APPLICATION FOR A PATENT

COMMONWEALTH OF AUSTRALIA
Patents Act 1952-1973

APPLICATION FOR A PATENT

We, YOSHITOMI PHARMACEUTICAL INDUSTRIES, LTD.
AND SENJU PHARMACEUTICAL CO., LTD.
of 35, Hiranomachi 3-chome, Higashi-ku, OSAKA 541, JAPAN and
6-1, Hiranomachi 3-chome, Higashi-ku, OSAKA 541, JAPAN,
respectively

hereby apply for a grant of a Patent for an invention entitled:

OPHTHALMIC SOLUTION

which is described in the accompanying complete specification.

This Application is a Convention Application and is based on the
Application(s) numbered: 39763/1984

for a Patent or similar protection made in Japan

on 1 March 1984

Our address for service is care of GRIFFITH HASSEL & FRAZER,
Patent Attorneys of 71 York Street, Sydney 2000, in the
State of New South Wales, Commonwealth of Australia.

Dated this 1st day of March 1985
YOSHITOMI PHARMACEUTICAL INDUSTRIES, LTD.
AND SENJU PHARMACEUTICAL CO., LTD.
By their Patent Attorneys

GRIFFITH HASSEL & FRAZER

TO: THE COMMISSIONER OF PATENTS
COMMONWEALTH OF AUSTRALIA
DECLARATION IN SUPPORT OF A CONVENTION OR NON-CONVENTION APPLICATION FOR A PATENT OR PATENT OF ADDITION

In support of the application No. (a), made by (b) (1) YOSHITOMI PHARMACEUTICAL INDUSTRIES., LTD., and (2) SENJU PHARMACEUTICAL CO., LTD., for a patent/patent of addition for an invention entitled (c),

OPHTHALMIC SOLUTION

1. (d) Shoji Yoshida

of (c) 6-1, Hiranomachi 3-chome, Higashi-ku, OSAKA 541, JAPAN

2. The basic application(s) as defined by Section 141 of the Act was/were made in the following country or countries on the following date(s) by the following applicant(s) namely:—

<table>
<thead>
<tr>
<th>Country</th>
<th>Applicant(s)</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Japan</td>
<td>Yoshitomi Pharmaceutical Industries, Ltd. and Senju Pharmaceutical Co., Ltd.</td>
<td>1 March 1984</td>
</tr>
</tbody>
</table>

3. (i) Kazumi OGATA; Yujiro YAMAMOTO and Yoshi OZAKI

of (n) Asahi-Plaza B-701, 8, Kamishinden 4-chome, Toyonaka-shi, OSAKA 565, JAPAN; CS-305, 1-1, Momoyamadai, Suita-shi, OSAKA 565, JAPAN and 1240, Uzumorida 2-chome, Higashinada-ku, Kobe-shi, Hyogo 652, JAPAN, respectively,

is/are the actual inventor(s) of the invention and the facts upon which the applicant(s) is/are entitled to make the application are as follows:—

(as regards entitlement under Section 34 of the Act:—(a) The applicants are the assignee of the said invention from the said inventors.

(as regards entitlement under Part XVI of the Act:—(a)

4. The basic application(s) referred to in paragraph 2 of this Declaration was/were the first application(s) made in a Convention country in respect of the invention the subject of the application.

Declared at Osaka, Japan this 31th day of January 1985
Senju Pharmaceutical Co., Ltd.

To: The Commissioner of Patents,
Commonwealth of Australia.

GRiffith, Hassel & Frazier Box 2133, G.P.O. SYDNEY 2001 AUSTRALIA
1. An anti-inflammatory ophthalmic solution comprising pranoprofen as an active ingredient and boric acid as an isotonicity-imparting agent which functions to reduce the eye-irritativeness of the pranoprofen.
Short Title:

Int. Cl:

Application Number:

Lodged:

Accept:

Lapse:

Published:

Priority:

Related Art:

TO BE COMPLETED BY APPLICANT

Name of Applicant: YOSHITOMI PHARMACEUTICAL INDUSTRIES, LTD.

and SENJU PHARMACEUTICAL CO., LTD.

Address of Applicant: 35, Hiranomachi 3-chome, Higashi-ku, OSAKA 541, JAPAN

and 6-1, Hiranomachi 3-chome, 7-chome, Higashi-ku, OSAKA 541, JAPAN, respectively

Actual Inventor: Kazumi OGATA ; Yujiro YAMAMOTO

and Yoshie OZAKI

Address for Service: GRIFFITH HASSEL & FRAZER

71 YORK STREET

SYDNEY, N.S.W. 2000, AUSTRALIA

Complete Specification for the Invention entitled: OPHTHALMIC SOLUTION

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

*Note: The description is to be typed in double spacing, pica type face, in an area not exceeding 250 mm in depth and 160 mm in width, on tough white paper of good quality and it is to be inserted inside this form.
OPHTHALMIC SOLUTION

Field of The Invention:

This invention relates to an ophthalmic solution comprising pranoprofen and boric acid.

Background of The Invention:

In the ophthalmic field, at the present time, patients contracting inflammatory diseases account for more than half all the patients of eye diseases. As an ophthalmic solution administered to them, various kinds of medicaments are used, for example, antibiotics, steroid compounds, non-steroid anti-inflammatory agents, FAD preparations, etc. The antibiotics and FAD preparations are categorized under medicaments acting on the causes for inflammation of the eyes (namely, medicaments for causal treatment) whereas the steroid compounds and non-steroid anti-inflammatory agents are categorized under medicaments acting on the inflammation per se of the living body (namely, medicaments for symptomatic treatment).

The steroid compounds are approved of clinically superior effects on inflammatory eye diseases of the external and front ocular parts, and nowadays are clinically indispensable ophthalmic agents. In contradiction to these favorable effects, however, the compounds are known to have severe side effects such as aggravation of steroid glaucoma, infectious eye diseases, particularly herpesvirus eye diseases, etc., so
that in the present situation, physicians clinically use them while having some apprehensions of these side effects. The non-steroid anti-inflammatory agents are used clinically in conjunction with the steroid compounds or alone, but are inevitably inferior to the steroid compounds in respect of their efficacy. An attempt has been heretofore made to provide ophthalmic solutions containing non-steroid anti-inflammatory agents as a main ingredient, but most of them are so irritant to the eyes and so strongly painful to the eyes that they cannot be practically used as an ophthalmic solution.

Hence, ophthalmic agents for herpesvirus eye diseases have not yet been found out.

A primary object of this invention is to provide an ophthalmic solution having potent anti-inflammatory action.

Another object of this invention is to provide an ophthalmic solution having no side effects and accordingly, capable of being dropped in the eyes to herpesvirus ophthalmia.

A further object of this invention is to provide an ophthalmic solution having less irritative anti-inflammatory property.

A still further object of this invention is to provide a method for treatment of herpesvirus ophthalmia.

With a view toward attaining the foregoing objects, namely solving the prior art technical problems, the present...
inventors have investigated extensively and as a result, have accomplished this invention by finding out that combined use of pranoprofen selected from innumerable compounds having anti-inflammatory activity and boric acid selected from various kinds of isotonicity-imparting agents can mitigate the foregoing problems.

According to this invention, there is provided an anti-inflammatory ophthalmic solution comprising pranoprofen as an active ingredient and boric acid as an isotonicity-imparting agent.

According to another embodiment of this invention, there is provided an anti-inflammatory ophthalmic solution to herpesvirus ophthalmia containing pranoprofen as an active ingredient.

According to further embodiment of this invention, there is provided a method of treatment for herpesvirus ophthalmia comprising dropping an efficient amount of pranoprofen in the eyes.

Pranoprofen whose chemical name is $\alpha$-methyl-5H-[1]-benzopyrano[2,3-b]pyridine-7-acetic acid is a novel non-steroid anti-inflammatory agent synthesized and developed by Yoshitomi Pharmaceutical Industries, Ltd. (Japan). This was revealed to have, as a result of fundamental tests, remarkable anti-inflammatory, analgesic and anti-pyretic actions and a wide safety range.

Furthermore, it
was confirmed, as a result of clinical tests, to have superior effects on inflammatory diseases and pain reactions. Pranoprofen is now commercially available under the trade name of "Niflan" (registered trademark), and characteristics and method for preparation of it are disclosed in U.S.P. No. 3,931,205.

The present inventors, however, have found that pranoprofen itself has eye irritativeness as shown in subsequent Experimental Example 1 and the irritativeness can be mitigated by this invention. Preferably, the concentration of pranoprofen as an anti-inflammatory active ingredient is usually in the range of 0.01 to 0.5 (w/v)% and can be adjusted appropriately depending on the intended objects.

Boric acid is incorporated in such an amount that its osmotic pressure ratio is about 1, and in general, in an amount on the order of 0.5 - 2 (w/v)%.

An essential feature of this invention resides in that pranoprofen is selected as an active ingredient and boric acid is selected as an isotonicity-imparting agent, and accordingly, it will be readily understood that further ingredients known per se in the preparation of ophthalmic solutions are incorporated in a usual amount.

Specific examples of other formulation ingredients than above and preferred formulation amounts of them will be exemplified hereinbelow.
As a dissolution-assisting agent, there may be mentioned for example, nonion surface active agents such as polyoxy-ethylenesorbitan monooleate, polyoxyethyleneoxystearic acid triglyceride, polyethylene glycol, etc.

A thickening agent includes for example, polyvinylpyrrolidone, methylcellulose, hydroxypropylmethylcellulose, hydroxyethylcellulose, etc.

As an ophthalmic antiseptic, those conventionally used may be mentioned, for example, benzalconium chloride, cetylpyridinium chloride, chlorobutanol, methylparaben, propylparaben, etc.

Ophthalmologically acceptable salts include, for example, alkali metal salts such as sodium salt or potassium salt, or alkali earth metal salts such as magnesium salt or calcium salt.

A chelating agent such as sodium ethylenediamine-tetraacetate (EDTA-Na) may be used.

The pH of the ophthalmic solution of this invention is preferred to be 6.5 - 8.5, particularly about 7.5.

The dosage of the anti-inflammatory active ingredient of this invention to be dropped in the eyes is an amount sufficient to render efficiently ophthalmia anti-inflammatory, and may vary depending on the disease conditions, kind of inflammation, etc., but is generally 5 - 200 Hg per dose. The administration frequency may be chosen appropriately in the range of 1 to 4 times a day. The foregoing amount and frequency to be dropped in the eyes are also true where pranoprofen is used for the treatment of ophthalmia ascribable to herpesvirus.

The effects and advantages of this invention will be
described by way of Examples only which are not intended to limit the invention in any way.

Experimental Example 1

In order to effect eye irritation test, its evaluation criterion was determined in the following manner. That is, Experimental formula Examples 1, 2, 3 and 4 were dropped in the eyes of ten healthy men and compared with one another with respect to the degree of eye irritation.

Experimental Formula Example 1:

An ophthalmic solution is prepared by dissolving 620 mg of sodium chloride into 100 ml of 0.04 M phosphate buffer having a pH of 7.4 and filtering and pasteurizing the solution.

Experimental Formula Example 2:

An ophthalmic solution is prepared by dissolving 660 mg of sodium chloride into 100 ml of 0.04 M phosphate buffer having a pH of 6.5 and filtering and pasteurizing the solution.

Experimental Formula Example 3:

An ophthalmic solution is prepared by dissolving 680 mg of sodium chloride into 100 ml of 0.04 M phosphate buffer having a pH of 5.5, and filtering and pasteurizing the solution.

Experimental Formula Example 4:

An ophthalmic solution is prepared by dissolving 680 mg of sodium chloride into 100 ml of 0.04 M phosphate buffer having a pH of 4.5 and filtering and pasteurizing
the solution.

Table 1

<table>
<thead>
<tr>
<th>Testing Person</th>
<th>Experimental Formula Ex.1</th>
<th>Experimental Formula Ex.2</th>
<th>Experimental Formula Ex.3</th>
<th>Experimental Formula Ex.4</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>-</td>
<td>+ 1</td>
<td>+ 2</td>
<td>+ 4</td>
</tr>
<tr>
<td>2</td>
<td>-</td>
<td>+ 1</td>
<td>+ 3</td>
<td>+ 4</td>
</tr>
<tr>
<td>3</td>
<td>-</td>
<td>+ 1</td>
<td>+ 2</td>
<td>+ 3</td>
</tr>
<tr>
<td>4</td>
<td>+ 1</td>
<td>+ 2</td>
<td>+ 3</td>
<td>+ 4</td>
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<td>+ 1</td>
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<td>+ 3</td>
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<td>-</td>
<td>+ 1</td>
<td>+ 2</td>
<td>+ 4</td>
</tr>
<tr>
<td>9</td>
<td>-</td>
<td>+ 1</td>
<td>+ 2</td>
<td>+ 4</td>
</tr>
<tr>
<td>10</td>
<td>+ 1</td>
<td>+ 1</td>
<td>+ 3</td>
<td>+ 4</td>
</tr>
</tbody>
</table>

From the test results of Table 1, the degree of irritation was evaluated according to the criterion:

<table>
<thead>
<tr>
<th>Rating</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
<td>No irritation, no unpleasant feeling (Experimental Formula Ex. 1 is dropped in the eyes.)</td>
</tr>
<tr>
<td>+ 1</td>
<td>Slight irritation feeling (Experimental Formula Ex. 2 is dropped in the eyes.)</td>
</tr>
<tr>
<td>+ 2 - + 3</td>
<td>Irritation feeling (Experimental Formula Ex. 3 is dropped in the eyes.)</td>
</tr>
</tbody>
</table>
Strong irritation feeling
(Experimental Formula Ex. 4 is dropped in the eyes.)

The following Experimental Formula Examples 5, 6, 7 and 8 were dropped in the eyes of ten healthy men and compared with one another in respect of eye irritation on the basis of this assessment criterion.

Experimental Formula Example 5:

One hundred mg of pranoprofen and 850 mg of sodium chloride are dissolved in purified water, and sodium hydroxide is added to the solution and dissolved to adjust the pH to about 7.5. Thereafter, purified water is added to make the total amount of the solution 100 ml, and it is filtered and pasteurized to prepare an ophthalmic solution.

Experimental Formula Example 6:

Pranoprofen, 100 mg, and 5000 mg of d-mannitol are incorporated in purified water, and sodium hydroxide is added and dissolved to adjust pH of the solution to about 7.5. Then purified water is added to make the total amount of the solution 100 ml, and it is filtered and pasteurized to prepare an ophthalmic solution.

Experimental Formula Example 7:

Pranoprofen, 100 mg, and 2500 mg of conc. glycerine are incorporated in purified water, and to the solution is added and dissolved sodium hydroxide to adjust pH to about 7.5. Then purified water is added to make the total amount
of the solution 100 ml, and the solution is filtered and pasteurized to prepare an ophthalmic solution.

Experimental Formula Example 8:

Pranoprofen, 100 mg, and 1600 mg of boric acid are dissolved in purified water, and 800 mg of borax is added to adjust pH of the solution to about 7.5. Thereafter, purified water is added to make the total amount of the solution 100 ml, and it is filtered and pasteurized to prepare an ophthalmic solution.

Table 2

<table>
<thead>
<tr>
<th>Testing Person</th>
<th>Experimental Formula Ex.5</th>
<th>Experimental Formula Ex.6</th>
<th>Experimental Formula Ex.7</th>
<th>Experimental Formula Ex.8 The Invention</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>2</td>
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<tr>
<td>5</td>
<td>4</td>
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<td>3</td>
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</tr>
<tr>
<td>6</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>7</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
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<tr>
<td>10</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>29</td>
<td>25</td>
<td>27</td>
<td>8</td>
</tr>
<tr>
<td>Average</td>
<td>2.9</td>
<td>2.5</td>
<td>2.7</td>
<td>0.8</td>
</tr>
</tbody>
</table>
From the results in Table 2, it will be apparent that irritativeness of the ophthalmic solution of this invention is statistically insignificant as compared with those of formulae each containing sodium chloride, d-mannitol and glycerine. Thus, the ophthalmic solution of this invention was corroborated to have low irritativeness.

Experimental Example 2

What influences non-steroid pranoprofen and steroid dexamethasone have on cornea herpes inflammation of rabbits was examined.

Method:

Herpesvirus:

50 μl of solution in which $6 \times 10^7$ PFU/ml is diluted to 10-fold is inoculated.

Group:

- Group to which 0.1% pranoprofen is dropped in the eyes ($n = 7$)
- Group to which 0.05% dexamethasone is dropped in the eyes ($n = 7$)
- Group to which isotonic sodium chloride solution is dropped in the eyes ($n = 6$)

Dropping of ophthalmic solution in the eyes:

One drop of ophthalmic solution is dropped in the eyes four times a day for five days before inoculation of virus.

Observation:
Groups to which ophthalmic solution was dropped in the eyes are dyed with 1% Rose Bengale and rated according to the list of ratings of Kaufman et al [Archives of Ophthalmology, 69, 926 (1963)].

Results:

Results are illustrated in the accompanying single figure which is a graphical representation showing effects of ophthalmic solution according to this invention on herpesvirus inflammation.

As will be apparent from the figure, the group to which pranoprofen was dropped in the eyes went through a similar curing process to the group to which isotonic sodium chloride solution was dropped in the eyes and did not affect on cornea herpes inflammation. On the other hand, the group to which doxamethasone was dropped in the eyes showed high peak ratings and a slow curing rate as compared with the group to which isotonic sodium chloride solution was dropped in the eyes.

From the results above, it is deemed that doxamethasone aggravates cornea herpes, but pranoprofen does not.

Example 1

One hundred mg of pranoprofen, 1600 mg of boric acid, 200 mg of polyoxyethylenesorbitan monooleate and 5 mg of benzalconium chloride are dissolved in purified water, and to the solution is added 800 mg of borax to adjust pH to about 7.5. Thereafter, purified water is added to make the
total amount of the solution 100 ml, and it is filtered and pasteurized to prepare an ophthalmic solution.

Example 2

One hundred mg of pranoprofen, 1600 mg of boric acid, 26 mg of methyl paraoxybenzoate and 14 mg of propyl paraoxybenzoate are dissolved in purified water and 800 mg of borax is added thereto to adjust pH to about 7.5. Then, purified water is added to make the total amount of the solution 100 ml, and the solution is filtered and pasteurized to prepare an ophthalmic solution.
THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. An anti-inflammatory ophthalmic solution comprising pranoprofen as an active ingredient and boric acid as an isotonicity-imparting agent which functions to reduce the eye-irritativeness of the pranoprofen.

2. A process for preparing an ophthalmic solution as defined in claim 1 which comprises dissolving pranoprofen or its ophthalmologically acceptable salt and boric acid into an aqueous medium and adjusting the pH of the solution to 6.5 - 8.5.

3. An ophthalmic solution as defined in claim 1 and substantially as herein described with reference to Example 1 or Example 2.

4. An ophthalmic solution as claimed in claim 1 comprising pranoprofen as an anti-inflammatory agent wherein the concentration of pranoprofen is in the range of 0.01 to 0.5 (w/v)%.

5. An ophthalmic solution as claimed in claim 1 comprising boric acid as an isotonicity-imparting agent wherein the concentration of boric acid is in the range 0.5-2 (w/v)%.


DATED this 14th day of October, 1988

YOSHITOMI PHARMACEUTICAL INDUSTRIES, LIMITED and

SENU PHARMACEUTICAL COMPANY, LIMITED

By their Patent Attorney

GRIFFITH HACK & CO
Day after inoculation

- - - : Isotonic NaCl-dropping group
○-○ : Pranoprofen-dropping group
←-← : Dexamethasone-dropping group