$_{\mathrm{X}}$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。上記アルキルアリー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】



【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ル４０（Ｐｏｌｙｏｘｙｌ　４０　ｓｔｅａｒａｔｅ）が特に好ましい。ステアリン酸ポリオキシル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、アルキルアリー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学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学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処方の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-ﾌﾞﾛﾓﾍﾞﾝｿﾞｲﾙ)ﾌｪﾆﾙ酢酸ﾅﾄﾘｳﾑ	0.1 g	0.1 g	0.1 g	0.1 g
ﾎｳ酸	1.5 g	1.5 g	1.5 g	1.5 g
塩化ﾍﾞﾝｻﾞﾙｺﾆｳﾑ	0.005g	0.005g	0.005g	0.005g
ﾎﾟﾘｿﾙﾍﾞｰﾄ80	0.15g	－	－	－
ｽﾃｱﾘﾝ酸ﾎﾟﾘｵｷｼﾙ40	－	0.15g	－	－
ﾁﾛｷｻﾎﾟｰﾙ	－	－	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-ﾌﾞﾛﾓﾍﾞﾝｿﾞｲﾙ)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
ﾎｳ酸		1.1 g	1.1 g	1.1 g	1.1 g	1.1 g
ﾎｳ砂		1.1 g	1.1 g	1.1 g	1.1 g	1.1 g
塩化ﾍﾞﾝｻﾞﾙｺﾆｳﾑ		0.005g	0.005g	0.005g	0.005g	0.005g
ﾎﾟﾘｿﾙﾍﾞｰﾄ80		－	－	－	－	－
ﾁﾛｷｻﾎﾟｰﾙ		0.02 g	0.05 g	0.03 g	－	－
ｽﾃｱﾘﾝ酸ﾎﾟﾘｵｷｼﾙ 40		－	－	－	0.02 g	0.05 g
ﾎﾟﾘﾋﾞﾆﾙﾋﾟﾛﾘﾄﾞﾝ(K-30)		2.0 g	2.0 g	2.0 g	2.0 g	1.0 g
ｴﾃﾞﾄ酸ﾅﾄﾘｳﾑ		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０．０５ｗ／ｖ％チロキサポールまたは０．０２、０．０５ｗ／ｖ％ステアリン酸ポリオキシル４０を配合した処方は６０℃、４週で残存率が９０％以上であり、点眼液剤として充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	6th	24th	1W	2W	3W	4W
S. aureus	2.1×10^{6}	3.0×10^{1}	0	0	0	0	0
E. coli	6.5×10^{6}	0	0	0	0	0	0
P. aeruginosa	5.8×10^{6}	0	0	0	0	0	0
C. albicans	3.2×10^{5}	—	—	0	0	0	0
A. niger	1.8×10^{5}	—	—	0	0	0	0

Unit : CFU/mL

表３－２

A－05	接種菌数	6th	24th	1W	2W	3W	4W
S. aureus	2.1×10^{6}	1.7×10^{5}	2.0×10^{1}	0	0	0	0
E. coli	6.5×10^{6}	0	0	0	0	0	0
P. aeruginosa	5.8×10^{6}	0	0	0	0	0	0
C. albicans	3.2×10^{5}	—	—	0	0	0	0
A. niger	1.8×10^{5}	—	—	0	0	0	0

Unit : CFU/mL

表３－３

A－07	接種菌数	6th	24th	1W	2W	3W	4W
S. aureus	2.7×10^{6}	3.1×10^{4}	0	0	0	0	0
E. coli	7.4×10^{6}	0	0	0	0	0	0
P. aeruginosa	8.8×10^{6}	0	0	0	0	0	0
C. albicans	4.6×10^{5}	—	—	0	0	0	0
A. niger	1.0×10^{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ＥＰ－Ａの基準1）、処方Ａ－０５およびＡ－０７の防腐効力はＥＰ－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	1.1g
塩化ベンザルコニウム	0.005 g
チロキサポール	0.02g
ポリビニルピロリドン（K—３０）	2.0g
エデト酸ナトリウム	0.02g
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	1.1g
塩化ベンザルコニウム	0.005 g
チロキサポール	0.05g
ポリビニルピロリドン（Ｋ－３０）	2.0g
エデト酸ナトリウム	0.02g
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	1.1g
塩化ベンザルコニウム	0.005 g
ステアリン酸ポリオキシル４０	0.02g
ポリビニルピロリドン（Ｋ－３０）	2.0g
エデト酸ナトリウム	0.02g
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ー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充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充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ー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

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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 14/261,720

APPLICATION AS FILED - PART I

	(Column 1)	(Column 2)	SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE($)	FEE($)		RATE($)	FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	280
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	600
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	720
TOTAL CLAIMS (37 CFR 1.16(i))	27 minus 20 =	* 7			OR	x 80 =	560
INDEPENDENT CLAIMS (37 CFR 1.16(h))	3 minus 3 =	*				x 420 =	0.00
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						0.00
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							0.00
			TOTAL			TOTAL	2160

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

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)	SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
AMENDMENT A		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE($)	ADDITIONAL FEE($)		RATE($)	ADDITIONAL FEE($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

		(Column 1)		(Column 2)	(Column 3)					
AMENDMENT B		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE($)	ADDITIONAL FEE($)		RATE($)	ADDITIONAL FEE($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

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

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
14/261,720	04/25/2014	1629	2160	2014-0545	27	3

CONFIRMATION NO. 1021

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

FILING RECEIPT

OC000000068364412

Date Mailed: 05/13/2014

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

Assignment For Published Patent Application
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 14/165,976 01/28/2014
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

Permission to Access - A proper **Authorization to Permit Access to Application by Participating Offices** (PTO/SB/39 or its equivalent) has been received by the USPTO.

Request to Retrieve - This application either claims priority to one or more applications filed in an intellectual property Office that participates in the Priority Document Exchange (PDX) program or contains a proper **Request to Retrieve Electronic Priority Application(s)** (PTO/SB/38 or its equivalent). Consequently, the USPTO will attempt to electronically retrieve these priority documents.

If Required, Foreign Filing License Granted: 05/09/2014
The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 14/261,720**
Projected Publication Date: 08/21/2014
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

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

SelectUSA

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 U.S. offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to promote and facilitate business investment. SelectUSA provides information assistance to the international investor community; serves as an ombudsman for existing and potential investors; advocates on behalf of U.S. cities, states, and regions competing for global investment; and counsels U.S. economic development organizations on investment attraction best practices. To learn more about why the United States is the best country in the world to develop technology, manufacture products, deliver services, and grow your business, visit http://www.SelectUSA.gov or call +1-202-482-6800.

Modified PTO/SB/05 (08/2008)
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1994, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

UTILITY
PATENT APPLICATION
TRANSMITTAL

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

Attorney Docket No.: 2014-0545

First Named Inventor: Shirou SAWA

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

Express Mail Label No.:

APPLICATION ELEMENTS
See MPEP chapter 600 concerning utility patent application contents.

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

1. [] Small Entity Status is hereby asserted.

2. [X] Specification *[Total Pages: 29]*
Both the claims and abstract must start on a new page
(For information on the preferred arrangement, see MPEP 608.01(a))

3. [] Drawing(s) *(35 USC 113)* *[Total Sheets:]*

4. [X] Declaration(s) *[Total Pages:2]*
    a. [] Copy from a prior application (37 CFR 1.63(d)(1))
    (for continuation/divisional with (37 CFR 1.63(d)(1)) completed)

5. [X] Application Data Sheet (see 37 CFR 1.76)

6. [] CD-ROM or CD-R in duplicate, large table or computer program *(Appendix)*

7. [] Nucleotide and/or Amino Acid Sequence Submission
(if applicable, all necessary)
    a. [] Computer Readable Form
    b. Specification Sequence Listing on:
        i. [] CD-ROM or CD-R (2 copies); or
        ii. [] Paper
    c. [] The paper and computer readable copies are identical

ACCOMPANYING APPLICATION PARTS

8. [X] Power of Attorney with Cover Letter

9. [X] Information Disclosure Statement (IDS)/PTO/SB/08
    [] Copies of IDS Citations

10. [X] Preliminary Amendment

11. [] 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.

12. [X] Other - **Certification and Request for Prioritized Examination**

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 :*

[] Continuation [X] Divisional [] Continuation-in-part (CIP) of prior application No. 14/165,976

Prior Application Information: Examiner: Layla Soroush Group Art Unit: 1627

19. CORRESPONDENCE ADDRESS

CUSTOMER NO.
00513

/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: 2014.04.25 10:57:56 -04'00'

Warren M. Cheek
Registration No. 33,367

WENDEROTH, LIND & PONACK, L.L.P.
1030 15th Street, N.W., Suite 400 East
Washington, D.C. 20005-1503
Phone:(202) 721-8200
Fax:(202) 721-8250

April 25, 2014

The USPTO is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16, 1.17, and 1.492, which may be required by this paper and for the entire pendency of the present application to Deposit Account No. 23-0975, except fees for multiple dependent claims.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	2014-0545
	Application Number	

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

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.
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.

Secrecy Order 37 CFR 5.2

☐ 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:

Inventor 1 Remove

Legal Name

Prefix	**Given Name**	**Middle Name**	**Family Name**	**Suffix**
	Shirou		SAWA	

Residence Information (Select One) ○ US Residency ● Non US Residency ○ Active US Military Service

City	Hyogo	Country of Residence i	JP

Mailing Address of Inventor:

Address 1	c/o SENJU PHARM. CO., LTD., Kobe Creative Center		
Address 2	5-4, Murotani 1-chome, Nishi-ku, Kobe-shi		
City	Hyogo	**State/Province**	
Postal Code	651-2241	**Country** i	JP

Inventor 2 Remove

Legal Name

Prefix	**Given Name**	**Middle Name**	**Family Name**	**Suffix**
	Shuhei		FUJITA	

Residence Information (Select One) ○ US Residency ● Non US Residency ○ Active US Military Service

City	Hyogo	Country of Residence i	JP

Mailing Address of Inventor:

Address 1	c/o SENJU PHARM. CO., LTD., Kobe Creative Center		
Address 2	5-4, Murotani 1-chome, Nishi-ku, Kobe-shi		
City	Hyogo	**State/Province**	
Postal Code	651-2241	**Country** i	JP

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	2014-0545
	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	Add Email Remove Email

Application Information:

Title of the Invention	AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL) PHENYLACETIC ACID		
Attorney Docket Number	2014-0545	**Small Entity Status Claimed**	☐
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	0	**Suggested Figure for Publication (if any)**	

Filing By Reference :

Only compete 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 i

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:	● Customer Number	○ US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	00513		

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	2014-0545
	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		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	Division of	14/165976	2014-01-28

Prior Application Status	Patented				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				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				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		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 **Add** button. 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) i 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).

			Remove
Application Number	Country i	Filing Date (YYYY-MM-DD)	Access Code i (if applicable)
2003-012427	JP	2003-01-21	

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button. Add

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	2014-0545
	Application Number	
Title of Invention	AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID	

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:

☒ Authorization to Permit Access to the Instant Application by the Participating Offices

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.

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.

In accordance with 37 CFR 1.14(c), access may be provided to information concerning the date of filing this Authorization.

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.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	2014-0545
	Application Number	
Title of Invention	AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID	

Applicant 1

Remove

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.

Clear

● Assignee ○ Legal Representative under 35 U.S.C. 117 ○ Joint Inventor

○ Person to whom the inventor is obligated to assign. ○ 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 :

If the Applicant is an Organization check here. ☒

Organization Name	SENJU PHARMACEUTICAL CO., LTD.

Mailing Address Information:

Address 1	5-8, Hiranomachi 2-chome, Chuo-ku, Osaka-shi		
Address 2			
City	Osaka	**State/Province**	
Country i	JP	Postal Code	541-0046
Phone Number		Fax Number	
Email Address			

Additional Applicant Data may be generated within this form by selecting the Add button. Add

Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not subsitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Assignee 1

Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication . An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

Remove

If the Assignee or Non-Applicant Assignee is an Organization check here. ☐

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	2014-0545
	Application Number	

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

Prefix	**Given Name**	Middle Name	**Family Name**	Suffix

Mailing Address Information For Assignee including Non-Applicant Assignee:

Address 1			
Address 2			
City		**State/Province**	
Country i		Postal Code	
Phone Number		Fax Number	
Email Address			

Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button. Add

Signature:

Remove

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

Signature	/ warren cheek /			Date (YYYY-MM-DD)	2014-04-25
First Name	Warren	Last Name	Cheek	Registration Number	33367

Additional Signature may be generated within this form by selecting the Add button. Add

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DESCRIPTION

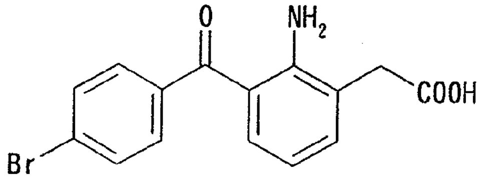
AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID

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.

BACKGROUND ART

Benzoylphenylacetic acid derivatives including bromfenac (generic name) of formula (I):



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 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.

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.

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.

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,

(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 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 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,

(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 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.

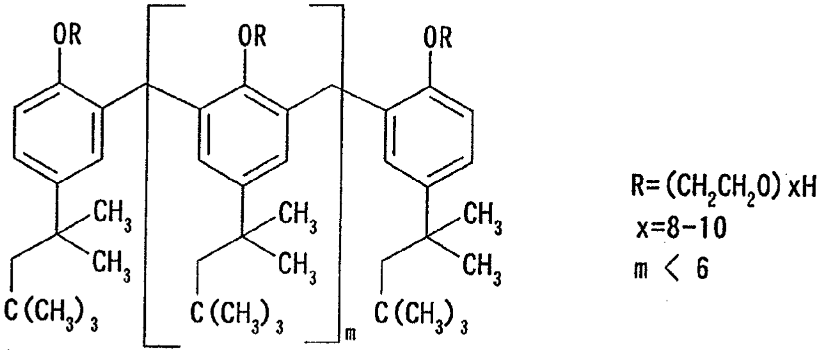
2-Amino-3-(4-bromobenzoyl)phenylacetic acid and its pharmacologically acceptable salt can be prepared according to the method as described in JP-A-23052/1977 (corresponding to US patent No. 4,045,576) or by a similar method thereof. These compounds can be obtained as their hydrate depending on synthetic 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, 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, 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, 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.

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 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 $C_{17}H_{35}COO(CH_2CH_2O)_nH$ 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 mamximum 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, thickners, 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 thickners 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 l-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、14th 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

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 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
Polyvinyl-pyrrolidone (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 inoculation	24 hours after inoculation	7 days after inoculation	14 days after inoculation	21 days after inoculation	28 days after inoculation
S. aureus	2.1×10^6	3.0×10^1	0	0	0	0	0
E. coli	6.5×10^6	0	0	0	0	0	0
P. aeruginosa	5.8×10^6	0	0	0	0	0	0
C. albicans	3.2×10^5	—	—	0	0	0	0
A. niger	1.8×10^5	—	—	0	0	0	0

Table 3-2

A−05	Cell count (CFU/mL)						
	Inoculum count	6 hours after inoculation	24 hours after inoculation	7 days after inoculation	14 days after inoculation	21 days after inoculation	28 days after inoculation
S. aureus	2.1×10^6	1.7×10^5	2.0×10^1	0	0	0	0
E. coli	6.5×10^6	0	0	0	0	0	0
P. aeruginosa	5.8×10^6	0	0	0	0	0	0
C. albicans	3.2×10^5	—	—	0	0	0	0
A. niger	1.8×10^5	—	—	0	0	0	0

Table 3-3

A—07	Cell count (CFU/mL)						
	Inoculum count	6 hours after inoculation	24 hours after inoculation	7 days after inoculation	14 days after inoculation	21 days after inoculation	28 days after inoculation
S. aureus	2.7×10^6	3.1×10^4	0	0	0	0	0
E. coli	7.4×10^6	0	0	0	0	0	0
P. aeruginosa	8.8×10^6	0	0	0	0	0	0
C. albicans	4.6×10^5	—	—	0	0	0	0
A. niger	1.0×10^5	—	—	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.

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.

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.

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.

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.

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.

2. The aqueous liquid preparation according to claim 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 claim 1 or 2, wherein the alkyl aryl polyether alcohol type polymer is tyloxapol.

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.

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 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 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-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 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.

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.

13. The aqueous liquid preparation according to any one of claims 1 to 12, wherein the aqueous liquid preparation is an eye drop.

14. The aqueous liquid preparation according to any one of claims 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.

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 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 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.

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.

Wenderoth, Lind & Ponack. LLP
Attorney Docket No.: 2014-0545/WMC/01736

Modified PTO/AIA/01 (06-12)

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): Shuhei FUJITA

Signature: Shuhei Fujita Date: 2012.11.19

Note: Use an additional form for each additional inventor.

Doc Code: TRACK1.REQ
Document Description: TrackOne Request

PTO/AIA/424 (03-14)

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), the prioritized examination fee set forth in 37 CFR 1.17(c), and if not already paid, the publication fee set forth in 37 CFR 1.18(d) have been filed with the request. 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.

3. The applicable box is checked below:

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

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

---OR---

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

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

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

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

Signature /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: 2014.04.25 11:00:26 -04'00'	Date April 25, 2014
Name (Print/Typed) Warren M. Cheek	Practitioner 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. Submit multiple forms if more than one signature is required.**

☐ *Total of 1 forms are submitted.

Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
Title of Invention:	AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID
First Named Inventor/Applicant Name:	Shirou SAWA
Filer:	Warren M. Cheek Jr./Donna King
Attorney Docket Number:	2014-0545

Filed as Large Entity

Track I Prioritized Examination - Nonprovisional Application under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
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
Pages:				
Claims:				
Miscellaneous-Filing:				
PROCESSING FEE, EXCEPT PROV. APPLS.	1830	1	140	140

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
	Total in USD ($)			**5740**

Electronic Acknowledgement Receipt

EFS ID:	18859825
Application Number:	14261720
International Application Number:	
Confirmation Number:	1021
Title of Invention:	AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID
First Named Inventor/Applicant Name:	Shirou SAWA
Customer Number:	513
Filer:	Warren M. Cheek Jr./pam veazey
Filer Authorized By:	Warren M. Cheek Jr.
Attorney Docket Number:	2014-0545
Receipt Date:	25-APR-2014
Filing Date:	
Time Stamp:	13:07:04
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$5740
RAM confirmation Number	12433
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	215179 dc077a4d220c0e972e776be89cf7fb2a038f4f62	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	1561451 94997a41d792893287a0ec78dfd76a86ad610711	no	7

Warnings:

Information:

3		AttachB_Spec.pdf	978059 7439c132861c928b3fdc660ae1813eada0b5752d	yes	29

Multipart Description/PDF files in .zip description

Document Description	Start	End
Specification	1	24
Claims	25	28
Abstract	29	29

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Information:

4	Oath or Declaration filed	AttachC1_Decl.pdf	91820 63012ff1a07d41c345d1dfa663596a255491f4b9	no	2

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Information:

5	Power of Attorney	AttachC2_Poa.pdf	239152 9ded83879ca7527b422c52fcb6b2fa26b056017c	no	2

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The page size in the PDF is too large. The pages should be 8.5 x 11 or A4. If this PDF is submitted, the pages will be resized upon entry into the Image File Wrapper and may affect subsequent processing

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Information:

6	Information Disclosure Statement (IDS) Form (SB08)	AttachD1_Ids.pdf	185862 a13cb285012d39555c36afb805eb1550d2b187eb	no	3

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7	Information Disclosure Statement (IDS) Form (SB08)	AttachD2_SB08.pdf	138502 91a01a55ddd6bbd140151954fe331d29937bc599	no	2

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Information:

This is not an USPTO supplied IDS fillable form

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8		AttachE_Pa.pdf	191159 ced4a00eff1a5db8279239765bc6b095f0c3f314	yes	7

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:

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Information:

9	TrackOne Request	AttachF.pdf	651389 4eca28ac6d402edac902f2cb0a2508a5ce3ff756	no	1

Warnings:

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Information:

10	Fee Worksheet (SB06)	fee-info.pdf	38868 df781d32aa34cdc4f8c8bbcb31fdd927f61993fb	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	4291441	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

<u>New Applications Under 35 U.S.C. 111</u>
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

<u>National Stage of an International Application under 35 U.S.C. 371</u>
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

<u>New International Application Filed with the USPTO as a Receiving Office</u>
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor :

Shirou SAWA :

Serial No. NEW :

Filed April 25, 2014

: Attorney Docket No. 2014-0545

AQUEOUS LIQUID PREPARATION
CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID
(Rule 1.53(b) Divisional
of Serial No. 14/165,976,
Filed January 28, 2014)

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 (Serial No. 14/165,976), 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. [X] 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.

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: 2014.04.25 10:59:36 -04'00'

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

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Washington, D.C. 20005-1503
Telephone (202) 721-8200
Facsimile (202) 721-8250
April 25, 2014

Sheet 1 of 2

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: April 25, 2014

ATTY DOCKET NO. 2014-0545

SERIAL NO. NEW

FIRST NAMED INVENTOR Shirou SAWA

FILING DATE April 25, 2014

GROUP

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	Cherng-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.			

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				

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

Sheet 2 of 2

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: April 25, 2014	**ATTY DOCKET NO.** 2014-0545	**SERIAL NO.** NEW
	FIRST NAMED INVENTOR Shirou SAWA	
	FILING DATE April 25, 2014	**GROUP**

	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				

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

	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.
	CB	ISTA Pharmaceuticals, "New Drug Applications: Xibrom", http://www.drugs.com/nda/xibrom_040525.htmt, 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	http://medical-dictionary.thefreedictionary.com/prophylactic accessed 12/15/2009.
	CH	H. Scott et al., "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.

EXAMINER	DATE CONSIDERED

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

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor :

Shirou SAWA :

Serial No. NEW :

Filed April 25, 2014 :

AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID : Attorney Docket No. 2014-0545
(Rule 1.53(b) Divisional
of Serial No. 14/165,976,
Filed November 28, 2012)

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:

The USPTO is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16, 1.17, and 1.492, which may be required by this paper to Deposit Account No. 23-0975.

AMENDMENTS TO THE CLAIMS

1-18. (Cancelled)

19. (New) A stable aqueous liquid preparation consisting essentially of: (a) a first component; (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; (c) boric acid; (d) sodium tetraborate; and (e) water; 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 and is present in the preparation at a concentration from about 0.05 w/v % to about 0.2 w/v %; the second component is tyloxapol and is present in said liquid preparation in an amount sufficient to stabilize said first component; and wherein said stable liquid preparation is formulated for ophthalmic administration.

20. (New) The aqueous liquid preparation according to claim 19, wherein the aqueous liquid preparation further consists of sodium sulfite.

21. (New) The aqueous liquid preparation according to claim 19, wherein the first component is a 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt.

22. (New) The aqueous liquid preparation according to claim 19, wherein the concentration of tyloxapol is from about 0.01 w/v % to about 0.05 w/v %.

23. (New) The aqueous liquid preparation according to claim 19, wherein the pH of the aqueous liquid preparation is from about 7.5 to about 8.5.

24. (New) The stable aqueous liquid preparation of claim 19; wherein the stable aqueous liquid preparation consists of: (a) 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt; (b) tyloxapol; (c) boric acid; (d) sodium tetraborate; (e) EDTA sodium salt; (f) polyvinylpyrrolidone; (g) sodium sulfite; and (h) water; wherein said liquid preparation is formulated for ophthalmic administration, 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 %, and wherein the concentration of tyloxapol is from about 0.01 w/v % to about 0.05 w/v %.

25. (New) A stable aqueous liquid preparation consisting essentially of: (a) a first component; (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; (c) boric acid; (d) sodium tetraborate; and (e) water; 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 and is present in the preparation at a concentration from about 0.05 w/v % to about 0.2 w/v %; the second component is tyloxapol; wherein said stable liquid preparation is formulated for ophthalmic administration; and 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.

26. (New) The aqueous liquid preparation according to claim 25, wherein the aqueous liquid preparation further consists of sodium sulfite.

27. (New) The stable aqueous liquid preparation of claim 25; 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.

28. (New) The aqueous liquid preparation according to claim 25; 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 0.05 w/v % to about 0.1 w/v %.

29. (New) The aqueous liquid preparation according to claim 28, wherein the pH is from about 7.5 to about 8.5.

30. (New) The stable aqueous liquid preparation of claim 25; wherein the stable aqueous liquid preparation consists 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) polyvinylpyrrolidone; (g) sodium sulfite; and (h) water; and wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.05 w/v % to about 0.1 w/v %, and the concentration of tyloxapol is about 0.02 w/v%.

31. (New) A stable aqueous liquid preparation consisting essentially of: (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; (c) boric acid; (d) sodium tetraborate; and (e) water; 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 and is present in the preparation at a concentration from about 0.05 w/v % to about 0.2 w/v %; the second component is tyloxapol; wherein said stable liquid preparation is formulated for ophthalmic administration; provided that the liquid preparation does not include mannitol.

32. (New) The aqueous liquid preparation according to claim 31, wherein the aqueous liquid preparation further consists of sodium sulfite.

33. (New) The aqueous liquid preparation according to claim 31, wherein the first component is a 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt.

34. (New) The aqueous liquid preparation according to claim 31, 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 0.1 w/v %.

35. (New) The aqueous liquid preparation according to claim 31, wherein the pH is from about 7.5 to about 8.5.

36. (New) The stable aqueous liquid preparation of claim 31; wherein the stable aqueous liquid preparation consists 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) polyvinylpyrrolidone; (g) sodium sulfite; and (h) water;

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 %, and the concentration of tyloxapol is from about 0.02 w/v% to about 0.05 w/v %.

37. (New) The stable aqueous liquid preparation of claim 31; 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.

38. (New) The stable aqueous liquid preparation of claim 37; 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.

39. (New) The stable aqueous liquid preparation 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 0.05 w/v % to about 0.1 w/v %.

40. (New) The aqueous liquid preparation according to claim 39, wherein the pH of the aqueous liquid preparation is from about 7.5 to about 8.5.

41. (New) The stable aqueous liquid preparation of claim 31; wherein the stable aqueous liquid preparation consists 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) polyvinylpyrrolidone; (g) sodium sulfite; and (h) water; 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 0.05 w/v % to about 0.1 w/v %.

42. (New) The aqueous liquid preparation of claim 19, wherein the aqueous liquid preparation does not include any preservative.

43. (New) The aqueous liquid preparation of claim 25, wherein the aqueous liquid preparation does not include any preservative.

44. (New) The aqueous liquid preparation of claim 31, wherein the aqueous liquid preparation does not include any preservative.

45. (New) The aqueous liquid preparation according to claim 19, optionally further consisting of one or more additives selected from the group consisting of buffers, thickeners, stabilizers, chelating agents, and pH controlling agents.

REMARKS

The present application is a divisional of Serial No. 14/165,976 filed January 28, 2014. The present Preliminary Amendment is submitted to cancel original claims 1-18, add new claims 19-45.

No new matter has been added.

Respectfully submitted,
/Warren M. Cheek, Jr./
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DN: cn=/Warren M. Cheek, Jr./, o, ou, email=wcheek@wenderoth.com, c=US
Date: 2014.04.25 11:00:09 -04'00'
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April 25, 2014

Modified PTO/AIA/82A (07-12)
(WLP version 9/2012)

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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	**NEW**
Filing Date	**April 25, 2014**
First Named Inventor	**Shirou SAWA**
Title	**AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID**
Art Unit	
Examiner Name	
Attorney Docket Number	**2014-0545**
Applicant's or Agent's Reference No.	

SIGNATURE of Applicant or Patent Practitioner

Signature	/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: 2014.04.25 10:59:16 -04'00'	Date	April 25, 2014
Name	**Warren M. Cheek**	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.

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I hereby revoke all previous powers of attorney given in the application referenced in the attached transmittal letter (form PTO/AIA/82A or equivalent).

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☐ Legal Representative of a Deceased or Legally Incapacitated Inventor

☒ Assignee or Person to Whom the Inventor is Under an Obligation to Assign

☐ 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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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 14/261,720	Filing Date 04/25/2014	☐ To be Mailed

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

(Column 1) (Column 2)

FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ 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 $ =	
☐ 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).			
☐ 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)

AMENDMENT	**04/25/2014**	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 27	Minus	** 27	= 0	x $80 =	0
	Independent (37 CFR 1.16(h))	* 3	Minus	***3	= 0	x $420 =	0
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	**0**

(Column 1) (Column 2) (Column 3)

AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	

LIE
/DIANA BATES/

* 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.

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