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SUPERINTENDENTE DE INDUSTRIA Y C
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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TÍTULO SOLICITADO: "POVIDONA YODADA, UN PRESERVATIVO
ALTERNATIVO NOVEDOSO PARA
COMPOSICIONES OFTALMOLOGICAS"

PUBLICACIÓN: Gaceta 634 de 20 de Abril de 2011, N° de publicación
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PRIORIDAD: US 61/129,222 de 21/11/2011; US 61/201,854 de
15/12/2008.

SOLICITANTE: FORESIGHT BIOTHERAPEUTICS INC.

APODERADO: JESUS MARIA MENDEZ BERMUDEZ.

TRÁMITE: SUSTENTACION DE OPOSICIÓN

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 44655 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad **TECNOQUIMICAS S.A.**, en ejercicio de lo dispuesto por el artículo 42 de la Decisión 486 de 2000, muy respetuosamente me permito formular la siguiente

I. PETICIÓN

Sírvase negar el beneficio patentario a la solicitud contenida en el expediente **11-002-094**, por no cumplir con lo dispuesto en la Decisión 486 de 2000, con base en los fundamentos que se expondrán a continuación.

II. LEGÍTIMO INTERÉS

Asiste a **TECNOQUIMICAS S.A.**, legítimo interés para presentar esta oposición, pues la eventual concesión de la solicitud restringiría injustificadamente el empleo de ciertas sustancias, derivados y procesos que a nuestro juicio carecen de nivel inventivo, en detrimento de sus legítimos intereses comerciales. De igual manera mis clientes están interesados, por su misma condición de industrias farmacéuticas, en evitar la concesión de privilegios de patente que incumplan los requisitos materiales de patentabilidad establecidos en las normas vigentes, y que supongan un riesgo para la libre competencia.

III. RATIFICACIÓN.

La solicitud en curso, que se refiere a una preparación oftálmica preservada que comprende povidona yodada (PVP-I) en una concentración suficiente para preservar dicha preparación y por lo menos un miembro seleccionado del grupo que consiste de un compuesto esteroidal antiinflamatorio, un compuesto no esteroidal antiinflamatorio, un compuesto antibacteriano, un compuesto antialérgico, y un compuesto antiglaucoma carece de los requisitos fundamentales para otorgársele el privilegio de patente de invención, particularmente en materia Nivel Inventivo.

IV. COMPLEMENTO DE INFORMACIÓN.

En primer lugar y teniendo en cuenta que la solicitud colombiana en cuestión, específicamente en sus reivindicaciones 1, 6 y 7, hace mención de la combinación entre compuestos antiinflamatorios, antibacterianos, antialérgicos y antiglaucoma, es relevante mencionar el concepto de la Doctora en Bioquímica Silvia Susana Giarcovich¹ en su opinión escrita a cerca de "Asociaciones y Patentes" en donde afirma que las asociaciones farmacológicas están restringidas por ciertos principios y lineamientos preestablecidos por varias entidades, puesto

¹ Profesora Regular Adjunta del Departamento de Farmacología de la Facultad de Farmacia y Bioquímica de la UBA y Directora Técnica y Gerente de Estudios Clínicos de DIFFUCAP-EURAND SACIFI

que dichas combinaciones deben estar bajo el precepto de eficacia, seguridad y eficiencia terapéutica, veamos:

“3.3.2. Lineamientos FDA:

A continuación se mencionarán lineamientos que la agencia sanitaria de EEUU ha establecido para el caso de los llamados “*Combination Drug Products*”:

3.3.2.1. CFR

El CFR establece la política en relación a las combinaciones de drogas a dosis fija para humanos en 21CFR300.50. Allí se establece que dos o más drogas pueden ser combinadas en una única unidad posológica cuando cada componente hace una contribución al efecto propuesto y la dosis de cada componente es tal que la combinación es segura y efectiva (se consideran casos especiales cuando se busca aumentar la seguridad y eficacia del principal componente o minimizar su potencial abuso).

**3.3.2.2. Guía “OTC Combination of Drug Products”
[Docket No. 78D-0322]²:**

Esta guía establece en detalle la política de la agencia para combinar dos o más ingredientes activos OTC, seguros y eficaces y caracteriza diferentes tipos de asociaciones de OTC:

- Ingredientes activos de diferentes categorías terapéuticas para tratar distintos síntomas simultáneamente: Sólo se acepta esta asociación si cada ingrediente está presente dentro de su rango de seguridad y eficacia.
- Ingredientes activos de la misma categoría terapéutica que tienen distintos mecanismos de acción para tratar los mismos síntomas o condición: Sólo se acepta esta asociación si es mejor o igual que cada ingrediente solo en su dosis terapéutica y también pueden usarse a dosis subterapéuticas si corresponde.
- Ingredientes activos de la misma categoría terapéutica que tienen el mismo mecanismo de acción: Estos no deberían ser combinados a menos que haya alguna ventaja con respecto a los ingredientes simples (mayor eficacia, seguridad, aceptación del paciente o calidad de la formulación).
- Ingredientes considerados adyuvantes, que aumenten o alteren el efecto de otro ingrediente activo, serán, considerados ingredientes activos.

² Anunciada en el Federal Register (1978), Vol. 43, No. 229.

3.3.2.3. Guía Draft "Current GMP for Combination Products":

Este documento provee una guía para la industria y para el *staff* de la FDA acerca de la aplicabilidad de la cGMP para las asociaciones (*combination products*) y define a un *combination product*, de acuerdo al CFR (21CFR3.2(e)), de forma que no sólo involucra drogas sino *devices*:

Un producto combinado es un producto compuesto de cualquier combinación de una droga y un dispositivo; un producto biológico y un dispositivo; una droga y un producto biológico; o una droga, dispositivo, y un producto biológico. Bajo 21 CFR 3.2 (e), un producto de combinación incluye:

- 1. Un producto que comprende dos o más componentes regulados (i.e., droga/dispositivo, biológico/dispositivo, droga/biológico, o droga/dispositivo/biológico) que son combinados físicamente, químicamente, o de otra forma, o mezclados y producidos como una entidad única;*
- 2. Dos o más productos separados, empaquetados juntos en un solo paquete, o como una unidad comprendiendo droga y productos del dispositivo, dispositivo y productos biológicos, o biológico y productos de droga;*
- 3. Una droga, dispositivo, o producto biológico empaquetado separadamente que, de acuerdo a su plan de investigación o el etiquetado propuesto, es destinado para utilizarse únicamente con una droga, dispositivo, o producto biológico aprobada especificada individualmente, dónde al mismo tiempo ambos son deben estar aceptados para la indicación o efecto y donde, luego de la aprobación del producto propuesto, el etiquetado del producto aprobado necesitaría ser cambiado (e.g., para reflejar un cambio en la indicación, forma farmacéutica, dosis, ruta de administración, cambio significativo en la posología); ó*
- 4. Cualquier droga en investigación, dispositivo, o producto biológico empaquetado separadamente que, de acuerdo al etiquetado propuesto es para utilizarse únicamente con otra droga en investigación especificada, dispositivo, o producto biológico, dónde a la vez se requiere que ambos sean aceptados para la misma indicación, uso y efecto.*

Además, dentro de esta guía es muy interesante el concepto de "parte constitutiva de un *combination product*" porque especifica su identidad regulatoria como droga, *device* o producto biológico.

3.3.2.4. Guía Draft "Combination Products Timeliness of Premarket Reviews":

Esta guía provee información a un postulante a reclamar la resolución de una disputa acerca de la duración de la revisión de una postulación referida a un producto combinado. Es una guía referida simplemente a un problema administrativo que demuestra cuán regulado se halla este ámbito que tiene una oficina destinada, la Office of Combination Products.

3.3.3. Lineamientos EMEA: Guía "Fixed Combination Medicinal Products":

Esta guía propone evaluar las potenciales ventajas de la asociación en cuanto a mejoramiento de la relación riesgo/beneficio y a simplificación de la terapia. Asimismo, establece criterios a respetar y requisitos a cumplimentar, tanto generales como particulares. Dentro de los particulares hace especial referencia a:

- La indicación.
- Los estudios farmacodinámicos y farmacocinéticos.
- Eficacia y Seguridad: En este caso diferencia dos escenarios concretos:
 - a) *Cuando la combinación fija corresponde exactamente a combinaciones que están ya en uso difundido, un análisis de los datos bibliográficos bien fundamentados debería ser presentado. Con tal que los datos estén bien documentados, este análisis puede ser útil en reducir la cantidad de ensayos clínicos a ser realizada y podría facilitar la selección de dosis para cada sustancia y el rango de dosis propuesto en la combinación fija.*
 - b) *Cuando la combinación fija es esencialmente nueva (las sustancias activas no son usualmente combinadas, la composición cuantitativa es inusual entre sustancias usualmente combinadas o una sustancia enteramente nueva), los datos necesarios son similares a los de una nueva entidad química en la situación donde la combinación fija será propuesta (primero línea o segunda de la línea de terapia). La existencia de experiencia con las sustancias debería ser tomada en cuenta.*

y especifica Régimen de dosis y Composición, Ensayos Terapéuticos y Aspectos de Seguridad.

- Paquetes combinados de diferentes productos medicinales para administración simultánea o secuencial.

Conclusión:

Las diferentes agencias sanitarias a nivel internacional han regulado fuertemente el registro de asociaciones de forma de garantizar la seguridad y eficacia de las mismas y la buena calidad en su elaboración. Todo estudio, investigación o análisis derivados de estos requisitos representan procedimientos de rutina y no originales ideas llevadas a la práctica."

Además, se puede considerar que todo efecto sinérgico o terapéutico entre fármacos no se refiere propiamente a una invención, sino que corresponde mejor a la categoría de un descubrimiento, dado que dicho efecto sinérgico o terapéutico conseguido mediante la combinación de fármacos ocurre dentro del organismo y se hace evidente a través de los respectivos ensayos preclínicos y/o clínicos por los que todo fármaco o combinación de fármacos se deben evaluar. Así mismo es importante volver a enfatizar en que la combinación de fármacos para tratar ciertas patologías, hace parte de las actividades de la profesión médica, y no de las actividades industriales.

En un segundo aspecto, y esta vez refiriéndonos a la utilización polivinilpirrolidona yodada (PVP-I) como sustancia preservante dentro de una formulación farmacéutica de aplicación oftálmica, podemos afirmar que dentro de las habilidades comunes de cualquier persona medianamente versada en la formulación de productos farmacéuticos, está la de seleccionar los excipientes adecuados al tipo de vía de administración, a la características fisicoquímicas del principio activo, y en general con todos los demás componentes de la formulación. Dicha selección es llevada a cabo a través de los ensayos rutinarios de preformulación y formulación.

Es de conocimiento común para cualquier persona medianamente versada en la elaboración de productos farmacéuticos el hecho que cuando la formulación farmacéutica de uso oftálmico se dispensa en envase multidosis, con el fin de mantener su esterilidad a lo largo de su utilización, deben incorporar conservantes en su fórmula³. Nuevamente la selección de dichos agentes perseverantes debe realizarse en base a la estabilidad y empatía con el resto de componentes de la formulación y en la inocuidad relacionada a la fisiología de la vía de administración.

³ Vila Jato J.L. Tecnología Farmacéutica. Volumen 2. Página 337.

Prueba de lo anterior, y en general de la versatilidad de compuesto que pueden ser usados como agentes perseverantes en formulaciones farmacéuticas, han sido usados compuestos organomercúricos como conservantes en formulaciones oftálmicas, incluyendo soluciones oftálmicas de fármacos ácidos. Estos compuestos organomercúricos incluyen timerosal, acetato fenilmercúrico y nitrato fenilmercúrico.

El ácido sórbico también ha sido utilizado para conservar las formulaciones oftálmicas.

El cloruro de benzalconio es un conservante ampliamente usado en las soluciones oftálmicas. Sin embargo, el cloruro de benzalconio y otros compuestos de amonio cuaternario se consideran generalmente incompatibles con las composiciones oftálmicas de fármacos con grupos ácidos, tales como fármacos antiinflamatorios no esteroides ("NSAIDS"). Estos conservantes pierden su capacidad para funcionar cuando forman complejos con compuestos de fármacos cargados.

El documento de patente U.S. No. 5.110.493 describe formulaciones oftálmicas (NSAID) estables que no contienen conservantes organomercúricos. Por el contrario, las formulaciones de referencia NSAID usan compuestos de amonio cuaternario, tales como bromuro de cetiltrimetilamonio, cloruro de cetilpiridinio y preferiblemente cloruro de benzalconio, y una cantidad estabilizante de un tensioactivo no iónico.

La solicitud PCT WO 94/15.597 describe el uso del cloruro de lauralconio, el homólogo C12 del cloruro de benzalconio, en formulaciones oftálmicas de fármacos que son incompatibles con el cloruro de benzalconio. A diferencia de la mezcla de cloruro de alquildimetilbencilamonio, conocido como cloruro de benzalconio, esta solicitud PCT describe que el cloruro de lauralconio es compatible con entidades de fármacos ácidos; aparentemente, no forma complejos iónicos insolubles con los compuestos de fármacos cargados.

Inclusive, en algunos casos, la ausencia de un único conservante que sea seguro, estable, y capaz de reunir tanto los requerimientos de efectividad para los conservantes de formulaciones oftálmicas y fármacos ácidos de la Farmacopea de

los Estados Unidos (USP) y como de la Farmacopea Europea (Ph. Eur.), ha obligado a las compañías farmacéuticas a desarrollar más de una formulación del mismo fármaco, conteniendo cada formulación un conservante diferente.

El documento de patente U.S. No. 4.960.799 describe composiciones oftálmicas acuosas estables al almacenamiento que contienen diclorofenaco, un fármaco no esteroide anti-inflamatorio, y/o sus sales farmacéuticamente aceptables. Las composiciones de referencia incluyen EDTA como agente estabilizante, un agente solubilizante tal como el aceite de ricino polietoxilado, y un bacteriostático. Los bacteriostáticos preferidos son el timerosal y el ácido sórbico.

Es conocido el uso de Polyquad y otros compuestos poliméricos de amonio cuaternario como desinfectante y conservante en el cuidado de lentes de contacto y soluciones de lágrimas artificiales. Véanse, por ejemplo, los documentos de patente U.S. 5.037.647; 4.525.346; y 4.407.791⁴.

Con lo anterior se hace evidente que a través de los diferentes desarrollos de formulaciones farmacéuticas oftálmicas, se han empleado diversos y diferentes agentes preservantes cuya efectividad y compatibilidad se evalúan previamente para su adición dentro de una composición específica; más cuando la solicitud colombiana en trámite revela varios de estos compuestos como otras alternativas de agentes estabilizantes en su reivindicación 8.

Nuevamente queremos resaltar el hecho que si bien la adición de un nuevo agente preservante a un tipo de formulaciones puede parecer un evento novedoso, no resulta válido como evento inventivo dado que es una práctica común el evaluar agentes que ayuden a obtener formulaciones farmacéuticas con los niveles de calidad y seguridad requeridos para todo medicamento.

Mucho más relevante resulta dicha carencia de nivel inventivo, cuando el compuesto seleccionado para cumplir la función de preservante tiene ampliamente descritas sus características útiles como desinfectante y microbicida, puesto que esto llevaría a cualquier persona medianamente versada en la formulación de

⁴ Patente Española ES 216722 publicada el 30 de octubre de 1996.

productos oftálmicos a querer involucrarlo en las formulaciones desarrolladas; tal y como lo demostramos a continuación:

En primer lugar es importante resaltar que este complejo fue descubierto en los laboratorios de toxicología industrial en Filadelfia por HA Shelanski y Shelanski MV, y ha sido comercializado desde 1995⁵.

La patente americana US 2739922 publicada el 27 de marzo de 1956 revela:

This invention relates to improved novel compositions containing halogens and polymeric N-vinyl pyrrolidone.

I have discovered that polymeric N-vinyl- α -pyrrolidone of the type described in U. S. P. 2,265,450 in combination with halogens and organic and inorganic substances derived from and containing halogens or capable of setting free halogens in solution materially lowers the toxicity and sensitizing effects of the halogens on animal life without affecting, and in fact, in many cases enhancing the killing effect of such halogen compounds on microorganisms, i. e., bacteria, yeasts, molds, fungi, protozoa, and metazoa.

(...)

Lo cual permite verificar la anterioridad con que se reconoce la actividad antiséptica de la PVP-I y su potencial combinación con otras sustancias e inclusión en otras formulaciones.

Por su parte la patente US 5126127 publicada el 30 de junio de 1992 revela lo siguiente:

Povidone-Iodine (PVP-I) solutions stable according to U.S.P. standards and a method for preparing the same are disclosed. The PVP-I solution includes a microbicidal effective amount of available iodine and an alkalizing agent in an effective amount to maintain the stability of the solution for a desired shelf-life of the solution when said solution is stored in a substantially nonpermeable container, the solution being non-buffered. In preferred embodiments, the iodophor solution is a microbicidal PVP-I solution for ophthalmic use.

⁵ <http://en.wikipedia.org/wiki/Povidone-iodine>

(...)

The present invention is related to stabilized povi-
done-iodine solutions and a novel method of preparing
the same. The present invention is further related to
microbicidal ophthalmic preparations comprising povi-
done-iodine.

(...)

TABLE 14			
Example	C	13	14
Ingredient	%	%	%
PVP-I	0.3*	0.3*	0.3*
Igepal Co-630	0.004	0.004	0.004
Methocel E4M	0.5	0.5	0.5
Sodium Chloride	0.50	0.0	0.90
Monobasic Sodium Phosphate	0.76	0.0	0.0
Dibasic Sodium Phosphate	0.47	0.0	0.0
Sodium Hydroxide (5%)	qs to pH 5.6	qs to pH 4.0	qs to pH 4.0
Purified water	qs to 100	qs to 100	qs to 100

*Plus a 20% overage, which is the maximum USP allowable overage.

(...)

2. The ophthalmic solution of claim 1, wherein said
iodophor solution comprises povidone-iodine.

Como se puede apreciar claramente la PVP-I ya se había logrado incluir con
anterioridad en formulaciones farmacéuticas para uso oftalmológico, previendo su
reconocida efectividad como ageste antiséptico. Del mismo modo se demuestra
que es posible formularlo para hacerlo inocuo frente a la fisiología ocular, y por lo
tanto poderse aplicar directamente sobre el tejido ocular.

En el mismo sentido, la patente americana US 2007/0219170 publicada el 20 de
septiembre de 2007 revela lo siguiente:

A topical ophthalmic composition comprised of povidone-iodine 0.01% to 10.0% combined with a steroid or non-steroidal anti-inflammatory drug. This solution is useful in the treatment of active infections of at least one tissue of the eye (e.g., conjunctiva and cornea) from bacterial, mycobacterial, viral, fungal, or amoebic causes, as well as treatment to prevent such infections in appropriate clinical settings (e.g. corneal abrasion, postoperative prophylaxis, post-LASIK/LASEK prophylaxis). Additionally the solution is effective in the prevention of infection and inflammation in the post-operative ophthalmic patient.

(...)

[0007] The invention is an ophthalmic composition comprised of povidone-iodine 0.01%-10% (weight/weight or weight/volume) combined with an anti-inflammatory medication, a steroid, or a combination of both anti-inflammatory and a steroid. In a preferred embodiment, the povidone-iodine (PVP-I) is between 0.1% and 2.5%, between 0.5 and 2%, between 0.75 and 2%, between 0.8 and 2%, between 0.9 and 2%, between 1% and 2% or between 1% and 1.5%. In another embodiment, the total weight of the PVP-I, anti-inflammatory and steroid is between 0.1% and 4.5%. This solution is useful in the treatment of infections of the conjunctiva and cornea. The broad spectrum of povidone-

(...)

[0025] Suitable anti-inflammatories for the compositions and methods of the invention include, at least, the following: ketotifen fumarate, diclofenac sodium, flurbiprofen sodium, ketorlac tromethamine, suprofen, celecoxib, naproxen, rofecoxib, or a derivative or combination thereof. Ketorolac (also called ketorlac, or ketorolac tromethamine) is a non-steroidal anti-inflammatory drug (NSAID) in the family of propionic acids.

(...)

[0032] As an optional ingredient, suitable antimicrobial preservatives may be added to prevent multi-dose package contamination. Such agents may include benzalkonium chloride, thimerosal, chlorobutanol, methyl paraben, propyl paraben, phenylethyl alcohol, EDTA, sorbic acid, Onamer M, other agents known to those skilled in the art, or a combination thereof. Typically such preservatives are employed at a level of from 0.001% to 1.0% by weight.

(...)

Viscosity Agents

[0034] The compositions of the invention may contain an optional viscosity agent—that is, an agent that can increase viscosity. Viscosity increased above that of simple aqueous solutions may be desirable to increase ocular absorption of the active compound, to decrease variability in dispensing the formulation, to decrease physical separation of components of a suspension or emulsion of the formulation and/or to otherwise improve the ophthalmic formulation. Such viscosity builder agents include as examples polyvinyl alcohol, polyvinyl pyrrolidone, methyl cellulose, hydroxy propyl methylcellulose, hydroxyethyl cellulose, carboxymethyl cellulose, hydroxy propyl cellulose, other agents known to those skilled in the art, or a combination thereof. Such agents are typically employed at a level of from 0.01% to 2% by weight.

(...)

5. The ophthalmic composition of claim 1 wherein said anti-inflammatory agent is selected from the group consisting of ketotifen fumarate, diclofenac sodium, flurbiprofen sodium, ketorlac tromethamine, suprofen, celecoxib, naproxen, rofecoxib, and a combination thereof.

(...)

23. The ophthalmic composition of claim 1, wherein said composition is in the form of a solution, suspension, emulsion, ointment, cream, gel, or a controlled-release/sustained-release vehicle.

Como se puede apreciar claramente, en esta anterioridad se involucran varias de las características esenciales de la formulación propuesta por la solicitud colombiana en trámite, específicamente en la inclusión de PVP-I en formulaciones farmacéuticas oftalmológicas en combinación con agentes anti-inflamatorios y agentes viscosantes. Inclusive las proporciones dentro de las cuales se encuentra el PVP-I coinciden, y a pesar de que el documento involucra a dicho compuesto como un principio activo y no como un agente preservante, para cualquier persona medianamente versada en la formulación de productos farmacéuticos que conociera las características del PVP-I junto con la información expuesta, estaría en condiciones más que suficientes para generar una formulación oftalmológica como la descrita en las reivindicaciones de la solicitud colombiana en cuestión.

En conclusión, la solicitud colombiana en trámite carece irrefutablemente de nivel inventivo, dado la obviedad que representa la utilización de PVP-I dentro de una formulación como agente preservante dadas sus reconocidas características antisépticas, así como la suficiente información que se encuentra en el estado de la técnica acerca de su involucramiento en formulaciones farmacéuticas para aplicación oftalmológica.

Por todo lo anterior, le solicito Señor Superintendente, que analice los argumentos citados con el rigor y detenimiento habituales y que decrete, además de la negación de la solicitud en comento, el archivo del citado expediente.

V. FUNDAMENTOS DE DERECHO.

Son fundamentos de derecho el Capítulo I, (Requisitos de Patentabilidad) y el artículo 42 (Oposiciones) de la Decisión 486 de 2000.

VI. ANEXOS.

- ❖ Copia de todos los documentos mencionados en el acápite de Complemento de información.

VII. NOTIFICACIONES

El suscrito recibirá notificaciones en la secretaría de su Despacho o en mi oficina localizada en la Carrera 17 No. 88-23, Oficina 205, Fax (1) 621.25.42 de esta ciudad. Tecnoquímicas S.A. las recibirá en sus oficinas localizadas en la Calle 23 N° 7-39 de Cali.

Señor Superintendente,



JOSÉ LUIS REYES VILLAMIZAR

C.C. 79'152.473 de Usaquén

T.P.A. 44.655 del C.S.J.

1

2,739,922

MIXTURES OF POLYMERIC N-VINYL PYRROLIDONE AND HALOGENS

Herman A. Shelanski, Philadelphia, Pa.

No Drawing. Application March 13, 1952,
Serial No. 276,449

12 Claims. (Cl. 167-70)

This invention relates to improved novel compositions containing halogens and polymeric N-vinyl pyrrolidone.

I have discovered that polymeric N-vinyl- α -pyrrolidone of the type described in U. S. P. 2,265,450 in combination with halogens and organic and inorganic substances derived from and containing halogens or capable of setting free halogens in solution materially lowers the toxicity and sensitizing effects of the halogens on animal life without affecting, and in fact, in many cases enhancing the killing effect of such halogen compounds on microorganisms, i. e., bacteria, yeasts, molds, fungi, protozoa, and metazoa.

This discovery makes possible the formulation of a wide variety of compositions containing such halogen compounds in conjunction with polyvinyl pyrrolidone which are of value in substantially the same use as the unmodified halogen compounds but are free of many of the objectionable properties of such unmodified halogen compounds and thus may be employed with greater safety than the unmodified compounds and in more effective concentrations.

The present invention does not relate to any novel halogen compounds per se but instead relates to the combination of known halogen compounds having bactericidal, therapeutic or diagnostic uses with polyvinyl pyrrolidone, such combinations having decreased toxicity and substantially less irritation and sensitizing effects than the halogen compounds per se, but in many cases showing synergistic effect. Such combinations, depending upon the particular halogen compound employed, may be employed for local application to the skin, in ointments, creams, jellies, suppositories and the like, or may be employed as parenteral or intramuscular injections. In addition to decreasing the toxicity and irritation and sensitization effects of the halogen compounds, it has been found that the presence of polyvinyl pyrrolidone substantially prolongs the application of the halogen when it is used therapeutically or otherwise in situ. Thus the addition of small amount of polyvinyl pyrrolidone to water, for instance, in a swimming pool, substantially prolongs the effect of a given quantity of chlorine.

As stated above, the polymeric N-vinyl- α -pyrrolidone compounds which I found to be useful combined with halogens and halogen containing compounds in the compositions of the present invention are the polymeric N-vinyl- α -pyrrolidones of the type described in the U. S. Patent 2,265,450. I have found that the water soluble polymers of N-vinyl pyrrolidone as a class are effective in the compositions of this invention and that the degree of polymerization (i. e. molecular weight of the polymer) has no apparent effect on its detoxifying action. However, for particular uses polymers of particular molecular weight range may be preferred for reasons other than their detoxifying effect. The Fickentscher K value is a convenient designation of relative degree of polymerization or relative molecular weight and will therefore be used to designate specific polymers in this specification.

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Thus, polymers having a K value below 15, and particularly below 10, are rapidly excreted from the body in the urine when administered in parenteral fluids, and when it is desired to detoxify a halogen compound and to have that compound excreted normally such low K value polymers will usually be preferred. Polymers having K values within the range of 15, to say 75 and preferably 25 to 50, appear to be excreted from the body more slowly. Moreover, the osmotic pressure of solutions of polymers within this range of K values appears to be better suited for the preparation of parenteral fluids and therefore such polymers will usually be preferred in compositions intended for use in parenteral fluids or where it is desired to prolong the presence and effect of the composition. The higher polymers, i. e. those having a K value above 50 and especially above 75, to say 90, appear to be stored in the liver for appreciable periods of time and such high molecular weight products may, therefore, be preferred in compositions intended for therapy of the liver or where it is desired to have the therapeutic or diagnostic agent incorporated therein remain in the body for long periods of time. The water soluble polymers of N-vinyl pyrrolidone have been extensively employed as blood plasma substitutes and appear to be entirely innocuous. While for certain purposes a polymer for a particular weight range may be desired, the detoxifying effect does not appear to be related to the molecular weight and the range of molecular weight of a particular polymer to be employed in any given application will be governed by considerations other than this detoxifying action. Such considerations are well known in the medical profession and the proper choice of polymer may readily be made. For external use the molecular weight (K value) of the polymer appears to be without effect save for its effect on the viscosity of the composition.

The present invention will first be described in detail in connection with its use with inorganic irritating forms of halogens. Thus the addition of a small amount of polyvinyl pyrrolidone to elemental iodine was effective in decreasing the toxicity of iodine solutions very substantially. The inorganic forms of iodine with which polyvinyl pyrrolidone may be used include elemental iodine, Lugol's solution, colloidal iodine suspensions, salts of iodine, iodides, iodates and iodites and acids of iodine, HI and HIO.

It was found that in such combinations of iodine and polyvinyl pyrrolidone, the acute toxicity of iodine was lowered approximately 10-fold average, and the lowering of the chronic toxicity resulted in very substantial increase in the average daily consumption. The irritation and sensitization effects of iodine were completely absent in iodine polyvinyl pyrrolidone combinations. The objectionable staining properties of the iodine were overcome, and the odor of iodine was not noticeable. At the same time, it was noted that the presence of a polyvinyl pyrrolidone in the composition did not effect the bactericidal function of the iodine as free elemental iodine and in fact it was found that combinations of iodine and polyvinyl pyrrolidone were more active bactericidally than free iodine itself. It was found that while there was no conclusive evidence of any chemical combination between the iodine and the polyvinyl pyrrolidone, it appears that such combination possesses distinctive properties which possibly may be due to the formation of a new form of matter. Thus when a small amount of polyvinyl pyrrolidone is added to Lugol's solution and the thus formed mixture heated on a steam bath, a starch test for iodine could not be obtained on paper suspended over the bath and no odor of iodine could be detected, the vapor pressure of iodine being substantially reduced to 0. This mixture of iodine and Lugol's solution was subjected

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to standard culture tube tests as illustrated in Series A of Table I below using 1 ml. 24 hour *Staph. aureus* broth culture to each tube of test broth culture and 1 per cent Lugol's iodine was added to the culture broth to the indicated dilution.

In the tables polyvinyl pyrrolidone is abbreviated as PVP.

Table I
SERIES A

Nutrient Broth in—	1/25	1/50	1/100	1/150	1/300	1/400	1/600
H ₂ O-base:							
24 hours.....	—	+	++	++	++	++	++
48 hours.....	—	++	++	++	++	++	++
1% PVP—H ₂ O-base:							
24 hours.....	—	—	++	++	—	++	++
48 hours.....	—	—	++	++	++	++	++

SERIES B

Nutrient Broth in—	1/20	1/40	1/80	1/160	1/320
H ₂ O-base:					
24 hours.....	—	++	++	++	
48 hours.....	—	++	++	++	
1% PVP—H ₂ O-base:					
24 hours.....	—	—	—	—	++
48 hours.....	—	—	—	++	++
72 hours.....	—	—	++	++	++

It will be noted that the Lugol's solution was effective at a dilution of 1 to 25, whereas the same solution containing 1 per cent polyvinyl pyrrolidone was effective at dilutions of 1 to 300. Substantially similar results were obtained in agar cup plat tests as indicated by the following tables in which 2.0 ml. of a 24 hour *Staph. aureus* culture was used per 100 ml. agar.

Table II

Dilutions in Width of—		Dilutions in Width of—	
H ₂ O	Zones, mm.	PVP—2.5%	Zones, mm.
1/2.....	10	1/2.....	13
1/10.....	3	1/10.....	8
1/50.....	0.5	1/50.....	2
1/100.....	0.0	1/100.....	0.0

Table III

Concentrations of PVP	Width of Zone, mm.
2.5%.....	7
1.25%.....	7
0.63%.....	6
0.31%.....	3
H ₂ O Control.....	3
2.5% Gelatin.....	1.5
2.5% Gelatin (no Iodine).....	0.0

The stability of iodine in polyvinyl pyrrolidone-iodine compositions is not to be regarded as due principally to I₃⁻ formation by the I⁻ present in these compositions. Spectrophotometric analysis shows that an ordinary dilute iodine-KI solution to have an absorption peak of 355 mu and a small shoulder of 420 mu. Polyvinyl pyrrolidone-iodine solutions of similar concentration, although showing a peak of 355 mu exhibit a pronounced broadening at 420 mu. The spectrum of polyvinyl pyrrolidone-iodine solution, using iodine-KI as a blank, showed a small peak of 355 mu and a high peak of 420 mu having more than twice the intensity. This indicates that there is some absorption due to I₃⁻ formation, but the greater proportion of the iodine is bound otherwise. The addition of KI to a polyvinyl pyrrolidone iodine solution causes a drastic decrease in the oxidation potential. The KI-iodine solutions have a much lower oxidation potential than polyvinyl pyrrolidone-iodine solutions of the same iodine

content. The addition of KI to a polyvinyl pyrrolidone-iodine solution causes a shift in color towards the ultra-violet. Oxygen containing organic iodine solutions give characteristically redder or browner solutions than I₃⁻ complexes. The formation of complexes such as I₅⁻, I₇⁻, and I₉⁻ take place, as a rule, only in higher polar organic solutions with cations certainly not to be found in polyvinyl pyrrolidone-iodine solutions.

This novel combination or complex of polyvinyl pyrrolidone and iodine is, as indicated previously, readily prepared by mixing a solution of polyvinyl pyrrolidone in a solvent such as methanol, ethanol, or methylene chloride with a solution of iodine in a similar solvent. Advantageously an aqueous solution of polyvinyl pyrrolidone may be added to an aqueous solution of iodine such as Lugol's solution and mixing; in this case the solution of polyvinyl pyrrolidone is preferably added to the Lugol's solution since mixing is readily effected when addition is in this order, while when the converse order or addition is used, there is a tendency for a precipitation to be formed and difficulty may be encountered in obtaining a uniform composition. The thus obtained mixed solutions which contain the polyvinyl pyrrolidone iodine complex may be used as such or, if desired, may be dried and the dry powder used as a powder. This dry powder is readily redissoluble in water and may be redissolved for use, if desired.

It has also been found that the polyvinyl pyrrolidone appears to act as solvent for iodine and the novel complex or combination of polyvinyl pyrrolidone and iodine of the present invention may be prepared by intimately mixing (for example, by grinding in a mortar and pestle or in a ball or pebble mill) elemental iodine and the dry polymer. As high as 35 per cent iodine by weight has been incorporated in polyvinyl pyrrolidone in this manner. Such dry mixtures are as readily dissolved in water as the polymer used in producing them and it has been found that polyvinyl pyrrolidone ground with iodine until as high as 25 per cent by weight of iodine is incorporated therein forms a homogenous solution in water from which iodine is not precipitated by further dilution. It appears that not all the iodine incorporated in polyvinyl pyrrolidone by dry mixing or grinding is in the form of a complex or some other combination, particularly where large amounts of iodine such as 20 to 25 per cent by weight of the polymer are used since an appreciable amount of iodine can be extracted by washing with ether and such dry compositions still retain a sensitizing or irritating effect on the skin although this sensitizing or irritating effect is markedly decreased. However, by first grinding dry iodine and dry polyvinyl pyrrolidone polymer together and then dissolving it in water and drying the solution, there is obtained a composition in which the iodine is in some way combined with the polymer so that iodine is no longer removed therefrom by washing with ether and the dry powder no longer has an irritating or sensitizing effect on the skin.

It has also been found that by heating a dried mixture of polyvinyl pyrrolidone and iodine while stirring the same or grinding in a ball mill that the iodine may be completely blended with the polyvinyl pyrrolidone so that a stable homogenous composition in which the iodine is completely combined with the polyvinyl pyrrolidone is obtained in a short time. This method of dry blending and stabilizing polyvinyl pyrrolidone composition is more fully described and claimed in the copending application Serial No. 282,458 of Beller et al., filed April 15, 1952; now Patent No. 2,706,701.

Dry products containing polyvinyl pyrrolidone and iodine in the form of a complex or other combination may also be prepared by suspending dry polyvinyl pyrrolidone in a solution of iodine in a non-solvent for polyvinyl pyrrolidone, for example, 5 grams of polyvinyl pyrrolidone were suspended in 100 ml. of a solution prepared by dissolving 2 grams of iodine in 10 ml. of methylene chloride and diluting to 250 ml. with benzene. This

suspension was allowed to stand for 18 hours with occasional agitation and the suspended polymer then filtered, washed with benzene and dried. There was obtained a brown powder of polyvinyl pyrrolidone which had combined with or dissolved iodine from the solution. This powder was soluble in water, alcohol, acetic acid, etc. and, when analyzed was found to contain 11.78 per cent iodine of which 3.64 per cent was detectable as iodine ion and 8.14 was detectable as free iodine. The product further had no odor of iodine and starch test for iodine could not be obtained holding a starch test over an aqueous solution of the powder on a water bath.

Regardless of the method by which the polyvinyl pyrrolidone and iodine are combined, it has been found that iodine is present in the final composition in three forms. A minor amount is present as bound iodine, and depending on the amount of iodine used, varying proportions of iodine are present as free or available iodine and as iodide ion. A distinction between these forms may be made on an analytical basis, free iodine being determined directly by titrating a solution of the product in water with 0.1 N-sodium thiosulfate ($\text{Na}_2\text{S}_2\text{O}_3$) solution, using starch as an indicator. The amount of iodine present as iodide ion is determined by reducing the iodine-polyvinyl pyrrolidone composition in solution with a 1-N sodium acid sulfite (NaHSO_3), adding enough to make the solution colorless, then adding 0.1 N-silver nitrate and enough nitric acid to make the solution acid and back-titrating with ammonium thiocyanate (NH_4SCN). The iodide ion is the difference between this figure and the available iodine as determined above. The total iodine may be determined by combustion methods such as that formulated by Hallet in Scott's Standard Methods of Chemical Analyses, vol. 2, pp. 2497-8 (D. Van Nostrand Co. N. Y. 1929): bound iodine then being determined by subtracting the sum of free iodine and iodine ion from the total iodine so determined.

It has been found that only relatively small amounts of iodine are present in polyvinyl pyrrolidone compositions of the present invention in the form of bound iodine. This loss of iodine in the form of bound iodine may represent the uptake of iodine by terminal unsaturation of the polyvinyl pyrrolidone. This combination takes place rapidly and it has been found that the amount of iodine present in my composition as bound iodine varies with different batches of polymer. However, the amount so combined is constant for any given batch of polymer. This loss is negligible except in preparing a composition having a low iodine concentration with large amounts of polyvinyl pyrrolidone.

It has also been found that when a freshly prepared polyvinyl pyrrolidone composition is allowed to stand that the relative proportions of iodine present as free iodine and iodide ion may vary somewhat. On standing, the amount of free iodine frequently slowly decreases while the amount of iodide ion increases. It has been found, however, that when the ratio of free iodine to iodide ion is substantially 2:1 that the product is stable and further variation in the relative proportions of free iodine to iodide ion occur only, if at all, very slowly. Such a stable composition of iodine and polyvinyl pyrrolidone in which the ratio of free iodine to iodide ion is about 2:1 are readily obtained in solution in a short time. In a dried blended product, considerable time is required for such a stable composition to be obtained. However, in accordance with the process described in the above mentioned Beller et al. application, such a stable product is obtained in a short time by heating while dry blending polyvinyl pyrrolidone and iodine. Once a polyvinyl pyrrolidone-iodine composition has become stabilized, there is no significant change in the iodine content over a long time. A small loss in iodine content may be ascribed to iodine evaporation, leakage and reaction with oxidizable closures. Thus, a polyvinyl pyrrolidone-iodine solution containing 11.5 per cent polyvinyl pyrrolidone and 1.8

per cent iodine was diluted 1:10 and 1:100. The undiluted solution and the two diluted solutions were stored in white glass 4-oz. bottles with plastic caps having a paper disc. At the start of the test, the analysis showed solutions containing 1.78%, 0.174% and 0.017% iodine, respectively. The pH values of the solutions were 1.9, 2.8 and 3.6, respectively. The solutions were analyzed five times during the test period. On the conclusion of the test, after five and one-half months, the iodine percentages were 1.61, .180 and 0.016 per cent; the pH values were 1.7, 2.7 and 3.7, respectively. Examination of the bottle caps showed considerable corrosion of the paper disc. The plastic cap, itself, was entirely unaffected. The caps were never screwed tightly to avoid difficulty in opening should some polyvinyl pyrrolidone remain on the threads.

A series of four polyvinyl pyrrolidone-iodine solutions were prepared from a polyvinyl pyrrolidone iodine powder containing 15% iodine, extra polyvinyl pyrrolidone was added to three solutions. The solutions were stored in white glass bottles with plastic caps, separated from the glass rim by paper discs. Solutions No. 0 and 1 had a detectable iodine odor; Nos. 2 and 3 had no iodine odor. After six months of storage the yellowing of the cap in solution No. 2 was slightly noticeable and the cap of No. 3 was hardly yellow. Caps No. 0 and No. 1 were appreciably yellow but not corroded at all. All the pertinent data, including iodine determinations, are given in Table IV below. The polyvinyl pyrrolidone powder used contained 5 per cent water.

Table IV

Soln.	Wt.15% Powder	Wt. Water	Wt. PVP	Calc. I ₂	3 hrs.	24 hrs.	72 hrs.	5 days	6 mos.
	G.	G.	G.	Per- cent	Per- cent	Per- cent	Per- cent	Per- cent	Per- cent
0-----	12.5	60	0	2.59	2.46	2.45	2.46	2.45	2.46
1-----	12.5	63.5	1	2.44	2.32	2.32	2.32	2.32	2.16
2-----	12.5	63.0	3	2.30	2.19	2.20	2.20	2.20	2.06
3-----	12.5	60.0	5	2.43	2.28	2.29	2.25	2.19	2.12

The novel compositions of the present invention, i. e., "complex" of polyvinyl pyrrolidone and iodine may be used either in dried form or in solution, aqueous solutions generally being preferred on account of their cheapness. From a practical standpoint, it is frequently preferable to obtain the product in the dry form and redissolve it in water at the point of use. However, both the solution and dry form of the novel "complex" of the composition of the present invention have wide fields of application.

A 10% solution of polyvinyl pyrrolidone containing about 5 per cent iodine based on the polyvinyl pyrrolidone has been found to be valuable as general antiseptic for first-aid and other purposes (both skin wounds and deep wounds).

The novel polyvinyl pyrrolidone iodine compositions of this invention are suitable for topical application in treatment of diseases and infections produced by bacteria, viruses, and fungi infections of the skin. Both the dried compositions themselves and aqueous solutions may be used on any surface of the body. In addition, the novel iodine polyvinyl pyrrolidone compositions of this invention may be incorporated in the solutions, powders, ointments, jellies, suppositories, etc., used for topical application.

Aqueous solutions of polyvinyl pyrrolidone and iodine have been administered intravenously. As a therapeutic regimen it is preferable to first inject a solution of polyvinyl pyrrolidone then a solution of polyvinyl pyrrolidone containing a small amount of iodine and then inject a solution of polyvinyl pyrrolidone containing a more effective amount of iodine which may also contain other therapeutic agents.

When there is substantial pain, due to wound injury or infection, it has been found that the novel polyvinyl

pyrrolidone-iodine compounds of the present invention may readily be combined with procaine or other anesthetics by mixing solutions thereof and such solutions employed intramuscularly. While there is no noticeable pain due to the injection of polyvinyl pyrrolidone iodine "complex" of the present invention in the form of solutions, it has been found that procaine in such solutions is of considerable help where there is pain due to wound injury, etc.

The polyvinylpyrrolidone iodine compositions of the present invention are not limited to any concentration. In general, based on dry weights of polyvinylpyrrolidone and iodine, at least about 5% iodine to 95% polyvinylpyrrolidone is preferred since this concentration has been found to be non-toxic when administered orally, intravenously, intramuscularly and topically. Compositions containing larger amounts of iodine up to 10 to 15% by weight based on the weight of polyvinylpyrrolidone have also been found to be non-toxic and non-irritating. They have not, however, been as fully investigated as the composition containing about 5% iodine and 95% polyvinylpyrrolidone having a K value of 30. These compositions, when administered in the form of solutions, for example, intravenously or intramuscularly, may be used in any wide range of concentrations. In other words, they may be employed in hypo- hyper- or isotonic solutions, the isotonic solutions being preferred. In general, an aqueous solution containing from 2.5 to 5% polyvinylpyrrolidone, having a K value of 30 and containing about 5% iodine based on the polyvinylpyrrolidone is to be recommended for intravenous and intramuscular administration. The amount of polyvinylpyrrolidone, in a solution to be administered intravenously or intramuscularly, which is required to produce a solution having the desired viscosity will vary to some extent with the relative degree of polymerization (molecular weight or K value) of the polymer employed. The higher the polymer, the more viscous the solution formed with a given amount of polymer. These solutions may be made up with distilled water and may be autoclaved, if desired, so that, if necessary, distilled water need not be used. Various salt solutions, such as Ringer's solution, may be employed in making up solutions of the polyvinylpyrrolidone iodine compositions of this invention since they are not affected by ordinary solutions of electrolytes.

Where the novel compositions of the present invention are intended for use in general sanitizing, larger amounts of iodine may be incorporated in polyvinylpyrrolidone. It has been found that up to 35% iodine can readily be incorporated in polyvinylpyrrolidone and, when this composition is dissolved in water, iodine is not precipitated on dilution. It may also be desirable to prepare polyvinylpyrrolidone iodine compositions of the present invention containing relatively large amounts of iodine, say 15 to 25%, which are mixed with iodine-free polyvinylpyrrolidone or an iodine-free solution of polyvinylpyrrolidone to produce a solution having the desired iodine content. Once the iodine polyvinylpyrrolidone composition of the present invention has been produced, it is readily soluble in water and further amounts of polyvinylpyrrolidone may readily be added thereto.

The polyvinylpyrrolidone iodine compositions of this invention have been spoken of at times as a "complex" or some form of combination because of the enhancement of the yellow color of an aqueous iodine solution on the addition of an aqueous solution of polyvinylpyrrolidone to it. This enhancement of the yellow color of the iodine solution is somewhat similar to the formation of a blue color by the addition of starch to an aqueous iodine solution. In preparing the novel iodine polyvinylpyrrolidone compositions of this invention by suspending polyvinylpyrrolidone in a solution of iodine in a non-solvent for the polyvinylpyrrolidone, it appears that the iodine transfers from the solution or adsorption on the polyvinyl-

pyrrolidone with the formation of some form of complex or combination. This phenomenon does not take place when other water soluble polymers, such as vinyl alcohol and carboxymethyl cellulose, are used in place of polyvinylpyrrolidone.

In certain respects the polyvinylpyrrolidone iodine compositions of this invention may be considered as a novel form of water soluble iodine or a novel process for solubilizing iodine so as to obtain an aqueous solution of brown iodine which is non-toxic and in which the vapor pressure of the iodine is substantially reduced. Polyvinylpyrrolidone is preferred for producing such aqueous solutions of iodine since its non-toxicity has been established through its extensive use as a blood plasma substitute, and therefore, compositions having a wide field of application may readily be prepared. However, for general sanitizing purposes, where the matter of toxicity is not controlling, it has been found that other related polymeric materials are capable of forming a similar type of complex with iodine which is water-soluble. Among such related products may be mentioned water-soluble interpolymers of polyvinylpyrrolidone with other vinyl monomers such as vinyl phthalimide, vinyl pyridine, acrylamide and simply substituted acrylamides, and vinyl caprolactam. As examples of related homopolymers which may be combined with iodine in a similar manner to produce a water-soluble composition may be mentioned polyvinyl caprolactam, polyvinyl- γ -valerolactam and polyvinyl- ϵ -valerolactam. The combinations of these related water-soluble polymers with iodine are also water-soluble and the iodine retains its killing action on microorganisms. However, the toxicity of such other polymers and of these combinations with iodine on humans and domestic animals has not been investigated and, therefore, these products cannot be recommended for use in applications where the toxicity is a controlling factor unless full investigation should show them to be safe. They are, however, useful in applications involving general sanitizing where toxicity is not a controlling factor.

The novel polyvinylpyrrolidone iodine compositions of the present invention, as well as the compositions of iodine with related water-soluble polymers, may be formulated with a wide variety of surface active agents such as anionic agents as soaps or alkylaryl sulfates and sulfonates, higher fatty alcohol sulfates and sulfonates, cationic agents such as quaternary ammonium surface active agents, and non-ionic surface active agents such as polyglycol ethers of alkyl phenols, and higher fatty alcohols or the polyglycol ether esters of higher fatty acids to produce valuable, cleaner sanitizers which have a wide field of application in cleaning and sanitizing operations, by washing, bathing, spraying, etc.

This application is a continuation-in-part of my co-pending application Serial No. 135,519, filed December 28, 1949, and now abandoned.

I claim:

1. A method of reducing the vapor pressure of free halogens selected from the group consisting of chlorine and iodine in compositions containing the same which comprises mixing with such free halogen containing products polymeric N-vinyl pyrrolidone.
2. Compositions containing free halogens selected from the group consisting of chlorine and iodine in which the vapor pressure of the free halogen is substantially reduced and characterized in that said compositions contain polymeric N-vinyl pyrrolidone.
3. The method of reducing the vapor pressure of free iodine in solutions containing the same which comprises mixing polymeric N-vinyl pyrrolidone with a solution containing free iodine.
4. A solution containing free iodine and polymeric N-vinyl pyrrolidone.
5. The method of reducing the vapor pressure of free halogens in solutions of alkali hypohalites which com-

prises mixing such solutions with polymeric N-vinyl pyrrolidone.

6. Method as defined in claim 5 wherein the alkali hypohalite is sodium hypochlorite.

7. A composition comprising a mixture of alkali hypo- 5 halite and polymeric N-vinyl pyrrolidone.

8. A composition comprising a mixture of sodium hypochlorite and polymeric N-vinyl pyrrolidone.

9. A composition containing free iodine and comprising a mixture of polymeric N-vinyl pyrrolidone and ele- 10 mental iodine and a surface active agent.

10. A composition as defined in claim 9 wherein the surface active agent is a nonionic polyglycol ether surface active agent.

11. A composition in the form of a dry powder, com- 15 prising polymeric N-vinylpyrrolidone, and free iodine, characterized in that the vapor pressure of the iodine is substantially zero.

12. A composition in the form of a dry powder, com-

prising polymeric N-vinylpyrrolidone, and free iodine, characterized in that the vapor pressure of the iodine is substantially zero; and, further characterized, in that the ratio of free iodine to iodide ion is substantially 2:1.

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DESCRIPCION

Composiciones conservadas de fármacos oftálmicos que contienen compuestos polímeros de amonio cuaternario.

Antecedentes del invento

El invento se refiere de manera general a composiciones oftálmicas. En particular, el presente invento se refiere al uso de un compuesto polimérico de amonio cuaternario y ácido bórico para proporcionar composiciones oftálmicas de fármacos ácidos bien conservadas y estables durante el almacenamiento.

Las formulaciones oftálmicas contienen generalmente uno o mas compuestos activos junto con excipientes tales como tensioactivos, agentes de acomodación, agentes acomplejantes, estabilizadores, sistemas de tamponamiento, agentes quelantes, agentes de viscosidad o polímeros gelificantes y antioxidantes. Las formulaciones oftálmicas que están destinadas para uso multidosis requieren un conservante.

Han sido usados compuestos órgano-mercúricos como conservantes en formulaciones oftálmicas, incluyendo soluciones oftálmicas de fármacos ácidos. Estos compuestos órgano-mercúricos incluyen timerosal, acetato fenil-mercúrico y nitrato fenil-mercúrico. Los compuestos órgano-mercúricos, sin embargo, tienen limitaciones debido a la potencial toxicidad del mercurio y a su deficiente estabilidad química.

El ácido sórbico también ha sido utilizado para conservar las formulaciones oftálmicas, pero tiene también una deficiente estabilidad química, así como una deficiente actividad antimicrobiana.

El cloruro de benzalconio es un conservante ampliamente usado en las soluciones oftálmicas. Sin embargo, el cloruro de benzalconio y otros compuestos de amonio cuaternario se consideran generalmente incompatibles con las composiciones oftálmicas de fármacos con grupos ácidos, tales como fármacos antiinflamatorios no esteroides ("NSAIDS"). Estos conservantes pierden su capacidad para funcionar cuando forman complejos con compuestos de fármacos cargados.

El documento de patente U.S. No. 5.110.493 describe formulaciones oftálmicas (NSAID) estables que no contienen conservantes órgano-mercúricos. Por el contrario, las formulaciones de referencia NSAID usan compuestos de amonio cuaternario, tales como bromuro de cetiltrimetilamonio, cloruro de cetilpiridinio y preferiblemente cloruro de benzalconio, y una cantidad estabilizante de un tensioactivo no iónico.

La solicitud PCT WO 94/15.597 describe el uso del cloruro de lauralconio, el homólogo C₁₂ del cloruro de benzalconio, en formulaciones oftálmicas de fármacos que son incompatibles con el cloruro de benzalconio. A diferencia de la mezcla de cloruro de alquildimetilbencilamonio, conocido como cloruro de benzalconio, esta solicitud PCT describe que el cloruro de lauralconio es compatible con entidades de fármacos ácidos; aparentemente, no forma complejos iónicos insolubles con los compuestos de fármacos cargados.

En algunos casos, la presente ausencia de un único conservante que sea seguro, estable, y capaz de reunir tanto los requerimientos de efectividad para los conservantes de formulaciones oftálmicas y fármacos ácidos de la Farmacopea de los Estados Unidos (USP) y como de la Farmacopea Europea (Ph. Eur.), ha obligado a las compañías farmacéuticas a desarrollar más de una formulación del mismo fármaco, conteniendo cada formulación un conservante diferente.

El documento de patente U.S. No. 4.960.799 describe composiciones oftálmicas acuosas estables al almacenamiento que contienen diclorofenaco, un fármaco no esteroide anti-inflamatorio, y/o sus sales farmacéuticamente aceptables. Las composiciones de referencia incluyen EDTA como agente estabilizante, un agente solubilizante tal como el aceite de ricino polietoxilado, y un bacteriostático. Los bacteriostáticos preferidos son el timerosal y el ácido sórbico. No se hace ninguna mención sobre ningún conservante polimérico de amonio cuaternario.

Es conocido el uso de Polyquad® y otros compuestos poliméricos de amonio cuaternario como desinfectante y conservante en el cuidado de lentes de contacto y soluciones de lágrimas artificiales. Véanse, por ejemplo, los documentos de patente U.S. 5.037.647; 4.525.346; y 4.407.791. Ninguna de estas referencias describe el uso de un compuesto polimérico de amonio cuaternario como conservante en ninguna de las formulaciones de fármacos oftálmicos.

Resumen del invento

Se ha descubierto ahora que el uso de una combinación de un compuesto polimérico de amonio cuaternario tal como Polyquad® y ácido bórico en composiciones oftálmicas de fármacos ácidos proporciona una composición estable al almacenamiento que tiene, sorprendentemente, buena eficacia como conservante. Esta combinación de conservante de un compuesto polimérico de amonio cuaternario y ácido bórico es útil en composiciones oftálmicas de fármacos ácidos tales como prostaglandinas, fungicidas, antibacterianos y agentes de diagnóstico. Esta combinación de conservantes es especialmente útil en soluciones oftálmicas de fármacos que contienen o bien un grupo carboxilo tal como las drogas anti-inflamatorias no esteroides (NSAIDS), o un grupo sulfonamida tal como los fármacos antibacterianos.

Entre otros factores, el presente invento está basado en el descubrimiento de que las composiciones oftálmicas que contienen un compuesto polimérico de amonio cuaternario y ácido bórico pueden ser conservadas eficazmente según los requerimientos de la USP y Ph. Eur. sobre efectividad de conservantes a pesar de la ausencia de EDTA, un agente quelante convencional conocido para potenciar la actividad antimicrobiana de conservantes tales como el cloruro de benzalconio y el ácido sórbico.

Descripción detallada del invento

Los compuestos poliméricos de amonio cuaternario, útiles en las composiciones del presente invento, son aquellos que tienen efecto antimicrobiano y que son aceptables oftálmicamente. Los compuestos preferidos de este tipo están descritos en los documentos de patente números 3.931.319; 4.027.020; 4.407.791; 4.525.346; 4.836.986; 5.037.647 y 5.300.287; y la solicitud PCT WO 91/09523 (Dziabo y col.). El compuesto polimérico de amonio más preferido es el polyquaternium-1, conocido también como Polyquad® u Onamer M®, con un peso molecular medio numérico entre 2.000 y 30.000. Preferiblemente, el peso molecular medio numérico está entre 3.000 y 14.000.

Los compuestos poliméricos de amonio cuaternario se usan generalmente en las composiciones del presente invento en una cantidad desde 0,00001 a aproximadamente 3 % en peso, preferiblemente desde 0,001 a aproximadamente 0,1 % en peso. Más preferiblemente, las composiciones del presente invento contienen desde 0,001 a aproximadamente 0,05 % en peso de los compuestos poliméricos de amonio cuaternario.

El ácido bórico usado en las composiciones del presente invento incluye no solamente ácido bórico, sino también sus sales de adición ácida oftálmicamente aceptables, así como complejos de poliol-boratos del tipo descrito en el documento de patente U.S. 5.342.620 (Chowhan). En general, la cantidad usada en las composiciones del presente invento está entre aproximadamente 0,3 y aproximadamente 5,0 % en peso. Es preferible el uso desde aproximadamente 0,3 a aproximadamente 3,0 % en peso, y lo más preferiblemente el uso desde aproximadamente 0,5 a aproximadamente 2,0 % en peso. Los complejos de borato-poliol solubles en agua útiles en las composiciones del presente invento, comprenden preferiblemente borato y poliol en una relación molar entre aproximadamente 1:1 y aproximadamente 1:10.

Los agentes oftálmicos adecuados que pueden estar incluidos y administrados en las composiciones del presente invento incluyen, aunque no se limitan a, las formas enantiómeras y racémicas y las sales oftálmicamente aceptables, amidas, ésteres y profármacos de los siguientes tipos de fármacos que contienen una funcionalidad ácida tal como grupos -COOH, -SO₂NH₂, o SO₂NHR: agentes anti-glaucoma, tales como inhibidores de la anhidrasa carbónica, prostaglandinas y derivados de la prostaglandina; agentes no esteroides anti-inflamatorios, incluyendo pero no limitándose a aquellos clasificados como ácidos aril- o heteroarilalcanoicos, tales como diclofenaco, bromfenaco, flurbiprofeno, suprofen, ceterolaco, indometacina y cetoprofeno; agentes antibacterianos y antiinfecciosos, incluyendo sulfafármacos, tales como sulfacetamida sódica, y beta-lactamas tales como penicilinas y cefalosporinas; y agentes de diagnóstico tales como la fluoresceína sódica. También pueden ser usadas combinaciones de agentes oftálmicos en las composiciones del presente invento.

Las composiciones del presente invento pueden incluir adicionalmente otros componentes oftálmicamente aceptables tales como agentes de acomodación, tampones (p. ej. fosfato, acetato, carbonato y citrato), otros conservantes (p. ej. cloruro de benzalconio y homólogos individuales del cloruro de benzalconio, parabenos, clorobutanol, y biguanidas tales como clorhexidina y metil hidroxipropil biguanida), tensioactivos (p. ej. poloxameros tales como Pluronic®; polisorbato tales como Tweens®; tiloxapol; sarcosinatos tales como Hamposyl®, y aceites de ricino polietoxilados tales como Cremophor® y agentes tónicos (p. ej. cloruro sódico, manitol, dextrosa y xilitol). Además, otros excipientes, tales como antioxidantes, agentes quelantes y agentes acomplejantes pueden ser añadidos a las composiciones del presente invento según se desee o cuando sea necesario.

Las composiciones del presente invento pueden incluir también agentes modificadores de la viscosidad tales como: ésteres celulósicos, tales como hidroxipropilmetilcelulosa (HPMC), hidroxietilcelulosa (HEC), etilhidroxietilcelulosa, hidroxipropilcelulosa, metilcelulosa, y carboximetilcelulosa; carbómeros (p. ej. Carbopol®); alcohol polivinílico; polivinilpirrolidona; alginatos; carragenatos; y gomas de guar, caraya, agarosa, algarroba, tragacanto y xantano. La concentración de tales modificadores de viscosidad varía entre aproximadamente 0,1 y aproximadamente 5 % en peso, pero tales formulaciones generalmente tendrán una viscosidad entre aproximadamente 10 y aproximadamente 5.000 m Pas (centipoises).

Las composiciones oftálmicas del presente invento pueden contener adicionalmente polímeros que experimentarán una transición sólido-gel tras la exposición a estímulos físicos o químicos, tales como cambios en el pH, concentración iónica, y/o temperatura. Ejemplos de tales polímeros incluyen, pero no están limitados a: ciertos carragenatos, y gomas gellan, de algarrobo y de xantano, tales como los descritos en el documento de patente U.S. 08/108.824 (Lang y col.), U.S. 4.861.760 (Mazuel y col.), U.S. 4.136.173 (Pramoda y col.), U.S. 4.136.177 (Lin y col.), y U.S. 4.136.178 (Lin y col.). Los contenidos de estas solicitudes de patente y patentes relacionadas con los polímeros citados anteriormente están aquí incorporados por referencia.

Los fármacos ácidos en las composiciones del presente invento también pueden estar encapsulados en micro-partículas tales como microcápsulas, microesferas, nanocápsulas, nanoesferas y liposomas para mejorar la comodidad, y/o proporcionar una liberación sostenida.

Los siguientes ejemplos se presentan para ilustrar adicionalmente diversos aspectos del presente invento, pero no se pretende que limiten el alcance del invento bajo ninguna consideración.

Ejemplo 1

Las formulaciones siguientes son representativas de las composiciones preferidas del presente invento.

Ingrediente	Formulación (% en peso)		
	A	B	C
Diclorofenaco sódico	0,1	—	—
Sulfacetamida sódica	—	10	—
Suprofeno	—	—	0,25
HPMC*	0,1	0,1	0,1
Trometamina	2,0	2,0	2,0
Ácido bórico	1,2	1,2	1,2
TPGS de Vitamina E**	3,0	3,0	3,0
Manitol	3,5	1,6	3,6
Polyquad®	0,005	0,005	0,005
ClH/NaOH	c.s. p. pH 7,4	c.s. p. pH 7,4	c.s. p. pH 7,4
Agua destilada	c.s. p. 100 %	c.s. p. 100 %	c.s. p. 100 %

* Hidroxipropilmetilcelulosa
** Succinato 1000 de Tocoferilpolietilenglicol de Vitamina E

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Preparación

Se detalla a continuación la preparación de la formulación A. Las formulaciones B y C se pueden preparar de manera similar.

Inicialmente, una solución patrón de TPGS al 10% y una solución patrón de HPMC al 2% fueron preparadas en agua con agitación constante. Para asegurar una completa disolución se aplicó calor en caso necesario.

Se añadió diclorofenaco sódico a un vaso de vidrio tarado que contenía aproximadamente 40 % del peso final en agua destilada. Esta mezcla se agitó hasta que el diclorofenaco estaba totalmente disuelto. Los siguientes ingredientes fueron entonces añadidos con agitación en el orden que se indica a continuación, y cada ingrediente se disolvió completamente antes de la adición del siguiente ingrediente: solución patrón de TPGS de Vitamina E; trometamina; ácido bórico; Polyquad®; manitol; y solución patrón de HPMC.

Se añadió entonces agua para llevar la formulación al 95 % de su peso final, y el pH de la formulación se ajustó a entre 7,0 y 7,4 utilizando NaOH y/o ClH. Se añadió entonces agua para llevar al 100 % el peso final. Las formulaciones resultantes eran aproximadamente isotónicas (sobre 300 miliosmoles por kilogramo (mOsm/kg)).

Ejemplo 2

La efectividad conservante antimicrobiana de la combinación del compuesto polimérico de amonio cuaternario con ácido bórico del presente invento se determinó utilizando un ensayo de provocación de organismos de acuerdo con los métodos descritos en la Farmacopea de los Estados Unidos (USP) y de la Farmacopea Europea (Ph. Eur.). Se inocularon muestras con niveles conocidos de bacterias vegetativas gram-positivas (*Staphylococcus aureus* ATCC 6538) y gram-negativas (*Pseudomonas aeruginosa* ATCC 9027 y *Escherichia coli* ATCC 8739), levaduras (*Candida albicans* ATCC 10231) y hongos (*Aspergillus niger* ATCC 16404) y se tomaron muestras a intervalos específicos para determinar si el sistema conservante antimicrobiano era capaz de suprimir o inhibir la propagación de organismos incorporados a propósito en la formulación. La tasa del nivel de actividad antimicrobiana se determinó de acuerdo con las normas de eficacia conservante para preparaciones oftálmicas de la USP y/o Ph. Eur.

Las normas resumidas para las preparaciones oftálmicas se presentan a continuación:

Para Bacterias:

Período de Tiempo	Log(Redución de la población de organismos)		
	USP	Ph. Eur. A (Objetivo)	Ph. Eur. B (Min)
6 horas	-	2	-
24 horas	-	3	1
7 días	-	-	3
14 días	3	-	-
28 días	NI	NR	NI

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Para hongos:

		Log(reducción de la población de organismos)		
5	Período de Tiempo	USP	Ph. Eur. A (Objetivo)	Ph. Eur. B (Min)
10	7 días	-	2	-
	14 días	NI	-	1
15	28 días	NI	NI	NI

- NR = Ningún organismo recuperado.
NI = Ningún incremento en éste o cualquier período de tiempo siguiente.
- = Ningún requerimiento establecido para este período de tiempo.

Los resultados del estudio de provocación de conservantes realizados sobre la Formulación A se muestran en la Tabla 1 a continuación. Estos resultados muestran que una formulación oftálmica de un fármaco ácido puede ser conservada globalmente, es decir, puede cumplir con los requerimientos de efectividad conservante de la USP y Ph. Eur. para preparaciones oftálmicas, usando una combinación de un compuesto polimérico de amonio cuaternario y ácido bórico.

TABLA 1
Resultados del ensayo de provocación para la Formulación A

	Organismo de ensayo	Recuento inicial	Número de microorganismos por mililitro*					
35			6 h	24 h	Día 7	Día 14	Día 21	Día 28
	S. aureus	1,5 x 10 ⁶	<10	<10	<10	<10	<10	<10
	P. aeruginosa	1,0 x 10 ⁶	<10	<10	<10	<10	<10	<10
40	E. coli	1,1 x 10 ⁶	<10	<10	<10	<10	<10	<10
	C. albicans	1,2 x 10 ⁶	6,3 x 10 ⁵	4,1 x 10 ⁵	4,1 x 10 ²	<10	<10	<10
	A. niger	1,3 x 10 ⁶	1,4 x 10 ⁶	3,9 x 10 ⁴	2,5 x 10 ²	8,0 x 10 ¹	6,5 x 10 ¹	<10

* Límite de detección: < 10 CFU/ml. (CFU = Unidades Formadoras de Colonias)

REIVINDICACIONES

1. Una composición oftálmica conservada, estable al almacenamiento, que comprende una cantidad terapéuticamente efectiva de uno o más agentes oftálmicos ácidos, una cantidad efectiva como conservante de una combinación de un compuesto de amonio cuaternario polimérico antimicrobiano y ácido bórico, y un vehículo oftálmicamente aceptable.
2. La composición de la reivindicación 1, en la que el agente oftálmico ácido se selecciona del grupo consistente en agentes anti-glaucoma, agentes anti-inflamatorios no esteroides, agentes anti bacterianos, agentes anti-infecciosos y agentes de diagnóstico.
3. La composición de la reivindicación 2, en la que el agente oftálmico es un agente anti-inflamatorio no esteroide.
4. La composición de la reivindicación 3, en la que el agente anti-inflamatorio no esteroide comprende un ácido aril o heteroarilalcanoico, o una sal oftálmicamente aceptable, éster, amida o profármaco del mismo.
5. La composición de la reivindicación 4, en la que el agente anti-inflamatorio no esteroide se selecciona del grupo consistente en: diclorofenaco, flurbiprofeno, suprofeno, bromfenaco, queterolaco, indometacina, quetaprofeno, y las sales oftálmicamente aceptables, ésteres, amidas o profármacos del mismo.
6. La composición de la reivindicación 5, en la que el agente anti-inflamatorio no esteroide se selecciona del grupo consistente en diclorofenaco y sus sales oftálmicamente aceptables, ésteres, amidas, o profármacos del mismo.
7. La composición de la reivindicación 5, en la que el agente anti-inflamatorio no esteroide se selecciona del grupo consistente en suprofeno y sus sales oftálmicamente aceptables, ésteres, amidas o profármacos del mismo.
8. La composición de la reivindicación 5, en la que el agente anti-inflamatorio no esteroide se selecciona del grupo consistente en bromfenaco y sus sales oftálmicamente aceptables, ésteres, amidas, o profármacos del mismo.
9. La composición de la reivindicación 8, en la que el compuesto de amonio cuaternario polimérico antimicrobiano es el polyquaternium-1.
10. La composición de la reivindicación 9, en la que el polyquaternium-1 tiene un peso molecular medio numérico entre 2.000 y 30.000.
11. La composición de la reivindicación 10, en la que el polyquaternium-1 tiene un peso molecular medio numérico entre 3.000 y 14.000.
12. La composición de la reivindicación 1, en la que la concentración del compuesto de amonio cuaternario polimérico antimicrobiano está entre 0,00001 y 3% en peso.
13. La composición de la reivindicación 12, en la que la concentración del compuesto de amonio cuaternario polimérico antimicrobiano está entre 0,001 y 0,1 por ciento en peso.
14. La composición de la reivindicación 13, en la que la concentración del compuesto de amonio cuaternario polimérico antimicrobiano está entre 0,001 y 0,05 por ciento en peso.
15. La composición de la reivindicación 1, en la que las formas oftálmicamente activas del ácido bórico son seleccionadas del grupo consistente en ácido bórico, sales de adición ácida oftálmicamente aceptables de complejos de ácido bórico y poliol-borato.
16. La composición de la reivindicación 1, en la que la concentración de ácido bórico está entre 0,3 y 6 por ciento en peso.
17. La composición de la reivindicación 16, en la que la concentración de ácido bórico o formas oftálmicamente activas del mismo está entre 0,3 y 3 por ciento en peso.

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18. La composición de la reivindicación 17, en la que la concentración de ácido bórico o formas oftálmicamente activas del mismo está entre 0,5 y 2 por ciento en peso.
19. La composición de la reivindicación 15, en la que las formas oftálmicamente activas de ácido bórico son complejos de poliol-borato solubles en agua que tienen una relación molar de borato a poliol desde 1:1 a 1:10.
20. Una formulación oftálmica conservada globalmente que comprende diclorofenaco o una sal oftálmicamente aceptable, éster, amida o profármaco del mismo, que usa una combinación de un compuesto de amonio cuaternario polimérico antimicrobiano y ácido bórico.
21. La formulación de la reivindicación 20, en la que la formulación comprende diclorofenaco sódico, ácido bórico, manitol, polyquaternium-1 y un agente de acomodación.
22. El uso de una composición de una cualquiera de las reivindicaciones del 1 a 21 para la preparación de un medicamento para el tratamiento o control de la inflamación ocular.

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NOTA INFORMATIVA: Conforme a la reserva del art. 167.2 del Convenio de Patentes Europeas (CPE) y a la Disposición Transitoria del RD 2424/1986, de 10 de octubre, relativo a la aplicación del Convenio de Patente Europea, las patentes europeas que designen a España y solicitadas antes del 7-10-1992, no producirán ningún efecto en España en la medida en que confieran protección a productos químicos y farmacéuticos como tales.

Esta información no prejuzga que la patente esté o no incluida en la mencionada reserva.



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United States Patent [19]
Bhagwat et al.

US005126127A

[11] **Patent Number:** **5,126,127**
[45] **Date of Patent:** **Jun. 30, 1992**

- [54] **STABILIZED PVP-I SOLUTIONS**
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[73] **Assignee:** **Euroceltique, S.A., Luxembourg, Luxembourg**
[21] **Appl. No.:** **730,462**
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[51] **Int. Cl.⁵** **A61K 31/74**
[52] **U.S. Cl.** **424/78.25; 424/427; 424/437; 424/78.24; 424/667; 424/668; 424/669; 424/670; 424/671; 424/672**
[58] **Field of Search** **424/78, 80, 150, 427, 424/437, 667, 668, 669, 670, 671, 672, 78.25, 78.24**

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[57] **ABSTRACT**
Povidone-Iodine (PVP-I) solutions stable according to U.S.P. standards and a method for preparing the same are disclosed. The PVP-I solution includes a microbicidal effective amount of available iodine and an alkalinizing agent in an effective amount to maintain the stability of the solution for a desired shelf-life of the solution when said solution is stored in a substantially nonpermeable container, the solution being non-buffered. In preferred embodiments, the iodophor solution is a microbicidal PVP-I solution for ophthalmic use.

23 Claims, No Drawings

STABILIZED PVP-I SOLUTIONS

BACKGROUND OF THE INVENTION

The present invention is related to stabilized povidone-iodine solutions and a novel method of preparing the same. The present invention is further related to microbicidal ophthalmic preparations comprising povidone-iodine.

Povidone-iodine (polyvinylpyrrolidone-iodine or PVP-I) U.S.P. (U.S. Pharmacopeia) is the raw material used in the preparation of all PVP-I containing formulations.

Provine-iodine is a complex of iodine with povidone. It contains not less than 9.0% by weight, and not more than 12% by weight of available-iodine (titratable iodine) calculated on a dry basis. Povidone Iodine USP has a specification for iodide ion of not more than 6.6% by weight on a dry basis.

PVP-I solutions, as well as other iodophor solutions, have been packaged for medicinal use, e.g. in soft plastic bottles or containers, which can be used for various medicinal purposes, e.g. douching. However, a severe problem that has been encountered with such packaged iodophor solutions, is that elemental iodine (equilibrium iodine) has leached through the packaging itself. In the past, this resulted both in a decrease in stability and medicinal capacity of the iodophor solution contained within the packaging, and made it difficult to handle such packaging since the elemental iodine which leached therethrough caused staining and burning if touched.

The problems associated with packaging such PVP-I solutions in soft plastic bottles or containers have been overcome through the addition of other stabilizers or iodine donating species such as iodate salts, as disclosed in U.S. Pat. No. 4,113,857 (Shetty), and the use of iodide salts, as disclosed in U.S. Pat. No. 4,996,048 (Bhagwat et al.).

In Bhagwat et al., for example, the iodophor solution itself preferably comprises about 0.01-0.03% of iodide therein, in addition to the additional amount of iodide that has been introduced which improves the stability of the iodophor and minimizes leaching of iodine through the packaging. As disclosed therein, at least about 0.01% by weight of the additional iodide, based on the iodophor solution, and up to about 4.0% of the additional iodide is introduced into the packaging. The additional iodide is preferably KI.

Although PVP-I solutions are known to exert microbicidal activity, stabilizing PVP-I solutions for ophthalmic use was problematic prior to the present invention, and in view of the stability problems associated with dilute PVP-I solutions, it has not been possible to date to provide an acceptable formulation of dilute PVP-I solutions, such as for ophthalmic use. For example, the introduction of donating species such as iodate into a PVP-I solution is not considered to be desirable when the solution is to be used as an ophthalmic preparation because iodate (and probably iodide) are known to be irritating and toxic to the pigment epithelium of the retina. Thus, a PVP-I solution stabilized via the addition of, for example, potassium iodide and/or potassium iodate would not be useful as an ophthalmic preparation.

It is generally recognized that an ophthalmic solution should have the same pH as human lacrimal fluid. Such a result can be obtained for an ophthalmic preparation

via the use of a buffer system approaching physiological pH. It is common practice to control the pH of solutions through the use of buffers, which are pairs of related chemical compounds capable of resisting large changes in the pH of a solution caused by the addition of small amounts of acid or base, regardless of the source. For example, borate buffers (which comprise weak acids and their conjugate bases) have been used in ophthalmic preparations.

Historically, PVP-I solutions have been buffered to at least a pH of 5. This prior art is a known requirement for physiological compatibility and stability of aqueous PVP-I solutions. It has also long been recognized in the art that the more dilute the PVP-I solution, the less stable it is.

It has been found that for dilute concentrations of PVP-I which are microbicidal, especially those concentrations of PVP-I which would be useful in ophthalmic preparations, the use of buffers do not stabilize the solution. For example, if a 0.3% PVP-I solution buffered at a pH of 5.4 is prepared without the use of stabilizers or iodine donating species, the stability of such solutions in glass bottles cannot be maintained.

It is therefore an object of the present invention to provide a novel stabilized solution of an iodophor, most particularly PVP-I, which can be stored in nonpermeable containers, such as glass bottles.

It is another object of the present invention to provide a novel stabilized microbicidal solution of PVP-I which can be stored in glass bottles and which is useful as an ophthalmic preparation.

It is a further object of the present invention to provide a novel stabilized microbicidal ophthalmic preparation containing a dilute solution of PVP-I which can be stored in glass bottles and which is not irritating or toxic to the eye.

It is a further object of the present invention to provide a method of using a PVP-I solution as an antimicrobial for ophthalmic use.

It is a further object of the present invention to provide a process for preparing a dilute PVP-I solution which is effective as a microbicidal for ophthalmic use and which is stable when stored in glass bottles.

It is a further object of the present invention to provide a method of treating the eye via the use of a microbicidal stabilized ophthalmic solution comprising PVP-I.

SUMMARY OF THE INVENTION

The above-mentioned objects and others are attained by the present invention, which is related to stabilized, microbicidal iodophor solutions which can be stored in a suitable nonpermeable containers.

More particularly, the present invention is related to a stable iodophor solution, such as according to U.S.P. or F.D.A. standards, comprising a microbicidal effective amount of available iodine which amount is insufficient by itself to render the iodophor solution stable (such as with respect to U.S.P. standards), and a suitable alkalinizing agent in an amount effective to maintain said amount of available iodine within acceptable limits during its stated shelf-life, for example, to maintain said amount of available iodine at a minimum of about 85% and a maximum of 120% of an initial amount of available iodine in the solution under accelerated aging conditions. The accelerated aging conditions may comprise, for example, subjecting the solution to elevated

temperatures, e.g. from about 35° to about 40° C., for about three months when the solution is stored in a glass or other suitably nonpermeable container, the solution being non-buffered.

In a preferred embodiment, the iodophor solution comprises a non-irritating ophthalmic solution which is microbicidal and stable according to U.S.P. standards but which solution is not buffered. In this embodiment the alkalinizing agent in the effective amount is non-toxic and non-irritating to the eye. Preferably, a sufficient amount of an agent is included to render the solution substantially isotonic to human lacrimal fluid.

In preferred embodiments, the iodophor solution comprises povidone-iodine.

In other preferred embodiments, the present invention is related to a substantially non-irritating povidone-iodine ophthalmic solution comprising povidone-iodine in an initial amount of available iodine of from about 0.03% to about 0.06%, which solution is microbicidal and non-buffered.

The present invention is further related to an iodophor solution stable according to U.S.P. standards, comprising a microbicidal effective amount of available iodine which is insufficient by itself to render said iodophor solution stable according to U.S.P. standards, and an alkalinizing agent in an amount effective to provide said solution with an initial pH of from about 2 to about 6.5, such that the solution is stable according to U.S.P. standards, the solution being non-buffered.

The present invention is also related to a method of preparing a povidone-iodine solution which is stable according to U.S.P. standards when stored in a glass container. In this method, povidone-iodine is provided in an effective amount of available iodine to render the solution microbicidal. A suitable alkalinizing agent is added in an amount effective to maintain the amount of available iodine at a minimum of about 85% and a maximum of 120% of an initial amount of said available iodine for about three months at a temperature of about 40° C. when the ophthalmic solution is stored in a glass container, and the solution is non-buffered.

In another method of the present invention, the povidone iodine solution is intended for use as an ophthalmic preparation, and the alkalinizing agent in the said effective amount is non-toxic and non-irritating.

The present invention is also related to a process for treating the eye with a microbicidal treatment which is stable according to U.S.P. standards. A povidone-iodine solution having an effective amount of available iodine to render the solution microbicidal but which in said amount is by itself insufficient to render the solution stable according to U.S.P. standards is prepared, and a suitable alkalinizing agent is added in an amount effective to maintain said amount of available iodine at a minimum of about 85% and a maximum of 120% of an initial amount of said available iodine for about three months at a temperature of about 40° C. The alkalinizing agent in the said effective amount is non-toxic and non-irritating, and the solution is non-buffered. The solution is rendered substantially isotonic to human lacrimal fluid, and stored in a glass container for at least three weeks. Thereafter, the eye is treated with the microbicidal solution by placing a sufficient amount of the solution onto the external surface of an eye.

DETAILED DESCRIPTION OF THE INVENTION

The combination of elemental iodine and certain organic polymers, e.g. polyvinylpyrrolidone and detergent polymers, have been termed iodophor. The organic polymers used to form an iodophor comprise a broad range of molecular weight and chain length, and may be either ionic or non-ionic in characters, as well as possessing either surfactant or non-surfactant properties. A loose bond forms between the iodine and organic polymer to form a complex. Aqueous solutions of up to about 30% in iodine content, may be prepared.

The general method for the preparation of a iodophor complex is to bring into intimate contact, elemental diatomic iodine with the selected polymer, either in the dry or powder form or in the presence of a suitable solvent. Heat may be used to accelerate complex formation. Upon completion of the reaction, the iodophor complex of the respective polymeric carrier with iodine is obtained in certain reproducible proportions of one to the other.

The iodophor preparation can then be introduced in any convenient manner into the appropriate packaging, for purposes of the present invention, preferably glass containers (e.g., bottles).

While PVP-I is the preferred iodophor, the present invention is applicable to any iodine-releasing material. With regard to embodiments of the present invention directed to ophthalmic solutions, the iodine-releasing material, must of course be one that is suitable, i.e., non-toxic and non-irritating.

For example, with regard to other embodiments of the present invention not directed to ophthalmic preparations, other iodophor complexes comprise non-ionic, cationic and anionic detergent carriers. A detailed discussion of these materials is found in U.S. Pat. No. 4,996,048 (Bhagwat et al.), hereby incorporated by reference.

Examples of iodide salts which can be added to such iodophor preparations include sodium iodide, potassium iodide, calcium iodide and zinc iodide, with potassium iodide specifically being preferred.

Iodophor preparations are described in terms of available or titratable iodine which is considered to be the iodine released from the complex to exert germicidal action thereof. However, such available iodine determinations do not reflect either the total iodine content of the iodophor, or its germicidal potency. The iodine moiety of polyvinylpyrrolidone (povidone)-iodine complex is present in an aqueous iodophor solution in the form of different thermodynamically stable anionic iodine species and diatomic iodine. The anionic iodine forms are capable of generating diatomic iodine in the course of their respective equilibrium reactions. The anionic species do not distribute themselves into an extracting solvent which removes only the nonionic iodine. Such iodine is generated in the course of the iodine equilibrium reaction and extraction thereof by a solvent fractionates the equilibrium state. The disturbed equilibrium reaction is soon re-established to restore new anionic iodine species, but now at a different concentration level since the previous aqueous iodine content of the solution has been reduced by the extracting solvent.

Since the iodophor iodine exerting microbicidal actions exists in solutions in dynamic equilibrium with ionic iodine species, removal of one or more of the

iodine species results in formations of new equilibrium forms. An extracting solvent removes or consumes iodine from the iodophor solution in a manner similar to that of a microbial and organic load during degerming use of the iodophor solution. The amount of iodine available for germicidal action in an iodophor preparation therefore is the amount of iodine in equilibrium in the solution at the time of use. Such equilibrium iodine content represents the germicidal potency of the preparation, but not the total iodine content titrated for the preparation nor the apparent distribution of the iodine forms. Although iodophor solutions have been assayed in the art for available or titratable iodine, it is the equilibrium iodine which is the particular form of iodine present in the iodophor solution that is instantly available to exert microbicidal action. This form of iodine differs from titratable iodine and the other iodine species present in the iodophor solution. Therefore, the equilibrium iodine content of an iodophor solution is to be distinguished from its titratable iodine content.

The titratable iodine content of a iodophor preparation includes the iodine reservoir of the iodophor preparation (povidone iodine), as well as the equilibrium iodine in solution.

Titratable iodine = Reservoir Iodine + Equilibrium Iodine

However, it is the equilibrium iodine alone that exerts the microbicidal action of the preparation at any given moment. The portion of the titratable iodine content remaining after subtracting the amount of equilibrium iodine present, serves as the iodine reservoir to generate new equilibrium iodine in solution as it is consumed by the microbial and bio-organic load in the course of microbicidal activity, but does not exert such germicidal action by itself.

The level of iodide ions inherently present in any PVP-I formulation using PVP-I raw material, therefore depends on the amount of iodide ion present in the raw material PVP-I used. For example, on a theoretical basis, if the PVP-I contains 6% by weight iodide ion, then a formulation containing 10% by weight of PVP-I would contain 0.6% by weight iodide ions. However, PVP-I raw material containing a level of iodide ion greater than specification of U.S. Pharmacopeia, could also be used in formulating a PVP-I containing product.

Thus, the minimum amount of iodide ion inherently present in a PVP-I formulation could be as low as 0.0% by weight, while the maximum amount of iodide ion inherently present in such a PVP-I formulation would be the amount contributed by the PVP-I raw material used to formulate the same. For example, on a theoretical basis, if a formulation contains 0.36% by weight PVP-I, and the PVP-I contains the maximum iodide allowable of 6.6% by weight, then the formulation will have 0.0237% by weight iodide present.

Typically, for PVP-I containing products, the U.S. Pharmacopeia (U.S.P.) allows a 20% overage (i.e., 120%) from label claim and requires a minimum 85% of label at the end of the stated product shelf-life, for example, as determined by accelerated aging (3 months/40° C.) of the product. This translates into an allowable drop of 35%. Therefore, for 0.3% PVP-I solutions, the maximum allowable limit is 0.36% PVP-I and the minimum is 0.25%. Thus, stability of a 0.30% solution should be above 0.25% PVP-I (or 0.025% available iodine) to be considered stable.

Generally, PVP-I solutions having a concentration greater than 1.0% are relatively stable in glass or other nonpermeable packaging. However, such a concentration of PVP-I is not suitable for many uses. For example, with regard to ophthalmic preparations, a concentration of PVP-I of 1.0% or greater is not desirable in ophthalmic preparations because such concentrations are irritating to the eye.

It has now been surprisingly discovered that when PVP-I solutions at dilute concentrations are not buffered, e.g. to a pH of about 5.6, but instead only adjusted to a suitable pH via the addition of a suitable alkalizing agent, e.g. to a pH of about 4.0, without the use of buffers, the stability of the PVP-I solution was maintained for a period of 3 years in glass bottles, using the U.S.P. allowable overage of 20% extra PVP-I.

Preferably, the PVP-I solution has a minimum concentration of 0.3% (0.03% available iodine) in order to maintain the stability of the solution according to U.S.P. stability standards. It has now surprisingly been further found that lower PVP-I concentrations, even as low as 0.2%, are as effective as known marketed products such as Neosporin® and Garamycin® eye drops, and that PVP-I solutions having concentrations as low as 0.12% (0.012% available iodine) are also effective as antimicrobials. Although at such concentrations the iodophor solutions of the present invention are not stable according to U.S.P. standards, the iodophor solutions of the present invention at such concentrations are surprisingly and substantially more stable than prior art iodophor solutions at such concentrations, and therefore are useful nonetheless where compliance with U.S.P. standards is not of concern.

For use as an ophthalmic preparation, the stabilized microbicidal solutions of the present invention preferably comprise from about 0.12% to about 0.72% PVP-I. A higher concentration of PVP-I may be used, the limiting factor, among other things, being that the ophthalmic solution should not be unduly irritating to the eye. The limiting factor for lower concentrations of PVP-I solutions, among other things, is stability and efficacy as a microbicidal.

As explained above, the PVP-I solutions of the present invention are stabilized by adding a suitable alkalizing agent. The amount of alkalizing agent needed is that amount which is effective to maintain the amount of available iodine at a minimum of about 85% and a maximum of 120% of an initial amount of said available iodine for about three months at a temperature of about 40° C. when the solution is stored in a glass container. The solution is non-buffered.

When the solution is prepared as an ophthalmic preparation, the alkalizing agent in the said effective amount is non-toxic and preferably non-irritating. Any such alkalizing agent known in the art which may be used in ophthalmic preparations in the said effective amount may be used in the present invention. In preferred embodiments, the alkalizing agent preferably comprises sodium hydroxide, potassium hydroxide, sodium bicarbonate, disodium phosphate, mixtures of any of the foregoing, or the like. An especially preferred alkalizing agent is sodium hydroxide.

In embodiments of the present invention where the stabilized iodophor solution is not intended for ophthalmic use, the choice of alkalizing agent is, of course, not as critical with respect to toxicity and irritating properties. In such embodiments, any alkalizing agent

known in the art may be used, depending upon the intended use of the product.

In general, the pH of a dilute PVP-I solution, i.e. a PVP-I solution having a concentration of about 1.0% has a pH of about 2, and a 0.3% PVP-I solution has a pH of about 2.7. Thus, the pH of a dilute PVP-I solution is dependent upon the concentration of the PVP-I. The pH of the PVP-I solution is adjusted via the addition of the alkalizing agent until a pH of from about 2 to about 6.5 is attained, preferably at least until a stabilized product is obtained according to U.S.P. standards. More preferably, the alkalizing agent is added to the PVP-I solution until a pH of from about 2 to about 4.5 is obtained. It is especially preferred that the alkalizing agent (i.e., sodium hydroxide) is added in a amount effective to adjust the pH of the PVP-I solution to a pH of from about 4 to about 4.5.

The pH of normal tear (lacrimal) fluid is about 7.4, although the pH of the film of tears in contact with the surface of the eye may higher, i.e. from 7.4-8.0, because of loss of carbon dioxide to the atmosphere. It has been reported that an uncomfortable condition exists when the pH is under 6 or over 8, but the eye is more sensitive to acid than to alkaline solutions. The eye has also been reported to tolerate isotonic solutions more alkaline than tear fluid better than it does isotonic solutions that are acid. The tear fluid itself has a certain buffer capacity, although it is not sufficiently strong to avoid discomfort when solutions of more strongly acidic drugs are applied.

Unexpectedly, it has been discovered that the stabilized, microbicidal PVP-I ophthalmic solutions of the present invention are substantially non-irritating to the eye despite the fact that these solutions are not buffered and generally have a pH in the acidic range, e.g. pH 4.

Lacrimal fluid has an isotonicity value approximately the same as that of a 0.9% sodium chloride solution. An ophthalmic solution which is isotonic with lacrimal fluid causes less discomfort than one that is hypotonic or hypertonic. It is therefore especially preferred that the ophthalmic preparations of the present invention be adjusted with a suitable agent so that they are isotonic with the eye (i.e., with human lacrimal fluid). An especially preferred agent is sodium chloride.

Antimicrobials are usually required in ophthalmic solutions. A suitable antimicrobial preservative should have a wide bacteriostatic, or bacteriocidal activity against organisms; must maintain its microbial properties during storage, etc. have a rapid action; be nonallergenic and nonsensitized; have rapid action; be non-toxic and non-irritating; be chemically and pharmacologically compatible with other ingredients of the system; be chemically stable and not undergo discoloration; and should be readily and adequately soluble in the appropriate vehicles.

The stabilized PVP-I solutions of the present invention possess the beneficial properties outlined above. The stabilized PVP-I solutions of the present invention when prepared in suitable concentrations for ophthalmic use, have microbicidal activity as effective as that of commercially available antibiotic solutions such as Neosporin® and Garamycin®, and are similar to such products with respect to their non-irritating properties. Thus, it is contemplated that the stabilized microbicidal PVP-I solutions of the present invention are useful as microbicidal ophthalmic preparations, as combination products (e.g. in combination with local anesthetics, anti-inflammatories, etc.) for example, for ophthalmic

and otic use. It is also contemplated that the stabilized PVP-I solutions of the present invention are useful in ophthalmic products and the like as a preservative.

Preferably, the containers for storing the iodophor solutions of the present invention are comprised of substantially nonpermeable materials. By "substantially nonpermeable", it is meant that the material comprising the packaging does not allow a substantial amount of elemental iodine (such as that available as equilibrium iodine from an iodophor solution) to leach through the packaging itself. Examples of suitable containers include those comprised of glass, high density polyethylene, fluorinated high density polyethylene, and other specially treated plastics which treatments render the plastics substantially nonpermeable. The glass containers for storing the iodophor solutions of the present invention are those which are composed of pharmaceutically acceptable glass, as defined in the U.S. Pharmacopeia or National Formulary (N.F.). Both the U.S.P. and N.F. define the same four glass types (highly resistant, borosilicate glass, treated soda-lime glass, soda-lime glass, and general purpose soda-lime glass) and their alkalinity limits. The glass containers may be colorless, opaque or colored. There are four types of clear containers available, colorless, green, blue and amber. Amber glass is most preferred.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The following examples illustrate various aspects of the present invention. They are not to be construed to limit the claims in any manner whatsoever. The percentage of ingredients for each example provided below are expressed as percentage weight/volume, unless otherwise indicated. The percent available iodine for each example provided below was determined by the method described in U.S. Pharmacopeia XXI under povidone iodine topical solution (page 864).

EXAMPLE 1

In order to determine the stability of a buffered, dilute solution of PVP-I, the following 0.3% PVP-I solution, isotonic and buffered at a pH of 5.6, is prepared without the use of stabilizers or iodine donating species:

TABLE I

0.3% PVP-I Solution - Buffered, Isotonic	
Ingredient	Percentage
PVP-I*	0.3
Igepal CO-630	0.004
Methocel E4M	0.5
Monobasic Sodium Phosphate	0.76
Dibasic Sodium Phosphate	0.47
Sodium Chloride	0.5
Sodium Hydroxide (5%)	qs to pH 5.6
Purified Water	qs to 100

*(plus 0.06% U.S.P. allowable overage)

Accelerated stability studies were conducted for the above formulation. In order to remain within the definition of stability for a PVP-I solution as defined in the USP for 0.3% PVP-I solutions, the maximum allowable limits for the above formulation was 0.36% PVP-I and minimum was 0.25% PVP-I. Thus, stability of a 0.30% solution should be above 0.25% PVP-I (or 0.025% available iodine) to be considered stable. The formulation fell below this level after three months at room temperature, and after one month at 40° C. and 80%

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relative humidity. Therefore, the stability of these solutions in glass bottles cannot be maintained.

EXAMPLE 2

A non-isotonic 0.3% PVP-I solution was prepared which was not buffered at the above pH of 5.4, but only with adjusting the pH at 4.0. The formula for this solution was as follows:

TABLE 2

0.3% PVP-I, NON-BUFFERED, NON-ISOTONIC	
Ingredient	Percent
PVP-I*	0.30
Igepal CO-630	0.004
Methocel E4M	0.5
Sodium Hydroxide	qs to pH 4.0
Purified water	qs to 100

*(plus 0.06% U.S.P. allowable overage)

Three batches of the above formula were made and tested for stability. The results are provided in Table 3 below.

TABLE 3

Testing Time	Available Iodine (% w/v) (0.025-0.036%)	pH (2.5-4.5)	Appearance	Viscosity (10-30 cps)
Batch 1 - Betadine Ophthalmic Drops				
Initial	0.036%	4.44	Clear viscous brown color	25.3
Room Temperature				
3 mos	0.035%	4.06	no change	24.3
6 mos	0.035%	3.99	no change	—
9 mos	0.032%	3.89	no change	—
12 mos	0.033%	3.97	no change	22.1
18 mos	0.034%	3.70	no change	—
24 mos	0.031%	3.78	no change	24.8
36 mos	0.028%	3.55	no change	19.4
37° C., 80% Relative Humidity				
1 mos	0.032%	3.90	no change	21.0
2 mos	0.031%	3.83	no change	—
3 mos	0.031%	3.80	no change	22.4
Batch 2 - Betadine Ophthalmic Drops				
Initial	0.036%	4.36	Clear viscous brown color	21.8
Room Temperature				
3 mos	0.034%	4.09	no change	23.0
6 mos	0.035%	3.96	no change	—
9 mos	0.031%	3.88	no change	—
12 mos	0.030%	3.82	no change	20.8
18 mos	0.029%	3.80	no change	—
24 mos	0.025%	3.73	no change	21.9
36 mos	0.0265%	3.51	no change	22.2
37° C., 80% Relative Humidity				
1 mos	0.030%	3.85	no change	19.8
2 mos	0.030%	3.79	no change	—
3 mos	0.029%	3.82	no change	21.1
Batch 3 - Betadine Ophthalmic Drops				
Initial	0.036%	4.35	Clear viscous brown color	21.1
Room Temperature				
3 mos	0.035%	4.08	no change	22.4
6 mos	0.033%	3.81	no change	—
9 mos	0.032%	3.84	no change	—
12 mos	0.031%	3.86	no change	20.2
18 mos	0.030%	3.8	no change	—
24 mos	0.027%	3.69	no change	20.8
36 mos	0.0265%	3.49	no change	18.9
37° C., 80% Relative Humidity				
1 mos	0.031%	3.80	no change	20.2
2 mos	0.029%	3.73	no change	—
3 mos	0.027%	3.75	no change	19.2

Surprisingly, it was discovered that stability of the PVP-I solution was maintained for a period of 3 years,

in amber glass bottles, using the USP allowable overage of 20% extra PVP-I.

EXAMPLE 3

Further studies were conducted in order to determine the effect upon stability when the 0.3% PVP-I solutions were adjusted to isotonicity. The formula tested is set forth in Table 4 as follows:

TABLE 4

0.3% PVP-I, Non-buffered, Isotonic	
Ingredient	Percent
PVP-I*	0.30
Igepal CO-630	0.004
Methocel E4M	0.50
Sodium Chloride	0.85
Sodium Hydroxide	qs to pH 4.0
Purified water	qs to 100

*(plus 0.06% U.S.P. allowable overage)

Three batches of the above formula were made and tested for stability. The results are provided in Table 5 below:

TABLE 5

Testing Time	Available Iodine (% w/v) (0.025-0.036%)	pH (2.5-4.5)	Appearance	Viscosity (10-30 cps)
Batch 1 - Betadine Ophthalmic Drops				
Initial	0.036%	3.92	clear viscous brown color	22.4
Room Temperature				
3 mos	0.036%	3.83	pass	22.4
6 mos	0.034%	3.73	pass	22.4
9 mos	0.032%	3.65	pass	—
12 mos	0.032%	3.63	pass	19.2
18 mos	0.028%	3.60	pass	—
24 mos	0.029%	3.58	pass	19.8
36 mos	0.028%	3.54	pass	17.1
37° C., 80% Relative Humidity:				
1 mos	0.029%	3.64	pass	18.6
2 mos	0.029%	3.60	pass	—
3 mos	0.029%	3.64	no change	17.9
Batch 2 - Betadine Ophthalmic Drops				
Initial	0.035%	4.04	clear viscous brown color	21.4
Room Temperature				
3 mos	0.035%	4.00	pass	22.4
6 mos	0.033%	3.89	pass	—
9 mos	0.032%	3.83	pass	—
12 mos	0.030%	3.79	pass	19.5
18 mos	0.031%	3.70	pass	—
24 mos	0.028%	3.62	pass	19.7
36 mos	0.028%	3.51	pass	17.7
37° C., 80% Relative Humidity:				
1 mos	0.031%	3.81	pass	19.2
2 mos	0.031%	3.72	pass	—
3 mos	0.030%	3.78	pass	19.2
Batch 3 - Betadin Ophthalmic Drops				
Initial	0.036%	4.08	clear viscous brown color	21.1
Room Temperature				
3 mos	0.034%	3.92	pass	21.8
6 mos	0.034%	3.77	pass	—
9 mos	0.032%	3.69	pass	—
12 mos	0.034%	3.67	pass	19.5
18 mos	0.031%	3.60	pass	—
24 mos	0.030%	3.59	pass	19.8
36 mos	0.029%	3.44	pass	16.0
37° C., 80% Relative Humidity:				
1 mos	0.032%	3.71	pass	18.6
2 mos	0.031%	3.62	pass	—
3 mos	0.030%	3.67	pass	19.2

As can be ascertained from the results set forth above, stability was not compromised by rendering the PVP-I solution isotonic.

Another study was conducted using the formula presented in Table 4 and packaged in plastic bottles. In Comparative Batch 1, a polypropylene container was used. In Comparative Batch 2, a low density polyethylene container was used. The results of stability testing are set forth in Table 6 below.

TABLE 6

Comparative Batch 1 - Betadine Ophthalmic Drops				
Testing Time	Available Iodine (% w/v) (0.025-0.036%)	pH (2.5-4.5)	Appearance	Viscosity (10-30 cps)
Initial	0.036%	3.90	clear red-brown solution free of particulate matter	15.36
37° C., 80% Relative Humidity:				
1 mos	0.021%	3.52	light amber solution	—
2 mos	0.013%	3.24	light amber solution	—
Comparative Batch 2 - Betadine Ophthalmic Drops				
Testing Time	Available Iodine (% w/v) (.025-.036%)	pH (2.5-4.5)	Appearance	Viscosity (10-30 cps)
Initial	0.036%	3.90	clear red-brown solution free of particulate matter	15.36
37°πC., 80% Relative Humidity:				
1 mos	0.004	3.50	very light yellow amber	—
2 mos	0.002	3.23	very light yellow amber	—

Stability of Comparative Batches 1 and 2 stored in plastic bottles was not even maintained after one month since all the solutions became colorless (indicating the PVP-I was lost).

EXAMPLES 4-6

Further investigations were conducted at different concentrations of PVP-I solutions packaged in amber glass bottles. The solutions made are set forth in Table 7 as follows:

TABLE 7

Ingredient	%	%	%
PVP-I	0.2*	0.4*	0.5*
Igepal CO-630	0.004	0.004	0.004
Methocel E4M	0.4	0.4	0.4
Sodium Chloride	0.85	0.85	0.85
Sodium Hydroxide	qs to pH 4.0	qs to pH 4.0	qs to pH 4.0
Purified water	qs to 100	qs to 100	qs to 100

*Plus a 20% overage, which is the maximum USP allowable overage.

Batches of the above formula were made and tested for stability. The results are provided in Table 8 below:

TABLE 8

PVP-I, Non-buffered, Isotonic 0.2% PVP-I Ophthalmic Drops				
Testing Time	Available Iodine (% w/v) (0.017-0.025%)	pH (2.5-4.5)	Appearance	Viscosity (10-30 cps)
Initial	0.025%	3.90	clear reddish brown solution free of particulate matter	11.61
Room Temperature				
3 mos	0.021%	3.80	no change	12.80
6 mos	0.023%	3.78	no change	—
9 mos	0.019%	3.70	no change	—
12 mos	0.021%	3.60	no change	—
18 mos	0.019%	3.60	no change	—

TABLE 8-continued

24 mos	0.016%	3.56	no change	—
36 mos	0.017%	3.59	no change	—
37° C.				
1 mos	0.020%	3.78	no change	—
2 mos	0.019%	3.69	no change	—
3 mos	0.017%	3.63	no change	11.52

0.4% PVP-I Ophthalmic Drops

Available

Viscosity

35

Testing Time	Iodine (% w/v) (0.034-0.048%)	pH (2.5-4.5)	Appearance	(10-30 cps)
Initial	0.048%	3.83	clear reddish brown solution free of particulate matter	11.90

Room Temperature

3 mos	0.044%	3.71	no change	12.16
6 mos	0.048%	3.60	no change	—
9 mos	0.043%	3.52	no change	—
12 mos	0.042%	3.50	no change	—
18 mos	0.041%	3.45	no change	—
24 mos	0.040%	3.41	no change	—
36 mos	0.0399%	3.39	no change	—

37° C.

45

1 mos	0.042%	3.61	no change	—
2 mos	0.042%	3.55	no change	—
3 mos	0.042%	3.43	no change	10.56

0.6% PVP-I Ophthalmic Drops

50

Testing Time	Available Iodine (% w/v) (0.0425-0.048%)	pH (2.5-4.5)	Appearance	Viscosity (10-30 cps)
Initial	0.058%	3.87	clear reddish brown solution free of particulate matter	13.70

Room Temperature

55

3 mos	0.056%	3.90	no change	11.52
6 mos	0.057%	3.61	no change	—
9 mos	0.054%	3.52	no change	—
12 mos	0.053%	3.40	no change	—
18 mos	0.051%	3.42	no change	—
24 mos	0.048%	3.37	no change	—
36 mos	0.047%	3.36	no change	—

37° C.

60

1 mos	0.054%	3.57	no change	—
2 mos	0.053%	3.55	no change	—
3 mos	0.052%	3.74	no change	10.24

From the results set forth above, it was observed that the 0.2% solution was only stable for 18 months, while the 0.4% and 0.5% were stable for at least three years.

EXAMPLES 7-10

PVP-I solutions having concentrations of 0.2%, 0.03%, 0.04%, and 0.05% were prepared in accordance with the formulas provided in Examples 3-6. These solutions were then tested for In vitro microbiology against two commercially available products.

Killing time tests were conducted with a series of log phase cultures of gram negative and gram positive organisms including Gentamicin resistant *Pseudomonas aeruginosa* and selected viruses. Controls used were ophthalmic preparations of Neosporin® and Garamycin® (Comparative Examples A and B, respectively). Bacterial samples were taken at 30 seconds, 1, 2, 5, 10 and 15 minutes and transferred into culture media containing inactivators for iodine. Similarly, virus killing time tests were sampled at one minute and transferred into inactivating media. The results obtained are set forth in Table 9 and Table 10:

TABLE 9

BACTERIAL KILLING TESTS						
Example	7	8	9	10	A	B
Available Iodine (% w/v)	0.02	0.03	0.04	0.05	0.0	0.0
Organic	Killing Time (in seconds unless otherwise noted)					
<i>C. albicans</i>	<30	<30	<30	<30	<30	<30
<i>P. mirabilis</i>	<30	<30	<30	<30	<15	3 min
<i>Ps. aeruginosa</i>	2 min	2 min	<30	<30	<30	5 min
<i>Ps. aeruginosa</i> , Gm+	2 min	<30	<30	<30	10 min	>15 min
<i>Ps. aeruginosa</i> , Gm+	5 min	<30	<30	<30	>15 min	>15 min
<i>Ps. aeruginosa</i> , Gm+	1 min	<30	<30	<30	>15 min	>15 min
<i>S. aureus</i>	1 min	<30	<30	<30	>15 min	<30
<i>E. coli</i>	<30	<30	<30	<30	<30	5 min
<i>S. pneumoniae</i>	<30	<30	<30	<30	>15 min	<30
<i>N. gonorrhea</i>	<30	<30	<30	<30	<30	<30

(anti-bacterial activity = 10⁶ kill of log phase culture at sample time point)

TABLE 10

VIRAL KILLING TESTS						
Example	7	8	9	10	A	B
Available Iodine (% w/v)	0.02	0.03	0.04	0.05	0.0	0.0
Anti-viral activity						
Estimation of Virus Kill at 1 Minute Sample Time Point						
HSV-II	≥99.999	≥99.999	≥99.999	≥99.999	≥99.999	≥99.999
Adenovirus 8	90	0	90	0	0	0
Adenovirus 19	90	90	90	99	90	90

It was therefore surprisingly further found conducting in-vitro bacterial and viral killing time tests, that low PVP-I concentrations, even as low as 0.2% are as effective as known marketed products as Neosporin® and Garamycin® eye drops.

The PVP-I Ophthalmic Drops of Example 8 were tested for ocular safety before the lot was released for human clinical trials. Two vials were taken from sterile vials set aside for clinical trials. A 0.1 ml sample of each tested vial was instilled into one eye of each of six albino rabbits. The animals were observed for 72 hours for signs of ocular corneal or conjunctival irritation. Results obtained at the end of the 72 hour test period found the contents of both test vials to be non-irritating in this standard ocular safety test.

EXAMPLES 11-12

In Examples 11 and 12, a study was conducted similar to that in Examples 7-10 above, with the anti-microbial effect of PVP-I solutions as dilute as 0.12% (Example 11) and as concentrated as 0.60% (Example 12) were determined, respectively. The formulations for these results are set forth in Tables 11 and 12, respectively, and the results are provided in Table 13 below:

TABLE 11

0.12% PVP-I, Non-buffered, Isotonic	
Ingredient	Percent
PVP-I	0.12
Igepal CO-630	0.004
Methocel E4M	0.50
Sodium Chloride	0.90
Sodium Hydroxide (5%)	qs to pH 4.0
Purified water	qs to 100

TABLE 12

0.6% PVP-I, Non-buffered, Isotonic	
Ingredient	Percent
PVP-I	0.60
Igepal CO-630	0.004
Methocel E4M	0.50
Sodium Chloride	0.90
Sodium Hydroxide (5%)	qs to pH 4.0
Purified water	qs to 100

TABLE 13

TEST - In vitro killing		
Organism	Example 11	Example 12
<i>N. gonorrhoea</i>	>15 min.	<30 sec.
<i>C. albicans</i>	1 min	<30 sec.
<i>P. Mirabilis</i>	2 min	<30 sec.
<i>Ps. aeruginosa</i>	>15 min.	<30 sec.
<i>S. aureus</i>	3 min.	<30 sec.
<i>E. coli</i>	>15 min.	<30 sec.
<i>G. vaginale</i>	5 min.	<30 sec.
<i>S. epidermidis</i>	2 min.	<30 sec.
<i>H. simplex II</i>	3 log kill	3 log kill

From the results obtained above, it can be seen that PVP-I solutions at least as dilute as 0.12% PVP-I (0.012% available iodine) and at least as concentrated as 0.060% PVP-I are also effective as an anti-microbial.

EXAMPLES 13-15

In Examples 13 and 14, rabbit eye irritation studies were conducted in order to compare the properties of unbuffered, non-isotonic solutions of PVP-I at pH 4 (Example 13) and unbuffered isotonic PVP-I solutions at pH 4 (Example 14) to isotonic solutions of PVP-I buffered to a pH of 5.6 (Comparative Example C; not stable). In the same study, rabbit eye irritation studies

were conducted with a saline solution control and two commercially available products, Neosporin® and Herplex®. The formulations for Examples 13 and 14, as well as Comparative Example C are set forth in Table 14 below:

TABLE 14

Example Ingredient	C %	13 %	14 %
PVP-I	0.3*	0.3*	0.3*
Igepal Co-630	0.004	0.004	0.004
Methocel E4M	0.5	0.5	0.5
Sodium Chloride	0.50	0.0	0.90
Monobasic Sodium Phosphate	0.76	0.0	0.0
Dibasic Sodium Phosphate	0.47	0.0	0.0
Sodium Hydroxide (5%)	qs to pH 5.6	qs to pH 4.0	qs to pH 4.0
Purified water	qs to 100	qs to 100	qs to 100

*Plus a 20% overage, which is the maximum USP allowable overage.

The results showed that the unbuffered solutions of Examples 3 and 14 at pH 4 (both isotonic and non isotonic) were non-irritating, as was the buffered solution of Comparative Example C. This result was not expected due to the low pH of the PVP-I solution. Rather, it was expected that only PVP-I solutions above pH 5 would be non-irritating.

In the same study, a rabbit eye irritation study was conducted with the PVP-I solution of Example 12 (0.6% PVP-I solution; 0.06% available iodine). This solution was also found to be non-irritating.

Finally, in Example 15, a randomized paired comparison comfort evaluation was conducted in 30 normal human volunteers with a solution of stabilized, unbuffered isotonic 0.3% PVP-I having the formulation provided for Example 14, with Garamycin® ophthalmic solution and Sodium Sulamyd® ophthalmic solution. The results of this study revealed that there was statistically no significant differences in the discomfort between all three solutions.

The examples provided above are not meant to be exclusive. Many other variations of the present invention would be obvious to those skilled in the art, and are contemplated to be within the scope of the appended claims.

What is claimed is:

1. A stabilized non-irritating ophthalmic solution comprising an iodophor solution containing a microbicidal effective amount of available iodine ions of from about 0.03% to about 0.06%, and an alkalinizing agent in an amount effective to maintain said amount of available iodine ions at a minimum of about 85% and a maximum of 120% of an initial amount of said available iodine, for about three months under accelerated aging conditions or for about three years at room temperature, when said ophthalmic solution is stored in a substantially non-permeable container, said alkalinizing agent in said effective amount being non-toxic and non-irritating, said ophthalmic solution being nonbuffered and therefore stable and non-irritating.

2. The ophthalmic solution of claim 1, wherein said iodophor solution comprises povidone-iodine.

3. The ophthalmic solution of claim 1, wherein said alkalinizing agent is selected from the group consisting of sodium hydroxide, potassium hydroxide, sodium bicarbonate, disodium phosphate, and mixtures of the foregoing.

4. The ophthalmic solution of claim 1, wherein said alkalinizing agent comprises sodium hydroxide.

5. The ophthalmic solution of claim 4, wherein said alkalinizing agent comprises a sufficient amount of sodium hydroxide to adjust the pH of solution to an initial value from about 2 to about 6.5.

6. The ophthalmic solution of claim 1 which has a pH from about 2 to about 4.5.

7. The ophthalmic solution of claim 3 which is isotonic to human lacrimal fluid.

8. The ophthalmic solution of claim 5, further comprising an effective amount of sodium chloride to render said solution isotonic to human lacrimal fluid.

9. An iodophor solution stable according to U.S.P. standards, comprising a microbicidal effective amount of available iodine ions which in said amount is insufficient by itself to render said iodophor solution stable according to U.S.P. standards, and an alkalinizing agent in an amount effective to maintain said amount of available iodine ions at a minimum of about 85% and a maximum of 120% of an initial amount of said available iodine for about three months at a temperature of about 37° C., or for about three years at about room temperature, when said solution is stored in a substantially non-permeable container, said solution being non-buffered.

10. The solution of claim 9, wherein said iodophor comprises PVP- and said alkalinizing agent is selected from the group consisting of sodium hydroxide, potassium hydroxide, sodium bicarbonate, disodium phosphate, and mixtures of any of the foregoing.

11. A microbicidal ophthalmic solution, comprising povidone-iodine solution in a microbicidal sufficient quantity to initially provide said ophthalmic solution with from about 0.03% to about 0.06% available iodine ions,

a sufficient quantity of an alkalinizing agent to provide said ophthalmic solution with an initial pH of about 2 to about 6.5, such that said solution is rendered stable according to U.S.P. standards when stored in glass, said quantity of alkalinizing agent being non-toxic and non-irritating to the human eye, and

said ophthalmic solution being isotonic to human lacrimal fluid, said ophthalmic solution being non-buffered, non-irritating, and stable.

12. The ophthalmic solution of claim 11, wherein said alkalinizing agent is selected from the group consisting of sodium hydroxide, potassium hydroxide, sodium bicarbonate, disodium phosphate, and mixtures in its place.

13. The ophthalmic solution of claim 12 which has a pH from about 2 to about 6.5.

14. The ophthalmic solution of claim 12 which has a pH from about 4 to about 4.5.

15. The stabilized iodophor solution, comprising a microbicidal effective amount of available iodine ions which in said amount is insufficient by itself to render said iodophor solution stable, and an alkalinizing agent in an amount effective to maintain said amount of available iodine ions at a minimum of about 85% and a maximum of 120% of an initial amount of said available iodine for about one month at a temperature of about 37° C. when said solution is stored in a glass container, said solution being non-buffered.

16. The stabilized iodophor solution of claim 15 which initially comprises from about 0.12% PVP-I to about 0.72% PVP-I.

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17. The stabilized iodophor solution of claim 15 which is non-irritating to the human eye.

18. A method of preparing a microbicidal ophthalmic solution comprising povidone-iodine which is stable according to U.S.P. standards when stored in a glass container, comprising

providing povidone-iodine in an effective amount of available iodine ions to render said solution microbicidal but which in said effective amount does not render said solution stable, and

adding a suitable alkalinizing agent in an amount effective to maintain said amount of available iodine ions at a minimum of about 85% and a maximum of 120% of an initial amount of said available iodine ions for about three months at a temperature of about 37° C., or for about three years at about room temperature, when said solution is stored in a substantially nonpermeable container, such that said alkalinizing agent in said effective amount is non-toxic and non-irritating, said solution being non-buffered.

19. The method of claim 18, further comprising adding an effective amount of sodium chloride to render said solution isotonic to human lacrimal fluid.

20. The product produced according to claim 18.

21. A method of preparing a non-irritating, microbicidal ophthalmic solution comprising povidone-iodine which is stable according to U.S.P. standards when stored in a glass container, comprising

providing povidone-iodine in a sufficient quantity to initially provide said ophthalmic solution from about 0.03% to about 0.06% available iodine ions, and

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adding a suitable alkalinizing agent in an amount effective to maintain said amount of available iodine at a minimum of about 85% and a maximum of 120% of an initial amount of said available iodine ions for about three months at a temperature of about 37° C., or for about three years at room temperature, when said solution is stored in a substantially nonpermeable container.

22. The product according to claim 21.

23. A process for treating the eye with a microbicidal treatment which is table according to U.S.P. standards, comprising

preparing a povidone-iodine solution having an effective amount of available iodine ions to render said solution microbicidal but which in said amount does not render said solution stable,

adding a suitable alkalinizing agent in an amount effective to maintain said amount of available iodine ions at a minimum of about 85% and a maximum of 120% of an initial amount of said available iodine ions for about three months under accelerated aging conditions or for about three years at about room temperature, when said solution is stored in a substantially nonpermeable container, said effective amount of said alkalinizing agent being non-toxic and non-irritating, said solution being non-buffered,

rendering said solution isotonic to human lacrimal fluid,

storing said solution in a substantially nonpermeable container for at least three weeks, and thereafter placing a medicinally effective amount of said solution onto a human eye.

* * * * *



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 Samson et al. (43) **Pub. Date: Sep. 20, 2007**

(54) OPHTHALMIC COMPOSITIONS COMPRISING POVIDONE-IODINE (76) Inventors: C. Michael Samson, New York, NY (US); Bo Liang, Lawrenceville, NJ (US); Joseph A. Capriotti, New York, NY (US) Correspondence Address: MINTZ LEVIN COHN FERRIS GLOVSKY & POPEO 666 THIRD AVENUE NEW YORK, NY 10017 (21) Appl. No.: 11/636,293 (22) Filed: Dec. 7, 2006 Related U.S. Application Data (60) Provisional application No. 60/782,629, filed on Mar. 14, 2006, provisional application No. 60/848,315, filed on Sep. 29, 2006.	Publication Classification (51) Int. Cl. A61K 31/56 (2006.01) (52) U.S. Cl. 514/171 (57) ABSTRACT A topical ophthalmic composition comprised of povidone-iodine 0.01% to 10.0% combined with a steroid or non-steroidal anti-inflammatory drug. This solution is useful in the treatment of active infections of at least one tissue of the eye (e.g., conjunctiva and cornea) from bacterial, mycobacterial, viral, fungal, or amoebic causes, as well as treatment to prevent such infections in appropriate clinical settings (e.g. corneal abrasion, postoperative prophylaxis, post-LASIK/LASEK prophylaxis). Additionally the solution is effective in the prevention of infection and inflammation in the post-operative ophthalmic patient.
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OPHTHALMIC COMPOSITIONS COMPRISING POVIDONE-IODINE

RELATED APPLICATIONS

[0001] This application claims the benefit of priority from U.S. Provisional Application Ser. No. 60/782,629 filed Mar. 14, 2006 and U.S. Provisional Application Ser. No. 60/848,315 filed Sep. 29, 2006. All patents, patent applications, and references cited anywhere in this specification are hereby incorporated by reference in their entirety.

BACKGROUND OF THE INVENTION

[0002] Infectious conjunctivitis is an ophthalmic disorder characterized by inflammation of the conjunctiva secondary to invasion of a microbe. Microbes capable of causing conjunctivitis in humans include bacteria (including *Mycobacteria* sp), viruses, fungi, or amoebae. Current treatment for bacterial conjunctivitis consists of antibiotic drops. Because antibiotic drops are ineffective against viral conjunctivitis, treatment of such infections consists only of relieving symptoms. Treatments for fungi and amoeba conjunctivitis consist of a small selection of medications which lacks anti-bacterial or anti-viral activity and which, in addition, is toxic to the ocular surface.

[0003] Diagnosis of the various causative agents such as bacteria, virus, or fungus, in infectious conjunctivitis is not economically feasible because accurate diagnosis requires sophisticated laboratory culture not easily integrated into the average healthcare practice. Because accurate diagnosis is impractical, most conjunctivitis is presumed to be bacterial without culturing and is treated with antibiotics. Antibiotic treatment is suboptimal because it is ineffective against viral or fungal conjunctivitis.

[0004] The use of steroids is approached cautiously in the setting of ocular infection. While steroids can have the benefit of reducing the severity of the inflammation in an acute infection, they are also known to increase susceptibility to certain infections.

[0005] Topical corticosteroids are routinely used to control ocular inflammation. Their mechanism of action involves the inhibition of the immune response and the subsequent tissue destruction that exuberant inflammation may cause. Corticosteroid has the undesirable side effect of limiting the body's intrinsic ability to fight infection. In fact, inopportune steroids usage can worsen the course of an infection secondary to mycobacteria, virus, or fungus. Thus, the use of a combined antimicrobial-steroid medication in ocular infections is recommended only under careful observation of a trained ophthalmologist because of these significant risks. In fact, Tobradex® (Alcon), the most commonly prescribed combination ophthalmic antimicrobial-steroid drug, specifically lists 'viral disease of the cornea and conjunctiva, mycobacteria infection, and fungal infection' as absolute contraindications to its use. Clearly, these combination drugs were not intended to be used in the face of infectious conjunctivitis in which bacterial infection cannot be confirmed.

[0006] In summary, there is currently no ophthalmic antimicrobial drug with broad activity against all the causes of conjunctivitis or keratitis, and there is currently no approved antimicrobial/steroid, or antimicrobial/non steroidal anti-

inflammatory combination drug that can be safely used in infectious conjunctivitis or keratitis that can potentially be viral or fungal in origin.

SUMMARY OF THE INVENTION

[0007] The invention is an ophthalmic composition comprised of povidone-iodine 0.01%-10% (weight/weight or weight/volume) combined with an anti-inflammatory medication, a steroid, or a combination of both anti-inflammatory and a steroid. In a preferred embodiment, the povidone-iodine (PVP-I) is between 0.1% and 2.5%, between 0.5 and 2%, between 0.75 and 2%, between 0.8 and 2%, between 0.9 and 2%, between 1% and 2% or between 1% and 1.5%. In another embodiment, the total weight of the PVP-I, anti-inflammatory and steroid is between 0.1% and 4.5%. This solution is useful in the treatment of infections of the conjunctiva and cornea. The broad spectrum of povidone-iodine would allow this combination to be used in cases of ocular conjunctival or corneal infection caused by mycobacteria, viruses, fungi, and amoeba; this is in distinction to currently available combination antimicrobial-steroid ophthalmic compositions, which are contraindicated in the aforementioned infections. Additionally the solution will be useful in the infectious prophylaxis and inflammatory control of patients recovering from recent ophthalmic surgery. There are no currently available antimicrobial/anti-inflammatory or antimicrobial/steroid combinations useful for viral, fungal, mycobacterial and amoebic infections in the post-operative period.

[0008] One embodiment of the invention is directed to an ophthalmic composition suitable for topical administration to an eye, effective for treatment and/or prophylaxis of a microorganism infection or a disorder of at least one tissue of the eye. Prophylaxis may be, for example, prophylaxis from infection following surgery, prophylaxis from infection after birth for the newborn, or prophylaxis from accidental contact with contaminating material. Accidental contact with contaminating material may occur, for example, during surgery or during food processing. The composition comprises povidone-iodine in a concentration between 0.01% to 10%, and an anti-inflammatory, a steroid, or a combination thereof.

[0009] The mammalian eye can be divided into two main segments: the anterior segment and the posterior segment. The anterior segment is the front third of the eye that includes the tissues in front of the vitreous humor: the cornea, iris, ciliary body, and lens. Within the anterior segment are two fluid-filled spaces: the anterior chamber and the posterior chamber. The anterior chamber is located between the posterior surface of the cornea (i.e. the corneal endothelium) and the iris. The posterior chamber is located between the iris and the front face of the vitreous. The posterior segment is the back two-thirds of the eye that includes the anterior hyaloid membrane and all tissues behind it: the vitreous humor, retina, choroid, and optic nerve. In some animals, the retina contains a reflective layer (the tapetum lucidum) which increases the amount of light each photosensitive cell perceives, allowing the animal to see better under low light conditions.

[0010] It was surprising to discover that the formulations of povidone-iodine combined with steroids, when present in a suitable pH range, eliminated the undesired irritating effect of PVP-I to the eye. The invention provides pH stable

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aqueous suspensions of water-insoluble drugs that remain in such a state even after extended periods of storage.

[0011] In a preferred embodiment, the ophthalmic composition contains povidone-iodine at a concentration between 0.1% and 2.5% by weight, or more preferably, between 0.5% and 2% by weight. In another preferred embodiment, the ophthalmic composition has a total weight of povidone-iodine, an anti-inflammatory, a steroid of between 0.1% to 2.5% (weight to volume, or weight to weight) or between 0.1% to 4.5%.

[0012] The steroid of the ophthalmic composition may be at a concentration of between 0.01 and 10%. In a preferred embodiment, the steroid is at a concentration of between 0.05 and 2%.

[0013] The ophthalmic composition may further comprise (1) a topical anesthetic which relieves pain (2) a penetration enhancer which enhances the penetration of povidone-iodine into the tissues of the eye (this may be a topical anesthetic) (3) an antimicrobial preservative, which, for example, may be at a concentration of about 0.001% to 1.0% by weight; (4) a co-solvent or a nonionic surface agent—surfactant, which, for example, may be about 0.01% to 2% by weight; (5) viscosity increasing agent, which, for example, may be about 0.01% to 2% by weight; and (6) a suitable ophthalmic vehicle.

[0014] The ophthalmic composition may be in the form of a solution, a suspension, an emulsion, an ointment, a cream, a gel, or a controlled-release/sustain-release vehicle. For example, the composition may be in the form of a contact lens solution, eyewash, eyedrop, and the like.

[0015] The ophthalmic composition may be used for treatment and/or prophylaxis of a microorganism infection. The microorganism may be a bacterium, a virus, a fungus, or an amoeba, a parasite, or a combination thereof. The bacteria may be a mycobacterium. Further, the solution may be used to treat or for prophylaxis of disorders such as conjunctivitis, corneal abrasion, ulcerative infectious keratitis, epithelial keratitis, stromal keratitis and herpesvirus-related keratitis.

[0016] For example, the ophthalmic composition may comprise the following: 0.5 to 2% (w/w) polyvinylpyrrolidinone-iodine complex; 0.05 to 2% (w/w) steroid; 0.005% to 0.02% (w/w) EDTA (ethylenediaminetetraacetic acid); 0.01 to 0.5% (w/w) sodium chloride; 0.02 to 0.1% (w/w) tyloxapol; 0.5% to 2% (w/w) sodium sulfate; and 0.1 to 0.5% (w/w) hydroxyethylcellulose; at pH range from 5 to 7. More specifically, the ophthalmic composition may comprise the following: 1.0% (w/w) polyvinylpyrrolidinone-iodine complex; 0.1% (w/w) steroid; 0.01% (w/w) EDTA dehydrate; 0.3% (w/w) sodium chloride salt; 0.05% (w/w) tyloxapol; 1.2% (w/w) sodium sulfate; and 0.25% (w/w) hydroxyethylcellulose; at pH range from 5.5 to 6.5. In one embodiment, the composition consists essentially of 0.5 to 2% (w/w) polyvinylpyrrolidinone-iodine complex; 0.05 to 2% (w/w) steroid; 0.005% to 0.02% (w/w) EDTA (ethylenediaminetetraacetic acid); 0.01 to 0.5% (w/w) sodium chloride; 0.02 to 0.1% (w/w) tyloxapol; 0.5% to 2% (w/w) sodium sulfate; and 0.1 to 0.5% (w/w) hydroxyethylcellulose; at pH range from 5 to 7. In another embodiment, the composition consists essentially of 1.0% (w/w) polyvinylpyrrolidinone-iodine complex; 0.1% (w/w) steroid; 0.01% (w/w) EDTA disodium salt; 0.3% (w/w) sodium chloride salt; 0.05% (w/w) tyloxapol; 1.2% (w/w) sodium sulfate; and 0.25% (w/w) hydroxyethylcellulose; at pH range from 5.5 to 6.5.

[0017] It is known, of course, that EDTA can be in many forms such as a free acid, disodium, or tetrasodium salts. The steroid may be dexamethasone, prednisolone or prednisone. These steroids may be in their sodium phosphate form (e.g., dexamethasone sodium phosphate, prednisolone sodium phosphate, or prednisone sodium phosphate) or acetate form (e.g., dexamethasone acetate, prednisolone acetate, or prednisone acetate). Prednisolone is an active metabolite of prednisone and it is understood that prednisone may be used instead of prednisolone.

[0018] In a preferred embodiment, the ophthalmic composition retains at least 90% of its PVP-I and at least 90% of its steroid after 1 month, 2 months, 3 months, 6 months or 1 year after it is manufactured. This can be accomplished, at least, by producing the ophthalmic composition according to the formula listed above (e.g. previous two paragraphs). This stability is maintained even when the composition is stored at room temperature in a lighted indoor environment of 100 lux to 1000 lux. In one preferred embodiment, the composition is an aqueous solution.

[0019] In another embodiment, the invention is directed to a method for treating and/or prophylaxis of an eye disorder or a microorganism infection of at least one tissue of the eye comprising the step of administering one of more doses of an ophthalmic composition, discussed above, to the eye. The eye disorder may be, for example, a microorganism infection of at least one tissue of the eye, conjunctivitis, corneal abrasion, ulcerative infectious keratitis, epithelial keratitis, stromal keratitis and herpesvirus-related keratitis. The microorganism may be a bacteria (e.g., mycobacteria), virus, fungi, or amoebae.

[0020] In the method, the treatment may comprise administering a solution of the invention where the sum of the povidone-iodine, the anti-inflammatory, and the steroid is between 0.001 mg to 5 mg per dose. Further, the dose volume may be between 10 microliters to 200 microliters or between 50 microliters to 80 microliters; about one drop per eye. Administration may be between 1 to 24 times a day, between 2 to 4 times a day or between 2 to 24 times a day.

[0021] In one embodiment, the method further comprises a step of storing the solution for at least one month, at least two months, at least three months, at least six months, or at least one year before it is administered. The storage may be in a clear bottle (a container that does not substantially block light) in a lighted environment. A lighted environment may be, for example, an indoor lighted environment with about 100 lux to 1000 lux of light.

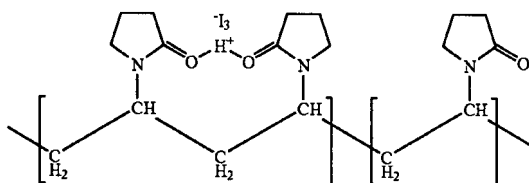
DETAILED DESCRIPTION OF THE INVENTION

[0022] In a preferred embodiment, the compositions of the present invention are administered topically. The dosage range is 0.001 to 5.0 mg/per eye; wherein the cited mass figures represent the sum of the three components: anti-inflammatory, povidone-iodine and topical anesthetic. Dosage for one eye is understood to be about one drop of solution. One drop of solution may be between 10 μ l to 200 μ l, between 20 μ l and 120 μ l, or between about 50 μ l (microliters) to about 80 μ l of solution or any values in between. For example, dispensers such as pipettors can dispense fluid drops from at least 1 μ l to 300 μ l and any value in between.

[0023] In a preferred embodiment, the solution may be administered as an eye drop using any of the many types of

eye drop dispensers on the market. Although not required, the container for the compositions of the invention may be clear, translucent, and opaque and may contain other properties or combination of properties such as being glass lined, tamper proof, packaged in single or few dose aliquots, and a combination thereof.

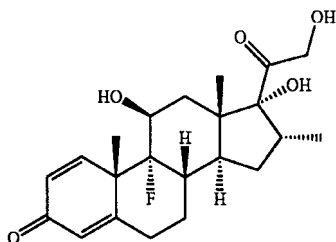
[0024] Povidone-iodine has the following chemical structure:



[0025] Suitable anti-inflammatories for the compositions and methods of the invention include, at least, the following: ketotifen fumarate, diclofenac sodium, flurbiprofen sodium, ketorolac tromethamine, suprofen, celecoxib, naproxen, rofecoxib, or a derivative or combination thereof. Ketorolac (also called ketorlac, or ketorolac tromethamine) is a non-steroidal anti-inflammatory drug (NSAID) in the family of propionic acids.

[0026] Suitable steroids for the compositions and methods of the invention include, at least: dexamethasone, dexamethasone alcohol, dexamethasone sodium phosphate, fluomethalone acetate, fluomethalone alcohol, lotoprendol etabonate, medrysone, prednisolone, prednisone, prednisolone acetate, prednisolone sodium phosphate, rimexolone, hydrocortisone, hydrocortisone acetate, lodoxamide tromethamine, or a derivative or combination thereof. It is understood, for any of the chemicals of this disclosure, that the chemicals may be in various modified forms such as acetate forms, and sodium phosphate forms, sodium salts, and the like.

[0027] Dexamethasone has the following chemical structure:



[0028] It is known that any of the reagents mentioned anywhere in this disclosure may be in chemically equivalent forms such as salts, hydrides, esters and other modifications of the basic chemical. For example, dexamethasone in any of the compositions and methods of the invention may be replaced with any of its derivatives, including esters and salts thereof. Examples of such derivatives include, at least, Dexamethasone-17-acetate (CAS RN: 1177-87-3), Dexamethasone Disodium Phosphate (CAS RN: 2392-39-4), Dexamethasone Valerate (CAS RN: 14899-36-6), Dexametha-

sone-21-isonicotinate (CAS RN: 2265-64-7), Dexamethasone Palmitate (CAS RN: 33755-46-3), Dexamethasone Propionate (CAS RN: 55541-30-5), Dexamethasone Acefurate (CAS RN: 83880-70-0), Dexamethasone-21-galactoside (CAS RN: 92901-23-0), dexamethasone 21-thiopivalate, dexamethasone 21-thiopentanoate, dexamethasone 21-thiol-2-methyl-butanoate, dexamethasone 21-thiol-3-methyl-butanoate, dexamethasone 21-thiohexanoate, dexamethasone 21-thiol-4-methyl-pentanoate, dexamethasone 21-thiol-3,3-dimethyl-butanoate, dexamethasone 21-thiol-2-ethyl-butanoate, dexamethasone 21-thiooctanoate, dexamethasone 21-thiol-2-ethyl-hexanoate, dexamethasone 21-thiononanoate, dexamethasone 21-thiodecanoate, dexamethasone 21-p-fluorothiobenzoate or a combination thereof. Dexamethasone derivatives are also described in U.S. Pat. No. 4,177,268.

[0029] Suitable topical anesthetics for the compositions and methods of the invention include, at least, proparacaine, lidocaine, tetracaine or a derivative or combination thereof.

[0030] The compositions of the present invention can be administered as solutions, suspensions, emulsions (dispersions), gels, creams, or ointments in a suitable ophthalmic vehicle.

[0031] In any of the compositions of this disclosure for topical administration, such as topical administration to the eye, the mixtures are preferably formulated as 0.01 to 2.0 percent by weight solutions in water at a pH of 5.0 to 8.0 (figures relate to combined presence of povidone-iodine and dexamethasone). This pH range may be achieved by the addition of buffers to the solution. We have found that, surprisingly, the formulation of the present invention is stable in buffered solutions. That is, there is no adverse interaction between the buffer and the iodine or other component that would cause the composition to be unstable. While the precise regimen is left to the discretion of the clinician, it is recommended that the resulting solution be topically applied by placing one drop in each eye 1 to 24 times daily. For example, the solution may be applied 1, 2, 4, 6, 8, 12, 18 or 24 times a day.

Antimicrobial Preservative

[0032] As an optional ingredient, suitable antimicrobial preservatives may be added to prevent multi-dose package contamination. Such agents may include benzalkonium chloride, thimerosal, chlorobutanol, methyl paraben, propyl paraben, phenylethyl alcohol, EDTA, sorbic acid, Onamer M, other agents known to those skilled in the art, or a combination thereof. Typically such preservatives are employed at a level of from 0.001% to 1.0% by weight.

Co-Solvents/Surfactants

[0033] The compositions of the invention may contain an optional co-solvent. The solubility of the components of the present compositions may be enhanced by a surfactant or other appropriate co-solvent in the composition. Such co-solvents/surfactants include polysorbate 20, 60, and 80, polyoxyethylene/polyoxypropylene surfactants (e.g. Pluronic F-68, F-84 and P-103), cyclodextrin, tyloxapol, other agents known to those skilled in the art, or a combination

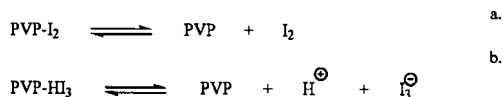
thereof. Typically such co-solvents are employed at a level of from 0.01% to 2% by weight.

Viscosity Agents

[0034] The compositions of the invention may contain an optional viscosity agent—that is, an agent that can increase viscosity. Viscosity increased above that of simple aqueous solutions may be desirable to increase ocular absorption of the active compound, to decrease variability in dispensing the formulation, to decrease physical separation of components of a suspension or emulsion of the formulation and/or to otherwise improve the ophthalmic formulation. Such viscosity builder agents include as examples polyvinyl alcohol, polyvinyl pyrrolidone, methyl cellulose, hydroxy propyl methylcellulose, hydroxyethyl cellulose, carboxymethyl cellulose, hydroxy propyl cellulose, other agents known to those skilled in the art, or a combination thereof. Such agents are typically employed at a level of from 0.01% to 2% by weight.

The Formulation

[0035] The following two reactions must be considered for the chemistry of PVP-I in aqueous solutions:



[0036] The affinity of free iodine (I₂) for reaction with —OH, —SH and —NH functional groups is well described in the literature and forms the basis for the anti-microbial activity of iodine-containing solutions (Rackur H. *J. Hosp. Infect.*, 1985; 6: 13-23, and references therein). Dexamethasone (9-Fluoro-11β, 17, 21-trihydroxy-16α-methylpregna-1, 4-diene-3, 20-dione) contains three such moieties (—OH) at the 11, 17 and 21 positions. A person in the field would conclude that these hydroxyl groups would be prone to covalent substitution reactions by the free iodine generated in the solution equilibrium reaction described above for PVP-I₂.

[0037] In deriving the present formulations, experiments of combinations of various anti-inflammatories and PVP-I, or steroids and PVP-I, were performed. It was observed that most formulations were unsuccessful because of the rapid reaction between PVP-I and the added reagent (anti-inflammatory or steroid). Some of these unsuccessful formulations are described elsewhere in this disclosure. Particularly, the limiting factor for lower concentrations of PVP-I solutions is stability and efficacy as a microbicidal.

[0038] It is thus the object of the present invention to discover novel formulation of combinations of PVP-I and an anti-inflammatory to solve three problems of stability, efficacy and non-irritating to the eye. We have found, unexpectedly, that a 1% PVP-I solution is effective for treatment of infection or prophylaxis of infections when combined with dexamethasone. The literature has previously indicated that while 1% PVP-I is desirable, the side effects of ocular administration precluded its use. The undesirable side effects include pain and irritation.

[0039] It was surprising to discover that the solution of PVP-I and dexamethasone remains stable for many months.

Based on the stability data disclosed, we conjecture that the compositions of the invention may be stable for years—although experiments are still ongoing at this point. It is a further unexpected result that the reaction of dexamethasone and PVP-I does not proceed to any appreciable extent at room temperature, in light or dark, over time. Unexpectedly the reaction between the free iodine in solution and the hydroxyl groups present on the dexamethasone molecule as compounded in our formulation does not proceed.

[0040] Due to the high propensity of oxidative potential of PVP-I, the resulted stable combination of PVP-I and dexamethasone is unexpected for the average worker/scientist/physician in this field. It was observed when the concentration of PVP-I is larger than 0.5%, a stable combination formulation can be achieved. Surprisingly, it was found that 0.3% PVP-I combination with dexamethasone was much less stable. This is once again unexpected because the lower concentrations of iodine are expected to be less reactive and hence, less destructive to either parts. After 8 weeks, the available iodine in the combination (0.3% PVP-I initially) decreased by 20%. Though 0.1% diluted PVP-I has the strongest antimicrobial activity (Gottardi W. *J. Hosp. Infect.*, 1985; 6(Suppl): 1-11) our data showed we need at least 0.5% PVP-I in combination with dexamethasone to show the best antimicrobial activity. We have observed PVP-I reacted with Ketorolac (a non-steroidal anti-inflammatory) rapidly and the Ketorolac was completely consumed and the available iodine in the PVP-I complex was reduced significantly depending on the ratio between Ketorolac and PVP-I. The combination of PVP-I and dexamethasone sodium phosphate also proved to be less successful but also useful. We observed some dissociation of PVP-I complex to an unknown polymeric complex in the UV spectra and the iodine reduction is around 5% after 12 weeks. It was further observed that PVP-I reacts immediately with proparacaine and releases free iodine rapidly.

[0041] Surprisingly, the combination formulation has contributed to the stability of diluted PVP-I solution. The available iodine of a 0.625% povidone-iodine solution was 91% at 25° C. and 98% at 4° C. after 5 weeks storage, respectively. (*Iryo Yakugaku* 2003, 29(1), 62-65). Our data showed that our formulation stabilized the diluted PVP-I solution. After 8 weeks at room temperature, the available iodine in solutions with 0.5% and 1% PVP-I were over 99%.

[0042] The use of topical steroids alone is contraindicated in suspected viral and fungal infections of the human eye. Furthermore the use of combination anti-bacterial/steroid solutions is contraindicated in the setting of suspected viral infection. There are no steroid-containing solutions described that are safe for use in the human eye in the setting of presumed viral or fungal infection. It is therefore unexpected to the authors and others in the field that a steroid-containing solution would be of use in the treatment of an acute viral or fungal ocular infection.

[0043] A potent anti-inflammatory steroid allows the temperance of the potentially devastating ocular immune response in the setting of an active infection. However, due to the antiseptic (antibacterial, antiviral, and antifungal, antiprotozoal) power of PVP-I, the compound is useable in the setting of active infection without the risk of worsening the infection. This unique property (poly-antimicrobicide and potent anti-inflammatory) is a significant improvement over all other ocular antibiotics and anti-inflammatory.

[0044] Although a topical steroid is of tremendous benefit in the treatment of ocular inflammation, its use is fraught with risks. Topical steroids applied to the eye act by a variety of well described genomic and non-genomic mechanisms to reduce the production of constituent proteins of the inflammatory cascade, decrease vascular permeability, decrease the production of pro-inflammatory cytokines, decrease the potency of soluble inflammatory factors, inhibit the production of acute phase proteins, decrease leukocyte migration and increase the stability of cell membranes. Through all of these mechanisms, topically applied steroids can reduce the local concentrations of activated products toxic to the eye including the gelatinase, collagenase and matrixmetalloproteinase families of proteins. With this reduction in potentially toxic substances comes the increased risk of prolonged infection and potential infection. If the topical steroid is given in combination with an appropriate antimicrobial (i.e. and antibacterial for bacterial infection, an antiviral for viral infection, an antifungal for fungal infection) its risk can be reduced and/or eliminated. The usual practicing ophthalmologist cannot reliably distinguish the causative agent in most cases of acute external eye infection in a time frame relevant to the prescription of treatment. Thus the beneficial effects one may gain from the prompt use of topical steroids are delayed or eliminated entirely as the clinician either waits for culture results or more likely delays treatment indefinitely. The novel combination of a polymicrobicidal effective against bacteria, viruses and fungi and a topical steroid eliminates this risk and allows the immediate control of inflammation and eradication of pathogen. In our view, this is the most preferred embodiment of the present invention.

[0045] We also noted that the other components in our preferred composition appear to further stabilize the formulation. That is, the EDTA, sodium chloride, tyloxapol, sodium sulfate and hydroxyethylcellulose appear to have additional beneficial effects of further stabilizing the composition.

[0046] The invention has been described herein by reference to certain preferred embodiments. However, as obvious variations thereon will become apparent to those skilled in the art, the invention is not to be considered as limited thereto. All patents, patent applications, and references cited anywhere is hereby incorporated by reference in their entirety.

EXAMPLES

[0047] Throughout this section the letter "A" in a sample name refers to Povidone-Iodine complex ("PVP-I"), A00 refers to PVP-I at 0.0%, A03 refers to PVP-I at 0.3%, A05 refers to PVP-I at 0.5%, A10 refers to PVP-I at 1.0%, A15 refers to PVP-I at 1.5%, A20 refers to PVP-I at 2.0%, A40 refers to PVP-I at 4.0% and so on.

[0048] Similarly, the letter "B, C, D, K, P" in a sample name refers to dexamethasone, dexamethasone sodium phosphate, prednisolone sodium phosphate, ketorolac (also called ketorlac) and proparacaine, respectively. B00 refers to dexamethasone at 0.0%, B01 refers to dexamethasone at 0.1%, C01 refers to dexamethasone sodium phosphate at

0.1%, D01 refers to prednisolone sodium phosphate at 0.1%, K01 refers to ketorolac at 0.1%, and P008 refers to proparacaine at 0.08%, and so on.

Example 1

Production of Povidone-Iodine/Dexamethasone Suspensions

[0049]

Amount (wt. %)	
Povidone-Iodine (PVP-I)	0.0 to 4.0
Dexamethasone, Micronized, USP	0.1
EDTA, USP	0.01
Sodium Chloride, USP	0.3
Sodium Sulfate, USP	1.2
Tyloxapol, USP	0.05
Hydroxyethylcellulose	0.25
Sulfuric Acid and/or	q.s. for pH adjustment to 5.7-6.0
Sodium hydroxide	
Sterile water, USP	q.s. to 100

[0050] Experimental Procedures:

[0051] In a 1000 mL beaker was added 400 g sterile water, hydroxyethylcellulose (2.25 g, 0.25% w/w) was added under vigorous stirring with an overhead stirrer. Sodium chloride (2.70 g, 0.3% w/w) was slowly added while dissolving, followed by addition of EDTA (0.09 g, 0.01% w/w) and sodium sulfate (10.8 g, 1.2% w/w). After stirring for 10 minutes, tyloxapol (0.45 g, 0.05% w/w) dissolved in water was transferred into the above solution. The reaction mixture was stirred for 1 hour and q.s. to 540 g with sterile water and was stirred for another 10 minutes to give "bulk solution 1."

[0052] 60 g each of the bulk solution 1 was transferred into two 125 mL beakers, and povidone-iodine complex (0.5 g, 1.5 g) was added into the respective solution while stirring. The pH value was adjusted to the range of 5.7 to 6.0 by addition of sodium hydroxide or sulfuric acid and q.s. the suspensions to 100 g with sterile water to give control samples A05B00 and A15B00, respectively.

[0053] The remaining 417 g of the bulk solution 1 was added dexamethasone (0.7 g, 0.1% w/w) and homogenized for 5 minutes and then q.s. to 420 g to give bulk solution 2.

[0054] 60 g each of the bulk solution 2 was transferred into seven 125 mL beakers, and povidone-iodine complex (0.0 g, 0.3 g, 0.5 g, 1.0 g, 1.5 g, 2.0 g, and 4.0 g) was added into the respective solution while stirring. The pH value was adjusted to the range from 5.7 to 6.0 by addition of sodium hydroxide or sulfuric acid and q.s. the suspensions to 100 g with sterile water to give samples A00B01, A03B01, A05B01, A10B01, A15B01, A20B01 and A40B01, respectively. The LC-MS spectra of all samples confirmed the finding that there was no reaction between PVP-I and dexamethasone at all. The dexamethasone (MH⁺=392.9) peak has not been altered to other mass peaks.

Example 2

Production of Solutions of Povidone-Iodine/Dexamethasone Sodium Phosphate; Povidone-Iodine/Prednisolone Sodium Phosphate; and Povidone-Iodine/Ketorolac

[0055] In a similar manner, solutions of A00C01, A03C01, A05C01, A10C01, A15C01, A00D01, A03D01, A05D01, A10D01, A15D01, A00K01, A05K01, A10K01, and A15K01 were produced.

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[0056] The LC-MS spectra of A05C01, A10C01, and A15C01 confirmed the dexamethasone phosphoric acid (MH⁺=472.9) peak. The LC-MS spectra of A05D01, A10D01, and A15D01 confirmed the prednisolone phosphoric acid (MH⁺=440.9) peak.

[0057] However, the LC-MS experiments of A05K01 and A10K01 confirmed the finding of reaction between PVP-I and ketorolac tromethamine. For A05K01, there was a small amount of ketorolac left in the sample (MH⁺=256.1), the major peak is: MH⁺=381.9. For A10K01 and A15K01, there was no ketorolac left and has converted to a new compound (MH⁺=381.9) completely.

[0058] LC-MS experiments of A00B01P008 (control), A05B01P008 and A10B01P008 confirmed the finding of reaction between PVP-I and proparacaine. For the control, two peaks: MH⁺=295.1 (proparacaine) and MH⁺=392.9 (dexamethasone) were observed in the LC-MS spectrum. Comparing A05B01P008 with A10B01P008, the proparacaine peak (MH⁺=295.1) relative to the dexamethasone peak (MH⁺=392.9) became much smaller, which suggests povidone iodine reacted with proparacaine.

Example 3

Production of Povidone-Iodine/Dexamethasone/
Proparacaine Suspensions

[0059]

Amount (wt. %)	
PVP-I	0.0 to 1.5
Dexamethasone, Micronized, USP	0.1
Proparacaine hydrochloride, USP	0.08%
EDTA, USP	0.01
Sodium Chloride, USP	0.3
Sodium Sulfate, USP	1.2
Tyloxapol, USP	0.05
Hydroxyethylcellulose	0.25
Sulfuric Acid and/or Sodium hydroxide	q.s. for pH adjustment to 5.7-5.9
Sterile water, USP	q.s. to 100

[0060] In a 400 mL beaker was added 100 g sterile water, hydroxyethylcellulose (0.75 g, 0.25% w/w) was added under vigorous stirring with an ARROW overhead stirrer. Sodium chloride (0.9 g, 0.3% w/w) was slowly added while dissolving, followed by addition of EDTA (0.03 g, 0.01% w/w), sodium sulfate (3.6 g, 1.2% w/w) and proparacaine hydrochloride salt (0.24 g, 0.08% w/w) sequentially. After stirring for 10 minutes, tyloxapol (0.15 g, 0.05% w/w) dissolved in water was transferred into the above solution. The reaction mixture was stirred for 1 hour and dexamethasone (0.3 g, 0.1% w/w) was added and homogenized for 10 minutes and then q.s. to 180 g with sterile water to give the bulk solution 5. 60 g each of the bulk solution 5 was transferred into four 125 mL beakers, and povidone-iodine complex (0.0 g, 0.5 g, 1.0 g) was added into the respective solutions while stirring. The pH value was adjusted to around 5.8 by addition of sodium hydroxide or sulfuric acid and q.s. the solution to 100 g to afford samples A00B01P008, A05B01P008, and A10B01P008.

[0061] During the production of these samples, strong smell of iodine was observed. It was speculated that PVP-I reacted with proparacaine very rapidly. The speculation was confirmed by LC-MS spectra. The dexamethasone and pro-

paracaine peaks in the combination samples with PVP-I became very small or even disappeared.

Stability of the Solutions

[0062] The amount of titratable iodine in the solutions was determined by titration method after various week of sample storage at room temperature.

[0063] Titration Method: 5 mL of each sample was transferred into a 125 mL beaker by pipette, and 1 mL of 1% (w/v) starch indicator solution was added. The solution was titrated with 0.0025N sodium thiosulfate solution until the blue color disappeared completely. The volume of sodium thiosulfate solution used was determined.

$$\text{Titratable Iodine (mg)} = V \text{ (mL, volume used for titration)} \times 12.69 \text{ (mg/mL)} / 2$$

[0064] The calculated titratable iodine (mg) is listed in Table 1.

TABLE 1

Stability Data Summary (Available Iodine)

sample	Iodine (mg) 0 wk	Iodine (mg) After 1 wk	Iodine (mg) change %	Iodine (mg) after 8 wks	Iodine (mg) change %
CLSA05B00	2.32	2.25	-3.02		
CLSA15B00	7.31	7.17	-1.92		
CLSA03B01	1.36	1.27	-6.62	1.08	-20.59
CLSA05B01	2.27	2.32	2.2	2.25	-0.88
CLSA10B01	4.28	4.28	0	4.25	-0.7
CLSA15B01	7.28	7.36	1.1	7.52	3.3
CLSA20B01	9.87	9.9	0.3	9.71	-1.62

	Iodine (mg) (After 4 wks)	Iodine (mg) (After 12 wks)	Iodine (mg) change %
CLSA10C01	4.25	4	-5.9
CLSA15C01	6.79	6.54	-3.7
CLSA10D01	4.6	4.38	-4.8
CLSA15D01	6.44	6.41	-0.5

	0 wk	After 5 wks	
CLSA05K01	1.81	0	-100
CLSA10K01	4.54	1.87	-58.8
CLSA15K01	7.17	4.57	-36.3

[0065] The data of concentration of PVP-Iodine after weeks of storage at room temperature, either at dark or light, have suggested that stable combination formulations have been achieved for PVP-iodine combinations with dexamethasone, or dexamethasone sodium phosphate or prednisolone sodium phosphate. The 0.3% (wt. %) PVP-I combination with dexamethasone is less stable than those of above 0.5% PVP-Iodine combinations with dexamethasone, which have less than 5% alteration of the available iodine concentration after 8 weeks.

[0066] Data has also suggested PVP-I reacted with ketorolac tromethamine. At 0.5% PVP-I in the sample after five weeks, there was no titratable iodine left. At 1.5% and 1.5% of PVP-I in the samples, the titratable iodine was depleted significantly at 58.8% and 36.3%, respectively.

[0067] Stability Test of Dexamethasone in the Sample Using HPLC

[0068] The USP method was performed. The concentration of dexamethasone data is tabulated in chart form below in Table 2:

TABLE 2

Samples	concentration (mg/mL)/3 wks	concentration (mg/mL)/7 wks	Concentration change %
CLS-A05B01	0.94	0.92	-2.13
CLS-A10B01	0.86	0.90	4.65
CLS-A15B01	0.93	0.86	-7.53

[0069] HPLC spectra have shown that there were no new peaks appearing compared with standard controls. The spectra suggested that there was no reaction between PVP-Iodine and dexamethasone at all.

[0070] Stability Test of Dexamethasone Sodium Phosphate in the Sample Using HPLC

[0071] The USP method was performed. The concentration data of dexamethasone sodium phosphate is tabulated in chart form below in Table 3. A05C01 (1 day), A10C01, A15C01 (3 days) in 40° C. oven.

TABLE 3

Sample name	Initial Concentration (mg/mL)	Concentration (mg/mL)	Concentration Change %
A05C01	1.273	1.244	-2.28
A10C01	0.948	1.075	13.40
A15C01	1.355	1.148	-15.28

[0072] HPLC spectra have shown that there was a new peak appearing in the samples of A10C01 and A15C01 compared with standard controls and A05C01. The concentrations of dexamethasone sodium phosphate were altered more than 10% in the samples of A10C01 and A15C01.

[0073] In another experiment, we have found, surprisingly, that eye drops of the following formulation: 0.5 to 2% (w/w) polyvinylpyrrolidone-iodine complex; 0.05 to 0.2% (w/w) steroid; 0.005% to 0.02% (w/w) EDTA; 0.01 to 0.5% (w/w) sodium chloride; 0.02 to 0.1% (w/w) tyloxapol; 0.5% to 2% (w/w) sodium sulfate; and 0.1 to 0.5% (w/w) hydroxyethylcellulose; wherein said steroid is dexamethasone, prednisolone, prednisone, or acetate forms thereof, or sodium phosphate forms thereof were stable for 1 month, 3 months and up to 6 months. Based on data gathered so far, such a solution appears to be capable of storage of up to at least 1 year from the date for manufacturer. Stability is defined as a deviation in concentration of the major components (PVP-I and steroid) by less than 10% over a period of time. Thus, the PVP-I was not reduced to less than 90% over the period of 1 month, 3 months, and 6 months while the solution is in storage and based on our data at 6 months, it appears that the solution would be stable for at least one year. Storage conditions was at room temperature, in clear bottles, in indoor lighting of 100 to 1000 lux of incandescent and/or fluorescent lighting. The stability may be attributed to the unique combination of PVP-I and dexamethasone, prednisolone, prednisone (including acetate forms and sodium phosphate forms of these steroids). We have additionally found that the other reagents (EDTA, sodium chloride, tyloxapol, sodium sulfate; and hydroxyethylcellulose) when present, further contributed to stability.

[0074] We have found, when comparing various formulations during development, that PVP-I confers a number of advantages in the formulation. Briefly, PVP-I formulations have the following improved properties compared to an

iodine solution: (1) less irritating to the skin and eye, (2) washable, (3) increased stability, (4) increased stability in light, (5) low systemic toxicity, (6) less side effects. Also, based on current knowledge, PVP-I is neutral with respect to scar tissue formation.

Example 4

Antimicrobial Assays

[0075] Solutions of PVP-iodine combinations with various anti-inflammatory steroids were tested for antimicrobial activity against common pathogenic bacteria, yeast, fungi and viruses. The broth inoculation method of Antimicrobial Assays (USP) was used to conduct the efficacy test of the treatment of various concentrations of the solutions of PVP-iodine combinations against pure ocular isolates. It was found that the concentrations of PVP-iodine from 0.03% can dose-dependently produce the suppressing effects on microbial growth. The antimicrobial effects can be further supported by completely eliminating all species tested within 72 hours of inoculating treatment with 0.03% solution. The optimal efficacy of antimicrobial effects can be achieved at concentrations above 0.5%. Above the concentrations, the solution can effectively kill and eliminate all species tested even under a condition of immediate contact without further inoculation. For example, a solution of 1% PVP-iodine and 0.1% dexamethasone (wt %) was found to kill on contact *Pseudomonas aeruginosa*, *Proteus mirabilis*, *Serratia marcescens*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus pneumoniae*, Methicilin Resistant *Staphylococcus Aureus*, *Klebsiella pneumoniae*, *Candida parapsilosis*, *Candida albicans* and *Aspergillus niger*. The results clearly demonstrated the efficacy of the solutions on eliminating microbial growth.

Example 5

Adenovirus Testing

[0076] Solutions of PVP-iodine combinations with dexamethasone were tested for antiviral activity against human adenovirus. A 0.5 mL aliquot of each test and control article was combined with 0.5 mL of virus stock in a sterile tube. The tubes were then incubated at 37° C. for 30 minutes. AOOBOI was used as the positive control. Hank's Balanced Salt Solution (HBSS) was used as the negative control. Immediately following incubation the test and control articles were titrated for infectious HAdV-4.

TABLE 4

Antiviral Activity	
Customer Sample Number	HAdV-4 Titer (Log ₁₀ TCID ₅₀ /mL)
A00B01	4.4
A10B01	≤1.6
A15B01	≤1.6
A20B01	≤1.6
HBSS	4.0

[0077] Following a 30 minute incubation of the test articles with virus, A00B01 had no effect on virus infectivity,

but compounds A10B01, A15B01 and A20B01 resulted in complete inactivation of the virus.

Example 6

Human Eye Irritation Studies

[0078] All volunteers were examined before testing and found to have healthy eyes with no signs of disease. 1.0% PVP-Iodine solution alone was made and tried in 15 healthy volunteers. Side effects of treatment were immediately reported. The side effects found included mild pain, discomfort, tearing, and redness. This is consistent because the literature has previously indicated that 1% PVP-iodine is unsuitable for use because of irritation that is unacceptable to the patient (e.g., U.S. Pat. No. 5,126,127). From the reported side effects, it is clear that a regiment of multiple applications to the volunteers would be intolerable.

[0079] The solution of A10B01, containing 1% PVP-1 and 0.1% dexamethasone, was tested by seven healthy volunteers. Administration was by eye drop. It was surprisingly found that the solution was tolerable to the eye (does not burn) and was comfortable at a range of pH. Specifically, the formulation of pH 5.9 formulation is comfortable upon instillation into the eye. One person used the solution as an eye drop four times a day for a period of 3 days with no adverse side effects. Other pH values, such as pH 6 to 8, are obtainable either by adjusting the pH alone, with a suitable chemical such as sulfuric acid or sodium hydroxide, or by the addition of a suitable buffer.

[0080] All volunteers were examined by physicians immediately after the trial period and in further follow-up examinations after a period of time. Further, volunteers were contacted by physicians at one month, two months and three months after trial and no adverse effects were reported for any of the volunteers.

We claim:

1. An ophthalmic composition suitable for topical administration to an eye, effective for treatment and/or prophylaxis of a microorganism infection or a disorder of at least one tissue of the eye, comprising

- a) povidone-iodine in a concentration between 0.01% and 10%, and
- b) An anti-inflammatory, a steroid, or a combination thereof.

2. The ophthalmic composition of claim 1 wherein said povidone-iodine is between 0.1% and 2.5% by weight.

3. The ophthalmic composition of claim 1 wherein said povidone-iodine is between 0.5% and 2% by weight.

4. The ophthalmic composition of claim 1 wherein a total weight of said povidone-iodine, said anti-inflammatory, and said steroid is between 0.1% and 4.5% in said solution.

5. The ophthalmic composition of claim 1 wherein said anti-inflammatory agent is selected from the group consisting of ketotifen fumarate, diclofenac sodium, flurbiprofen sodium, ketorlac tromethamine, suprofen, celecoxib, naproxen, rofecoxib, and a combination thereof.

6. The ophthalmic composition of claim 1 wherein said steroid is at a concentration of between 0.01 and 10%.

7. The ophthalmic composition of claim 1 wherein said steroid is at a concentration of between 0.05 and 2%.

8. The ophthalmic composition of claim 1 wherein said steroid is selected from the group consisting of dexametha-

sone, dexamethasone alcohol, dexamethasone sodium phosphate, and salts, esters, and derivatives and combinations thereof.

9. The ophthalmic composition of claim 1 wherein said steroid is selected from the group consisting of fluomethalone acetate, fluomethalone alcohol, lotoprendol etabonate, medrysone, prednisolone, prednisone, prednisolone acetate, prednisolone sodium phosphate, rimexolone, hydrocortisone, hydrocortisone acetate, Iodoxamide tromethamine and a combination thereof.

10. The ophthalmic composition of claim 1 wherein said composition further comprises a topical anesthetic which relieves pain.

11. The ophthalmic composition of claim 10 wherein said topical anesthetic is selected from the group consisting of proparacaine, lidocaine, tetracaine and a combination thereof.

12. The ophthalmic composition of claim 1 wherein said composition further comprises a penetration enhancer which enhances the penetration of povidone-iodine into the tissues of the eye.

13. The ophthalmic composition of claim 12 wherein said penetration enhancer is a topical anesthetic.

14. The ophthalmic composition of claim 1 wherein said composition further comprises an antimicrobial preservative.

15. The ophthalmic composition of claim 14 wherein said antimicrobial preservative is selected from the group consisting of benzalkonium chloride, thimerosal, chlorobutanol, methyl paraben, propyl paraben, phenylethyl alcohol, EDTA, sorbic acid, Onamer M and a combination thereof.

16. The ophthalmic composition of claim 14 wherein said antimicrobial preservative is at a concentration of about 0.001% to 1.0% by weight in said solution.

17. The ophthalmic composition of claim 1 wherein said composition further comprises a co-solvent/surfactant.

18. The ophthalmic composition of claim 17 wherein said co-solvent/surfactant is selected from the group consisting of polysorbate 20, polysorbate 60, polysorbate 80, Pluronic F-68, Pluronic F-84, Pluronic P-103, cyclodextrin, tyloxapol and a combination thereof.

19. The ophthalmic composition of claim 17 wherein said co-solvent/surfactant is at a concentration of about 0.01% to 2% by weight in said composition.

20. The ophthalmic composition of claim 1 wherein said composition further comprises viscosity increasing agent.

21. The ophthalmic composition of claim 20 wherein said viscosity increasing agent is selected from the group consisting of polyvinyl alcohol, polyvinyl pyrrolidone, methyl cellulose, hydroxy propyl methylcellulose, hydroxyethyl cellulose, carboxymethyl cellulose, hydroxy propyl cellulose, and a combination thereof.

22. The ophthalmic composition of claim 20 wherein said viscosity increasing agent is at a concentration of about 0.01% to 2% by weight in said solution.

23. The ophthalmic composition of claim 1, wherein said composition is in the form of a solution, suspension, emulsion, ointment, cream, gel, or a controlled-release/sustained-release vehicle.

24. The ophthalmic composition of claim 1, wherein said microorganism is selected from the group consisting of bacteria, viruses, fungi, and amoebae.

25. The ophthalmic composition of claim 24 wherein said bacteria is mycobacteria.

26. The ophthalmic composition of claim 1 wherein said eye disorder is selected from the group consisting of a microorganism infection of at least one tissue of the eye, conjunctivitis, corneal abrasion, ulcerative infectious keratitis, epithelial keratitis, stromal keratitis and herpesvirus-related keratitis.

27. The ophthalmic composition of claim 1 wherein said prophylaxis is prophylaxis of infection following corneal abrasion or ocular surgery.

28. The ophthalmic composition of claim 1, comprising: 0.5 to 2% (w/w) polyvinylpyrrolidinone-iodine complex; 0.05 to 2% (w/w) steroid; 0.005% to 0.02% (w/w) EDTA; 0.01 to 0.5% (w/w) sodium chloride; 0.02 to 0.1% (w/w) tyloxapol; 0.5% to 2% (w/w) sodium sulfate; and 0.1 to 0.5% (w/w) hydroxyethylcellulose;

wherein said steroid is selected from the group consisting of dexamethasone, prednisolone, prednisone, acetate forms thereof, and sodium phosphate forms thereof.

29. The ophthalmic composition of claim 1, comprising: 1.0% (w/w) polyvinylpyrrolidinone-iodine complex; 0.1% (w/w) steroid; 0.01% (w/w) EDTA; 0.3% (w/w) sodium chloride salt; 0.05% (w/w) tyloxapol; 0.2% (w/w) sodium sulfate; and 0.25% (w/w) hydroxyethylcellulose

wherein said steroid is selected from the group consisting of dexamethasone, prednisolone, prednisone, acetate forms thereof, and sodium phosphate forms thereof.

30. The ophthalmic composition of claim 1 wherein said composition retains 90% of its polyvinylpyrrolidinone-iodine and 90% of its steroid after a period of 3 months in a lighted environment.

31. The ophthalmic composition of claim 1 wherein said composition retains 90% of its polyvinylpyrrolidinone-iodine and 90% of its steroid after a period of 1 year in a lighted environment.

32. The ophthalmic composition of claim 1 wherein said composition is an aqueous solution.

33. A method for treating and/or prophylaxis of an eye disorder or a microorganism infection of at least one tissue of the eye comprising the step of administering one of more doses of an ophthalmic composition of claim 1 to said eye.

34. The method of claim 33 wherein said prophylaxis is prophylaxis of infection following corneal abrasion or ocular surgery.

35. The method of claim 33 wherein said eye disorder is selected from the group consisting of a microorganism infection of at least one tissue of the eye, conjunctivitis, corneal abrasion, ulcerative infectious keratitis, epithelial keratitis, stromal keratitis and herpesvirus-related keratitis.

36. The method of claim 33, wherein said microorganism is a bacteria, virus, fungi, or amoebae.

37. The method of claim 36 wherein said bacteria is mycobacteria.

38. The method of claim 33 wherein the sum of said povidone-iodine, said anti-inflammatory, and said steroid is between 0.001 mg to 5 mg per dose.

39. The method of claim 33 wherein each dose is between 10 microliters to 200 microliters.

40. The method of claim 33 wherein each dose is between 50 microliters to 80 microliters.

41. The method of claim 33 wherein said administering comprises administering said solution to said eye one to four times a day.

42. The method of claim 33 wherein said administering comprises administering said solution to said eye one to twenty-four times a day.

43. The method of claim 33 further comprising the step of storing the composition for at least one month, at least three months, at least six months, or at least 1 year before said administration step.

44. The method of claim 43 wherein said storing is in a lighted environment.

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