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(54) **Ketorolac tromethamine készítmények a szem fájdalmának kezelésére vagy megelőzésére**

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(54) **Ketorolac tromethamine compositions for treating or preventing ocular pain**

Ketorolac tromethamin-Zusammensetzungen zur Behandlung oder Vorbeugung von Augenschmerzen

Compositions de kétorolac trométhamine pour traiter ou prévenir la douleur oculaire

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(56) References cited:
EP-A1- 0 524 587
WO-A2-2005/101982
WO-A2-2006/071601
US-A1- 2008 039 398

- **DONNENFELD E D ET AL: "Double-masked study of the effects of nepafenac 0.1% and ketorolac 0.4% on corneal epithelial wound healing and pain after photorefractive keratectomy", ADVANCES IN THERAPY, HEALTH COMMUNICATIONS, METUCHEN, NJ, US, vol. 24, no. 4, 1 July 2007 (2007-07-01), pages 852-862, XP009148763, ISSN: 0741-238X, DOI: 10.1007/BF02849978**

EP 2 446 878 B1

Description

Field of the Invention

[0001] This invention relates to pharmaceutical compositions. More particularly, this invention relates to topical ophthalmic solutions comprising 5-benzoyl-2,3-dihydro-1*H*-pyrrolizine-1-carboxylic acid, otherwise known as ketorolac, and the use of ketorolac for treating or preventing ocular pain.

Description of the Related Art

[0002] Topical nonsteroidal anti-inflammatory drugs (NSAIDs) are used to control pain and postoperative inflammation. All drugs are associated with some adverse effects. With the use of NSAIDS in topical ophthalmic treatment of patients, surface toxicity has been a concern, and incidents of keratitis, corneal subepithelial infiltrates, ulceration, and corneal melts have been reported (Guidera et al, Ophthalmology, 2001, 108 (5), pp. 936-944; Solomon et al, J Cataract Refract Surg, 2001, 27 (8), pp. 1232-1237; Teal et al, J Cataract Refract Surg, 1995, 21(5), pp. 516-518). Further, patients often report burning or stinging on instillation (Jaanus et al, Antiinflammatory Drugs. Clinical Ocular Pharmacology, Bartlet. J.D. and Jaanus, S.D., Ed., Boston: Heineman, 2001, pp. 265-298). The burning or stinging could be related to the concentration of the active component of the formulation.

[0003] US 2008/0039398 discloses ophthalmic formulations comprising ketorolac tromethamine and carboxymethyl cellulose.

[0004] Ketorolac tromethamine 0.5% (w/v) ophthalmic solution, available from Allergan, Inc., under the tradeneme ACULAR®, is a safe and effective NSAID with proven analgesic and anti-inflammatory activity. The most common adverse event associated with the use of the 0.5% ketorolac formulation is ocular irritation, primarily burning and stinging upon instillation. Keterolac tromethamine 0.4% (w/v) ophthalmic solution, under the tradename ACULAR LS ®, has shown improved bioavailability and less stinging on instillation than ACULAR®, but there remains a need for an improved keterolac tromethamine formulation with greater bioavailability and greater tolerability, minimized ocular surface toxicity, improved patient comfort, increased retention time of the active ingredient and improved wound healing capabilities during use.

[0005] It is one object of this invention to provide a keterolac formulation for instillation in the eye to eliminate or reduce ocular irritation, to improve tolerability, compliance, duration and effect of keterolac, to allow for dosing from four times daily to twice daily, and to increase the effectiveness of treatment by being free of benzalkonium chloride or other preservatives.

[0006] It is another object of the invention to improve bioavailability and increase the ocular absorption of ketorolac yet provide an aqueous solution having an optimized concentration of ketorolac.

[0007] It is another object of the invention to extend the effects of keterolac and allow for a decrease in required daily dosage.

[0008] It is another object of the invention to provide reduction of inflammation associated with cataract surgery and reduction of pain associated with cataract surgery in comparison to other keterolac formulations.

[0009] It is another object of the invention to create a keterolac formulation with improved wound healing capabilities.

[0010] Other objects of this invention will become apparent from a reading of the present specification.

Summary of the Invention

[0011] The present invention provides an aqueous ophthalmic formulation according to claim 1 comprising an effective amount of ketorolac but having an optimized concentration of keterolac in comparison other commercially available keterolac products. The aqueous ophthalmic soloution of the present invention comprises carboxymethyl cellulose, e.g. sodium carboxymethyl cellulose, having a pH within the range of from about 6.8 to 7.4, which is comfortable when topically applied to the eye of a patient, wherein the concentration of carboxymethyl cellulose and, preferably, the pH, is selected to provide an increased absorption of ketorolac in the eye of a patient as compared to a comparative keterolac solution that differs only in not including the carboxymethyl cellulose. That is, the absorption of keterolac may be 130% or greater than the absorption of a comparative aqueous ketorolac ophthalmic solution having the same or higher concentration of ketorolac.

[0012] More preferably, the aqueous ophthalmic solution of this invention has a pH within the range of from 6.8 to 7.4, particularly 6.8.

[0013] More preferably, the aqueous ophthalmic solution of the present invention has a concentration of carboxymethyl cellulose of from about 0.2 to about 2 percent, by weight, even more preferably from about 0.5 to 1.5 percent, by weight, and most preferably about 0.5% w/v.

[0014] Even more preferably, the aqueous ophthalmic solution of the present invention comprises a mixture of medium

viscosity and high viscosity sodium carboxymethyl cellulose.

[0015] The aqueous ophthalmic solution of the invention comprises an effective amount of ketorolac of 0.45 percent, by weight/volume.

[0016] More preferably, the aqueous ophthalmic solution of the invention has a viscosity of from 5 to 50 cps, preferably from 10 to 30 cps.

[0017] It has been surprisingly discovered that optimizing the concentration of ketorolac tromethamine reduces the occurrence of adverse events while maintaining clinical efficacy. Additionally, it has been discovered that the optimized concentration of ketorolac tromethamine in combination with carboxymethyl cellulose offers surprising and clear benefits in terms of formulation in that no preservative, chelating agent, and surfactant are required for formulation. Thus, finding a way to increase the absorption of ketorolac benefits the patient who can use a solution having an optimized concentration of ketorolac and obtain similar results in terms of efficiency as compared to a ketorolac solution having a higher concentration of ketorolac.

[0018] Thus, this invention relates to an aqueous topical ophthalmic composition comprising 0.45 % ketorolac tromethamine by weight/volume. The present invention also contains from 0.2 to 2 percent by weight, more preferably from 0.5 to 1.5 percent by weight and most preferably about 0.5 % w/v percent of medium and high molecular weight sodium carboxymethyl cellulose. Another aspect of this invention relates to a method of treating or preventing ocular pain in a person comprising topically administering to said patient a sterile composition comprising 0.45% w/v ketorolac tromethamine in combination with from 0.2 to 2 percent, by weight, preferably from 0.5 to 1.5 percent by weight, and most preferably 0.5% percent by weight/volume, sodium carboxymethyl cellulose and mixtures thereof.

[0019] While not intending to limit the scope of this invention in any way, of particular interest in relationship to this invention is the use of aqueous topical ophthalmic compositions of 0.45% (w/v) ketorolac tromethamine for the treatment of ocular pain, especially for the treatment of ocular pain in postoperative photorefractive keratectomy (pork) surgery patients which improves healing. It is surprising that the lower concentration of ketorolac as compared to the Acular® product, discussed herein, would reduce the incidence of adverse events and enhance comfort while maintaining clinical efficacy. Two drops (0.1 mL) of 0.5% ketorolac tromethamine ophthalmic solution instilled into the eyes of patients 12 hours and 1 hour prior to cataract extraction achieved measurable levels in 8 of 9 patients' eyes (mean ketorolac concentration 95 ng/mL aqueous humor, range 40 to 170 ng/mL). Ocular administration of ketorolac tromethamine reduces prostaglandin E_2 (PGE_2) levels in aqueous humor. The mean concentration of PGE_2 was 80 pg/mL in the aqueous humor of eyes receiving vehicle and 28 pg/mL in the eyes receiving 0.5% ketorolac tromethamine ophthalmic solution.

[0020] Ocular administration of 0.45% w/v ketorolac tromethamine ophthalmic solution increases relative bioavailability of ketorolac in the aqueous humor of rabbits to greater than 200% and in the iris-ciliary body to nearly 300%, compared with 0.5% ketorolac tromethamine ophthalmic solution. This enhanced ketorolac bioavailability allows for a reduction in dosing frequency from QID with 0.5% ketorolac tromethamine ophthalmic solution to BID with 0.45% keterolac solution. Preclinical data indicate systemic ketorolac exposure levels achieved following ocular administration of 0.45% keterolac solution are comparable to levels achieved with 0.5% ketorolac tromethamine ophthalmic solution.

Detailed Description of the Invention

[0021] During the reformulation of Allergan's marketed Acular LS® product (0.40 % w/v keterolac), it was surprisingly found that a test formulation containing 0.45% ketorolac tromethamine and sodium carboxymethylcellulose (NaCMC) exhibited significantly better ocular absorption in rabbits than did the currently marketed product, i.e. Acular LS®.

[0022] Since the viscosities of the two test solutions were virtually identical, the mechanism for achieving increased ocular penetration compared to the control formulation cannot be accounted for only by the viscosity of the test solutions. In fact, a comparison of two identical carboxymethyl cellulose-containing solutions which differ only in having viscosity of 11 and 22 cps shows similar absorption of ketorolac into the aqueous humor. While not wishing to be bound by theory, it is believed that there is a functional relationship between the sodium carboxymethyl cellulose and either,the ketorolac or some component of the ocular surface that facilitates absorption of ketorolac.

[0023] All of the aqueous topical ophthalmic solutions of this invention are contemplated for use in treating or preventing ocular pain. Preferably, all of the solutions of this invention are contemplated for use when said ocular pain is a result of photorefractive keratectomy surgery (PRK).

[0024] One important aspect of this invention is that the solutions of the present invention have a concentration of ketorolac tromethamine, which is optimized to reduce side effects, while maintaining clinical efficacy in treating ocular pain. As such, the concentration of ketorolac tromethamine in compositions related to this invention is 0.45% ketorolac tromethamine, by weight/volume.

[0025] Carboxymethyl cellulose (CMC) is a carboxymethyl derivative of cellulose formed by the reaction of cellulose with alkali and chloroacetic acid. As a result of said reaction, carboxymethyl groups are bound to some of the hydroxyl groups of the glucopyranose units that make up the backbone of cellulose. The degree of substitution of carboxymethyl

varies from about 0.6 to 0.95 per glucopyranose unit. CMC is used in aqueous solutions usually as the sodium salt to increase viscosity.

[0026] Carboxymethyl cellulose is available in various molecular weights. Low molecular weight carboxymethyl cellulose has a Mw of about 90,000 and a 2% solution thereof will have a viscosity of about 1.1 cP at 25° C. Medium weight carboxymethyl cellulose has a Mw of about 250,000. High molecular weight carboxymethylcellulose has a Mw of about 700,000 and a 2% solution will have a viscosity of about 12 cP at 25° C.

[0027] For the purpose of the present invention, it is desirable to use a mixture of medium and high molecular weight sodium carboxymethyl cellulose. For example, from 25/75 to 75/25 carboxymethyl cellulose, preferably from 30/70 to 70/30 and most preferably about 35/65 medium/high molecular weight sodium carboxymethyl cellulose.

[0028] The fact that the concentration of ketorolac tromethamine in compositions related to this invention achieves greater or equal absorption of ketorolac into the aqueous humor of the eye and includes carboxymethyl cellulose, allows the solutions of the present invention to be prepared with no preservative, surfactant and chelating agent. This is a significant advantage over prior art keterolac formulations as preservatives, surfactants and chelating agents can cause irritation to the eye resulting in less patient compliance and less effectiveness of prior art keterolac formulations.

[0029] The term preservative has the meaning commonly understood in the ophthalmic art. Preservatives are used to prevent bacterial contamination in multiple-use ophthalmic preparations, and, while not intending to be limiting, examples include benzalkonium chloride, stabilized oxychloro complexes (otherwise known as Purite®), phenylmercuric acetate, chlorobutanol, benzyl alcohol, parabens, and thimerosal. Preferably, the keterolac solution of the present invention is preservative free.

[0030] The term surfactant used in this invention has the meaning commonly understood in the art. Surfactants are used to help solubilize the therapeutically active agent or other insoluble components of the composition. Anionic, cationic, amphoteric, zwitterionic, and nonionic surfactants may all be used in this invention. If a surfactant is included in the solutions of this invention, preferably, a nonionic surfactant is used. While not intending to limit the scope of the invention, some examples of useful nonionic surfactants are polysorbates, poloxamers, alcohol ethoxylates, ethylene glycol-propylene glycol block copolymers, fatty acid amides, and alkylphenol ethoxylates, and phospholipids. Most preferably, the surfactant is an octylphenol ethoxylate with an average of 40 ethoxylate groups. This type of surfactant, also known as octoxynol-40 or Igepal CA-897®, can be purchased under the Igepal CA-897® tradename from Rhône-Poulenc. Preferably, the keterolac solution of the present invention is surfactant free.

[0031] The term chelating agent refers to a compound that is capable of complexing a metal, as understood by those of ordinary skill in the chemical art. Chelating agents are used in ophthalmic compositions to enhance preservative effectiveness. While not intending to be limiting, some useful chelating agents for the purposes of this invention are edetate salts like edetate disodium, edetate calcium disodium, edetate sodium, edetate trisodium, and edetate dipotassium. Preferably, the keterolac solution of the present invention is chelator free.

[0032] In addition to surfactants, preservatives, and chelating agents, tonicity agents and other excipients are often used in ophthalmic compositions. Tonicity agents are often used in ophthalmic compositions to adjust the concentration of dissolved material to the desired isotonic range. Tonicity agents are known to those skilled in the ophthalmic art, and, while not intending to be limiting, some examples include glycerin, mannitol, sorbitol, sodium chloride, and other electrolytes. Preferably, the tonicity agent is sodium chloride.

[0033] One preferred embodiment of this invention relates to an aqueous topical ophthalmic composition comprising 0.4% ketorolac tromethamine, from 0.2 to 2.0 %, by weight, sodium carboxymethyl cellulose.

[0034] The most preferred embodiment of this invention relates to an aqueous topical ophthalmic composition consisting of 0.45% (w/v) of ketorolac tromethamine, 0.5 % w/v of carboxymethylcellulose sodium, e.g. a mixture of medium and high viscosity sodium carboxymethyl cellulose, sodium chloride, sodium citrate dehydrate, sodium hydroxide, hydrochloric acid and purified water.

Example 1 (Reference)

[0035] Unless otherwise specified, all steps in this procedure were carried out at room temperature. The following procedure was followed in accordance with the amounts listed in Table 1 below. Purified water was charged into the main batch vessel. Mixing was initiated to produce a vortex sufficient to disperse and/or dissolve all product ingredients without excessive aeration or foam formation. The following components were added directly into the vortex in order, allowing each to dissolve before adding the next: sodium chloride, calcium chloride, dihydrate magnesium chloride, hexahydrate, boric acid, sodium borate, sodium carboxymethyl cellulose as a an percent aqueous solution comprising including a mixture of 65% medium molecular weight and 35% high molecular weight carboxymethyl cellulose. The solution was mixed for no longer than 15 minutes. A specified amount of 1N sodium hydroxide, was then added. The pH was checked and, if needed, was adjusted to 7.3 with 1N sodium hydroxide or 1N hydrochloric acid. Ketorolac tromethamine was then added based on "as is" assay and mixed until completely dissolved based on visual inspection. When dissolved, the solution pH was again checked and if needed adjusted to pH 7.3 - 7.5 (final target pH is 7.4) with

1N sodium hydroxide or 1N hydrochloric acid. Purified water was then added to bring the bulk solution to final volume and allowed to mix for at least 15 minutes to ensure uniformity. The solution was then sterile filtered for use.

Table 1. 0.4% Ketorolac Tromethamine Ophthalmic Solution of the Invention

Keterolac Tromethamine	0.4%
CMC, Med Visc.	.65%
CMC Low Visc.	.35%
Potassium chloride	0.14%
Calcium chloride, dihydrate	0.060%
Magnesium chloride, hexahydrate	0.060%
Boric acid	.060%
Sodium borate	.1225%

Example 2 (Reference)

[0036] Unless otherwise specified, all steps in this procedure were carried out at room temperature. The following procedure was followed in accordance with the amounts listed in Table 2 below. Purified water at 90% of batch size was charged into the main batch vessel. Mixing was initiated to produce a vortex sufficient to disperse and/or dissolve all product ingredients without excessive aeration or foam formation. The following components were added directly into the vortex in order, allowing each to dissolve before adding the next: sodium chloride, edetate disodium, octoxynol-40 (as a 70% stock solution) and benzalkonium chloride (as a 10 % stock solution). The amount of benzalkonium chloride added took into account the assay of the stock solution used. The solution was mixed for no longer than 15 minutes. A specified amount of 1N sodium hydroxide, 1.85 mL per liter of final bulk product, was then added. The pH was checked and if needed was adjusted to 10.7 - 11.0 with 1N sodium hydroxide or 1N hydrochloric acid. Ketorolac tromethamine was then added based on "as is" assay and mixed until completely dissolved based on visual inspection. When dissolved, the solution pH was again checked and if needed adjusted to pH 7.3 - 7.5 (final target pH is 7.4) with 1N sodium hydroxide or 1N hydrochloric acid. Purified water was then added to bring the bulk solution to final volume and allowed to mix for at least 15 minutes to ensure uniformity. The solution was then sterile filtered for use.

Table 2. 0.4% Ketorolac Tromethamine Ophthalmic Solution (Comparative)

Ketorolac Tromethamine	0.4%
Edetate Disodium	0.015%
NaCl	0.79%
Benzalkonium Chloride	0.006%
Octoxynol-40	0.003%
Ph	7.4

Example 3 (Reference)

[0037] This example was prepared according to the procedure of Example 1, except that hydroxypropyl cellulose was used in place of the sodium carboxymethyl cellulose in an amount sufficient to provide a viscosity equivalent to the viscosity of the composition of Example 1.

Example 4

[0038] The following composition was manufactured on a volume basis at ambient temperates from two principal parts. Each part is manufactured separately and then combined under controlled sequences to form a sterile bulk product: the first part (Part 1) involves the dissolution of carboxymethylcellulose sodium in water followed by bulk heat sterilization, and the second part (Part 2) involves dissolution of keterolac tromethamine and salts in water sterile filtration throng a 0.2 micron membrane into a sterile pressure vessel. The sterile bulk solution is then clarity filtered through a 20 micron polypropylene membrane filter into the filling machine reservoir.

[0039] The sterile post-clarity filtered solution is then filled by a UD filling machine via blow-fill-seal process into UD vials using virgin LDPE resin without colorant. The filling is done in an ISO Class 5 environment. The nominal fill is 0.4 mL into 0.9 mL capacity vials.

Table 3: 0.45 % w/v Ketorolac Tromethamine Ophthalmic Solution

Ingredient	Function	Concentration (% w/v)
Keterolac tromethamine	Active	0.45%
Carboxymethycellulose Sodium (Med. Viscosity)	Thickening Agent	0.325%
Carboxymethycellulose Sodium (High Viscosity)	Thickening Agent	0.175%
NaCl	Tonicity Agent	0.7%
Sodium Citrate Dihydrate	Buffer	0.2%
Sodium Hydroxide (IN)	pH adjustment	Adjust to pH 6.8
Hydrochloric Acid (1N)	pH adjustment	Adjust to pH 6.8
Purified Water	Vehicle	Q.S.

Example 5

[0040] Comparison of Aqueous Humor Ketorolac Pharmacokinetics Following a Single Ocular Instillation of 0.45% Ketorolac Tromethamine Formulations with Varying pH to Acular LS® in New Zealand White Rabbits.

Study Objectives:

[0041]

1) To compare aqueous humor ketorolac pharmacokinetics following a single ocular instillation of 0.45% ketorolac tromethamine formulations with varying pH and Acular LS® to New Zealand White rabbits;

2) This Example was designed to determine whether decreasing the pH of the composition would increase the absorption of ketorolac into the eye; and,

3) In addition, one arm of this trial was designed to test the effect of decreasing viscosity of the composition from 22 cps to 11 cps.

[0042] The specifics of this study are as follows:

Rabbit Aqueous Humor Ketorolac Concentrations following Administration of Three 0.45% Ketorolac Tromethamine Formulations and Acular LS

Table 4

Treatment Groups	0.45% Ketorolac Tromethamine 22 cps pH=7.4
	0.45% Ketorolac Tromethamine 22 cps pH=7.2
	0.45% Ketorolac Tromethamine 22 cps pH=7.0
	0.45% Ketorolac Tromethamine 11 cps pH=7.0
	0.45% Ketorolac Tromethamine 22 cps pH=6.8
	Acular LS pH=7.4
Dosing Route:	Topical ocular
Animal Gender:	NZW Rabbits/Female
Dosing Regimen	Single dose, bilateral
Timepoints:	1, 2 and 4 hrs post-dose
# Rabbits:	3 rabbits/timepoint +1 rabbit blank
	Total = 39 rabbits
Tissues/Matrices:	Aqueous Humor
Bioanalysis:	LC-MS/MS

(continued)

Data analysis: AUC_{0-t}, C_{max}

[0043] The results of the study are reported in Table 5, below.

Table 5

PK Parameters			
Formulation	AUC_{0-4}± SE (ng·h/ml)	C_{max}±SD (ng/ml)	Relative %F*
0.45% CMC 22 cps pH 7.4 w.o "outlier"	627±51	265±71	135
045% CMC 22 cps pH 7.4	713±96	322±153	153
045% CMC 22 cps pH 7.2	620±50	240±84	133
045% CMC 22 cps pH 7.0	658±73	268±125	142
045% CMC 22 cps pH 6.8	939±163	389±258	202
045% CMC 11 cps pH 7.0	649±74	347±218	139
Acular LS®	465±65	211±106	100

Summary of the results:

[0044] The sodium carboxymethyl cellulose-containing formulations perform better than Acular LS® with a relative bioavailability ranging from 133% (0.45% Keto 22 cps pH 7.2) to 202% (0.45% Keto 22 cps pH 6.8). However, there is not a clear pH effect-because the 0.45% Keto 22 cps pH 7.4 has a relative bioavailability of 153%, although one anomalous result maybe driving this observation. Nevertheless, the solution having a pH of 6.8 shows the best bioavailability.

Example 6 (Reference)

[0045] A multicenter, randomized, double-masked, parallel-group study is carried out using the 0.4% ketorolac tromethamine formulations of Examples 2 and 3. The study subjects consisted of 157 patients (78-79/group) undergoing unilateral PRK surgery. The key inclusion criteria for the study is that each subject a) is a candidate for unilateral photorefractive keratectomy surgery (PRK) within 7 days after the initial visit, b) have best-corrected ETDRS visual acuity of 20/100 or better, and c) is capable of wearing a soft bandage contact lens. Key exclusion criteria are a history of refractive ocular surgery and sensitivity to study medication or its vehicle, Tylenol #3®, or Ocuflox®. The patient demographics are shown in Table 6. A total of 157 patients are enrolled with an age range of 20-66 years. There are no significant demographic differences between treatment groups.

Table 6: Patient Demographics

	n	%
Gender		
Female	91	58
Male	66	42
Age, mean ± SD	39 ± 10	
Race		
Caucasian	148	94
Black	5	3
Hispanic	2	1
Asian	1	1
Other	1	1

[0046] Each subject receives the Ocuflox® 5 min prior to study medication. The study subjects then receive ketorolac tromethamine 0.4% ophthalmic solution of Example 2 or Example 3, 1 drop QID for up to 4 days. Then all subjects are then instructed to take Tylenol #3® as needed for intolerable pain (escape medication). Patients use electronic diaries with date and time stamp to record the ocular pain they experience as one of the following: no pain, mild, moderate, severe, intolerable.

[0047] The pain intensity is less for the subjects who receive the solution of Example 2 during the first 12 hours post-PRK compared to those who receive the solution of Example 3. In particular, during the first 12 hours post-PRK, the group that receive the solution of Example 2 had fewer patients with severe or intolerable pain compared with the receive the solution of Example 3. In particular, the median pain intensity reported by the group which receive the solution of Example 2 was 1 grade less than with the group which receive the solution of Example 3 (moderate vs. severe on a 5-point scale of 0 = no pain to 4 = intolerable pain). Additionally, pain intensity is also less for the group which receive compared with the group which receive the solution of Example 3.

[0048] This clinical study shows that the solution of invention provides a greater degree of absorption of ketorolac as compared to the solution without sodium carboxymethylcellulose despite the fact that the solutions have the same concentration of ketorolac and are at the same viscosity.

[0049] In summary, the 0.4% ketorolac formulation is clinically effective in treating post PRK ocular pain. In patients treated with 0.4 ketorolac tromethamine-the patients treated with the solution comprising sodium carboxymethyl cellulose experienced significantly greater and faster pain relief, and used less escape medication compared to the patients treated with the solution comprising hydroxypropylcellulose.

Example 7

[0050] Rabbit Ocular Pharmacokinetic Evaluation of Keterolac Tromethamine 0.45%

NZW Rabbits/Female

[0051]

Dosing Regimen:	Single ocular dose, bilateral
Timepoints:	0.5, 1, 2, 4, 8, 10 and 24 hrs post-dose
Tissues/Matrices:	Aqueous Humor and Iris-ciliary body
Bioanalysis:	LC-MS/MS
Data Analysis:	Pharmacokinetic analyses and simulation

Table 7: Ocular Pharmacokinetics, Aqueous Humor: Increased and Prolonged Keterolac Exposure

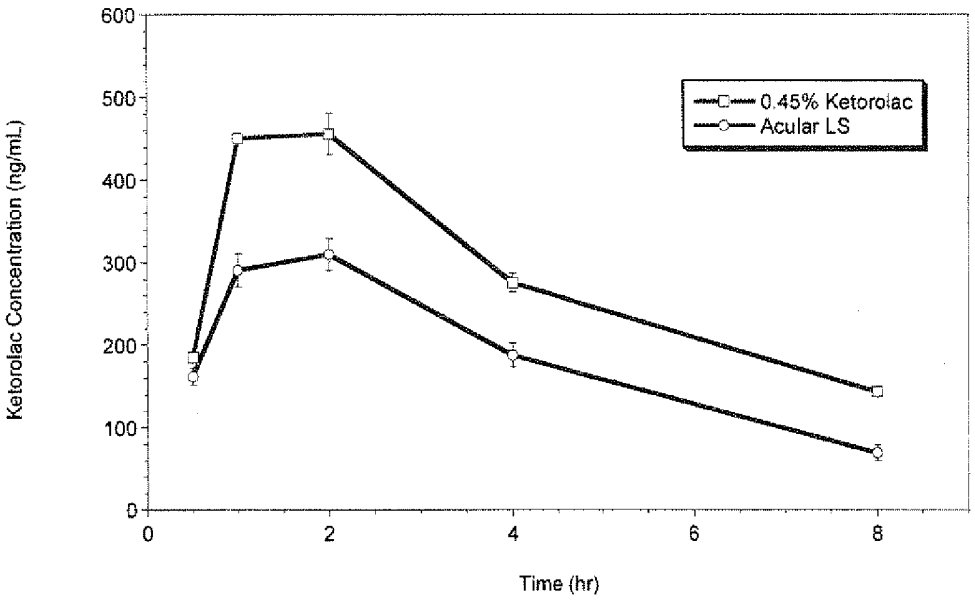


Table 8: Ocular Pharmacokinetics, Aqueous Humor Relative bioavailability based on AUC0-t comparison to Acular LS®

	0.45% Ketorolac	**Acular LS®**
Cmax (ng/mL)	456	310
AUC0-t (ng·h/mL)	2230	1467
% Relative Bioavailability	178	100

Table 9: Ocular pharmacokinetics in Iris-ciliary body

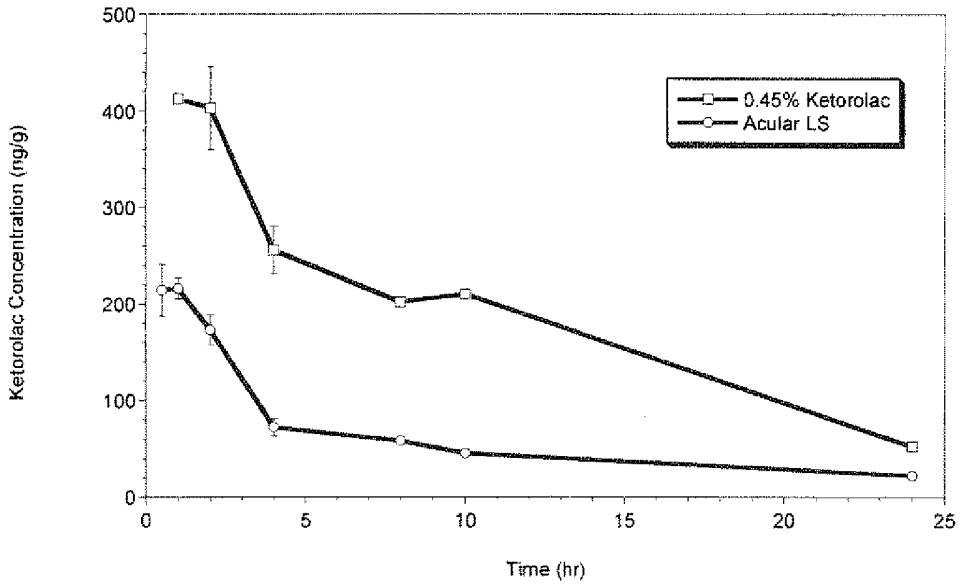
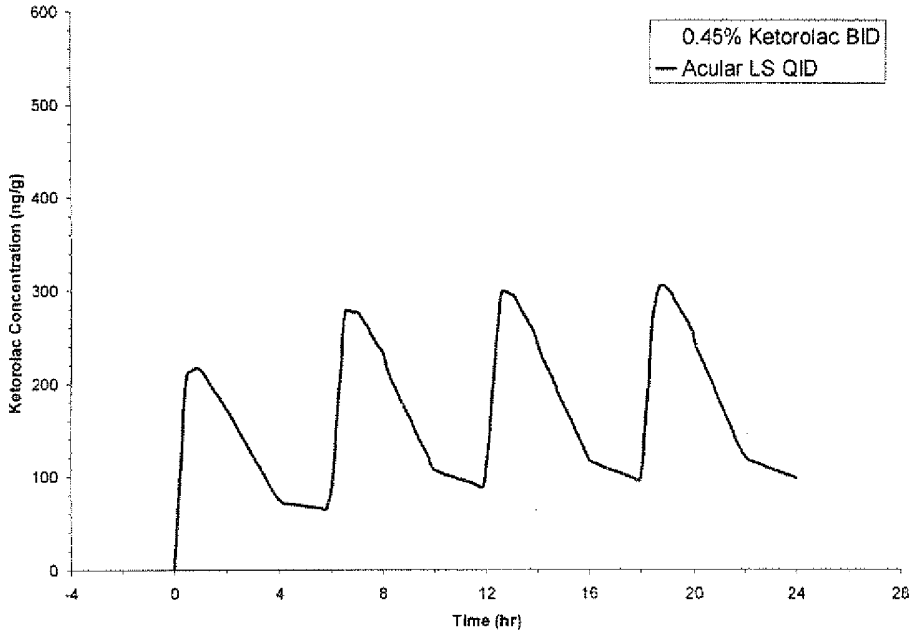


Table 10: Ocular Pharmacokinetics: Iris Ciliary Body, Relative bioavailability based on dose normalized AUC comparison to Acular LS®, Increased and Prolonged Keterolac Exposure

	0.45% Ketorolac	**Acular LS®**
Cmax (ng/g)	429	216
AUC0-∞ (ng·h/g)	5090	1860
%Relative Bioavailability	285	100

Table 11: Multiple Dose Simulation: Iris-Ciliary Body_0.45% Ketorolac BID vs. Acular LS® QID



	0.45% Ketorolac BID	Acular LS® QID
AUC0-τ (ng·hr/g)	2910	725

Conclusions:

[0052]

1) Increase in relative bioavailability of keterolac as compared to Acular LS®;
2) Increased ketorolac concentrations are maintained longer post-dose; and
3) Together these data support a reduction in dosing frequency from 4X/day to 2X/day.

Table 12: Safety and Tolerability Results

Variable	**Keterolac 0.45%**	**ACULAR LS 0.40%**
Ocular AEs-Irritation	**10.0% (2/20)**	**15.4% (6/39)**
Symptoms-Burning/stinging (≥ 1 grade increase)	**10.0% (2/20)**	**12.8% (5/39)**
Bulbar hyperemia (≥ trace)	**10.0% (2/20)**	**23.1% (9/39)**
Ocular comfort (≥ comfortable)	**90-100%**	**84-100%**

Conclusion:

[0053] Acular 0.45% is safe and well-toleraled when given 5 times over a half-day and compares very favorably to ACULAR LS.

[0054] The present invention is not to be limited in scope by the exemplified embodiments, which are only intended as illustrations of specific aspects of the invention. Various modifications of the invention, in addition to those disclosed herein, will be apparent to those skilled in the art by a careful reading of the specification, including the claims, as originally

filed. It is intended that all such modifications will fall within the scope of the appended claims.

[0055] The present invention can be summarized by reference to the following embodiments (embs.):

emb. 1. A topical aqueous ophthalmic solution comprising keterolac tromethamine, carboxymethyl cellulose and no preservative

emb. 2. The topical aqueous ophthalmic solution of emb. 1 wherein the keterolac tromethamine is present in a concentration of approximately 0.40 - 0.45 percent by weight/volume.

emb. 3. The topical aqueous ophthalmic solution of emb. 1 wherein the carboxymethyl cellulose is a combination of medium and high viscosity carboxymethyl cellulose.

emb. 4. The topical aqueous ophthalmic solution of emb. 1 wherein the keterolac tromethamine is present in a concentration of 0.45 percent by weight/volume.

emb. 5. The topical aqueous ophthalmic solution of emb. 4 having a pH between 6.8 and 7.4.

emb. 6. The topical aqueous ophthalmic solution of emb. 5 wherein the concentration of carboxymethylcellulose is from 0.2 to 2 percent by weight.

emb. 7. The topical aqueous ophthalmic solution of emb. 5 having a pH of approximately 6.8.

emb. 8. The topical aqueous solution of emb. 4 wherein the solution is surfactant and chelator free..

emb. 9. The topical aqueous solution of emb. 8 for use in treatment of ocular pain associated with postoperative photorefractive keratectomy.

emb. 10. The topical aqueous solution of emb. 4 further comprising a mixture of medium and high molecular weight sodium carboxymethyl cellulose.

emb. 11. The topical aqueous solution of emb. 4 further comprising a mixture of medium and high viscosity sodium carboxymethyl cellulose, sodium chloride, sodium citrate dehydrate, sodium hydroxide, hydrochloric acid and purified water.

emb. 12. The topical aqueous solution of emb. 10 wherein the combination of carboxymethyl cellulose and keterolac increases the absorption in the eye of a patient more than a solution of keterolac alone.

emb. 13. The topical aqueous solution of emb. 1 wherein the keterolac tromethamine is present as a racemic mixture of R-(+) and S-(-)- ketorolac tromethamine

emb. 14. The topical aqueous solution of emb. 1 wherein the keterolac tromethamine is present in a mixture of crystal forms.

emb. 15. The topical aqueous solution of emb. 5 wherein the viscosity is from 10 to 30 cps.

emb. 16. The topical aqueous solution of emb. 6 wherein the carboxymethylcellulose is present in the amount of 0.5% percent by weight.

emb. 17. The topical aqueous solution of emb. 4 wherein the solution may be administered before or after eye surgery to prevent ocular pain.

emb. 18. The topical aqueous solution of emb. 4 wherein the solution increases healing time of the eye after surgery in comparison to keterolac solutions containing a preservative.

emb. 19. The topical aqueous solution of emb. 4 wherein the topical aqueous solution is instilled twice daily to achieve proper efficacy.

emb. 20. The topical aqueous solution of emb. 4 wherein the aqueous solution is surfactant free.

Claims

1. A topical aqueous ophthalmic solution comprising ketorolac tromethamine and carboxymethylcellulose, wherein the concentration of ketorolac tromethamine is 0.45% weight/volume.

2. The solution of claim 1 wherein the carboxymethylcellulose is a combination of medium and high viscosity carboxymethylcellulose.

3. The solution of claim 1 having a pH between 6.8 and 7.4.

4. The solution of claim 3 wherein the concentration of carboxymethylcellulose is from 0.2 to 2 percent by weight.

5. The solution of claim 3 having a pH of 6.8.

6. The solution of claim 1 wherein the solution is surfactant-free and optionally chelator-free.

7. The solution of claim 6 for use in treatment of ocular pain associated with postoperative photorefractive keratectomy.

8. The solution of claim 1 further comprising a mixture of medium and high molecular weight sodium carboxymethylcellulose.

9. The solution of claim 1 further comprising a mixture of medium and high viscosity sodium carboxymethylcellulose, sodium chloride, sodium citrate dihydrate, sodium hydroxide, hydrochloric acid and purified water.

10. The solution of claim 8 wherein the combination of carboxymethylcellulose and ketorolac increases the absorption in the eye of a patient more than a solution of ketorolac alone.

11. The solution of claim 1 wherein the ketorolac tromethamine is present as a racemic mixture of R-(+) and S-(-)-ketorolac tromethamine, and/or wherein the ketorolac tromethamine is present in a mixture of crystal forms.

12. A solution according to claim 1, consisting of 0.45% (w/v) ketorolac tromethamine, 0.5% (w/v) carboxymethylcellulose sodium, sodium chloride, sodium citrate dehydrate, sodium hydroxide, hydrochloric acid and purified water.

13. A solution according to claim 12, wherein the carboxymethylcellulose sodium is a mixture of medium and high viscosity carboxymethylcellulose sodium.

Patentansprüche

1. Topische, wässrige, ophthalmische Lösung, umfassend Ketorolactromethamin und Carboxymethylcellulose, wobei die Konzentration an Ketorolactromethamin 0,45 % Gewicht/Volumen beträgt.

2. Lösung gemäss Anspruch 1, wobei die Carboxymethylcellulose eine Kombination von mittel- und hochviskoser Carboxymethylcellulose ist.

3. Lösung gemäss Anspruch 1, die einen pH-Wert zwischen 6,8 und 7,4 aufweist.

4. Lösung gemäss Anspruch 3, wobei die Konzentration an Carboxymethylcellulose 0,2 bis 2 Gew.% beträgt.

5. Lösung gemäss Anspruch 3, die einen pH-Wert von 6,8 aufweist.

6. Lösung gemäss Anspruch 1, wobei die Lösung tensidfrei und gegebenenfalls chelatbildnerfrei ist.

7. Lösung gemäss Anspruch 6 zur Verwendung bei der Behandlung von Augenschmerzen, die mit postoperativer photorefraktiver Keratektomie assoziiert sind.

8. Lösung gemäss Anspruch 1, die ferner eine Mischung von mittel- und hochmolekulargewichtiger Natriumcarboxymethylcellulose umfasst.

9. Lösung gemäss Anspruch 1, die ferner eine Mischung von mittel- und hochviskoser Natriumcarboxymethylcellulose, Natriumchlorid, Natriumcitratdihydrat, Natriumhydroxid, Salzsäure und gereinigtem Wasser umfasst.

10. Lösung gemäss Anspruch 8, wobei die Kombination von Carboxymethylcellulose und Ketorolac die Absorption im Auge eines Patienten stärker erhöht als eine Lösung von Ketorolac allein.

11. Lösung gemäss Anspruch 1, wobei das Ketorolactromethamin als racemische Mischung von R-(+)- und S-(-)-Ketorolactromethamin vorhanden ist und/oder wobei das Ketorolactromethamin in einer Mischung von Kristallformen vorhanden ist.

12. Lösung gemäss Anspruch 1, die aus 0,45 % (G/V) Ketorolactromethamin, 0,5 % (G/V) Natriumcarboxymethylcellulose, Natriumchlorid, Natriumcitratdehydrat, Natriumhydroxid, Salzsäure und gereinigtem Wasser besteht.

13. Lösung gemäss Anspruch 12, wobei die Natriumcarboxymethylcellulose eine Mischung von mittel- und hochviskoser Natriumcarboxymethylcellulose ist.

Revendications

1. Solution ophtalmique aqueuse topique comprenant de la kétorolac trométhamine et de la carboxyméthylcellulose, dans laquelle la concentration en kétorolac trométhamine est de 0,45 % en poids/volume.

2. Solution selon la revendication 1, dans laquelle la carboxyméthylcellulose est une combinaison de carboxyméthylcellulose de hautes et moyennes viscosités.

3. Solution selon la revendication 1, ayant un pH entre 6,8 et 7,4.

4. Solution selon la revendication 3, dans laquelle la concentration en carboxyméthylcellulose est de 0,2 à 2 pour cent en poids.

5. Solution selon la revendication 3, ayant un pH de 6,8.

6. Solution selon la revendication 1, dans laquelle la solution est exempte de tensioactif et éventuellement exempte de chélateur.

7. Solution selon la revendication 6 pour utilisation dans le traitement d'une douleur oculaire associée à une kératectomie photoréfractive post-opératoire.

8. Solution selon la revendication 1, comprenant en outre un mélange de carboxyméthylcellulose sodique de poids moléculaires moyens et élevés.

9. Solution selon la revendication 1, comprenant en outre un mélange de carboxyméthylcellulose sodique de hautes et moyennes viscosités, de chlorure de sodium, de citrate de sodium dihydraté, d'hydroxyde de sodium, d'acide chlorhydrique et d'eau purifiée.

10. Solution selon la revendication 8, dans laquelle la combinaison de carboxyméthylcellulose et de kétorolac augmente l'absorption dans l'oeil d'un patient plus qu'une solution de kétorolac seule.

11. Solution selon la revendication 1, dans laquelle la kétorolac trométhamine est présente sous la forme d'un mélange racémique de R-(+)- et S-(-)-kétorolac trométhamine et/ou dans laquelle la kétorolac trométhamine est présente dans un mélange de formes cristallines.

12. Solution selon la revendication 1, constituée de 0,45 % (en poids/volume) de kétorolac trométhamine, de 0,5 % (en poids/volume) de carboxyméthylcellulose sodique, de chlorure de sodium, de citrate de sodium dihydraté, d'hydroxyde de sodium, d'acide chlorhydrique et d'eau purifiée.

13. Solution selon la revendication 12, dans laquelle la carboxyméthylcellulose sodique est un mélange de carboxyméthylcellulose sodique de hautes et moyennes viscosités.

REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

- US 20080039398 A **[0003]**

Non-patent literature cited in the description

- **GUIDERA et al.** *Ophthalmology,* 2001, vol. 108 (5), 936-944 **[0002]**
- **SOLOMON et al.** *J Cataract Refract Surg,* 2001, vol. 27 (8), 1232-1237 **[0002]**
- **TEAL et al.** *J Cataract Refract Surg,* 1995, vol. 21 (5), 516-518 **[0002]**
- Antiinflammatory Drugs. **JAANUS et al.** Clinical Ocular Pharmacology. Heineman, 2001, 265-298 **[0002]**

KETOROLAC TROMETHAMINE KÉSZÍTMÉNYEK A SZEM FÁJDALMÁNAK KEZELÉSÉRE VAGY MEGELŐZÉSÉRE

SZABADALMI IGÉNYPONTOK

1. Helyi szemészeti vizes oldat, amely ketorolac tromethamine-t és karboximetil-cellulózt tartalmaz, ahol a ketorolac tromethamine koncentrációja 0,45% (súly/térfogat) vegyes százalékban kifejezve.

2. Az 1. igénypont szerinti oldat, ahol a karboximetil-cellulóz közepes és nagy viszkozitású karboximetil-cellulóz keveréke.

3. Az 1. igénypont szerinti oldat, amelynek pH-értéke 6,8 és 7,4 között van.

4. A 3. igénypont szerinti oldat, ahol a karboximetil-cellulóz koncentrációja 0,2% és 2% között van súlyszázalékban kifejezve.

5. A 3. igénypont szerinti oldat, amelynek pH-értéke 6,8.

6. Az 1. igénypont szerinti oldat, ahol az oldat felületaktív anyag mentes és opcionálisan ketlátképző mentes.

7. A 6. igénypont szerinti oldat a fotorefraktív keratektómia műtét utáni szemfájdalom kezelésében való felhasználásra.

8. Az 1. igénypont szerinti oldat, amely tartalmaz még egy közepes és nagy molekulasúlyú nátrium-karboximetil-cellulózból álló keveréket.

9. Az 1. igénypont szerinti oldat, amely tartalmaz még egy közepes és nagy viszkozitású nátrium-karboximetil-cellulózból álló keveréket, nátrium-kloridot, nátrium-citrát-dihidrátot, nátrium-hidroxidot, sósavat és tisztított vizet.

10. A 8. igénypont szerinti oldat, ahol a karboximetil-cellulóz és a ketorolac keveréke jobban megnöveli a beteg szemében az abszorpciót, mint a ketorolac oldata egyedül.

11. Az 1. igénypont szerinti oldat, ahol a ketorolac tromethamine az R-(+) és S-(-)-ketorolac tromethamine racém keverékeként van jelen, és/vagy ahol a ketorolac tromethamine kristályformák keverékében van jelen.

12. Az 1. igénypont szerinti oldat, amely a következőket tartalmazza: 0,45% (w/v) ketorolac tromethamine, 0,5% (w/v) karboximetil-cellulóz-nátrium, nátrium-klorid, nátrium-citrát-dihidrát, nátrium-hidroxid, sósav és tisztított víz.

13. A 12. igénypont szerinti oldat, ahol a karboximetil-cellulóz -nátrium közepes és nagy viszkozitású karboximetil-cellulóz-nátrium keveréke.