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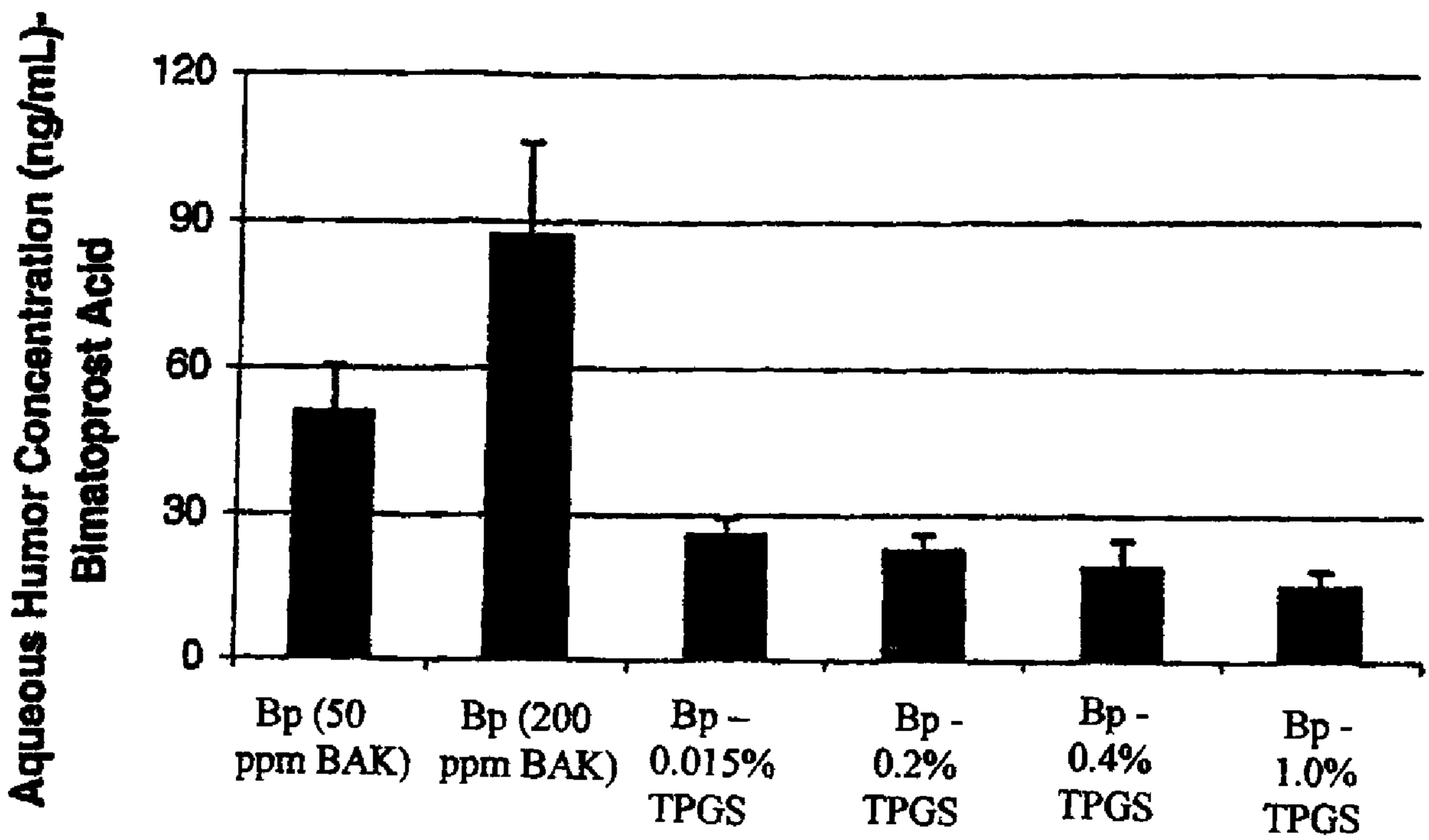
(54) Title: ENHANCED BIMATOPROST OPHTHALMIC SOLUTION



(57) Abrégé/Abstract:
A composition comprising from 0.005% to 0.02% bimatoprost by weight and from 100 ppm to 250 ppm benzalkonium chloride, wherein said composition is an aqueous liquid which is formulated for ophthalmic administration is disclosed herein. A method which is useful in treating glaucoma or ocular hypertension related thereto is also disclosed herein.

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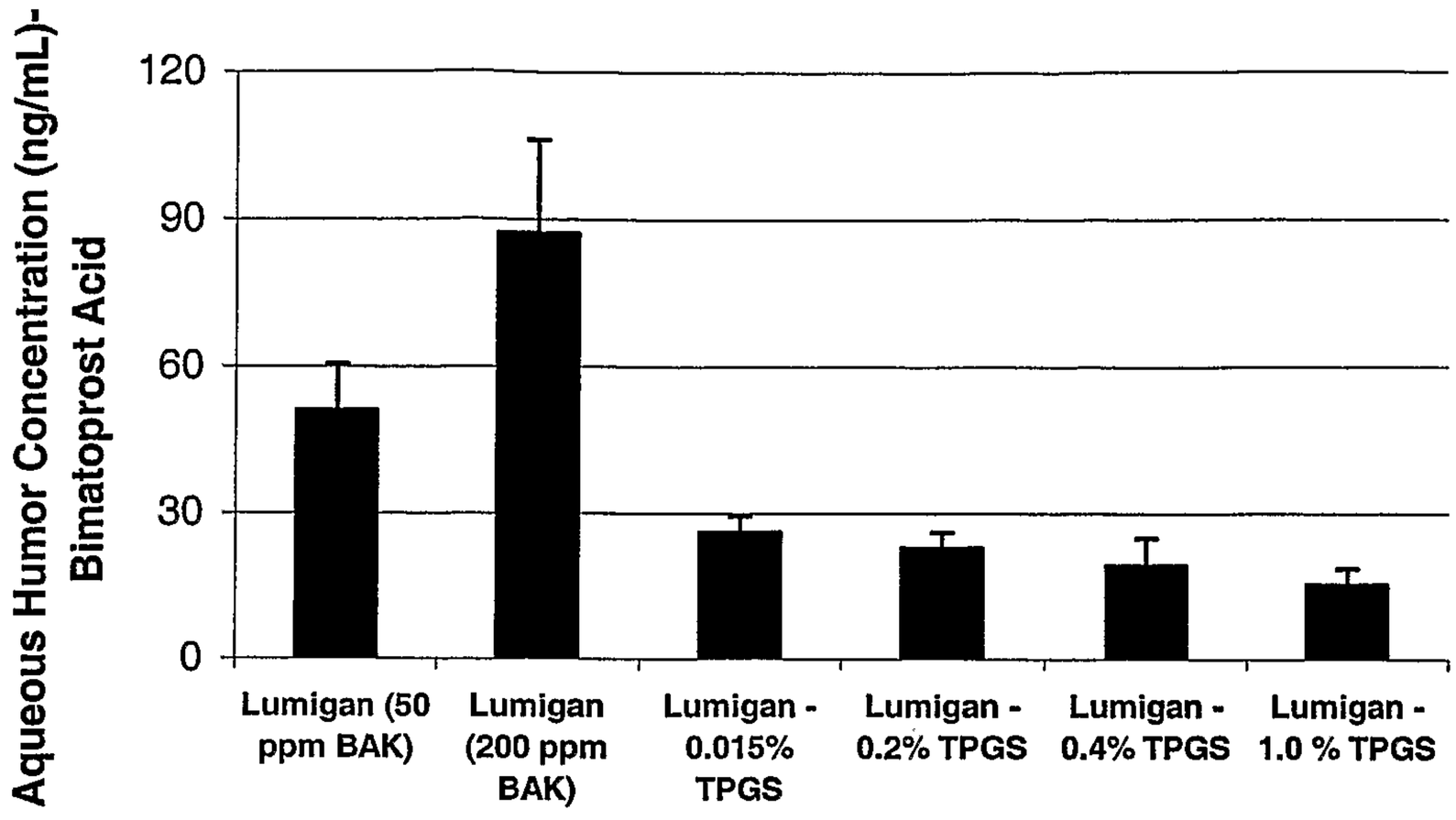
(54) Title: ENHANCED BIMATOPROST OPHTHALMIC SOLUTION



(57) Abstract: A composition comprising from 0.005% to 0.02% bimatoprost by weight and from 100 ppm to 250 ppm benzalkonium chloride, wherein said composition is an aqueous liquid which is formulated for ophthalmic administration is disclosed herein. A method which is useful in treating glaucoma or ocular hypertension related thereto is also disclosed herein.

WO 2006/101839 A3

ENHANCED BIMATOPROST OPHTHALMIC SOLUTION

By Inventors

Chin-Ming Chang, James N. Chang, Rhett M. Schiffman, R. Scott Jordan, and Joan-En Chang-Lin

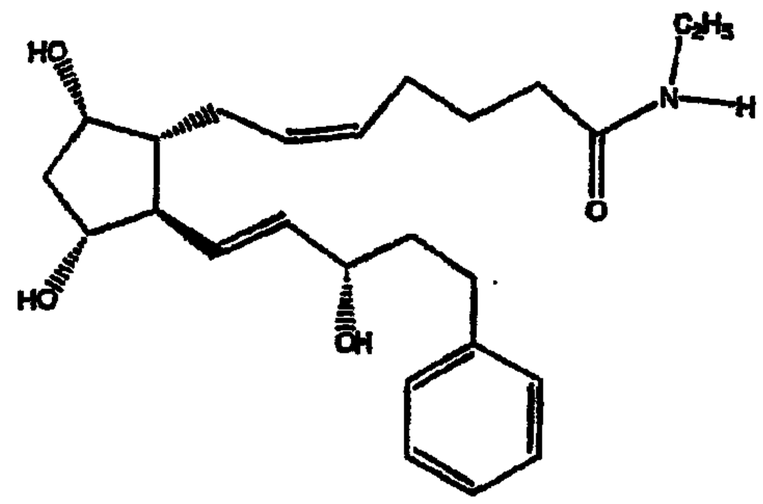
FIELD OF THE INVENTION

This invention relates to pharmaceutical compositions comprising bimatoprost.

BACKGROUND OF THE INVENTION

Description of Related Art

Bimatoprost, shown below, is a prostamide marketed commercially for the treatment of glaucoma and ocular hypertension.



Formula I

Benzalkonium chloride (BAK) is a preservative used in many commercial ophthalmic products to prevent microbial contamination in multi-use products. The commercial eye drops (Lumigan*, Allergan, Inc., Irvine, CA) contain 0.03% bimatoprost and 0.005% BAK. Although no other prostamides are currently marketed for the treatment of glaucoma, several prostaglandin analogs

* Trademark

are commercially available which use BAK as a preservative. These include latanoprost (Xalatan)*, travoprost (Travatan)*, and unoprostone isopropyl (Rescula)*, which require significantly more BAK, from 150-200 ppm, to meet antimicrobial effectiveness tests in the United States and Europe.

United States Patent No. 6,596,765 B2 discloses a composition comprising 0.005% or 0.0005% latanoprost and 0.2 mg/mL BAK.

United States Patent No. 6,646,001 B2 discloses compositions comprising 0.03% bimatoprost and 0.01% BAK or "0.01% + 5% excess" BAK.

BRIEF DESCRIPTION OF THE DRAWING FIGURES

Figure 1 is a plot showing the aqueous humor concentration of the parent acid of bimatoprost (Bp) after topical administration of several formulations.

Figure 2 is a plot showing the membrane permeability of bimatoprost (Bp) in several different formulations.

DETAILED DESCRIPTION OF THE INVENTION

A composition comprising from 0.005% to 0.02% bimatoprost by weight and from 100 ppm to 250 ppm benzalkonium chloride, wherein said composition is an aqueous liquid which is formulated for ophthalmic administration is disclosed herein.

A method which is useful in treating glaucoma or ocular hypertension related thereto is also disclosed herein.

An aqueous liquid which is formulated for ophthalmic administration is formulated such that it can be administered topically to the eye. The comfort should be maximized as much as possible, although sometimes formulation considerations (e.g. drug stability) may necessitate less than optimal comfort.

In certain compositions the concentration of bimatoprost is from 0.01% to 0.02%. In other compositions the concentration of bimatoprost is from 0.015% to 0.02%.

* Trademark

In certain compositions the concentration of BAK is from 150 ppm to 200 ppm. In other compositions the concentration of BAK is from 150 ppm to 200 ppm. In other compositions the concentration of BAK is from 150 ppm to 250 ppm.

In ophthalmic compositions, a chelating agent may be used to enhance preservative effectiveness. Suitable chelating agents are those known in the art, and, while not intending to be limiting, edetate salts (EDTA) are useful chelating agents.

In certain compositions, concentration of EDTA is at least 0.001%. In other compositions, the concentration of EDTA is at least 0.01%. In other compositions the concentration of EDTA is 0.15% or less. In other compositions the concentration of EDTA is 0.1% or less. In other compositions the concentration of EDTA is 0.05% or less.

Certain compositions comprise from 150 to 250 ppm BAK and an effective amount of EDTA.

As is known in the art, buffers are commonly used to adjust the pH to a desirable range for ophthalmic use. Generally, a pH of around 6-8 is desired, and in certain compositions a pH of 7.4 is desired. Many buffers including salts of inorganic acids such as phosphate, borate, and sulfate are known.

Another commonly used excipient in ophthalmic compositions is a viscosity-enhancing, or a thickening agent. Thickening agents are used for a variety of reasons, ranging from improving the form of the formulation for convenient administration to improving the contact with the eye to improve bioavailability. The viscosity-enhancing agent may comprise a polymer containing hydrophilic groups such as monosaccharides, polysaccharides, ethylene oxide groups, hydroxyl groups, carboxylic acids or other charged functional groups. While not intending to limit the scope of the invention, some examples of useful viscosity-enhancing agents are sodium carboxymethylcellulose, hydroxypropylmethylcellulose, povidone, polyvinyl alcohol, and polyethylene glycol.

In ophthalmic solutions, tonicity agents often are used to adjust the composition of the formulation to the desired isotonic range. Tonicity agents

are well known in the art and some examples include glycerin, mannitol, sorbitol, sodium chloride, and other electrolytes.

One composition has a pH of 7.4 and consists essentially of 0.015% bimatoprost, 200 ppm benzalkonium chloride, from 0 to 0.03% EDTA, a phosphate buffer, NaCl, and water.

Another composition has a pH of 7.4 and comprises 0.02% bimatoprost, 200 ppm benzalkonium chloride, from 0 to 0.03% EDTA, a phosphate buffer, NaCl, and water.

Another composition has a pH of 7.4 and consists of 0.01% bimatoprost, 200 ppm benzalkonium chloride, from 0 to 0.03% EDTA, a phosphate buffer, NaCl, and water.

The best mode of making and using the present invention are described in the following examples. These examples are given only to provide direction and guidance in how to make and use the invention, and are not intended to limit the scope of the invention in any way.

One embodiment comprises 0.01% Bimatoprost, 0.02% Benzalkonium Chloride, 0.268% Sodium Phosphate Dibasic, Heptahydrate, 0.014% Citric Acid, Monohydrate, 0.81% Sodium Chloride, and water, wherein the pH is 7.3.

Another embodiment comprises 0.015% Bimatoprost, 0.02% Benzalkonium Chloride, 0.268% Sodium Phosphate Dibasic, Heptahydrate, 0.014% Citric Acid, Monohydrate, 0.81% Sodium Chloride, and water, wherein the pH is 7.3.

Another embodiment comprises 0.015% Bimatoprost, 0.02% Benzalkonium Chloride, 0.268% Sodium Phosphate Dibasic, Heptahydrate, 0.014% Citric Acid, Monohydrate, 0.81% Sodium Chloride, 0.03%, EDTA, and water, wherein the pH is 7.3.

Another embodiment comprises 0.02% Bimatoprost, 0.02% Benzalkonium Chloride, 0.268% Sodium Phosphate Dibasic, Heptahydrate, 0.014% Citric Acid, Monohydrate, 0.81% Sodium Chloride, and water, wherein the pH is 7.3.

Another embodiment consists essentially of 0.01% Bimatoprost, 0.02% Benzalkonium Chloride, 0.268% Sodium Phosphate Dibasic, Heptahydrate,

0.014% Citric Acid, Monohydrate, 0.81% Sodium Chloride, and water, wherein the pH is 7.3.

Another embodiment consists essentially of 0.015% Bimatoprost, 0.02% Benzalkonium Chloride, 0.268% Sodium Phosphate Dibasic, Heptahydrate, 0.014% Citric Acid, Monohydrate, 0.81% Sodium Chloride, and water, wherein the pH is 7.3.

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Another embodiment consists essentially of 0.02% Bimatoprost, 0.02% Benzalkonium Chloride, 0.268% Sodium Phosphate Dibasic, Heptahydrate, 0.014% Citric Acid, Monohydrate, 0.81% Sodium Chloride, and water, wherein the pH is 7.3.

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Another embodiment consists of 0.02% Bimatoprost, 0.02% Benzalkonium Chloride, 0.268% Sodium Phosphate Dibasic, Heptahydrate, 0.014% Citric Acid, Monohydrate, 0.81% Sodium Chloride, and water, wherein the pH is 7.3.

Another embodiment comprises 0.0125% bimatoprost, 0.02% benzalkonium chloride, 0.268% sodium phosphate dibasic heptahydrate,

0.014% citric acid monohydrate, 0.81% sodium chloride, sufficient sodium hydride and/or hydrochloric acid to adjust the pH to 7.3, and water.

Another embodiment consists essentially of 0.0125% bimatoprost, 0.02% benzalkonium chloride, 0.268% sodium phosphate dibasic heptahydrate, 0.014% citric acid monohydrate, 0.81% sodium chloride, sufficient sodium hydride and/or hydrochloric acid to adjust the pH to 7.3, and water.

Another embodiment consists of 0.0125% bimatoprost, 0.02% benzalkonium chloride, 0.268% sodium phosphate dibasic heptahydrate, 0.014% citric acid monohydrate, 0.81% sodium chloride, sufficient sodium hydride and/or hydrochloric acid to adjust the pH to 7.3, and water.

Example 1

Formulations containing 0.268% sodium phosphate dibasic heptahydrate, 0.014% citric acid, 0.83% sodium chloride, with the pH adjusted to 7.3 in qs water, and the amounts of bimatoprost, BAK, and EDTA listed in Table 1 below were prepared by conventional methods well known in the art.

Table 1

Formulation
1. 0.03% Bimatoprost (50 ppm BAK) Control
2. 0.03% Bimatoprost – 200 ppm BAK
3. 0.03% Bimatoprost – 0.015% TPGS (no preservative)
4. 0.03% Bimatoprost – 0.2% TPGS (no preservative)
5. 0.03% Bimatoprost – 0.4% TPGS (no preservative)
6. 0.03% Bimatoprost – 1.0% TPGS (no preservative)

Example 2

Studies were carried out to determine the effect of benzalkonium chloride (BAK) and d-alpha tocopheryl polyethylene glycol 1000 succinate (TPGS) on ocular absorption of bimatoprost *in vivo*. For the *in vivo* study, eighteen female rabbits were given a single 28 μL eyedrop bilaterally and aqueous humor samples were collected (n=3 animals with 6 eyes per formulation) at 60 min postdose. Two rabbits (4 eyes) remained untreated to serve as pre-dose bioanalytical controls. Bimatoprost and its parent carboxylic

acid extracted from aqueous humor and *in vitro* samples were analyzed by a liquid chromatography tandem mass spectrometry (LC-MS/MS) method with a quantitation range of 0.25-60 ng/mL.

Due to extensive metabolism of bimatoprost in rabbit eyes, its parent acid was used as a surrogate for determining ocular absorption of bimatoprost. Concentration of the acid in rabbit aqueous humor following single dose of 6 different bimatoprost formulations are summarized in Figure 1 and Table 2 below.

Table 2

Formulation	**Aqueous Humor[a] (ng/mL)**
1. 0.03% Bimatoprost (50 ppm BAK) Control	51.0 ± 9.4
2. 0.03% Bimatoprost – 200 ppm BAK	87.2 ± 19.0*
3. 0.03% Bimatoprost – 0.015% TPGS (no preservative)	26.1 ± 3.3*
4. 0.03% Bimatoprost – 0.2% TPGS (no preservative)	22.9 ± 3.2*
5. 0.03% Bimatoprost – 0.4% TPGS (no preservative)	19.3 ± 5.6*
6. 0.03% Bimatoprost – 1.0% TPGS (no preservative)	15.4 ± 3.3*

a Mean ± SD. Per formulation, N=3 rabbits (6 eyes).

* Statistically different ($p<0.05$) compared to 0.03% Bimatoprost

Test formulations containing 0.015%, 0.2%, 0.4% and 1.0% TPGS resulted in a lower aqueous humor carboxylic acid concentration compared to Bimatoprost by 52%, 59%, 62% and 72%, respectively. In contrast, 0.03% Bimatoprost containing 200 ppm BAK resulted in 57% higher aqueous humor AGN 191522 concentration compared to Bimatoprost (50 ppm BAK).

While not intending to limit the scope of the invention in any way, or be bound by theory, compared to the Bimatoprost control, formulations containing TPGS resulted in decrease bimatoprost permeability. In contrast, formulations with higher BAK resulted in higher permeability.

Example 3

Formulations containing 0.268% sodium phosphate dibasic heptahydrate, 0.014% citric acid, 0.83% sodium chloride, with the pH adjusted to 7.3 in qs

water, and the amounts of bimatoprost, BAK, and EDTA listed in Table 3 below were prepared by conventional methods well known in the art.

Table 3

Formulation
A. 0.03% Bimatoprost (50 ppm BAK) - Control
B. 0.015% Bimatoprost (50 ppm BAK)
C. 0.015% Bimatoprost (50 ppm BAK) 0.03% EDTA
D. 0.015% Bimatoprost (200 ppm BAK)
E. 0.015% Bimatoprost (200 ppm BAK) 0.03% EDTA
F. 0.015% Bimatoprost (50 ppm BAK) 0.015% EDTA
G. 0.015% Bimatoprost (200 ppm BAK) 0.015% EDTA
H. 0.015% Bimatoprost (125 ppm BAK)
I. 0.015% Bimatoprost (125 ppm BAK) 0.03% EDTA
J. 0.015% Bimatoprost (125 ppm BAK) 0.015% EDTA
K. 0.015% Bimatoprost (150 ppm BAK)
L. 0.015% Bimatoprost (150 ppm BAK) 0.1% EDTA
M. 0.015% Bimatoprost
N. 0.03% Bimatoprost

Example 4

The effect of benzalkonium chloride (BAK) and ethylenediaminetetraacetic acid (EDTA) on bimatoprost permeability across primary culture of rabbit corneal epithelial cell layers (RCECL). Corneal epithelial cells were harvested from New Zealand White rabbits and cultured on Transwell™ filters until confluency (Day 5). For the transport experiment, cells were first equilibrated in transport buffer for 1 hour at 37°C. Dosing solution containing 0.015% or 0.03% bimatoprost with varying concentrations of BAK and EDTA was then applied to the apical compartment of the Transwell™ (2 cultures; n=3-4 per culture) and the cells were incubated at 37°C. At 30, 60, 90 and 120 minutes postdose, 200 μL samples were taken from the basolateral chamber for apical to basolateral (AB) transport. The samples were analyzed by a liquid chromatography tandem mass spectrometry (LC-MS/MS) method with quantitation range of 1-600 ng/mL.

The results are presented in Figure 2.

Example 5

A drop of formulation J is administered once daily topically to the eye of a person suffering from glaucoma. After a few hours, intraocular pressure drops more and less hyperemia is observed than would be observed for formulation A. Lowered intraocular pressure persists for as long as the treatment continues.

CLAIMS:

1. A composition comprising from 0.005% to 0.02% bimatoprost by weight and from 0.01% to 0.025% by weight benzalkonium chloride, wherein said composition is an aqueous liquid which is formulated for ophthalmic administration.

2. The composition of claim 1 which further comprises EDTA.

3. The composition of claim 2 wherein the concentration of benzalkonium chloride is from 0.015% to 0.02%.

4. The composition of claim 3 having a pH of 7.4 which consists essentially of 0.015% bimatoprost, 0.02% benzalkonium chloride, from 0 to 0.03% EDTA, and further comprising a phosphate buffer, NaCl, and water.

5. The composition of claim 1 wherein the concentration of bimatoprost is from 0.01% to 0.02%.

6. The composition of claim 5 wherein the concentration of bimatoprost is from 0.015% to 0.02%.

7. The composition of claim 6 wherein the concentration of benzalkonium chloride is from 0.015% to 0.020%.

8. The composition of claim 7 wherein the concentration of benzalkonium chloride is 0.02%.

9. The composition of claim 6 which further comprises EDTA.

10. A composition comprising 0.015% by weight bimatoprost, 0.02% by weight benzalkonium chloride, from 0 to 0.03% EDTA, a phosphate buffer, NaCl, wherein said composition has a pH of 7.4 and is an aqueous liquid.

11. The composition of claim 2 comprising from 0.001% to 0.15% EDTA.

12. The composition of claim 11 comprising from 0.01% to 0.1% EDTA.

13. The composition of claim 12 comprising from 0.01% to 0.05% EDTA.

14. The composition of claim 2 comprising from 0.015% to 0.025% benzalkonium chloride.

15. A composition comprising by weight 0.0125% bimatoprost, 0.02% benzalkonium chloride, 0.268% sodium phosphate dibasic heptahydrate, 0.014% citric acid monohydrate, 0.81% sodium chloride, water, and wherein said composition is an aqueous liquid with a pH adjusted to 7.3.

16. A composition comprising by weight 0.01% bimatoprost, 0.02% benzalkonium chloride, 0.268% sodium phosphate dibasic heptahydrate, 0.014% citric acid monohydrate, 0.81% sodium chloride, water, and wherein said composition is an aqueous liquid with a pH adjusted to 7.3.

17. Use of a composition comprising from 0.005% to 0.02% bimatoprost by weight and from 0.01% to 0.02% by weight benzalkonium chloride for treating glaucoma or intraocular hypertension in a mammal.

18. Use of a composition comprising from 0.005% to 0.02% bimatoprost by weight and from 0.01% to 0.02% by weight benzalkonium chloride for the preparation of a medicament for treating glaucoma or intraocular hypertension in a mammal.

19. Use of a composition according to any one of claims 1 to 16 for treating glaucoma or intraocular hypertension in a mammal.

20. Use of a composition according to any one of claims 1 to 16 for the preparation of a medicament for treating glaucoma or intraocular hypertension in a mammal.

Fig. 1

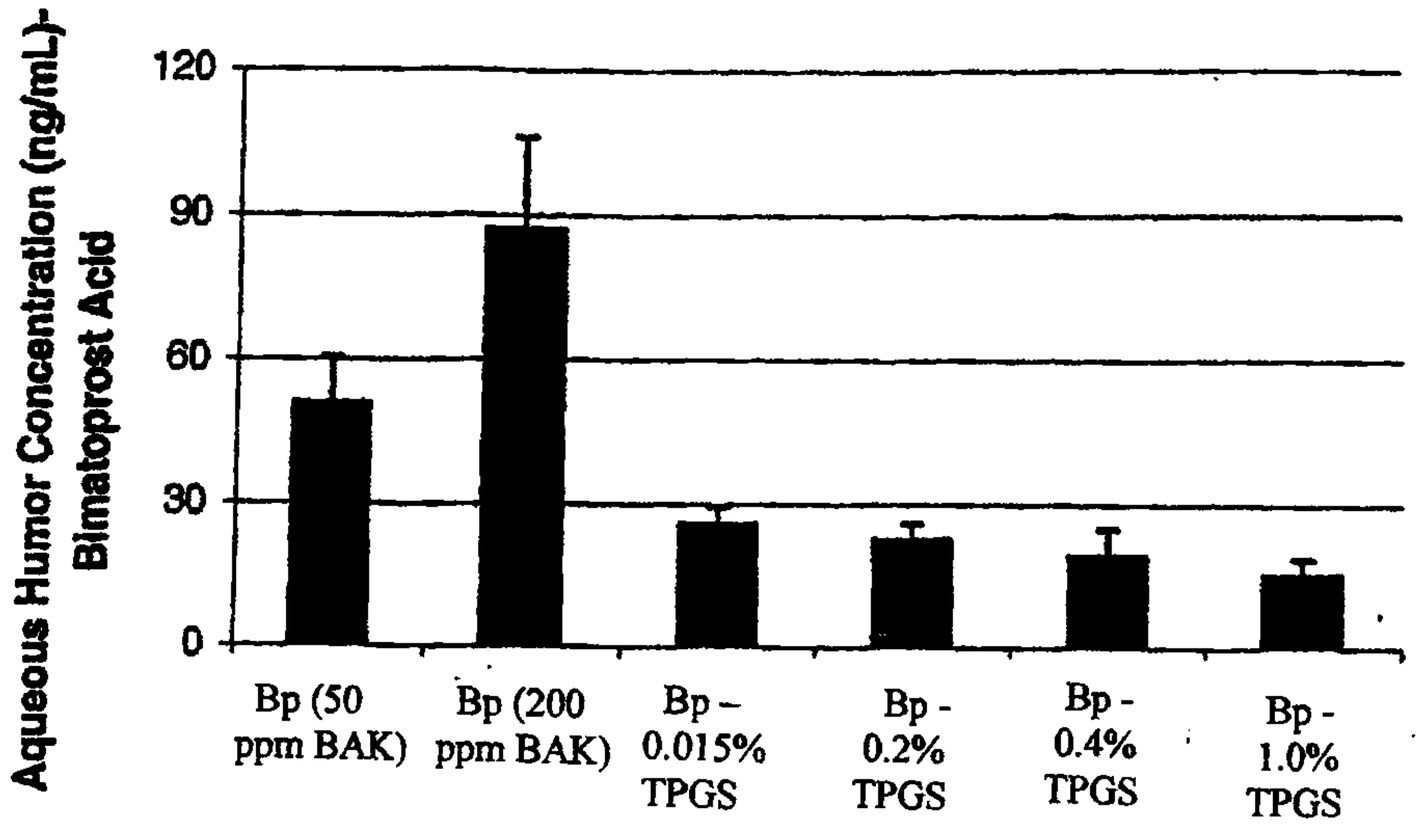
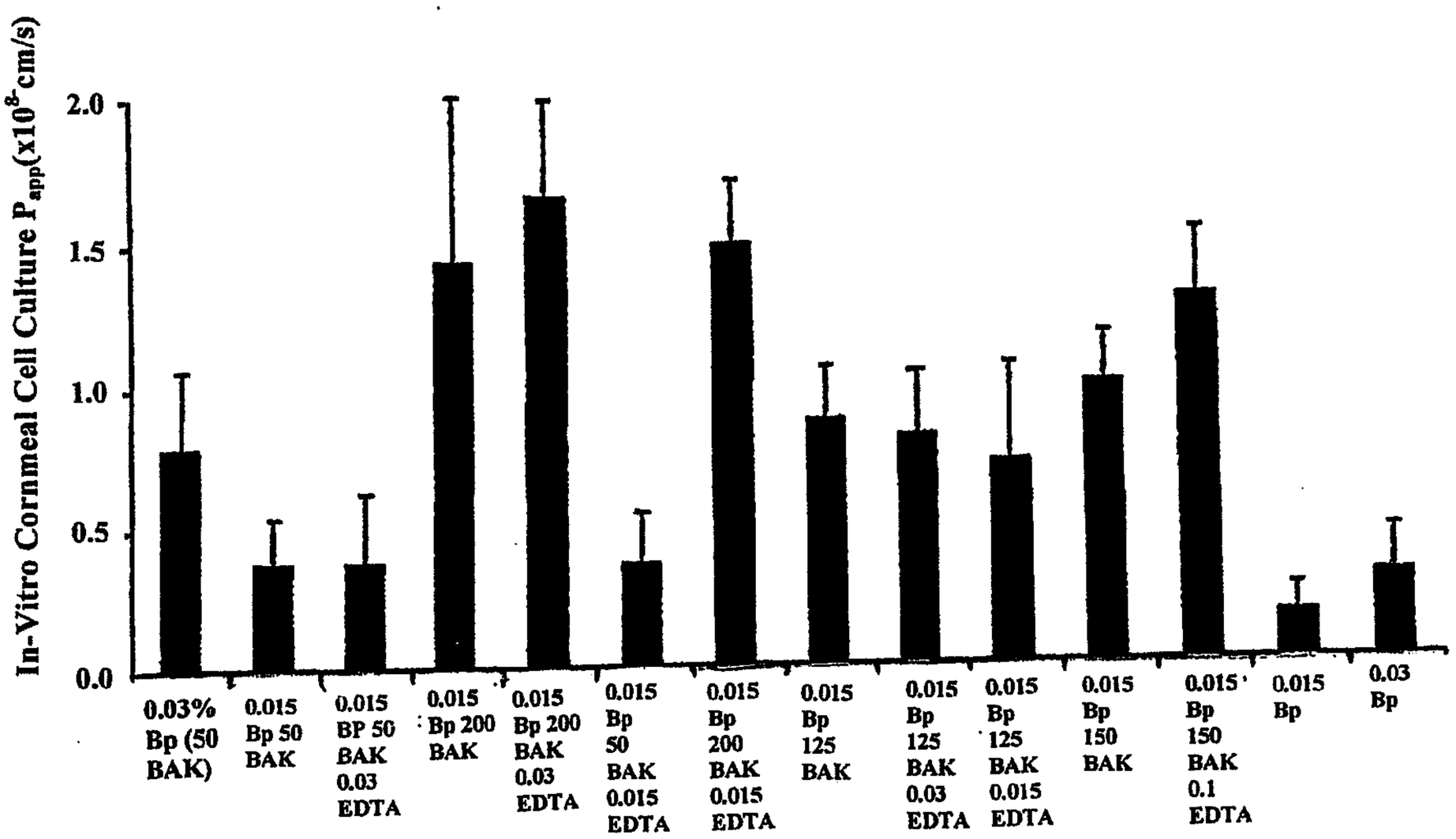
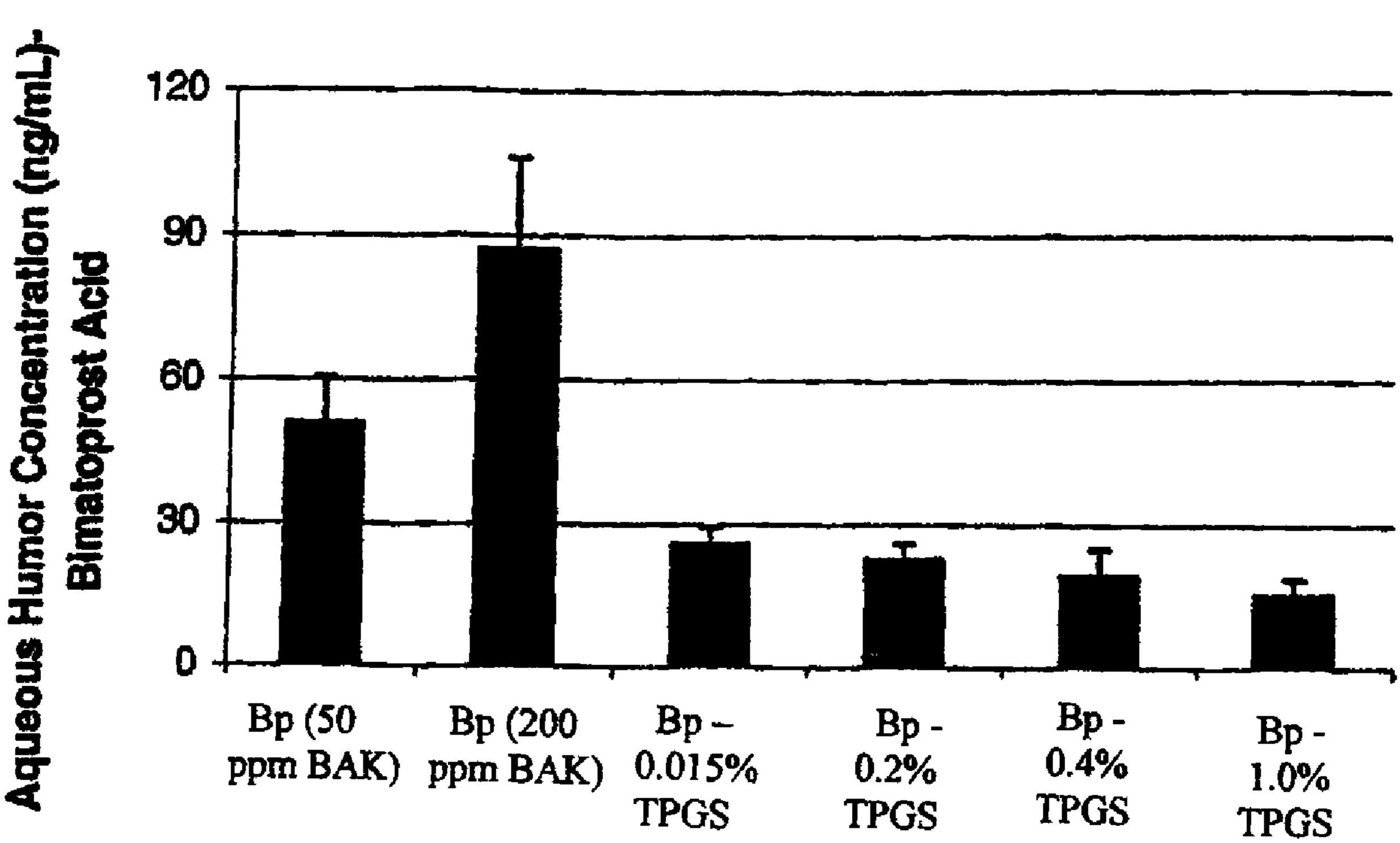

Aqueous Humor Concentration (ng/mL)-
Bimatoprost Acid
120
90
60
30
0
Bp (50 ppm BAK)
Bp (200 ppm BAK)
Bp – 0.015% TPGS
Bp - 0.2% TPGS
Bp - 0.4% TPGS
Bp - 1.0% TPGS

FIG. 2


In-Vitro Cornmeal Cell Culture P_{app}(x10^{-6}cm/s)
2.0
1.5
1.0
0.5
0.0
0.03% Bp (50 BAK)
0.015 Bp 50 BAK
0.015 BP 50 BAK 0.03 EDTA
0.015 Bp 200 BAK
0.015 Bp 200 BAK 0.03 EDTA
0.015 Bp 50 BAK 0.015 EDTA
0.015 Bp 200 BAK 0.015 EDTA
0.015 Bp 125 BAK
0.015 Bp 125 BAK 0.03 EDTA
0.015 Bp 125 BAK 0.015 EDTA
0.015 Bp 150 BAK
0.015 Bp 150 BAK 0.1 EDTA
0.015 Bp
0.03 Bp


Aqueous Humor Concentration (ng/mL)-
Bimatoprost Acid
120
90
60
30
0
Bp (50 ppm BAK)
Bp (200 ppm BAK)
Bp – 0.015% TPGS
Bp - 0.2% TPGS
Bp - 0.4% TPGS
Bp - 1.0% TPGS