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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
28 March 2002 (28.03.2002)

PCT

(10) International Publication Number
WO 02/24116 A1

(51) International Patent Classification[7]: A61F 2/14, A61K 47/30

(21) International Application Number: PCT/US01/29485

(22) International Filing Date:
20 September 2001 (20.09.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/234,319 20 September 2000 (20.09.2000) US

(71) Applicant: **SHAHINIAN, Lee, Jr.** [US/US]; 1506 Country Club Drive, Los Altos, CA 94024 (US).

(74) Agent: **VERNY, Hana**; Peters, Verny, Jones & Biksa, LLP, Suite 6, 385 Sherman Avenue, Palo Alto, CA 94306 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

**Published:**
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

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

WO 02/24116 A1

(54) Title: SELF-PRESERVED NASAL, INHALABLE, AND TOPICAL OPHTHALMIC PREPARATIONS AND MEDICATIONS

(57) Abstract: Self-preserved nasal, inhalable and topical ophthalmic preparations and medications which destroy, inhibit or therapeutically significantly limit microbial growth within said preparations or medications. The nasal, inhalable, and topical ophthalmic preparations and medications are mildly buffered and maintain a stable pH at pH 3.5 or lower.

# SELF-PRESERVED NASAL, INHALABLE, AND TOPICAL OPHTHALMIC PREPARATIONS AND MEDICATIONS

This application is based on and claims priority of the Provisional application Serial No. 60/234,319, filed on September 20, 2000.

## Field of the Invention

The current invention concerns buffered, low pH, self-preserved nasal, inhalable and topical ophthalmic preparations and medications which destroy, inhibit or sufficiently limit microbial growth within said preparations or medications. In particular, the current invention involves nasal, inhalable and topical ophthalmic preparations and medications having low pH of about 3.5 or lower, to inhibit microbial growth, wherein immediately upon application to the eye surface or a mucosal surface, the pH rises to physiologic levels.

## BACKGROUND OF THE INVENTION

To prevent infection with use, currently available multidose preparations and medications are sterilized during manufacture and have a variety of preservatives added to destroy or inhibit the growth of microorganisms inadvertently introduced into the product after opening.

It is well recognized that the preservatives used in topical ophthalmic medications and preparations can be toxic to the eye surface and respiratory mucosa. The most widely used ophthalmic preservative, benzalkonium chloride (BAK), can cause damage to the conjunctival and corneal epithelium (Cornea, 1:221-225 (1992); Arch Opthalmol, 110:528-532 (1992) and CLAO J, 18:260-266 (1992)). BAK is now thought to be also a significant cause of rhinitis medicamentosa, as described in Allergy, 52:627-632 (1997), and has been also shown to damage respiratory mucosa (Am Rev Respir Dis, 141:1405-1408 (1990)

and Acta Otolaryngol, 116:868-875 (1996)). Reducing the concentration of BAK reduces its toxic effect, but at too low a concentration, BAK is no longer effective as a preservative. Although alternatives to BAK are available, all preservatives have some potential for toxicity.

Pressurized aerosol containers used for inhalation or as a spray are an exception, needing no preservative since no air or contamination enters the container as doses are extracted. However, such packaging is relatively bulky and expensive, often contains CFC propellants which can harm the atmosphere, and precludes drop administration.

In recent years, preparations and medications have been packaged in unit-dose containers, thus avoiding the need for potentially toxic preservatives. In this arrangement, a single dose of medicine is provided by a given container. With sterile packaging, microbial contamination is theoretically not a concern, since the consumer/patient is instructed to discard the container after each single use. However, there are several problems with unit dose containers. First, the packaging is bulky and inconvenient. Second, cost per dose is significantly higher than with multidose containers. Third, patients often retain the opened container for many hours or even more than one day, contradicting the package instructions. This pattern of use increases the probability of microbial contamination of the medication or preparation.

Thus, it would be desirable to have available preservative-free preparations and medications suitable for topical, mucosal and inhalation use that could be stored in multi-dose containers without risk of microbial contamination.

All patents, patent applications and publications are hereby incorporated by reference.

## SUMMARY OF THE INVENTION

One aspect of the current invention is a topical

ophthalmic, nasal, or inhalable preparation or medication which is self-preserved, that is, which destroys, inhibits or sufficiently limits growth and multiplication of various microorganisms without the addition of preservative agents.

Another aspect of the current invention is a mildly buffered, topical ophthalmic, nasal, or inhalable preparation which is self-preserved by having a pH of from about 1.5 to about 3.5 with preferred pH at about 2.5 or lower.

Another aspect of the current invention is a self-preserved topical ophthalmic, nasal, or inhalable preparation or medication comprising a pharmaceutically acceptable excipient or additive selected from the group consisting of dextrose, polyethylene glycol (PEG), hydroxypropyl methylcellulose (HPMC), sodium chloride, potassium chloride, calcium chloride, magnesium chloride, phosphoric acid, disodium edetate, bicarbonate, phosphate, povidone, carboxymethylcellulose, hydroxyethylcellulose, methylcellulose, microcrystalline cellulose, glycerin, polyvinyl alcohol, dextran 40, dextran 70, mannitol, gelatin, polyol, polysorbate 80, propylene glycol, zinc sulfate, poloxamer 188, 282, 407, ephedrine hydrochloride, naphazoline hydrochloride, oxymetazoline hydrochloride, phenylephrine hydrochloride, tetrahydrozoline hydrochloride, xylometazoline hydrochloride, lecithin, oleic acid, sorbitan, pheniramine maleate, pyrilamine maleate, antazoline phosphate, glycine, camphor, eucalyptol, menthol, benzyl alcohol, lavender oil, tyloxapol, bornyl acetate, and phenylethyl alcohol, and a buffering agent, said preparation or medication adjusted to a low pH between about 1.5 to about pH 3.5, with most preferred pH at about pH 2.5 or lower, said medication optionally containing analgesics, anti-inflammatories, mast cell stabilizers, diagnostic aids, antibiotics, antiglaucoma drugs, decongestants, bronchodilators, vasoconstricting or

hypertonicity agents, astringents and topical anesthetics.

Still another aspect of the current invention is a physiologically compatible self-preserved lightly buffered topical ophthalmic, nasal, or inhalable preparation or medication containing no preservation agents, formulated and maintained at about pH 2.5 or lower, wherein immediately upon application to the eye or a mucosal surface, such preparation permits the pH to rise to physiologic levels to maintain patient comfort, prevent tissue damage, and enhance drug delivery.

Still yet another aspect of the current invention is a multidose topical ophthalmic, nasal, or inhalable preparation or medication lightly buffered to maintain a stable pH in the multidose container, thereby maintaining its self-preserving characteristic.

Still another aspect of the current invention is a method for preparation of a topical ophthalmic, nasal or inhalable self-preserved solution comprising steps of:

a) preparing a formulation comprising

a pharmaceutically acceptable excipient or additive selected from the group consisting of dextrose, polyethylene glycol (PEG), hydroxypropyl methylcellulose (HPMC), sodium chloride, potassium chloride, calcium chloride, magnesium chloride, phosphoric acid, disodium edetate, bicarbonate, phosphate, povidone, carboxymethylcellulose, hydroxyethylcellulose, methylcellulose, microcrystalline cellulose, other cellulose derivatives, glycerin, polyvinyl alcohol, dextran 40, dextran 70, mannitol, gelatin, polyols, polysorbate 80, propylene glycol, zinc sulfate, poloxamer 188, 282, 407, ephedrine hydrochloride, naphazoline hydrochloride, oxymetazoline hydrochloride, phenylephrine hydrochloride, tetrahydrozoline hydrochloride, xylometazoline hydrochloride, lecithin, oleic acid and sorbitan, pheniramine maleate,

DOCKET ALARM

# Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

## Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

## Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

## Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

## API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

**LAW FIRMS**
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

**FINANCIAL INSTITUTIONS**
Litigation and bankruptcy checks for companies and debtors.

**E-DISCOVERY AND LEGAL VENDORS**
Sync your system to PACER to automate legal marketing.