Industria y Comercio
SUPERINTENDENCIA

FORMULARIO UNICO DE OPOSICION
2000-12

1 **OPOSICION A:**

- [x] Patente de Invención
- [ ] Patente de Modelo de Utilidad
- [ ] Diseño Industrial
- [ ] Esquema de Trazado para Circuitos Integrados
- [ ] Marcas de Productos o Servicios
- [ ] Marca Colectiva
- [ ] Marca de Certificación
- [ ] Lema Comercial

2 **SOLICITUD PUBLICADA**

Número del expediente: 07 055.028
Solicitante: JOHNSON & JOHNSON CONSUMER COMPANIES, INC.
Apoderado: JIMENA ESCOBAR URIBE.
Título de la nueva creación o denominación del signo: COMPOSICIONES Y MÉTODOS PARA TRATAR IRRITACIÓN Y EQUIPO DEL MISMO.
Gaceta: 596 de 30 de Septiembre de 2008, número de publicación 868.

3 **OPOSICION PRESENTADA POR:**

OPOSITOR	Nombre: **Lafrancol S.A.** Dirección: **Carrera 1 No. 46-84** Teléfono: **(092) 449.30.51** Fax: Domicilio: **Cali – Valle**	**IDENTIFICACION** C.C. ☐ NIT ☒ C.E. ☐ Otro ☐ Número: **890 301 463 -8**
REPRESENTANTE O APODERADO (74)	Nombre: **José Luis Reyes Villamizar** Dirección: **Cra. 17 No. 88-23, Of. 205** Teléfono: **621.26.31** E-mail: **info@reyes-abogados.com** Fax: **621.25.42** Domicilio: **Bogotá, D.C.**	**IDENTIFICACION** C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Número: **79'152.473 de Usaquén** **TP 44655**

4 **FUNDAMENTOS DE LA OPOSICION:**

Causal: Incumplimiento de requisitos de patentabilidad (Título II, Capítulo I, Decisión 486 de 2000). Se violan los artículos 14, 16 (las patentes de invención deben ser nuevas, tener nivel inventivo y ser suceptibles de aplicación industrial),18 (una invención tiene nivel inventivo si no es obvia para una persona versada en la materia).

Justificación: VER ANEXO

5 **Comprobante de pago No.** 08 - 101.582 (Oposición) **Fecha** Diciembre 30 de 2008
_____ (Prórroga) Fecha _____

6 **Anexos:**

- [x] Comprobante de pago de la tasa
- [x] Poderes, si fuere el caso
- [x] Pruebas de los fundamentos de la oposición
- [x] Certificado de existencia y representación legal de las partes, cuando sean personas jurídicas
- [ ] Documentos que acrediten el legítimo interés, si fuere el caso
- [x] Copia de la oposición para el traslado al solicitante.

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NOMBRE: JOSÉ LUIS REYES VILLAMIZAR

FIRMA: _____

C.C.No. 79.152.473 T.P. No. 44655

REYES & REYES
A B O G A D O S

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Señor
SUPERINTENDENTE DE INDUSTRIA Y COMERCIO
E. S. D.

REF: **Expediente 07 055.028**

TÍTULO SOLICITADO: **COMPOSICIONES Y MÉTODOS PARA TRATAR IRRITACIÓN Y EQUIPO DEL MISMO.**

PUBLICACIÓN: **Gaceta 596 de 30 de Septiembre de 2008, número de publicación 868.**

PRIORIDAD: **US 60/632,151 de 01/12/2004**

SOLICITANTE: **JOHNSON & JOHNSON CONSUMER COMPANIES, INC.**

APODERADO: **JIMENA ESCOBAR URIBE**

TRÁMITE: **PRESENTACIÓN DE OPOSICION**

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 **LABORATORIO FRANCO COLOMBIANO S.A., LAFRANCOL 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 **07 055.028**, por no cumplir con lo dispuesto por los artículos 14, 16, 18 y 20 literal d) de la Decisión 486 de 2000, con base en los fundamentos que se expondrán a continuación.

(69)

II. LEGÍTIMO INTERÉS

Asiste a **LABORATORIO FRANCO COLOMBIANO S.A., LAFRANCOL 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. FUNDAMENTO DE LA OPOSICIÓN

La solicitud colombiana en trámite que reivindica un método para tratar una condición vaginal (infección) a través de una composición que contiene un principio activo (antiviral, antifúngico o antibiótico), un agente mejorador (anestésico local o antihistamínico), un ingrediente refrescante (alcoholes inferiores, mentol, alcanfor y azucares como sorbitol) y un portador farmacéuticamente aceptable, a través de un dispositivo de aspersión de bomba invertida o de aerosol; incumple con los requisitos indispensables para otorgársele el privilegio de patente de invención tal y como se demuestra con los siguientes argumentos:

Para comenzar, todas las reivindicaciones de dicha solicitud colombiana en trámite incurren en una improcedencia directa de patentabilidad, en cuanto a que explícitamente se refieren a un tratamiento terapéutico, que involucra la aplicación de una formulación farmacéutica que contiene un principio activo (antiviral, antifúngico o antibiótico), un agente mejorador (anestésico local o antihistamínico), un ingrediente refrescante (alcoholes inferiores, mentol, alcanfor y azucares como sorbitol) y un portador farmacéuticamente aceptable, a través de un dispositivo de aspersión de bomba invertida o de aerosol, para así tratar la sintomatología asociada a una infección vaginal; lo cual va en contra de lo

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expuesto por la decisión 486 de 2000 que explícitamente revela en su articulo 20 literal d) "*No serán patentables (...) los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnostico aplicados a los seres humanos o a animales.*"

En segundo lugar y si lo anteriormente expuesto no fuese suficiente para no otorgársele el privilegio de patente de invención a dicha solicitud en trámite; existen también muchos documentos que exponen con anterioridad, información que contiene la esencia de lo reivindicado por la misma, y que por lo tanto demuestran la carencia de novedad y de nivel inventivo de la misma, veamos:

- La publicación internacional WO 00/56353 publicada el 28 de septiembre de 2000 revela:

1. A uro-genital condition treatment system comprising:

a carrier;

at least one polypeptide including an amino acid sequence selected from a group consisting of KPV (SEQ. ID. NO. 1), MEHFRWG (SEQ. ID. NO. 2), HFRWGKPV (SEQ. ID. NO. 3), SYSMEHFRWGKPV (SEQ. ID. NO. 4), or a biologically functional equivalent of any of the foregoing; and

wherein the carrier carries the at least one polypeptide.

(...)

8. The uro-genital condition treatment system of claim 7 wherein a part of the applicator is for insertion into the vagina, urethra, or rectum.

9. The uro-genital condition treatment system of claim 1 wherein the uro-genital condition is an infection, inflammation, or both.

(...)

25. The uro-genital condition treatment system of claim 1 wherein the uro-genital condition includes vaginitis.

(...)

51. The method of claim 49 wherein the local application is achieved through a cream, an ointment, a balm, a gel, an aerosol foam, an aerosol spray, or a dissolvable pill.

❖ La publicación internacional WO 99/27922 publicada el 10 de Junio de 1999 revela:

1. The use of polyols for the preparation of a composition to be administered in the treatment or prophylaxis of mucosal yeast infection in mammals, comprising mixing at least one pharmacologically acceptable carrier with an amount of polyol sufficient to reduce or inhibit mucosal infection caused by yeasts such as *Candida s.p.* in said mammal.

2. The use according to claim 1 wherein the polyol is selected from the group consisting of xylitol, lactitol, sorbitol, mannitol and mixtures therof, preferably xylitol.

(...)

7. The use according to any one of the preceding claims, wherein said mucosal yeast infection is a vaginal infection.

(...)

10. The use according to claim 9, wherein said composition is prepared in the form of an orally administrable preparation selected from the group comprising a liquid, a tablet, a pill, a chewing gum or tablet, a powder, a spray, a syrup, a sugar substitute, a candy or sweet, an ice-cream, a pet food, an animal feed, and the like, by mixing at least one pharmacologically acceptable carrier and an amount of xylitol sufficient to reduce or inhibit the infectious activity of yeasts on the mucosa of said mammal.

(...)

12. The use according to claim 10 or 11, wherein said composition additionally includes another antifungal drug effective against said yeast infection.

13. The use according to claim 9, wherein said composition is prepared in the form of a topically administrable preparation selected from the group comprising a liquid, a spray, an aerosol, a cream, a paste, a cement, an ointment, a jelly or gel, a lubricant, a plaster, a membrane, a mouth wash or rinse, a tooth paste, and eye drops, by mixing at least one topical carrier and an amount of xylitol sufficient to reduce or inhibit the infectious activity of yeasts on the mucosa of said mammal.

14. The use according to claim 7 or 13, wherein said composition is in a form suitable for vaginal yeast infection and xylitol is included in a cream, jelly, lubricant, or liquid or is applied onto the surface of a condom.

(...)

16. A device suitable for the treatment or prophylaxis of mucosal yeast infection in mammals, characterized in that it comprises a condom having polyol added thereto for administration of polyol into an orifice of the body, such as vagina.

❖ La publicación internacional WO 01/13956 publicada el 01 de Marzo de 2008 revela:

1. A composition comprising a lactic acid-producing bacterial species in a pharmaceutically-acceptable carrier which is suitable for topical application to skin or a mucous membrane of a mammal and Emu Oil.

(...)

10. The composition of claim 1, wherein said carrier is selected from a group comprising an emulsion, cream, lotion, gel, oil, ointment, suspension, aerosol spray, powder, aerosol powder, or semi-solid formulation.

(...)

17. The composition of claim 1, further comprising one or more anti-microbial agents selected from a group consisting of: a quartenary ammonium chloride, an iodine or iodifer compound, a phenolic compound, and an alcohol compound or tincture.

18. The composition of claim 1, further comprising one or more systemic anti-fungal compounds selected from a group consisting of: Amphotericin B, Dapsone, Fluconazole, Flucytosine, Griseofulvin, Itraconazole, Ketoconazole, and Miconazole KI.

19. The composition of claim 1, further comprising one or more topical anti-fungal compounds selected from a group consisting of: Amphotericin B, Carbol-Fuchsin, Ciclopirox, Clotrimzole, Econazole, Haloprogin, Ketoconazole, Mafenide, Miconazole, Naftifine, Nystatin, Oxiconazole, Silver Sulfadiazine, Sulconazole, Terbinafine, Tioconazole, Tolnaftate, and Undecylenic acid.

20. The composition of claim 1, further comprising one or more vaginal anti-fungal compounds selected from a group consisting of: Butoconazle, Clotrimazole, Econazole, Gentian Violet, Miconazole, Nystatin, Terconazole, and Tioconazole.

Como se puede apreciar claramente, en estas anterioridades se revela la formulación de compuestos anti-infecciosos para la aplicación vaginal, a través de

formulaciones tipo spray, aerosol y crema; así como la mención explícita del uso de polióles dentro de dicha formulación, específicamente el uso de sorbitol.

En el mismo sentido, y teniendo en cuenta que cualquier persona medianamente versada en la materia, reconoce que dentro la sintomatología de una infección vaginal, especialmente por hongos, la comezón y/o el escozor son unos de los síntomas que resultan mas molestos; es entonces mas que obvia la asociación entre los agentes anti-infecciosos usados para dado caso y los agentes anestésicos locales o antihistamínicos, lo cual se puede confirmar a través de la publicación de diversos documentos. Dentro de algunos de estos documentos se pueden mencionar la patente europea EP 1206937 publicada el 22 de Mayo de 2002 en donde se exponen en el capitulo reivindicatorio la combinación de derivados de nitromidazol con dichos agentes antihistamínicos o anestésicos locales en el tratamiento de candidiasis vaginal. Por su parte la publicación internacional WO 03/032985 publicada el 24 de Abril de 2003 también menciona el tratamiento de infecciones fúngicas o bacteriales a nivel vaginal a través de la combinación de diversos agentes activos y el uso concomitante de anestésicos locales. Así mismo la patente americana US 4478822 publicada el 23 de octubre de 1984 revela nuevamente composiciones para aplicación vaginal que contienen diversos agentes anti-infecciosos en combinación con agentes antihistamínicos y/o anestésicos locales.

Para finalizar, y teniendo en cuenta que la solicitud colombiana reivindica también que la aspersión de dicha formulación farmacéutica se hace a través de dispositivos del tipo botella de aspersión de bomba invertida y/o una botella de aspersión de aerosol invertida; es relevante también mencionar que existen con anterioridad, una gran diversidad de documentos que revelan dispositivos con las mismas características técnicas, y muchos de estos implicados en la administración de fármacos, tal y como sucede en el capítulo reivindicatorio de la solicitud colombiana en tramite en cuestión. Dentro de algunos de estos documentos se pueden mencionar la patente americana US 2345854 publicada el 04 De Abril de n1944; la patente americana US 3043524 publicada el 10 de Julio de 1962; la patente europea EP 1222938 publicada el 17 de Julio de 2002; la patente americana US 6708846 publicada el 23 de marzo de 2004; la patente americana US 3818908 publicada el 25 de Junio de 1974 y la patente americana US 4702415 publicada el 27 de Octubre de 1987.

En conclusión, la solicitud colombiana en trámite carece absolutamente de todos los requisitos fundamentales para otorgársele el privilegio de patente de invención; primero que todo, porque incurre en una improcedencia directa de patentabilidad al reivindicar un método terapéutico, y en segundo lugar, y como ha quedado demostrado, carece de novedad y de nivel inventivo, puesto que todos los aspectos esenciales que resumen la invención de dicha solicitud, se encuentran descritos con anterioridad en el mismo estado de la técnica.

Así las cosas, y con fundamento en los argumentos expuestos a lo largo del presente escrito, respetuosamente reitero la solicitud para que su despacho se abstenga de conceder el privilegio de patente solicitado, y ordene en consecuencia el archivo del expediente respectivo.

IV. FUNDAMENTOS DE DERECHO

Son fundamentos de derecho el Capítulo I, artículos **14, 16, 18 y 20 literal d)** de (Requisitos de Patentabilidad) y el artículo 42 (Oposiciones) de la Decisión 486 de 2000.

V. PRUEBAS

Ruego que se tengan como tales, sin perjuicio de las que puedan presentarse al vencimiento de la prórroga solicitada, y de aquellas que el Despacho considere oficiosamente, las siguientes:

- Capítulos reivindicatorios de todos los documentos mencionados en el acápite de Fundamentos de la Oposición.

VI. ANEXOS

Para efectos del trámite correspondiente, me permito anexar al presente escrito los siguientes anexos

1. Certificado de existencia y representación legal de de LAFRANCOL S.A.
2. Poder para actuar.
3. Constancia de pago de las tasas de tramitación de oposición.
4. Copia para correr traslado al solicitante.
5. El mencionado en el acápite de pruebas.

VIII. NOTIFICACIONES

El suscrito recibirá notificaciones en la secretaría de su Despacho o en mi oficina localizada en la Carrera 17 No. 88-23, Oficina 207, Fax (1) 621.25.42 de esta ciudad. Tecnoquímicas S.A., las recibirá en la secretaría de su Despacho o en su sede localizada en la Calle 23 # 7-39, de la ciudad de Cali.

Señor Superintendente,

JOSÉ LUIS REYES VILLAMIZAR
C.C. 79'152.473 de Usaquén
T.P.A. 44.655 del C.S.J.

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

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60/126,233 24 March 1999 (24.03.99) US

(71) Applicant *(for all designated States except US)*: ZENGEN INC. [US/US]; Suite 980, 21800 Oxnard Street, Woodland Hills, CA 91367 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: LIPTON, James [US/US]; 5800 Owensmouth Street #10, Woodland Hills, CA 91367 (US). CATANIA, Anna [IT/IT]; #15 Corsa Italia, I-20122 Milan (IT).

(74) Agent: WISE, Michael; Lyon & Lyon LLP, 633 West Fifth Street, Los Angeles, CA 90071 (US).

(81) Designated States: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

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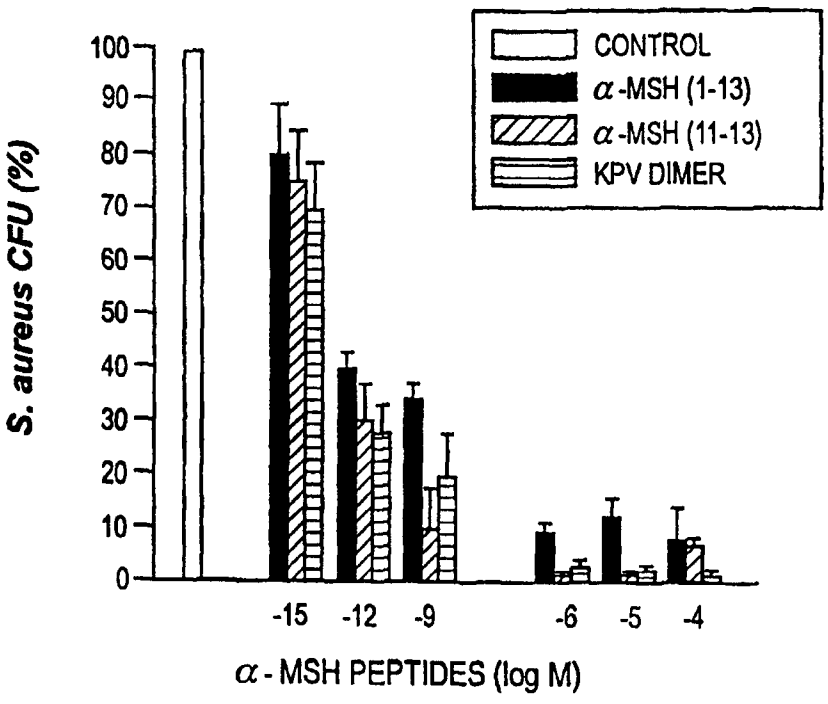
Without international search report and to be republished upon receipt of that report.

(54) Title: A URO-GENITAL CONDITION TREATMENT SYSTEM

(57) Abstract

The present invention is directed to a system for treating uro-genital conditions. One aspect of this invention involves the treatment system comprising one or more polypeptides with an amino acid sequence including KPV (SEQ. ID. NO. 1), MEHFRWG (SEQ. ID. NO. 2), HFRWGKPV (SEQ. ID. NO. 3), SYSMEHFRWGKPV (SEQ. ID. NO. 4), for treatment of uro-genital conditions. The one or more polypeptides can also be a dimer formed from any of the amino acid sequence above. Uro-genital conditions can include infections, inflammation, or both. In one preferred embodiment of the invention, the uro-genital condition includes infection and/or inflammation of the vagina, vulva, urinary tract, penis, and/or the rectum. In another preferred embodiment of the invention, the one or more polypeptides are dissolved in a carrier. In another preferred embodiment of the invention, the one or more polypeptides are associated with a tampon for preventing toxic shock syndrome. In another preferred embodiment, the one or more polypeptides are associated with a contraceptive for prevention of sexually transmitted diseases or infections. In another preferred embodiment, the one or more polypeptides are associated with a suppository for insertion into the vagina or rectum.



WHAT IS CLAIMED IS:

1. A uro-genital condition treatment system comprising:

a carrier;

at least one polypeptide including an amino acid sequence selected from a group consisting of KPV (SEQ. ID. NO. 1), MEHFRWG (SEQ. ID. NO. 2), HFRWGKPV (SEQ. ID. NO. 3), SYSMEHFRWGKPV (SEQ. ID. NO. 4), or a biologically functional equivalent of any of the foregoing; and

wherein the carrier carries the at least one polypeptide.

2. The uro-genital condition treatment system of claim 1 wherein the at least one polypeptide includes a dimer formed from any amino acid sequence in the group in claim 1.

3. The uro-genital condition treatment system of claim 2 wherein the dimer is a KPV dimer.

4. The uro-genital condition treatment system of claim 1 wherein the amino acid sequence KPV (SEQ. ID. NO. 1), HFRWGKPV (SEQ. ID. NO. 3), or SYSMEHFRWGKPV (SEQ. ID. NO. 4) is located at the C-terminal of the at least one polypeptide.

5. The uro-genital condition treatment system of claim 1 wherein the amino acid sequence KPV (SEQ. ID. NO. 1), MEHFRWG (SEQ. ID. NO. 2), HFRWGKPV (SEQ. ID. NO. 3), SYSMEHFRWGKPV (SEQ. ID. NO. 4), includes at least one amino acid in the D-form.

6. The uro-genital condition treatment system of claim 1 wherein the at least one polypeptide is N-acetylated or C-amidated or both.

7. The uro-genital condition treatment system of claim 1 further comprises an applicator for applying the carrier to a site of the uro-genital condition.

8. The uro-genital condition treatment system of claim 7 wherein a part of the applicator is for insertion into the vagina, urethra, or rectum.

9. The uro-genital condition treatment system of claim 1 wherein the uro-genital condition is an infection, inflammation, or both.

10. The uro-genital condition treatment system of claim 1 wherein the uro-genital condition includes the presence of bacteria or fungi in a uro-genital area.

11. The uro-genital condition treatment system of claim 1 wherein the uro-genital condition includes the presence of a virus in a uro-genital area.

12. The uro-genital condition treatment system of claim 1 the uro-genital condition is caused by a bacterial infection or a fungal infection or both.

13. The uro-genital condition treatment system of claim 1 wherein the uro-genital condition is caused by a viral infection, bacterial infection, fungal infection, or any combination thereof.

14. The uro-genital condition treatment system of claim 10 wherein the bacteria is a gram-positive bacteria.

15. The uro-genital condition treatment system of claim 10 wherein the bacteria is from the genus of *Staphylococcus*.

16. The uro-genital condition treatment system of claim 10 wherein the bacteria is *Staphylococcus aureus*.

17. The uro-genital condition treatment system of claim 10 wherein the fungi is from the genus *Candida*.

18. The uro-genital condition treatment system of claim 10 wherein the fungi is *Candida albicans*.

19. The uro-genital condition treatment system of claim 11 wherein the virus is a HIV.

20. The uro-genital condition treatment system of claim 11 wherein the virus is HSV.

21. The uro-genital condition treatment system of claim 1 wherein the uro-genital condition is located in a female reproductive cavity or on a genitalia or both.

22. The uro-genital condition treatment system of claim 1 wherein the uro-genital condition is located in the urinary tract.

23. The uro-genital condition treatment system of claim 1 wherein the uro-genital condition is located on a penis.

24. The uro-genital condition treatment system of claim 1 wherein the uro-genital condition is located in a rectal cavity or on a rectal area or both.

25. The uro-genital condition treatment system of claim 1 wherein the uro-genital condition includes vaginitis.

26. The uro-genital condition treatment system of claim 1 wherein the uro-genital condition includes cystitis or urethritis.

27. The uro-genital condition treatment system of claim 1 wherein the uro-genital condition includes balanoposthitis.

28. The uro-genital condition treatment system of claim 1 whercin the carrier is a cream, an ointment, a balm, an aerosol foam, an aerosol spray, or a dissolvable pill.

29. A tampon comprising:

an absorbent material;

at least one polypeptide including an amino acid sequence selected from the group consisting of KPV (SEQ. ID. NO. 1), MEHFRWG (SEQ. ID. NO. 2), HFRWGKPV (SEQ. ID. NO. 3), SYSMEHFRWGKPV (SEQ. ID. NO. 4), or a biologically functional equivalent of any of the foregoing; and

wherein the absorbent material is associated with the at least one polypeptide.

30. The tampon of claim 29 wherein the at least one polypeptide includes a dimer formed from any amino acid sequence in the group in claim 29.

31. The tampon of claim 30 wherein the dimer is a KPV dimer.

32. The tampon of claim 29 wherein the amino acid sequence KPV (SEQ. ID. NO. 1), HFRWGKPV (SEQ. ID. NO. 3), or SYSMEHFRWGKPV (SEQ. ID. NO. 4) is located at the C-terminal of the at least one polypeptide.

33. The tampon of claim 29 wherein the amino acid KPV (SEQ. ID. NO. 1), MEHFRWG (SEQ. ID. NO. 2), HFRWGKPV (SEQ. ID. NO. 3), SYSMEHFRWGKPV (SEQ. ID. NO. 4) includes at least one amino acid in the D-form.

34. The tampon of claim 29 wherein the at least one polypeptide is N-acetylated or C-amidated or both.

35. A contraceptive comprising:

a barrier;

a carrier associated with the barrier;

at least one polypeptide including an amino acid sequence selected from the group consisting of KPV (SEQ. ID. NO. 1), MEHFRWG (SEQ. ID. NO. 2), HFRWGKPV (SEQ. ID. NO. 3), SYSMEHFRWGKPV (SEQ. ID. NO. 4), or a biologically functional equivalent of any of the foregoing; and

wherein the carrier carries the at least one polypeptide.

36. The contraceptive of claim 35 wherein the at least one polypeptide includes a dimer formed from any amino acid sequence in the group in claim 35.

37. The contraceptive of claim 36 wherein the dimer is a KPV dimer.

38. The contraceptive of claim 35 wherein the amino acid KPV (SEQ. ID. NO. 1), HFRWGKPV (SEQ. ID. NO. 3), or SYSMEHFRWGKPV (SEQ. ID. NO. 4) is located at the C-terminal of the at least one polypeptide.

39. The contraceptive of claim 35 wherein the amino acid sequence KPV (SEQ. ID. NO. 1), MEHFRWG (SEQ. ID. NO. 2), HFRWGKPV (SEQ. ID. NO. 3), SYSMEHFRWGKPV (SEQ. ID. NO. 4) includes at least one amino acid in the D-form.

40. The contraceptive of claim 35 wherein the at least one polypeptide is N-acetylated or C-amidated or both.

41. The contraceptive of claim 35 wherein the barrier is a condom, a diaphragm, or a sponge.

42. A suppository comprising:

a carrier;

at least one polypeptide including an amino acid sequence selected from the group consisting of KPV (SEQ. ID. NO. 1), MEHFRWG (SEQ. ID. NO. 2), HFRWGKPV (SEQ. ID. NO. 3), SYSMEHFRWGKPV (SEQ. ID. NO. 4), or a biologically functional equivalent of any of the foregoing; and

wherein the carrier carries the at least one polypeptide.

43. The suppository of claim 42 wherein the at least one polypeptide includes a dimer formed from any amino acid sequence in the group in claim 42.

44. The suppository of claim 43 wherein the dimer is a KPV dimer.

45. The suppository of claim 42 wherein the amino acid sequence KPV (SEQ. ID. NO. 1), HFRWGKPV (SEQ. ID. NO. 3), or SYSMEHFRWGKPV (SEQ. ID. NO. 4) is located at the C-terminal of the at least one polypeptide.

46. The contraceptive of claim 42 wherein the amino acid sequence KPV (SEQ. ID. NO. 1), MEHFRWG (SEQ. ID. NO. 2), HFRWGKPV (SEQ. ID. NO. 3), SYSMEHFRWGKPV (SEQ. ID. NO. 4) includes at least one amino acid in the D-form.

47. The suppository of claim 42 wherein the at least one polypeptide is N-acetylated or C-amidated or both.

48. A method of treating uro-genital condition comprising:

using at least one polypeptide including an amino acid sequence selected from the group consisting of KPV (SEQ. ID. NO. 1), MEHFRWG (SEQ. ID. NO. 2), HFRWGKPV (SEQ. ID. NO. 3), SYSMEHFRWGKPV (SEQ. ID. NO. 4), or a biologically functional equivalent of any of the foregoing.

49. The method of claim 49 further comprising:

locally applying the at least one polypeptide at a site of the uro-genital condition.

50. The method of claim 49 wherein the local application is achieved through a suppository, a tampon, or a contraceptive.

51. The method of claim 49 wherein the local application is achieved through a cream, an ointment, a balm, a gel, an aerosol foam, an aerosol spray, or a dissolvable pill.

52. The method of claim 48 wherein the at least one polypeptide includes a dimer formed from any amino acid sequence in the group in claim 48.

53. The method of claim 52 wherein the dimer is a KPV dimer.

54. The method of claim 48 wherein the amino acid sequence KPV (SEQ. ID. NO. 1), HFRWGKPV (SEQ. ID. NO. 3), or SYSMEHFRWGKPV (SEQ. ID. NO. 4) is located at the C-terminal of the at least one polypeptide.

55. The method of claim 48 wherein the amino acid sequence KPV (SEQ. ID. NO. 1), MEHFRWG (SEQ. ID. NO. 2), HFRWGKPV (SEQ. ID. NO. 3), SYSMEHFRWGKPV (SEQ. ID. NO. 4) includes at least one amino acid in the D-form.

56. The method of claim 48 wherein the at least one polypeptide is N-acetylated or C-amidated or both.

57. A method of preventing toxic shock syndrome comprising:

using at least one polypeptide including an amino acid sequence selected from the group consisting of KPV (SEQ. ID. NO. 1), MEHFRWG (SEQ. ID. NO. 2), HFRWGKPV (SEQ. ID. NO. 3), SYSMEHFRWGKPV (SEQ. ID. NO. 4), or a biologically functional equivalent of any of the foregoing.

58. The method of claim 57 wherein the toxic shock syndrome is associated with toxic shock syndrome toxin-1 produced by *Staphylococcus aureus*.

59. The method of claim 57 further comprising:

locally applying the at least one polypeptide in the vagina.

60. The method of 59 wherein the local application is achieved through a tampon.

61. The method of 57 wherein the at least one polypeptide is associated with a tampon.

62. A method for preventing infection from sexually transmitted diseases comprising:

using a contraceptive together with at least one polypeptide including an amino acid sequence selected from the group consisting KPV (SEQ. ID. NO. 1), MEHFRWG (SEQ. ID. NO. 2), HFRWGKPV (SEQ. ID. NO. 3), SYSMEHFRWGKPV (SEQ. ID. NO. 4), or a biologically functional equivalent of any of the foregoing.

63. A method of claim 62 wherein the contraceptive is a condom, a diaphragm, or a sponge.

64. A method of claim 63 wherein at least one polypeptide is carried by a lubricant present on the condom.

65. A method of treating an antibiotic resistant microorganism comprising:

using at least one polypeptide including an amino acid sequence selected from the group consisting of KPV (SEQ. ID. NO. 1), MEHFRWG (SEQ. ID. NO. 2), HFRWGKPV

(SEQ. ID. NO. 3), SYSMEHFRWGKPV (SEQ. ID. NO. 4), or a biologically functional equivalent of any of the foregoing.

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(54) Title: THE USE OF POLYOLS IN COMBATING YEAST INFECTION AND POLYOL PREPARATIONS FOR SAID USE

(57) Abstract

The invention relates to the use of polyols such as xylitol for the preparation of a composition to be administered in the treatment or prophylaxis of mucosal yeast infection in mammals, as well as to preparations for use in the systemic or topical therapeutic or prophylactic treatment of mucosal yeast infections. The invention relates specifically but not solely to the combating of infections caused by *Candida s.p.* in mucosa in connection with exocrine glands of the mammalian body.

Claims

1. The use of polyols for the preparation of a composition to be administered in the treatment or prophylaxis of mucosal yeast infection in mammals, comprising mixing at least one pharmacologically acceptable carrier with an amount of polyol sufficient to reduce or inhibit mucosal infection caused by yeasts such as *Candida s.p.* in said mammal.

2. The use according to claim 1 wherein the polyol is selected from the group consisting of xylitol, lactitol, sorbitol, mannitol and mixtures therof, preferably xylitol.

3. The use according to claims 1 or 2, wherein said yeast is a *Candida s.p.* such as *Candida albicans*.

4. The use according to claim 1, 2 or 3, wherein said mucosal infection is an infection of the mucosa in connection with exocrine glands of the body of said mammal.

5. The use according to claim 1 or 2, wherein said mammal is selected from the group comprising human beings, mammalian pet animals such as cats and dogs, mammalian farm animals such as horses, cattle, pigs, and the like.

6. The use according to any one of the preceding claims, wherein said mucosal yeast infection is an oral infection, especially oral candidiasis.

7. The use according to any one of the preceding claims, wherein said mucosal yeast infection is a vaginal infection.

8. The use according to any one of the preceding claims, wherein said mucosal yeast infection is an udder infection.

9. The use according to any one of the preceding claims, wherein xylitol is incorporated into a pharmaceutical composition to be administered via systemic or topical administration.

10. The use according to claim 9, wherein said composition is prepared in the form of an orally administrable preparation selected from the group comprising a liquid, a tablet, a pill, a chewing gum or tablet, a powder, a spray, a syrup, a sugar substitute, a candy or sweet, an ice-cream, a pet food, an animal feed, and the like, by mixing at least one

pharmacologically acceptable carrier and an amount of xylitol sufficient to reduce or inhibit the infectious activity of yeasts on the mucosa of said mammal.

11. The use according to claim 10, wherein said composition includes an amount of xylitol sufficient to provide an oral daily intake of about 0.05 to 1.0 g/kg of said mammal, preferably 0.1 to 0.8 g/kg of said mammal, most preferably about 0.2 to 0.5 g/kg of said mammal.

12. The use according to claim 10 or 11, wherein said composition additionally includes another antifungal drug effective against said yeast infection.

13. The use according to claim 9, wherein said composition is prepared in the form of a topically administrable preparation selected from the group comprising a liquid, a spray, an aerosol, a cream, a paste, a cement, an ointment, a jelly or gel, a lubricant, a plaster, a membrane, a mouth wash or rinse, a tooth paste, and eye drops, by mixing at least one topical carrier and an amount of xylitol sufficient to reduce or inhibit the infectious activity of yeasts on the mucosa of said mammal.

14. The use according to claim 7 or 13, wherein said composition is in a form suitable for vaginal yeast infection and xylitol is included in a cream, jelly, lubricant, or liquid or is applied onto the surface of a condom.

15. The use according to claim 8 or 14, wherein said composition is in a form suitable for udder yeast infection and xylitol is included in a spray, dip, or tissue.

16. A device suitable for the treatment or prophylaxis of mucosal yeast infection in mammals, c h a r a c t e r i z e d in that it comprises a condom having polyol added thereto for administration of polyol into an orifice of the body, such as vagina.

17. The device according to claim 16, wherein said polyol is xylitol.

18. A method for the therapeutic or prophylactic treatment of mammals suffering from or being subject to an increased risk of mucosal yeast infection, said method comprising administering xylitol to said mammal in an amount which is effective in reducing or inhibiting mucosal infections caused by yeasts such as *Candida s.p* in said mammal, or effective in enhancing the effect of other antifungal drugs used in the treatment of said infection.

19. The method according to claim 18, wherein said xylitol is mixed with or replaced by another polyol.

20. The method according to claim 18, wherein said yeast is a *Candida s.p.* such as *Candida albicans*.

21. The method according to claim 19 or 20, wherein said mucosal infection is an infection of the mucosa in connection with exocrine glands of the body of said mammal.

22. The method according to claim 19, wherein said mammal is selected from the group comprising human beings, mammalian pet animals such as cats and dogs, mammalian farm animals such as horses, cattle, pigs, and the like.

23. The method according to claim 22, wherein said mammal is a human being suffering from AIDS.

24. The method according to claim 19, wherein said xylitol is administered by systemic or topical administration, alone or in combination with other antifungal drugs.

25. The method according to claim 24, wherein said xylitol is administered orally.

26. The method according to claim 24 or 25, wherein said xylitol is administered as a sugar substitute in the diet of said mammal.

27. The method according to claim 26, wherein said mucosal yeast infection is an oral infection, especially oral candidiasis.

28. The method according to claim 19, wherein said mucosal yeast infection is a vaginal infection.

29. The method according to claim 19, wherein said mucosal yeast infection is mastitis or an udder infection.

30. A composition for use in the therapeutic or prophylactic treatment of mammals suffering from or being subject to an increased risk of mucosal yeast infections, containing at least one pharmacologically acceptable carrier and an amount of xylitol sufficient to

reduce or inhibit mucosal infection caused by yeasts such as *Candida s.p.* in said mammal, or sufficient to enhance the effect of other antifungal drugs used in the treatment of said infection.

31. The composition according to claim 30, wherein said xylitol is mixed with or replaced by another polyol.

32. A pharmaceutical preparation for use in the systemic or topical therapeutic or prophylactic treatment of mucosal yeast infections, said preparation containing at least one pharmacologically acceptable carrier and an amount of polyol sufficient to reduce or inhibit mucosal infection caused by yeasts, such as *Candida s.p.* in said mammal, or sufficient to enhance the effect of other antifungal drugs used in the treatment of said infection.

33. The preparation according to claim 32, which is in the form of an orally administrable preparation selected from the group comprising a liquid, a tablet, a pill, a chewing gum or tablet, a powder, a lozenge, a spray, a syrup, a sugar substitute, a candy or sweet, an ice-cream, pet food, animal feed, and the like, by mixing at least one pharmacologically acceptable carrier and an amount of xylitol sufficient to reduce or inhibit the infectious activity of yeasts on the mucosa of said mammal.

34. The preparation according to claim 33, wherein said preparation includes an amount of xylitol sufficient to provide an oral daily intake of about 0.05 to 1.0 g/kg of said mammal, preferably 0.1 to 0.8 g/kg of said mammal, most preferably about 0.2 to 0.5 g/kg of said mammal.

35. The preparation according to claim 33 or 34, wherein said composition additionally includes another antifungal drug effective against said yeast infection.

36. The preparation according to claim 32, which is in the form of a topically administrable preparation selected from the group comprising a liquid, a spray, an aerosol, a cream, a paste, a cement, an ointment, a jelly or gel, a lubricant, a plaster, a membrane, a mouth wash or rinse, a tooth paste, and eye drops, by mixing at least one topical carrier and an amount of xylitol sufficient to reduce or inhibit the infectious activity of yeasts on the mucosa of said mammal.

37. The preparation according to claim 36, which is in a form suitable for reducing or

inhibiting vaginal yeast infection and xylitol is included in a cream, jelly, lubricant, or liquid or is applied onto the surface of a condom.

38. The preparation according to claim 36, which is in a form suitable for reducing or inhibiting udder yeast infection and xylitol is included in a spray, dip, or tissue.

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[Continued on next page]

(54) Title: THE USE OF EMU OIL AND ITS VARIOUS FRACTIONS AS A CARRIER FOR ANTIFUNGAL, ANTIBACTERIAL, AND ANTIVIRAL MEDICATIONS AND PREPARATIONS

Characteristic	*Bacillus coagulans* Response
Catalase production	Yes
Acid from D-Glucose	Yes
Acid from L-Arabinose	Variable
Acid from D-Xylose	Variable
Acid from D-Mannitol	Variable
Gas from Glucose	Yes
Hydrolysis of Casein	Variable
Hydrolysis of Gelatin	No
Hydrolysis of Starch	Yes
Utilization of Citrate	Variable
Utilization of Propionate	No
Deamidation of Tyrosine	No
Degradation of Phenylalanine	No
Nitrate reduced to Nitrite	Variable
Allatoin or Urate Required	No

(57) Abstract: Pharmaceutical composition and methods of treatment which include Emu Oil, an animal-derived lipid that is useful as a carrying agent for anti-microbial formulations, are disclosed that are useful components in anti-bacterial, anti-fungal, and anti-viral treatments. The present invention also discloses therapeutic compositions and method of treatment comprising Emu Oil, and various fractions thereof, in combination with one or more of the following: a lactic acid-producing vegetative bacteria or spores thereof, an extracellular product derived from said lactic acid-producing bacterial species, and an anti-microbial agent, suitable for topical application to the skin or mucosal membranes of a mammal so as to inhibit the growth of bacterium, yeast, fungi, virus, and combinations thereof. In a preferred embodiment of the present invention, the extracellular product is derived form cultures of *Bacillus coagulans* and/or *Pseudomonas lindbergii*. Also disclosed herein are articles of manufacture comprising the aforementioned composition.

WO 01/13956 A2

WHAT IS CLAIMED IS:

1. A composition comprising a lactic acid-producing bacterial species in a pharmaceutically-acceptable carrier which is suitable for topical application to skin or a mucous membrane of a mammal and Emu Oil.

2. The composition of claim 1, wherein said lactic acid-producing bacterial species is a *Bacillus* species selected from the group consisting of: *Bacillus subtilis*, *Bacillus uniflagellatus*, *Bacillus lateropsorus*, *Bacillus laterosporus* BOD, *Bacillus megaterium*, *Bacillus polymyxa*, *Bacillus licheniformis*, *Bacillus pumilus*, and *Bacillus sterothermophilus*, *Bacillus coagulans*, *Bacillus thermophilus*, *Bacillus mycoides*, *Bacillus cereus*, and *Bacillus circulans*.

3. The composition of claim 1, wherein said lactic acid-producing bacterial species is a member of the *Lactobacillus* genus selected from the group consisting of: *Lactobacillus acidophilus*, *Lactobacillus plantarum*, *Lactobacillus salivarius*, *Lactobacillus delbrukil*, *Lactobacillus rhamnosus*, *Lactobacillus bulgaricus*, *Lactobacillus gaserli*, *Lactobacillus jensenii* and *Lactobacillus sporogenes*.

4. The composition of claim 1, wherein said lactic acid-producing bacterial species is a member of the genus *Enterococccus* selected from the group consisting of: *Bacillus facium* and *Enterococccus thermophilus*.

5. The composition of claim 1, wherein said lactic acid-producing bacterial species is a member of the *Bifidiobacterium* genus selected from the group consisting of: *Bacillus longum*, *Bacillus infantis*, *Bacillus bifidus*, and *Bacillus bifidum*.

6. The composition of claim 1, wherein said lactic acid-producing bacterial species is a member of the genus *Pseudomonas* selected from a group consisting of: *Pseudomonas aeruginosa*, *Pseudomonas putida*, *Pseudomonas lindbergii*, *Pseudomonas cepacia*, *Pseudomonas florescenes*, and *Pseudomonas* 679-2.

7. The composition of claim 1, wherein said lactic acid-producing bacterial species is a member of the genus selected from a group consisting of: *Micromonospora*, *Sporolactobacillus*, *Micrococcus*, *Berkholderia*, and *Rhodococcus*.

8. The composition of claim 1, wherein said lactic acid-producing bacterial species is a *Bacillus coagulans* strain.

9. The composition of claim 1, wherein said lactic acid-producing bacterial stain is included in said composition in a form selected from a group consisting of: vegetative cells, a dried bacterial cell mass, a flowable concentrate, a stabilized gel, a stabilized paste, and spores.

10. The composition of claim 1, wherein said carrier is selected from a group comprising an emulsion, cream, lotion, gel, oil, ointment, suspension, aerosol spray, powder, aerosol powder, or semi-solid formulation.

11. The composition of claim 1, wherein the Emu Oil comprises approximately 0.5 % to approximately 99.9%, by weight of said composition.

12. The composition of claim 1, wherein the Emu Oil comprises approximately 10% to approximately 75%, by weight of said composition.

13. The composition of claim 1, wherein the Emu Oil comprises approximately 25% to approximately 60%, by weight of said composition.

14. The composition of claim 1, wherein the concentration of the lactic acid-producing bacteria ranges from approximately 1% to approximately 90%, by weight of said composition.

15. The composition of claim 1, wherein the concentration of the lactic acid-producing bacteria ranges from approximately 10% to approximately 75%, by weight of said composition.

16. The composition of claim 1, further comprising one or more compounds selected from a group consisting of: dimethyl sulfoxide (DMSO), methylsulfonylmethane (MSM), and Lignisul MSM.

17. The composition of claim 1, further comprising one or more anti-microbial agents selected from a group consisting of: a quartenary ammonium chloride, an iodine or iodifer compound, a phenolic compound, and an alcohol compound or tincture.

18. The composition of claim 1, further comprising one or more systemic anti-fungal compounds selected from a group consisting of: Amphotericin B, Dapsone, Fluconazole, Flucytosine, Griseofulvin, Itraconazole, Ketoconazole, and Miconazole KI.

19. The composition of claim 1, further comprising one or more topical anti-fungal compounds selected from a group consisting of: Amphotericin B, Carbol-Fuchsin, Ciclopirox, Clotrimzole, Econazole, Haloprogin, Ketoconazole, Mafenide, Miconazole, Naftifine, Nystatin, Oxiconazole, Silver Sulfadiazine, Sulconazole, Terbinafine, Tioconazole, Tolnaftate, and Undecylenic acid.

20. The composition of claim 1, further comprising one or more vaginal anti-fungal compounds selected from a group consisting of: Butoconazle, Clotrimazole, Econazole, Gentian Violet, Miconazole, Nystatin, Terconazole, and Tioconazole.

21. A composition comprising an extracellular product of a lactic acid-producing bacterial species in a pharmaceutically-acceptable carrier which is suitable for topical application to skin or a mucous membrane of a mammal and Emu Oil.

22. The composition of claim 21, wherein said extracellular product is a hydrophilic supernatant or filtrate of a culture of a lactic acid-producing bacterial strain fractionated using a method selected from the group consisting of sub-micron filtration, ion exchange chromatography, and High Performance Liquid Chromatography (HPLC).

23. The composition of claim 21, wherein said extracellular product is derived from a culture of *Bacillus coagulans*.

24. The composition of claim 21, wherein said extracellular product is derived from a culture of a *Pseudomonas lindbergii*.

25. The composition of claim 21, wherein said carrier is selected from a group comprising an emulsion, cream, lotion, gel, oil, ointment, suspension, aerosol spray, powder, aerosol powder, or semi-solid formulation.

26. The composition of claim 21, wherein the Emu Oil comprises approximately 0.5 % to approximately 99.9%, by weight of said composition.

27. The composition of claim 21, wherein the Emu Oil comprises approximately 10% to approximately 75%, by weight of said composition.

28. The composition of claim 21, wherein the Emu Oil comprises approximately 25% to approximately 60%, by weight of said composition.

29. The composition of claim 21, wherein the concentration of the lactic acid-producing bacterial extracellular product ranges from approximately 1% to approximately 90%, by weight of said composition.

30. The composition of claim 21, wherein the concentration of the lactic acid-producing bacterial extracellular product ranges from approximately 10% to approximately 75%, by weight of said composition.

31. The composition of claim 21, further comprising one or more compounds selected from a group consisting of: dimethyl sulfoxide (DMSO), methylsulfonylmethane (MSM), and Lignisul MSM.

32. The composition of claim 21, further comprising one or more anti-microbial agents selected from a group consisting of: a quartenary ammonium chloride, an iodine or iodifer compound, a phenolic compound, and an alcohol compound or tincture.

33. The composition of claim 21, further comprising one or more systemic anti-fungal compounds selected from a group consisting of: Amphotericin B, Dapsone, Fluconazole, Flucytosine, Griseofulvin, Itraconazole, Ketoconazole, and Miconazole KI.

34. The composition of claim 21, further comprising one or more topical anti-fungal compounds selected from a group consisting of: Amphotericin B, Carbol-Fuchsin, Ciclopirox, Clotrimzole, Econazole, Haloprogin, Ketoconazole, Mafenide, Miconazole, Naftifine, Nystatin, Oxiconazole, Silver Sulfadiazine, Sulconazole, Terbinafine, Tioconazole, Tolnaftate, and Undecylenic acid.

35. The composition of claim 21, further comprising one or more vaginal anti-fungal compounds selected from a group consisting of: Butoconazle, Clotrimazole, Econazole, Gentian Violet, Miconazole, Nystatin, Terconazole, and Tioconazole.

36. A composition comprising a lactic acid-producing bacterial species, an extracellular product of a lactic acid-producing bacterial species, a pharmaceutically-acceptable carrier which is suitable for topical application to skin or a mucous membrane of a mammal, and Emu Oil.

37. The composition of claim 36, wherein said lactic acid-producing bacterial species is a member of the genus selected from a group consisting of: the *Bacillus* genus, the *Lactobacillus* genus, the *Enterococccus* genus, the *Bifidiobacterium* genus, the *Pseudomonas* genus, the *Micromonospora* genus, the *Sporolactobacillus* genus, the *Micrococcus* genus, the *Berkholderia* genus, and the *Rhodococcus* genus.

38. The composition of claim 36, wherein said lactic acid-producing species is *Bacillus coagulans.*

39. The composition of claim 36, wherein said lactic acid-producing bacterial stain is included in said composition in a form selected from a group consisting of: vegetative cells, a dried bacterial cell mass, a flowable concentrate, a stabilized gel, a stabilized paste, and spores.

40. The composition of claim 36, wherein said extracellular product is a hydrophilic supernatant or filtrate of a culture of a lactic acid-producing bacterial strain fractionated using a method selected from the group consisting of sub-micron filtration, ion exchange chromatography, and High Performance Liquid Chromatography (HPLC).

41. The composition of claim 36, wherein said extracellular product is derived from a culture of *Bacillus coagulans.*

42. The composition of claim 36, wherein said extracellular product is derived from a culture of *Pseudomonas lindbergii.*

43. The composition of claim 36, wherein said carrier is selected from a group comprising an emulsion, cream, lotion, gel, oil, ointment, suspension, aerosol spray, powder, aerosol powder, or semi-solid formulation.

44. The composition of claim 36, wherein the Emu Oil comprises approximately 0.5 % to approximately 99.9%, by weight of said composition.

45. The composition of claim 36, wherein the Emu Oil comprises approximately 10% to approximately 75%, by weight of said composition.

46. The composition of claim 36, wherein the Emu Oil comprises approximately 25% to approximately 60%, by weight of said composition.

47. The composition of claim 36, wherein the concentration of the lactic acid-producing bacteria ranges from approximately 1% to approximately 90%, by weight of said composition.

48. The composition of claim 36, wherein the concentration of the lactic acid-producing bacteria ranges from approximately 10% to approximately 75%, by weight of said composition.

49. The composition of claim 36, wherein the concentration of the lactic acid-producing bacterial extracellular product ranges from approximately 1% to approximately 90%, by weight of said composition.

50. The composition of claim 36, wherein the concentration of the lactic acid-producing bacterial extracellular product ranges from approximately 10% to approximately 75%, by weight of said composition.

51. The composition of claim 36, further comprising one or more compounds selected from a group consisting of: dimethyl sulfoxide (DMSO), methylsulfonylmethane (MSM), and Lignisul MSM.

52. The composition of claim 36, further comprising one or more anti-microbial agents selected from a group consisting of: a quartenary ammonium chloride, an iodine or iodifer compound, a phenolic compound, and an alcohol compound or tincture.

53. The composition of claim 36, further comprising one or more systemic anti-fungal compounds selected from a group consisting of: Amphotericin B, Dapsone, Fluconazole, Flucytosine, Griseofulvin, Itraconazole, Ketoconazole, and Miconazole KI.

54. The composition of claim 36, further comprising one or more topical anti-fungal compounds selected from a group consisting of: Amphotericin B, Carbol-Fuchsin, Ciclopirox, Clotrimzole, Econazole, Haloprogin, Ketoconazole, Mafenide, Miconazole, Naftifine, Nystatin, Oxiconazole, Silver Sulfadiazine, Sulconazole, Terbinafine, Tioconazole, Tolnaftate, and Undecylenic acid.

55. The composition of claim 36, further comprising one or more vaginal anti-fungal compounds selected from a group consisting of: Butoconazle, Clotrimazole, Econazole, Gentian Violet, Miconazole, Nystatin, Terconazole, and Tioconazole.

56. A method of preventing bacterial, yeast, fungal or viral infection comprising the topical application, to the skin or a mucous membrane of a mammal, a lactic acid-producing bacterial species in a pharmaceutically-acceptable carrier which is suitable for topical application to skin or a mucous membrane of a mammal and Emu Oil; and allowing said lactic acid-producing bacterial species and Emu Oil to contact the skin or mucous membrane for sufficient time to inhibit growth of bacteria, yeast, fungus or virus.

57. The method of claim 56, wherein said lactic acid-producing bacterial species is a *Bacillus* species selected from the group consisting of: *Bacillus, subtilis*, *Bacillus uniflagellatus*, *Bacillus lateropsorus*, *Bacillus laterosporus* BOD, *Bacillus megaterium*, *Bacillus polymyxa*, *Bacillus licheniformis*, *Bacillus pumilus*, and *Bacillus sterothermophilus, Bacillus coagulans, Bacillus thermophilus, Bacillus mycoides, Bacillus cereus,* and *Bacillus circulans*.

58. The method of claim 56, wherein said lactic acid-producing bacterial species is a member of the *Lactobacillus* genus selected from the group consisting of: *Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus salivarius, Lactobacillus delbrukil, Lactobacillus rhamnosus, Lactobacillus bulgaricus, Lactobacillus gaserli, Lactobacillus jensenii* and *Lactobacillus sporogenes*.

59. The method of claim 56, wherein said lactic acid-producing bacterial species is a member of the genus *Enterococccus* selected from the group consisting of: *Bacillus facium* and *Enterococccus thermophilus*.

60. The method of claim 56, wherein said lactic acid-producing bacterial species is a member of the *Bifidiobacterium* genus selected from the group consisting of: *Bacillus longum, Bacillus infantis, Bacillus bifidus,* and *Bacillus bifidum*.

61. The method of claim 56, wherein said lactic acid-producing bacterial species is a member of the genus *Pseudomonas* selected from a group consisting of: *Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas lindbergii, Pseudomonas cepacia, Pseudomonas florescenes,* and *Pseudomonas* 679-2.

62. The method of claim 56, wherein said lactic acid-producing bacterial species is a member of the genus selected from a group consisting of: *Micromonospora, Sporolactobacillus, Micrococcus, Berkholderia,* and *Rhodococcus*.

63. The method of claim 56, wherein said lactic acid-producing bacterial stain is included in said composition in a form selected from a group consisting of: vegetative cells, a dried bacterial cell mass, a flowable concentrate, a stabilized gel, a stabilized paste, and spores.

64. The method of claim 56, wherein said lactic acid-producing bacterial species is a *Bacillus coagulans* strain.

65. The method of claim 56, wherein said carrier is selected from a group comprising an emulsion, cream, lotion, gel, oil, ointment, suspension, aerosol spray, powder, aerosol powder, or semi-solid formulation.

66. The method of claim 56, wherein the Emu Oil comprises approximately 0.5 % to approximately 99.9%, by weight of said composition.

67. The method of claim 56, wherein the Emu Oil comprises approximately 10% to approximately 75%, by weight of said composition.

68. The method of claim 56, wherein the Emu Oil comprises approximately 25% to approximately 60%, by weight of said composition.

69. The method of claim 56, wherein the concentration of the lactic acid-producing bacterial extracellular product ranges from approximately 1% to approximately 90%, by weight of said composition.

70. The method of claim 56, wherein the concentration of the lactic acid-producing bacterial extracellular product ranges from approximately 10% to approximately 75%, by weight of said composition.

71. The method of claim 56, wherein said composition further comprises one or more compounds selected from a group consisting of: dimethyl sulfoxide (DMSO), methylsulfonylmethane (MSM), and Lignisul MSM.

72. The method of claim 56, wherein said composition further comprises one or more anti-microbial agents selected from a group consisting of: a quartenary ammonium chloride, an iodine or iodifer compound, a phenolic compound, and an alcohol compound or tincture.

73. The method of claim 56, wherein said composition further comprises one or more systemic anti-fungal compounds selected from a group consisting of: Amphotericin B, Dapsone, Fluconazole, Flucytosine, Griseofulvin, Itraconazole, Ketoconazole, and Miconazole KI.

74. The method of claim 56, wherein said composition further comprises one or more topical anti-fungal compounds selected from a group consisting of: Amphotericin B, Carbol-Fuchsin, Ciclopirox, Clotrimzole, Econazole, Haloprogin, Ketoconazole, Mafenide, Miconazole, Naftifine, Nystatin, Oxiconazole, Silver Sulfadiazine, Sulconazole, Terbinafine, Tioconazole, Tolnaftate, and Undecylenic acid.

75. The method of claim 56, wherein said composition further comprises one or more vaginal anti-fungal compounds selected from a group consisting of: Butoconazle, Clotrimazole, Econazole, Gentian Violet, Miconazole, Nystatin, Terconazole, and Tioconazole.

76. The method of claim 56, wherein the step of allowing the lactic acid-producing bacteria to contact the skin or mucous membrane inhibits growth of one or more microbes selected from the group consisting of: *Staphylococcus* species, *Pseudomonas* species, *Clostridium* species, *Escherichia coli, Proteus* species, *Klebsiella* species, *Gardnereia vaginails, Proponbacterium acnes, Aeromonas hydrophia, Candida* species, *Trichophyton* species, *Aspergillus* species, *Acremonium* species, *Scopulariopis* species, Herpes simplex I, Herpes simplex II, and Herpes zoster.

77. A method of preventing bacterial, yeast, fungal or viral infection comprising the topical application, to the skin or a mucous membrane of a mammal, an extracellular product of a lactic acid-producing bacterial species in a pharmaceutically-acceptable carrier which is suitable for topical application to skin or a mucous membrane of a mammal and Emu Oil; and allowing said extracellular product and Emu Oil to contact the skin or mucous membrane for sufficient time to inhibit growth of bacteria, yeast, fungus, or virus.

78. The method of claim 77, wherein said extracellular product is a hydrophilic supernatant or filtrate of a culture of a lactic acid-producing bacterial strain fractionated using a method selected from the group consisting of sub-micron filtration, ion exchange chromatography, and High Performance Liquid Chromatography (HPLC).

79. The composition of claim 77, wherein said extracellular product is derived from a culture of *Bacillus coagulans.*

80. The composition of claim 77, wherein said extracellular product is derived from a culture of a *Pseudomonas lindbergii.*

81. The method of claim 77, wherein said carrier is selected from a group comprising an emulsion, cream, lotion, gel, oil, ointment, suspension, aerosol spray, powder, aerosol powder, or semi-solid formulation.

82. The method of claim 77, wherein the Emu Oil comprises approximately 0.5 % to approximately 99.9%, by weight of said composition.

83. The method of claim 77, wherein the Emu Oil comprises approximately 10% to approximately 75%, by weight of said composition.

84. The method of claim 77, wherein the Emu Oil comprises approximately 25% to approximately 60%, by weight of said composition.

85. The method of claim 77, wherein the concentration of the lactic acid-producing bacterial extracellular product ranges from approximately 1% to approximately 90%, by weight of said composition.

86. The method of claim 77, wherein the concentration of the lactic acid-producing bacterial extracellular product ranges from approximately 10% to approximately 75%, by weight of said composition.

87. The method of claim 77, further comprising one or more compounds selected from a group consisting of: dimethyl sulfoxide (DMSO), methylsulfonylmethane (MSM), and Lignisul MSM.

88. The method of claim 77, further comprising one or more anti-microbial agents selected from a group consisting of: a quartenary ammonium chloride, an iodine or iodifer compound, a phenolic compound, and an alcohol compound or tincture.

89. The method of claim 77, further comprising one or more systemic anti-fungal compounds selected from a group consisting of: Amphotericin B, Dapsone, Fluconazole, Flucytosine, Griseofulvin, Itraconazole, Ketoconazole, and Miconazole KI.

90. The method of claim 77, further comprising one or more topical anti-fungal compounds selected from a group consisting of: Amphotericin B, Carbol-Fuchsin, Ciclopirox, Clotrimzole, Econazole, Haloprogin, Ketoconazole, Mafenide, Miconazole, Naftifine, Nystatin, Oxiconazole, Silver Sulfadiazine, Sulconazole, Terbinafine, Tioconazole, Tolnaftate, and Undecylenic acid.

91. The method of claim 77, further comprising one or more vaginal anti-fungal compounds selected from a group consisting of: Butoconazle, Clotrimazole, Econazole, Gentian Violet, Miconazole, Nystatin, Terconazole, and Tioconazole.

92. The method of claim 77, wherein the step of allowing the extracellular product of the lactic acid-producing bacteria to contact the skin or mucous membrane inhibits growth of one or more microbes selected from the group consisting of: *Staphylococcus* species, *Pseudomonas* species, *Clostridium* species, *Escherichia coli, Proteus* species, *Klebsiella* species, *Gardnereia vaginails, Proponbacterium acnes, Aeromonas hydrophia, Candida* species, *Trichophyton* species, *Aspergillus* species, *Acremonium* species, *Scopulariopis* species, Herpes simplex I, Herpes simplex II, and Herpes zoster.

93. A method of preventing bacterial, yeast, fungal or viral infection comprising the topical application, to the skin or a mucous membrane of a mammal, a lactic acid-producing bacterial species, an extracellular product of a lactic acid-producing bacterial in a pharmaceutically-acceptable carrier which is suitable for topical application to skin or a mucous membrane of a mammal and Emu Oil; and allowing said lactic acid-producing bacteria, extracellular product, and Emu Oil to contact the skin or mucous membrane for sufficient time to inhibit growth of bacteria, yeast, fungus or virus.

94. The method of claim 93, wherein said lactic acid-producing bacterial species is a member of the genus selected from a group consisting of: the *Bacillus* genus, the *Lactobacillus* genus, the *Enterococccus* genus, the *Bifidiobacterium* genus, the *Pseudomonas* genus, the *Micromonospora* genus, the *Sporolactobacillus* genus, the *Micrococcus* genus, the *Berkholderia* genus, and the *Rhodococcus* genus.

95. The method of claim 93, wherein said lactic acid-producing species is *Bacillus coagulans*.

96. The method of claim 93, wherein said lactic acid-producing bacterial stain is included in a form selected from a group consisting of: vegetative cells, a dried bacterial cell mass, a flowable concentrate, a stabilized gel, a stabilized paste, and spores.

97. The method of claim 93, wherein said extracellular product is a hydrophilic supernatant or filtrate of a culture of a lactic acid-producing bacterial strain fractionated using a method selected from the group consisting of sub-micron filtration, ion exchange chromatography, and High Performance Liquid Chromatography (HPLC).

98. The composition of claim 93, wherein said extracellular product is derived from a culture of *Bacillus coagulans.*

99. The composition of claim 93, wherein said extracellular product is derived from a culture of a *Pseudomonas lindbergii.*

100. The method of claim 93, wherein said carrier is selected from a group comprising an emulsion, cream, lotion, gel, oil, ointment, suspension, aerosol spray, powder, aerosol powder, or semi-solid formulation.

101. The method of claim 93, wherein the Emu Oil comprises approximately 0.5 % to approximately 99.9%, by weight of said composition.

102. The method of claim 93, wherein the Emu Oil comprises approximately 10% to approximately 75%, by weight of said composition.

103. The method of claim 93, wherein the Emu Oil comprises approximately 25% to approximately 60%, by weight of said composition.

104. The method of claim 93, wherein the concentration of the lactic acid-producing bacteria ranges from approximately 1% to approximately 90%, by weight of said composition.

105. The method of claim 93, wherein the concentration of the lactic acid-producing bacteria ranges from approximately 10% to approximately 75%, by weight of said composition.

106. The method of claim 93, wherein the concentration of the lactic acid-producing bacterial extracellular product ranges from approximately 1% to approximately 90%, by weight of said composition.

107. The method of claim 93, wherein the concentration of the lactic acid-producing bacterial extracellular product ranges from approximately 10% to approximately 75%, by weight of said composition.

108. The method of claim 93, further comprising one or more compounds selected from a group consisting of: dimethyl sulfoxide (DMSO), methylsulfonylmethane (MSM), and Lignisul MSM.

109. The method of claim 93, further comprising one or more anti-microbial agents selected from a group consisting of: a quartenary ammonium chloride, an iodine or iodifer compound, a phenolic compound, and an alcohol compound or tincture.

110. The method of claim 93, further comprising one or more systemic anti-fungal compounds selected from a group consisting of: Amphotericin B, Dapsone, Fluconazole, Flucytosine, Griseofulvin, Itraconazole, Ketoconazole, and Miconazole KI.

111. The method of claim 93, further comprising one or more topical anti-fungal compounds selected from a group consisting of: Amphotericin B, Carbol-Fuchsin, Ciclopirox, Clotrimzole, Econazole, Haloprogin, Ketoconazole, Mafenide, Miconazole, Naftifine, Nystatin, Oxiconazole, Silver Sulfadiazine, Sulconazole, Terbinafine, Tioconazole, Tolnaftate, and Undecylenic acid.

112. The method of claim 93, further comprising one or more vaginal anti-fungal compounds selected from a group consisting of: Butoconazle, Clotrimazole, Econazole, Gentian Violet, Miconazole, Nystatin, Terconazole, and Tioconazole.

113. The method of claim 93, wherein the step of allowing the extracellular product of the lactic acid-producing bacteria to contact the skin or mucous membrane inhibits growth of one or more microbes selected from the group consisting of: *Staphylococcus* species, *Pseudomonas* species, *Clostridium* species, *Escherichia coli, Proteus* species, *Klebsiella* species, *Gardnereia vaginails, Proponbacterium acnes, Aeromonas hydrophia, Candida* species, *Trichophyton* species, *Aspergillus* species, *Acremonium* species, *Scopulariopis* species, Herpes simplex I, Herpes simplex II, and Herpes zoster.

114. An article of manufacture comprising a flexible article and an effective amount of a lactic acid-producing bacterial species in a pharmaceutically-acceptable carrier which is suitable for topical application to skin or a mucous membrane of a mammal and Emu Oil, applied to said flexible article, wherein said flexible article is intended to be worn by or attached to skin or a mucous membrane of a mammal so as to allow the indigenous anti-microbial activity of the extracellular product derived from the lactic acid-producing bacterial species to occur adjacent to, or on the skin or mucous membrane.

115. The article of manufacture of claim 114, wherein said lactic acid-producing bacterial species is a member of the genus selected from a group consisting of: the *Bacillus* genus, the *Lactobacillus* genus, the *Enterococccus* genus, the *Bifidiobacterium* genus, the *Pseudomonas* genus, the *Micromonospora* genus, the *Sporolactobacillus* genus, the *Micrococcus* genus, the *Berkholderia* genus, and the *Rhodococcus* genus.

116. The article of manufacture of claim 114, wherein said lactic acid-producing bacterial species is a *Bacillus coagulans* strain.

117. The article of manufacture of claim 114, wherein said article of manufacture is selected from the group consisting of: a diaper, a pliable material for wiping skin or a mucous membrane, a dermal patch, adhesive tape, an absorbent pad, a tampon, a feminine hygiene napkin, and an article of clothing.

118. The article of manufacture of claim 114, wherein the applying step comprises impregnating said composition into a fibrous or non-fibrous solid matrix.

119. The article of manufacture of claim 114, further comprising an extracellular product derived from a hydrophilic supernatant or filtrate of a culture of a lactic acid-producing bacterial strain fractionated using a method selected from the group consisting of sub-micron filtration, ion exchange chromatography, and High Performance Liquid Chromatography (HPLC).

120. The article of manufacture of claim 119, wherein said extracellular product is derived from a culture of *Bacillus coagulans*.

121. The article of manufacture of claim 119, wherein said extracellular product is derived from a culture of a *Pseudomonas lindbergii*.

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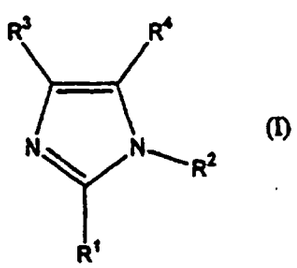
(54) **NITROIMIDAZOLE EXTERNAL PREPARATIONS FOR DERMATOSIS**

(57) An external preparation for skin disease which comprises a nitroimidazole derivative represented by the following formula (I):



(I)

wherein R^1, R^3 and R^4 may be the same or different and represent a hydrogen atom, a nitro group, a lower alkyl group, a substituted lower alkyl group, a lower alkenyl group, or a substituted lower alkenyl group; and R^2 represents a hydrogen atom, a lower alkyl group, a substituted lower alkyl group and a lower alkenyl group or a substituted lower alkenyl group, provided that any one of R^1, R^3 and R^4 is a nitro group.

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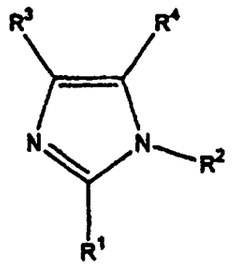
[0833] The external preparations of the present invention exhibited no changes in appearance or pH, and did not exhibit any significant changes in content or viscosity.

[0834] Thus, the external preparations provided by the present invention were clearly determined to be pharmacologically stable.

Claims

1. An external preparation for therapeutic or prophylactic treatment, or amelioration of skin disease which comprises a nitroimidazole derivative represented by the following formula (I), a pharmaceutically acceptable salt thereof, an ester thereof or other derivatives thereof as an active ingredient:



(I)

wherein R^1, R^3 and R^4 may be the same or different and each independently represents a hydrogen atom, a nitro group, a lower alkyl group, a lower alkyl group substituted by 1 or more substituents which may be the same or different selected from Substituent group α and Substituent group β, a lower alkenyl group, or a lower alkenyl group substituted by 1 or more substituents which may be the same or different selected from the Substituent group α and the Substituent group β; and R^2 represents a hydrogen atom, a lower alkyl group, a lower alkyl group substituted by 1 or more substituents which may be the same or different selected from the Substituent group α and the Substituent group β, a lower alkenyl group or a lower alkenyl group substituted by 1 or more substituents, which may be the same or different selected from the Substituent group α and the Substituent group β, provided that any one of R^1, R^3 and R^4 is a nitro group, wherein.

The Substituent group α comprises

a lower alkyloxy group, a lower alkyloxy group substituted by 1 or more substituents which may be the same or different selected from the Substituent group β, a lower alkylcarbonyloxy group, a lower alkylcarbonyloxy group substituted by 1 or more substituents which may be the same or different selected from the Substituent group β, a lower alkylsulfonyl group, a lower alkylsulfonyl group substituted by 1 or more substituents which may be the same or different selected from the Substituent group β, a cycloalkyl group, a cycloalkyl group substituted by 1 or more substituents which may be the same or different selected from the Substituent group β, a heteroaryl group, a heteroaryl group substituted by 1 or more substituents which may be the same or different selected from the Substituent group β, an aryl group and an aryl group substituted by 1 or more substituents which may be the same or different selected from the Substituent group β; and

the Substituent group β comprises

a hydroxy group, a mercapto group, a halogen atom, an amino group, a lower alkylamino group, a lower alkyloxy group, a lower alkenyl group, a cyano group, a carboxy group, a carbamoyloxy group, a carboxyamide group, a thiocarboxyamide group and a morpholino group.

2. The external preparation according to Claim 1, wherein R^4 is a nitro group.

3. The external preparation according to Claim 2, wherein R^1 and R^2 are the same or different and represent a lower alkyl group, a lower alkyl group substituted by 1 or more substituents selected from the Substituent group α and the Substituent group β, a lower alkenyl group, or a lower alkenyl group substituted by 1 or more substituents which may be the same or different selected from the Substituent group α and the Substituent group β, and R^3 is a hydrogen atom.

4. The external preparation according to Claim 3, wherein the Substituent group α is a lower alkyloxy group and the Substituent group β is a hydroxy group, an amino group, a halogen atom, a cycloalkyl group, a heteroaryl group

or an aryl group.

5. The external preparation according to Claim 4, wherein the Substituent group β is a hydroxy group, an amino group, a halogen atom or a heteroaryl group.

6. The external preparation according to Claim 5, wherein R^1 is a lower alkyl group.

7. The external preparation according to any one of Claims 5 and 6, wherein R^2 is a lower alkyl group substituted by a hydroxy group.

8. The external preparation according to Claim 4, which comprises 2-(2-methyl-5-nitroimidazole-1-yl)ethanol (general name: metronidazole), a pharmaceutically acceptable salt thereof, an ester thereof or other derivatives thereof as an active ingredient.

9. The external preparation according to Claim 3, wherein the Substituent group α is a lower alkylsulfonyl group or a lower alkylsulfonyl group substituted by substituents which may be the same or different selected from the Substituent group β and the Substituent group β is a hydroxy group, a halogen atom, an amino group, a lower alkylamino group, a lower alkyloxy group, a lower alkenyl group, a cyano group, a carboxy group, a cycloalkyl group or an aryl group.

10. The external preparation according to Claim 9, wherein R^1 is a lower alkyl group or lower alkyl group substituted by substituents which may be the same or different selected from the Substituent group β.

11. The external preparation according to Claim 9 or 10, wherein R^2 is a lower alkylsulfonyl group or a lower alkyl group substituted by a lower alkylsulfonyl group substituted by substituents which may be the same or different selected from the Substituent group β.

12. The external preparation according to Claim 9, which comprises 1-(2-ethylsulfonylethyl)-2-methyl-5-nitroimidazole (general name: tinidazole) or a pharmaceutically acceptable salt thereof as an active ingredient.

13. The external preparation which comprises at least one compound of the nitroimidazole derivatives as defined in any one of Claims 1 to 12 and at least one medicine selected from the group consisting of an antimycotic agent, antibacterial agent, sulfa, immunosuppressant, antiinflammatory agent, antibiotic, antiviral agent, metabolic antagonist, antihistamine, tissue repair promoter, vitamin, antiallergic, local anesthetic, hair agent and steroid being administered simultaneously or separately with an interval.

14. The external preparation according to Claim 13, wherein the antimycotic agent, the antibacterial agent, the sulfa, the immunosuppressant, the antiinflammatory agent, the antibiotic, the antiviral agent, the metabolic antagonist, the antihistamine, the tissue repair promoter, the vitamin, the antiallergic, the local anesthetic, the hair agent or the steroids is used with a concentration at which the agent itself does not demonstrate any pharmacological effect.

15. The external preparation according to any one of Claims 1 to 14, which further comprises crotamiton.

16. The external preparation according to any one of Claims 1 to 15, wherein the skin disease is atopic dermatitis.

17. The external preparation according to Claim 16, wherein the skin disease is facial atopic dermatitis.

18. The external preparation according to Claim 16 or 17, wherein the skin disease is infant atopic dermatitis.

19. The external preparation according to any one of Claims 1 to 15, wherein the skin disease is blotches, pigmentation or scars of the skin.

20. The external preparation according to any one of Claims 1 to 15, wherein the skin disease is psoriasis.

21. The external preparation according to any one of Claims 1 to 15, wherein the skin disease is hircus, body odor or osmidrosis.

22. The external preparation according to any one of Claims 1 to 15, wherein the skin disease is contact dermatitis,

plant dermatitis or insect bites.

23. The external preparation according to any one of Claims 1 to 15, wherein the skin disease is dermal pruritis or drug rash.

24. The external preparation according to any one of Claims 1 to 15, wherein the skin disease is chilblain.

25. The external preparation according to any one of Claims 1 to 15, wherein the skin disease is erythroderma.

26. The external preparation according to any one of Claims 1 to 15, wherein the skin disease is tinea.

27. The external preparation according to any one of Claims 1 to 15, wherein the skin disease is suppurative skin disease.

28. The external preparation according to any one of Claims 1 to 15, wherein the skin disease is pressure sore.

29. The external preparation according to any one of Claims 1 to 15, wherein the skin disease is wound.

30. The external preparation according to any one of Claims 1 to 15, wherein the skin disease is palmoplantar pustulosis, lichen planus, lichen nitidus, pityriasis rubra pilaris, pityriasis rosea, erythema (including polymorphic exudative erythema, erythema nodosum and Darier's erythema annulare centrifugum), discoid lupus erythematosus, drug rash and toxic rash, alopecia areata, burns (including scars and keloids), pemphigus, Duhring dermatitis herpetiformus (including pemphigoid), seborrheic dermatitis, dermal stomatitis, Candidiasis (including interdigital erosion, intertrigo, dermal Candidiasis, infantile parasitic erythema, perionychia and vaginal Candidiasis) or tinea versicolor.

31. The external preparation according to any one of Claims 1 to 30, wherein the form is selected from cream, lotion, shampoo, gel, rinse, face lotion wash, milky lotion, paste, shaving cream, foundation, cologne, pack, ointment, patch, semi-solid, solid or liquid.

32. The external preparation according to any one of Claims 1 to 31, wherein a concentration of the nitroimidazole derivative is 1.5 to 10 % by weight based on the amount of the preparation.

33. Use of the nitroimidazole derivative as claimed in any one of Claims 1 to 12 for production of an external preparation used for therapeutic or prophylactic treatment of atopic dermatitis.

34. Use of the nitroimidazole derivative as claimed in any one of Claims 1 to 12 for production of an external preparation used for amelioration of bloches, pigmentation or scars.

35. Use of the nitroimidazole derivative as claimed in any one of Claims 1 to 12 for production of an external preparation used for therapeutic or prophylactic treatment of psoriasis.

36. Use of the nitroimidazole derivative as claimed in any one of Claims 1 to 12 for production of an external preparation used for therapeutic or prophylactic treatment of hircus, body odor or osmidrosis.

37. A therapeutic or prophylactic treatment of atopic dermatitis utilizing the external preparation as claimed in any one of Claims 1 to 15.

38. Amelioration of bloches, pigmentation or scars utilizing the external preparation as claimed in any one of Claims 1 to 15.

39. A therapeutic or prophylactic treatment of psoriasis utilizing the external preparation as claimed in any one of Claims 1 to 15.

40. A therapeutic or prophylactic treatment of hircus, body odor or osmidrosis utilizing the external preparation as claimed in any one of Claims 1 to 15.

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(54) Title: NOVEL METHODS OF TREATING LOCAL FUNGAL AND BACTERIAL INFECTIONS

(57) Abstract: This invention relates to novel compositions, methods of use, regimens and kits for treating local fungal and bacterial infections that are susceptible to treatment administered either locally or topically and systemically. The methods of this invention relate to ways in which to relieve symptoms of such infections in an unexpectedly shorter timespan than with conventional treatment with greater predictability than those methods currently known.

WHAT IS CLAIMED IS:

1. A method of treating a local fungal or bacterial infection comprising oral administration of an effective amount of anti-infective agent and concurrent local administration of an external topical composition comprising an effective amount of a topical relief agent to ameliorate local symptoms.

2. A method of treating a local fungal infection comprising oral administration of an antifungal-effective amount of an antifungal agent and concurrent local administration of an external topical composition comprising an antifungal agent

3. A method of treating a vaginal fungal infection comprising oral administration of an antifungal-effective amount of an antifungal agent and concurrent vulvar administration of an external topical composition comprising an antifungal agent.

4. A method of treating a vaginal fungal infection comprising oral administration of fluconazole and concurrent vulvar administration of an external topical composition comprising fluconazole.

5. A method of treating a vaginal fungal infection comprising oral administration of fluconazole in an amount of from about 75 to about 150 mg/day for one to three days and concurrent vulvar administration of an external topical composition comprising an antifungal agent selected from the group consisting of miconazole nitrate, fluconazole, terconazole, butoconazole, clotrimazole, and combinations thereof.

6. A method of treating a vaginal fungal infection comprising oral administration of fluconazole in an amount of from about 75 to about 150 mg/day and concurrent vulvar administration of an external topical composition comprising an anti-inflammatory agent.

7. A method of treating a vaginal fungal infection comprising oral administration of fluconazole in an amount of from about 125 to about 150 mg and concurrent vulvar administration of an external topical composition comprising an emollient agent.

8. A method of treating a vaginal bacterial infection comprising oral administration of metronidazole in an amount of from about 500 single oral dose and concurrent vulvar administration of an external topical composition comprising 0.75% metronidazole gel.

9. A method of treating a local viral infection comprising oral administration of acyclovir (Zovirax), famcyclovir (Famvir), valcyclovir (Valtrex) in a daily dosage of from about 250 mg to about 2000 mg/day and concurrent local administration of an external topical composition comprising emollient or local anesthetic ingredients.

10. A kit comprising an oral dosage form of fluconazole and an external topical composition.

11. An applicator containing an external topical composition comprising stick, wipe, sanitary pad, pantyliner, wash, spray and roll-on.

12. A method of treating a topical infection comprising oral administration of an effective amount of anti-infective agent and concurrent local administration of an external topical composition comprising an effective amount of a topical relief agent to ameliorate local symptoms.

13. A method according to claim 12 wherein said oral administration comprises administering a composition comprising fluconazole and said topical composition comprises miconazole nitrate.

14. A method of treating onychomycosis comprising oral administration of an effective amount of anti-fungal agent and concurrent local administration of an external composition to a nail affected by onychomycosis comprising an effective amount of an anti-fungal agent to ameliorate local symptoms.

15. A method of treating a local bacterial infection comprising oral administration of an effective amount of anti-infective agent and concurrent local administration of an external topical composition comprising an effective amount of a topical relief agent to ameliorate local symptoms.

16. A method according to claim 14 wherein said anti-fungal agent is fluconazole.

United States Patent [19]

Haslam et al.

[11] **Patent Number: 4,478,822**

[45] **Date of Patent: Oct. 23, 1984**

[54] **DRUG DELIVERY SYSTEM UTILIZING THERMOSETTING GELS**

[75] Inventors: **John L. Haslam; Takeru Higuchi; Arthur R. Mlodozeniec,** all of Lawrence, Kans.

[73] Assignee: **Merck & Co., Inc.,** Rahway, N.J.

[21] Appl. No.: **495,239**

[22] Filed: **May 16, 1983**

[51] **Int. Cl.**[3] **A61K 31/74;** A61K 31/70; A61K 31/135; A61K 31/54; A61K 31/415; A61K 31/435; A61K 31/19; A61K 31/66

[52] **U.S. Cl.** ..... **424/78;** 424/285; 424/300; 424/85; 424/309; 424/311; 424/94; 424/313; 424/317; 424/114; 424/321; 424/322; 424/116; 424/324; 424/326; 424/177; 424/330; 424/343; 424/180; 424/181; 424/209; 424/211; 424/220; 424/221; 424/224; 424/230; 424/238; 424/243; 424/246; 424/248.51; 424/251; 424/253; 424/254; 424/256; 424/258; 424/263; 424/265; 424/267; 424/270; 424/271; 424/273 P; 424/273 R; 424/274; 424/275; 424/283

[58] **Field of Search** ..... 424/78, 85, 94, 177, 424/180, 181, 209, 211, 220, 221, 224, 230, 238, 243, 246, 248.51, 251, 253, 254, 256, 258, 263, 265, 267, 270, 271, 273 P, 273 R, 274, 275, 283, 285, 300, 309, 311, 313, 317, 321, 322, 324, 326, 330, 343

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Primary Examiner—Douglas W. Robinson
Attorney, Agent, or Firm—Manfred Polk; Michael C. Sudol, Jr.

[57] **ABSTRACT**

This invention relates to a unique drug delivery system for delivering drugs to a body cavity. The drug delivery system comprises a medicament and a polymer such that the drug delivery system is a liquid at room temperature but forms a semi-solid or gel at the body temperature in the body cavity.

55 Claims, 1 Drawing Figure

EXAMPLE 6

Sodium acetate	2%
Tetronic ® 1307	21%
Benzalkonium chloride	0.01%
pH adjusted with HCl to 5	
sufficient purified water to	100%
gel-sol transition temperature	25° C.

EXAMPLE 7

	Solution 1	Solution 2
Timolol maleate	0.68%	0.68%
Tetronic ® 1307	22%	27%
pH adjusted with HCl to	4	4
sufficient purified water	100%	100%
gel-sol transition temperature	30° C.	26° C.

If the pharmaceutical compositions of Example 1-7 were compared with similar compositions but without the polymer, it would be expected that the compositions of Examples 1-7 would result in greater sustained concentrations of the drug at the site of administration.

Following the procedure of Examples 1-7 one can use an appropriate amount of the polymers listed below in place of the Tetronic ®1307 or Tetronic ®1508 polymer used in Examples 1-7.

Tetronic 1107

Tetronic 908

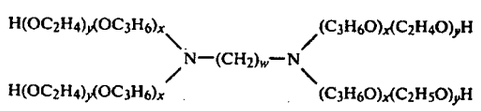
Tetronic 707

Following the procedure of Examples 1-7 one can use an appropriate amount of the drugs previously enumerated in this application.

What is claimed is:

1. An aqueous pharmaceutical composition for rectal, urethral, nasal, vaginal, optical or oral in the buccal pourch administration to a body cavity to treat a condition requiring pharmacological treatment comprising

a. 10% to 50% by weight of a polymer of the formula:



wherein w is an integer of from 2-6 containing approximately 40% to 80% poly(oxyethylene) and approximately 20 to 60% poly(oxypropylene) and having a molecular weight of 7,000 to 50,000; and x and y are any integers within the above constraints; and

b. a pharmacologically effective amount of drug selected from the group consisting of anti-bacterial substances, antihistamines and decongestants, anti-inflammatories, anti-parasitics, antiviral, local anesthetics, antifungal, amebecidal, or trichomonocidal agents, analgesics, antiarthritics, antiasthmatics, anticoagulants, anticonvulsants, antidepressants, antidiabetics, antineoplastics, antipsychotics, antihypertensives, and muscle relaxants and antiprotozoals; and

c. a pharmaceutically acceptable acid or base being in sufficient quantity to adjust the pH of the composition to range from 2 to 9 and wherein the composition is liquid at about room temperature or below.

2. The composition of claim **1** wherein the polymer is one wherein w is 2.

3. The composition of claim **1** wherein the polymer is Tetronic ®1307.

4. The composition of claim **1** wherein the gel-sol transition temperature of the composition is room temperature or below and said composition is liquid at this temperature.

5. The composition of claim **1** wherein the antibacterial substances are selected from the group consisting of beta-lactam antibiotics, tetracyclines, chloramphenicol, neomycin, gramicidin, bacitracin, sulfonamides, aminoglycoside antibiotics, tobramycin, nitrofurazone, nalidixic acid and analogs and the antimicrobial combination of fludalanine/pentizidone.

6. The composition of claim **1** wherein the antihistaminics and decongestants are selected from the group consisting of perilamine, chlorpheneramine, tetrahydrozaline and antazoline.

7. The composition of claim **1** wherein the anti-inflammatory drugs are selected from the group consisting of cortisone, hydrocortisone, betamethasone, dexamethasone, fluocortolone, prednisolone, triamcinolone, indomethacin, sulindac and its salts and corresponding sulfide.

8. A composition of claim **1** wherein the antiparasitic compound is ivermectin.

9. The composition of claim **1** wherein the antiviral effective compounds are selected from the group consisting of acyclovir and interferon.

10. A composition of claim **1** wherein the local anesthetics are selected from the group consisting of benzocaine, lidocaine and procaine.

11. The composition of claim **1** wherein the antifungal, antiprotozoal, amebecidal or trichomonacidal agent is selected from the group consisting of polyoxyethylene nonylphenol, alkylaryl sulfonate, oxyquinoline sulfate, miconazole nitrate, sulfanilamide, condicidin, sulfisoxazole, nystatin, chlotrimazole, metronidazole, chloramphenicol, chloroquine, trimethoprim or sulfamethoxazole.

12. The composition of claim **1** wherein the analgesic drug is selected from the group consisting of diflunisal, aspirin or acetaminophen.

13. The composition of claim **1** wherein the antiarthritics are selected from the group consisting of phenylbutazone, indomethacin, sulindac, dexamethasone, ibuprofen, allopurinol, oxyphenbutazone or probenecid.

14. The composition of claim **1** wherein the antiasthma drugs are selected from the group consisting of theophylline, ephedrine, beclomethasone diproprionate and epinephrine.

15. The composition of claim **1** wherein the anticoagulants are selected from the group consisting of heparin, bishydroxycoumarin, and warfarin.

16. The composition of claim **1** wherein the anticonvulsants are selected from the group consisting of diphenylhydantoin and diazepam.

17. The composition of claim **1** wherein the antidepressants are selected from the group consisting of amitriptyline, chlordiazepoxide perphenazine, protriptyline, imipramine and doxepin.

18. The composition of claim **1** wherein the antidiabetics are selected from the group consisting of insulin, tolbutamide, tolazamide, acetohexamide and chlorpropamide.

19. The composition of claim 1 wherein the antineoplastics are selected from the group consisting of adriamycin, flurouracil, methotrexate and asparaginase.

20. The composition of claim 1 wherein the antipsychotics are selected from the group consisting of prochlorperazine lithium carbonate, lithium citrate, thioridazine, molindone, fluphenazine, trifluoperazine, perphenazine, amitriptyline and triflupromazine.

21. The composition of claim 1 wherein the antihypertensives are selected from the group consisting of spironolactone, methyldopa, hydralazine, clonidine, chlorothiazide, deserpidine, timolol, propranolol, metoprolol, prazosin hydrochloride and reserpine.

22. The composition of claim 1 wherein the muscle relaxants are selected from the group consisting of melphalan, danbrolene, cyclobenzoprine, methocarbamol and diazepam.

23. The composition of claim 1 which includes a buffering agent or salt of from 0 to 5% by weight of the composition.

24. The composition of claim 23 wherein the buffering agent or salt is selected from the group consisting of alkali or alkali earth carbonates, chlorides, sulfates, phosphates, bicarbonates, citrates, borates, acetates and succinates.

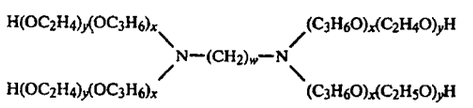
25. The composition of claim 1 which includes from 0.001% to 5% by weight of the composition of a preservative.

26. The composition of claim 25 wherein the preservatives are selected from the group consisting of sodium bisulfite, sodium thiosulfate, ascorbate, benzalkonium chloride, chlorobutanol, thimerosal, phenylmercuric borate, parabens, benzylalcohol and phenylethanol.

27. The composition of claim 1 wherein the acid or base is selected from the group consisting of hydrochloric acid or sodium hydroxide.

28. A method of treating a condition requiring pharmacological treatment which comprises administering rectal, urethral, nasal, vaginal, optical or oral in the buccal pourch to a body cavity a liquid drug delivery device comprising:

a. 10% to 50% by weight of a polymer of the formula



wherein w is an integer of from 2 to 6 containing approximately 40% to 80% poly(oxyethylene) and approximately 20–60% poly(oxypropylene) and having a molecular weight of 7,000 to 50,000; and x and y are any integers within the above constraints; and

b. a pharmacologically effective amount of drug selected from the group consisting of antibacterial substances, antihistamines and decongestants, anti-inflammatories, antiparasitics, antivirals, local anesthetics, antifungal, amebecidal, or trichomonocidal agents, analgesics, antiarthritics, antiasthmatics, anticoagulants, anticonvulsants, antidepressants, antidiabetics, antineoplastics, antipsychotics, antihypertensives, muscle relaxants and antiprotozoals; and

c. a pharmaceutically acceptable acid or base being in sufficient quantity to adjust the pH of the composition to range from 2 to 9 and wherein the composition is liquid at about room temperature or below.

29. A method of treatment according to claim 28 wherein the polymer is one wherein w is 2.

30. A method of treatment according to claim 23 wherein the polymer is Tetronic ®1307.

31. A method of treatment according to claim 28 wherein the gel-sol transition temperature of the composition is room temperature or below and said composition is liquid at this temperature.

32. A method of treatment of claim 28 wherein said pharmaceutical composition is administered rectally, urethrally, nasally, vaginally, otically or orally within the buccal pouch.

33. A method of treatment according to claim 28 wherein the antibacterial substances are selected from the group consisting of beta-lactam antibiotics, tetracyclines, chloroamphenicol, neomycin, gramicidin, bacitracin, sulfonamides, aminoglycoside antibiotics, tobramycin, nitrofurazone, nalidixic acid and analogs and the antimicrobial combination of fludalanine/pentizidone.

34. A method of treatment according to claim 28 wherein the antihistaminics and decongestants are selected from the group consisting of perilamine, chlorpheniramine, tetrahydrozaline and antazoline.

35. A method of treatment according to claim 28 wherein the anti-inflammatory drugs are selected from the group consisting of cortisone, hydrocortisone, betamethasone, dexamethasone, fluocortolone, prednisolone, triamcinalone, sulindac and its salts and corresponding sulfide.

36. A method of treatment of claim 28 wherein the antiparasitic compound is ivermectin.

37. A method of treatment according to claim 28 wherein the antiviral effective compounds are selected from the group consisting of acyclovir and interferon.

38. A method of treatment according to claim 28 wherein the local anesthetics are selected from the group consisting of benzocaine, lidocaine and procaine.

39. A method of treatment according to claim 28 wherein the antifungal, antiprotozoal, amebecidal or trichomonacidal agent is selected from the group consisting of polyoxyethylene nonylphenol, alkylaryl sulfonate, oxyquinoline sulfate, miconazole nitrate, sulfonilamide, condicidin, sulfisoxazole, nystatin, clotrimazole metronidazole, chloramphenicol, chloroquine, trimethoprim or sulfamethoxazole.

40. A method of treatment according to claim 28 wherein the analgesic drug is selected from the group consisting of diflunisal, aspirin or acetaminophen.

41. A method of treatment according to claim 28 wherein the antiarthritics are selected from the group consisting of phenylbutazone, indomethacin, sulindac and its salts and corresponding sulfide, dexamethasone, ibuprofen, allopurinol, oxyphenbutazone or probenecid.

42. A method of treatment according to claim 28 wherein the antiasthma drugs are selected from the group consisting of theophylline, ephedrine, beclomethasone diproprionate and epinephrine.

43. A method of treatment according to claim 28 wherein the anticoagulants are selected from the group consisting of heparin, bishydroxycoumarin, and warfarin.

44. A method of treatment according to claim 28 wherein the anticonvulsants are selected from the group consisting of diphenylhydantoin and diazepam.

45. A method of treatment according to claim 28 wherein the antidepressants are selected from the group

consisting of amitriptyline, chlordiazepoxide perphenazine, protriptyline, imipramine and doxepin.

46. A method of treatment according to claim 28 wherein the antidiabetics are selected from the group consisting of insulin, tolbutamide, tolazamide, acetohexamide and chlorpropamide.

47. A method of treatment according to claim 28 wherein the antineoplastics are selected from the group consisting of adriamycin, flurouracil, methotrexate and asparaginase.

48. A method of treatment according to claim 28 wherein the antipsychotics are selected from the group consisting of prochlorperazine lithium carbonate, lithium citrate, thioridazine, molindone, fluphenazine, trifluoperazine, perphenazine, amitriptyline and triflupromazine.

49. A method of treatment according to claim 28 wherein the antihypertensives are selected from the group consisting of spironolactone, methyldopa, hydralazine, clonidine, chlorothiazide, deserpidine, timolol, propranolol, metoprolol, prazosin hydrochloride and reserpine.

50. A method of treatment according to claim 28 wherein the muscle relaxants are selected from the group consisting of melphalan, danbrolene, cyclobenzaprine, methocarbamol and diazepam.

51. A method of treatment according to claim 28 wherein the composition includes a buffering agent or salt of from 0% to 5% by weight of the composition.

52. A method of treatment according to claim 51 wherein the buffering agent or salt is selected from the group consisting of alkali or alkali earth carbonates, chlorides, sulfates, phosphates, bicarbonates, citrates, borates, acetates and succinates.

53. A method of treatment according to claim 28 wherein the composition includes from 0.001% to 5% by weight of the composition of a preservative.

54. A method of treatment according to claim 53 wherein the preservatives are selected from the group consisting of sodium bisulfite, sodium thiosulfate, ascorbate, benzalkonium chloride, chlorobutanol, thimerosal, phenylmercuric borate, parabens, benzylalcohol and phenylethanol.

55. A method of treatment according to claim 28 wherein the acid or base is selected from the group consisting of hydrochloric acid or sodium hydroxide.

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UNITED STATES PATENT OFFICE

2,345,854

POCKET SPRAY DEVICE

Samuel L. Margolies, Brooklyn, N. Y.

Application September 10, 1940, Serial No. 356,151

1 Claim. (Cl. 299—89)

This invention relates to pocket spray devices and more particularly relates to atomizers and spray devices for perfumes, cosmetics, medicinals and the like, having parts which can be fitted into approximately the size of an ordinary fountain pen or pencil, and thus when carried will simulate a pen or pencil both in size and in shape.

It has previously been proposed to provide spray devices which allegedly can be carried in the pocket of the user, but such devices have either been bulky, and thus inconvenient to carry, or, even if of small enough size to render carriage convenient, have been leaky and thus impractical for the purpose intended.

It is an object of this invention to provide a pocket spray device which may coveniently be fitted within an outside casing of substantially the size and shape of an ordinary fountain pen.

It is a further object of this invention to provide a spray device having a combination of parts which will produce a finely divided spray of the material stored in the device, which parts may be mounted within a casing substantially the size and shape of an ordinary fountain pen.

It is an object of this invention to provide a pocket spray device having the liquid containing portion and the air containing portion completely separable so that the two parts may be carried separately and may be replaced individually so that loss or destruction of one part will not necessitate discarding the other part.

It is a further object of the invention to provide such pocket spray device or atomizer which will be completely leak-proof when not in use.

It is a further object of the invention to provide a pocket spray device which may be simply and conveniently operated.

Further objects and advantages will appear from the following description and the drawings appended thereto in which

Figure 1 is a longitudinal section of a spray device embodying the principles of this invention;

Figure 2 is a longitudinal section of a modified form of spray device;

Figure 3 is a section taken on the line 3—3 of Fig. 1;

Figure 4 is a section similar to Fig. 1 of a modified form of spray device;

Figure 5 is a section similar to Fig. 1 of a further modification; and

Figure 6 is an enlarged sectional view of a part of Figure 5.

Referring particularly now to Figure 1, a construction is shown having an outside casing 11 which is generally cylindrical in shape and is preferably constructed approximately the size of a customary pocket pen or pencil. The casing 11 consists preferably of the top cap 12 which is hinged at 13 to swing open and which contains the gasket 14 which may be of rubber or any other convenient insulating material. The cap may be held in closed position by any convenient means such as the snap catch shown which includes the resilient finger 9 which snaps over boss 10. The casing 11 also includes the upper cylindrical portion 15, lower portion 16 which may be connected to portion 15 as by threads 17, and the bottom member 18. If desired the clip member 19 may be provided for convenience in carrying.

Near the bottom of the upper portion 15 of the casing 11 is provided the closure member 21 which is threaded into the member 15 and provides a liquid seal at this point in the casing. The top portion of the casing 15 is provided with the closure member 22 which is also threaded into the interior of the casing 15 providing a liquid seal. The casing 15 and the top and bottom closures 21 and 22 define the liquid containing compartment 25. Threaded plug 26 screws into the closure member 22 and may be removed for refilling the liquid reservoir. The tube 27 is inserted into the liquid reservoir, its lower end terminating in the lower portion of the reservoir in the curved portion 28, and its upper end extending through the closure member 22 and terminating substantially flush with the top of the cap. The curved portion 28 of the tube 27 insures that no leakage will occur out of the top of the tube when the atomizer is not in use, as no matter what position the reservoir is placed in, no leakage will occur if no air is allowed to enter compartment 25. In addition the rubber gasket 14 doubly insures the absence of leakage.

To provide for atomizing the liquid in the container 25 the piston 30 is mounted within the lower wall 16 of the container 11. The piston is secured to the plunger 31 which extends downwardly through the bottom member 18 of the outside casing, and is provided at its end with the thumb piece 32. The spring 33 tends to draw the piston inwardly and preferably is provided with just sufficient strength to hold the piston, plunger and finger piece in position inside of the casing 16 when the device is not in use.

The piston includes the cup member 35 and cup member 34 which may be of leather placed back to back. The member 34 mounts the valve member 36. The valve plate 38 is limited in its upward movement by fingers 37 and the hair spring 39 tends to push the valve plate 38 downward. Port 40 is provided extending through the members 36, 34, and 33.

The tube 45 is provided extending from closure member 21 through the liquid containing chamber 25 and terminating in an outwardly turned portion 46 which is directed over the top end of the tube 27. The curved air connection 47 is provided near the top of the tube 45 to permit air to enter the liquid compartment 25 to com-

pensate for the removal of liquid so that a vacuum will not obtain within the chamber 25, thus preventing the removal of liquid. The curved member 47 insures that no leakage will take place through this air vent no matter the position of the device, and the gasket 14 further insures from undesired leakage.

The operation of the device is simple. The plunger 31 is drawn down, the valve plate 38 moving up against the annular flange 37 and permitting air to pass. The plunger 31 is then pushed up and valve plate 38 seals the port 40, thus sending air at high velocity through the tube 45, which in passing over the end of the tube 27 draws liquid from the liquid chamber 25 according to atomizer principles. The displacement of liquid in the chamber 25 is compensated for by reintroduction of air through the tube 47 and the device will operate smoothly and continuously, the liquid being atomized in a fine spray which may be sprayed in any desired direction by the operator.

In Figure 2 is shown a construction of atomizer which is adapted to be confined in a tube of the same cross sectional diameter, but which may conveniently be reduced in longitudinal dimension. No further description of the liquid chamber and atomizing means is necessary, reference being made to Fig. 1 for this construction. The construction for producing the blast of air at the opening of the tube 45, however, includes the cylindrical member 50 in which is confined the piston 30 as shown. The plunger 31 is secured to a cylindrical member 51 of a diameter adapted to fit snugly over the cylindrical member 50 in sliding substantially air tight relationship. Spring 52 tends to retract the plunger 31 and has just sufficient strength to hold the same in retracted position. The device may conveniently be operated by up and down movement of the outside cylinder 51.

An alternate construction is illustrated in Fig. 4 wherein the plunger 31 and cap 32 will be located at the top of the construction comparable to the top of a fountain pen when the device is in non-operative position. The construction is similar in operation and construction to that shown in Fig. 1 and differs only in modified location of parts. Thus the casing 60 which is comparable to the upper portion 15 of the casing 11 of Fig. 1, is exteriorly threaded at its top. The casing 61, comparable to the portion 16 in Fig. 1 and in the rest position of the device inverted over the top of casing 60, is provided with the interiorly threaded portion 64 into which the threaded portion of the casing 60 is screwed. The gasket 65 seals the liquid and air openings of the tubes 45 and 27. The lower portion of casing 60 is exteriorly threaded at 67.

To place the device in operative position the casing 61 is unscrewed from the top of casing 60, inverted and screwed to the bottom portion at 67, whereupon the device operates in the manner described in connection with Fig. 1. The advantage of this construction lies in the fact that the plunger 31 with its cap 32 is thus kept away from the bottom of the user's pocket and further that the liquid and air openings are positively sealed within the casing and do not depend to any extent whatsoever upon the presence of a hinged cap member, as shown in Fig. 1.

A modified construction of spray device is illustrated in Figs. 5 and 6 in which the means for producing a blast of air are the same as that described in connection with Figs. 1 and 4 and thus require no further description. This construction, however, is particularly directed to a device which will permit spraying of liquids of greater specific gravity than those for which the constructions of Figs. 1 through 4 are especially adapted, and to this end the liquid reservoir 70 is provided, including the cylindrical casing 71, the top closure 72 having refill plug 73 and the bottom closure 74. Tube 75 is directly connected to the source of air. It has a descending portion 75a, an ascending portion 75b and a descending portion 75c which extends through the plate 74 and turns outwardly to the portion 76 of enlarged diameter. The enlarged portion 76 contains a screw 77 adapted to revolve freely in the portion 76.

The portion 75b of the tube 75 contains holes 78 and 79 one of which will always be below the liquid level, except when the liquid in the reservoir is substantially exhausted, and one of which will always be in the air space above the liquid level. These holes serve a combined purpose. Air entering through tube 75 will, in the position of the spray device shown in Fig. 5, blow out of hole 79 displacing some of the liquid into the tube 75. In the event that the removal of liquid from the liquid container is insufficiently compensated for so that a vacuum is formed, air will also escape from 79 and permit continuous removal of the liquid, thus providing an even delivery of spray from the portion 77. The two holes 78 and 79 further insure that the device will operate in any position in which it is held.

The cap 80 hinged at 81 is similar to the cap 12 of Fig. 1, the gasket 82 being adjusted to accommodate the open portion of the screw spray device. The reservoir 70 may be refilled by removing it from the piston containing portion 80 and unscrewing the plug 73.

It will be observed that in all forms of the invention the liquid containing portion forms a complete leakproof unit which may be carried separately from the piston containing portion. Either portion may be replaced if lost or destroyed thus saving the expense of obtaining an entire new device.

While I have illustrated and described in detail certain preferred forms of my invention, it is to be understood that changes may be made therein and the invention embodied in other structures. I do not, therefore, desire to limit myself to the specific constructions illustrated, but intend to cover my invention broadly in whatever form its principle may be utilized.

I claim:

A pocket atomizer comprising a pair of members separably connected end to end, the first of said members having storage means for storage of liquid, the second of said members having air compressing means including a piston, a plunger to operate said piston, said plunger having a cap, said cap comprising a cylindrical member snugly slidable over said second member to actuate said piston, means in said first member to conduct air compressed by said air compressing means under high velocity to the end of said first member remote from the connective end of said member, a tube in communication with the lower portion of said storage means and mounted in atomizing relation to said air conducting means at the end of said first member remote from its connected end, said air conducting means having communication with said liquid storage means in the upper part thereof.

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United States Patent Office

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Patented July 10, 1962

3,043,524

METERING SPRAYER DEVICE

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10 Claims. (Cl. 239—350)

This invention relates to an improved sprayer device having means for metering the quantity of material sprayed at each actuation of the device.

Conventional sprayer devices generally comprise a container for a store of material, e.g. liquid, to be sprayed, another container containing a store of gas under pressure, a jet or spray-nozzle such as a Venturi nozzle, and a manually-operable valve member, usually in the form of a spring pressed, finger-actuated, plunger, actuation of which connects the gas container with the spray nozzle for discharging therethrough a jet of the gas with minute droplets of liquid entrained therewith.

The quantity of spray discharged in such a device at each actuation of the valve member depends on the length of time the valve member remains actuated since throughout such time the delivery of gas to the spray nozzle remains established. This precludes the possibility of accurately metering the quantity of spray discharged. An object of the invention therefore is to provide a sprayer device in which such metering is made possible with a high degree of accuracy. Another object is to provide a sprayer device having two different modes of operation, in one (conventional or continuous) mode the device acting to discharge spray for so long as the valve member remains actuated, while in the other or metering mode the device acts to discharge a limited metered amount of spray per actuation of the valve member, means being provided for easily switching from one to the other mode of operation.

Basically the sprayer device of the invention may be characterized in that it includes a metering chamber adapted to be alternately placed in communication with the gas container or with the spray nozzle. When the chamber communicates with the gas container it is filled with an amount of gas at the high pressure existing in the container. On thereafter being placed in communication with the nozzle, the said amount of gas entrapped in the metering chamber is discharged through the nozzle entraining liquid droplets therewith in the usual way in the form of spray, the quantity of spray thus discharged being strictly limited or metered in accordance with the metering chamber volume.

A sprayer device according to the invention may be either of the type using a conventional dipper tube adapted for use in normal position i.e. with the liquid container held upright, or of the type adapted for use in inverted position of the liquid container, and wherein the liquid is delivered to the nozzle by gravity or by the suction created in said nozzle by the discharge of gas therethrough.

In one specific embodiment of the invention the metering chamber is provided as an e.g. annular recess formed in a spool-like valve member formed integrally with an actuating plunger or push-botton, and slidable in a valve bore into which discharge two axially-spaced passages respectively connected with the spray nozzle and the gas reservoir, the spacing between the points at which said conduits open into the valve bore being greater than the axial length of the metering chamber, whereby only one or the other of said passages can at any time be effectively connected with the chamber, depending on the position of the valve member.

The metering chamber may be formed with an extension in the form of a longitudinally extending groove, so that by imparting to the valve spool a rotational displacement to position such groove in register with that one of said passages connected to the gas store, a continuous communication may be established between the gas reservoir and the nozzle, whereupon the sprayer device will operate in the conventional mode to discharge a jet of spray as long as the valve member remains in actuated position.

Preferably, the valve member or spool is arranged simultaneously to operate a cutoff valve element adapted to cut off the connection from the liquid container (or dipper tube) to the spray nozzle in the position of the valve member in which the chamber communicates with the gas container, and establish such connection in the alternate position of the valve member. Spring means may be provided for urging the valve member to said first position. The said cut-off valve may be operated from the valve member by way of a lost-motion connection or the like, to ensure that the connection from the liquid container to the spray nozzle is effectively established at the time the connection from the metering chamber to the spray nozzle is established, this arrangement being of especial advantage in sprayer constructions where a dipper tube is included.

Exemplary embodiments of the invention will now be described for purposes of illustration but not of limitation with reference to the accompanying drawings, wherein:

FIG. 1 is an axial cross sectional view of a first sprayer construction according to the invention, using an inverted liquid container, shown in its inverted position of use;

FIG. 2 is an end view from the bottom of FIG. 1;

FIG. 3 shows a portion of the sprayer of FIG. 1 in the operated position of the valve member;

FIG. 4 shows a portion of the sprayer of FIG. 1 in the operated position of the valve member, but with the valve member being set to the continuous-spray mode of operation;

FIG. 5 is an axial cross sectional view of another sprayer according to the invention embodying an upright liquid container and dipper tube.

As shown in FIG. 1, the sprayer device comprises a body **1** threadedly connected with the neck **2***a* of a container **2** containing a store of liquid to be sprayed, through a sealing gasket **3**.

Slidably mounted in a blind axial bore **4** of body **1** is a valve member or spool **5** which projects beyond the lower end of the body to provide an actuating plunger or button **6**. The valve spool is formed with an annular recess providing a metering chamber **7** which is adapted to communicate either with a passage or port **8** connected with the inlet end of a conventional Venturi-type spray nozzle, or with a passage or port **10** communicating at its other end with the interior of a container or reservoir **11** for compressed gas, e.g. air. The spacing between ports **8** and **10** is greater than the axial length of chamber **7**, so that the chamber cannot communicate with both ports at the same time. A passage **12** connects the throat section of Venturi spray nozzle **9** with the bottom opening of the liquid container **2**, which opening however is normally sealed by a cut-off valve head **13** secured to the end of a rod **14** coaxially and integrally projecting from the valve member **5**. A spring **15** acting between an inner end surface of bore **4** and a shoulder of valve member **5** urges the valve member and valve head to an idle position in which the meeting chamber **7** communicates with gas-reservoir port **10** but not with the nozzle **9**, and wherein cut-off valve head **13** seals the liquid-container orifice.

In a side of valve member **5** is a longitudinal groove **20** one end of which connects with metering chamber **7**, and the valve member **5** can be selectively rotated about

its axis to either of two angular positions in one of which (as shown in FIGS. 1 and 3) the groove **20** is positioned out of register with port **10**, and in the other of which (FIG. 4) the groove **20** registers with port **10**. For this purpose a centrally perforated disk **16** is slidably but non-rotatably keyed to an outer end portion of valve member **5** by means of an inward projection **16***a* of perforated disk **16** slidably projecting into a keyway **17** formed in the valve member **5** (in the portion thereof constituting the push-button **6**). Disk **16** is formed with an arcuate slot **19** through which extends a screw **18** threaded into a tapped hole formed in the bottom end of body **1**. Thus the valve member and disk can be bodily rotated together between a "continuous-spray" position in which groove **20** registers with port **10**, which position is indicated by means of an index mark **21** (FIG. 2) on the disk registering with an index mark "C" on the sprayer body, and a "metered-spray" position in which groove **20** is displaced out of register with port **10**, this position being indicated by index mark **21** registering with an index mark "D" on the sprayer body.

The sprayer device operates as follows: It is first assumed that the indexing disk **16** and valve member have been rotated to the "D" position so that the sprayer operates in the "metered-spray" mode. Normally owing to the action of spring **15** the valve member is positioned as in FIG. 1 so that metering chamber **7** communicates with gas passage **10** only and valve head **13** seals the liquid-container orifice. Metering chamber **7** therefore contains a certain volume of gas at the relatively high pressure obtaining in reservoir **11**.

With the sprayer held in the inverted position shown, if the push-button **6** is depressed to displace the valve member **6** upwardly, as shown in FIG. 3, valve head **13** uncovers the liquid container orifice so that liquid can now flow through conduit **12** to the throat of nozzle **9**. Simultaneously valve member **5** is moved to disconnect the metering chamber **7** from the gas passage **10** and connect the chamber with nozzle passage **8**, whereby the metered volume of gas entrapped in chamber **7** is discharged through the spray nozzle **9**, carrying with it an amount of liquid in finely divided form to produce a jet of spray. It will thus be evident that the quantity of spray discharged is strictly limited and metered in accordance with the volume of metering chamber **7**.

If now the valve member **5** and disk **16** are rotated by action on button **6** so as to bring index **21** to the "D" setting, groove **20** is brought into register with gas port **10** (FIG. 4). In this condition, depression of button **6** will bring metering chamber **7** into communication with nozzle port **8**, as before, but the communication of the chamber **7** with gas port **10** will not be discontinued owing to the presence of groove **20**. Gas is now enabled to flow continuously from gas reservoir **11** to spray nozzle **20** and the sprayer operates in the so-called "continuous-spray" mode.

In the embodiment of FIG. 5, the sprayer body has a dipper tube **22** depending therefrom into the liquid reservoir. The connection between the upper end of the dipper tube and the passage **12** leading to the throat of Venturi nozzle **9** is normally sealed by a cutoff valve head **23** provided at the end of a rod **24** slidably extending through an axial perforation in valve member **5** and carrying at its upper end a stop **25** movable in an axial recess **26** of the push-button **6** portion of valve member **5**. A relatively weak spring **27** acts between an end face of valve member **5** and a shoulder of cutoff valve shank **24** to urge the stop **25** into engagement with the valve member **5**.

The operation of this embodiment is generally similar to that previously described except for the lost-motion connection provided from valve member **5** to cutoff valve head **23** through the shank **24**. Thus, on depression of button **6** valve head **23** is first unseated to connect the dipper tube **22** with conduit **12** until the movement of valve head **23** and shank **24** is arrested by engagement

with the top of the dipper tube, whereupon further depression of button **6** compresses weak spring **27**, and then establishes communication from the metering chamber to the nozzle inlet port as previously described. Releasing the button **6** will first cause upward movement of valve member **5** to disconnect the metering chamber from the nozzle port, and only thereafter will actuate the cutoff valve **23** to seal the dipper tube orifice, after the valve member **5** has engaged the stop **25** to raise the shank **24**.

It will be understood that various modifications may be made in the constructions illustrated and described, as by including certain features of one construction in the other construction, or other changes.

What I claim is:

1. A sprayer device comprising a spray nozzle, a container for gas under pressure having an outlet for the latter, a container for material to be sprayed having an outlet for the latter extending to said nozzle, means defining a metering chamber and being movable between a first position, in which only said outlet for gas under pressure opens into said metering chamber, and a second position, in which said metering chamber communicates with said nozzle, and actuating means for selectively disposing said means defining a metering chamber in said first and second positions thereof so that, when in said first position, a metered quantity of gas under pressure determined by the volume of said metering chamber enters the latter from said container for the gas and, when moved to said second position, the metered quantity of gas under pressure escapes from said metering chamber through said nozzle along with material to be sprayed from said container for such material.

2. A sprayer device as in claim 1; further comprising a valve for closing said outlet for the material to be sprayed, said valve being movable with said means defining a metering chamber to close and open said outlet for the material to be sprayed in said first and second positions, respectively, of the means defining a metering chamber.

3. A sprayer device comprising a body having a bore therein with first and second passages extending from said bore at axially spaced apart locations along the latter, a first container for gas under pressure having an outlet communicating with said first passage, a spray nozzle carried by said body and communicating with said second passage, a plunger slidable in said bore and having a recess in the surface of the plunger to define a metering chamber, the axial extent of said recess on the plunger being less than the axial distance along said bore between said first and second passages so that said chamber can only alternatively communicate with said first and second passages, a second container for material to be sprayed, conduit means extending from said second container to said nozzle, and means for displacing said plunger axially from a first position, where said metering chamber communicates with said first passage to receive a metered quantity of gas under pressure from said first container determined by the volume of said chamber, to a second position, where said chamber communicates with said second passage for discharging said metered quantity of gas under pressure through said nozzle along with material to be sprayed reaching said nozzle from said second container by way of said conduit means.

4. A sprayer device as in claim 3; wherein said spray nozzle is of the venturi type having a throat at which said conduit means opens while said second passage opens axially into the venturi type spray nozzle so that the discharge of the metered quantity of gas under pressure through said nozzle induces the flow of material to be sprayed from said second container through said conduit means to said nozzle for atomizing by said gas.

5. A sprayer device as in claim 3; wherein said conduit means has a valve seat interposed therein between said second container and nozzle; and further comprising a

valve movable with said plunger to engage said valve seat and close said conduit means when said plunger is in said first position, and to move away from said valve seat and thereby open said conduit means when said plunger is moved to said second position.

6. A sprayer device as in claim 5; wherein said valve is axially aligned with said plunger and fixed relative to the latter.

7. A sprayer device as in claim 5; wherein said valve is axially aligned with said plunger, and lost-motion connection means is provided between said valve and said plunger to unseat and seat said valve during a portion of the movement of said plunger from and to said first position.

8. A sprayer device as in claim 3; wherein said recess extends annularly around said plunger and the latter further has a second recess of limited angular extent extending axially from the first mentioned recess in the direction opposed to the axial movement of said plunger from said first position to said second position; and wherein said plunger is turnable in said bore to selectively angularly space and register said second recess with respect to said first passage so that, when said plunger is

in said second position, registration of said second recess with said first passage, permits gas under pressure to flow from said first passage and through said second and first recesses and said second passage to said spray nozzle for continuous spraying from the latter of material reaching the nozzle from said second container.

9. A sprayer device as in claim 3; wherein said second container for the material to be sprayed is inverted and carried by said body above said nozzle.

10. A sprayer device as in claim 3; wherein said second container for the material to be sprayed is suspended from said body below said nozzle, and said conduit means includes a dipper tube depending from said body into said second container.

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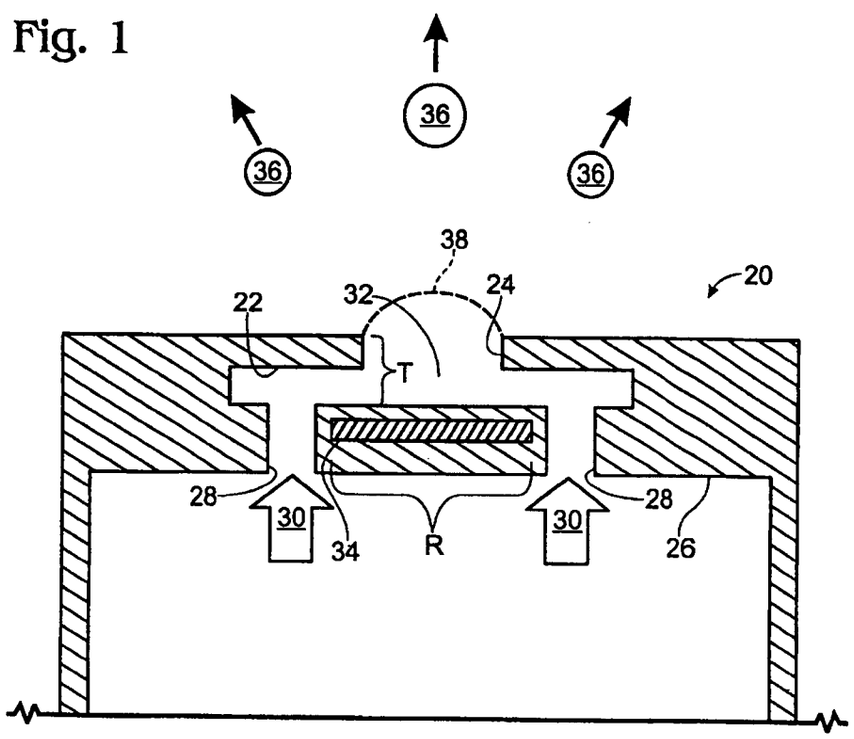
(54) Thermal generation of droplets for aerosol

(57) A thermal-type drop generator (20) having a geometry that is configured so that the ejection of liquid from the chamber (33) has the effect of separating the ejected volume into a number of small droplets. The relationship between the thickness of the liquid chamber and the area of the heat transducer (35) used to eject the liquid is controlled to provide the separating aspect so that the resultant droplets (36) have very small volumes, in the range of tens of femtoliters. Such small droplets are readily entrained in an aerosol and especially useful for pulmonary delivery of medicinal fluid.

Fig. 1



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that the liquid in the supply is directed to the drop generator head 72 that carries the multiple drop generators as described above in connection with Fig. 2. Preferably, the conduit and drop generator head are primed (as by applying suction to the orifices in the head) upon manufacture or by the user before the inhaler is operated to eject drops as described next.

[0055] The above-mentioned flex circuit 60 may be bonded, for example, to the inhaler 71 in a correspondingly shaped recess 61 in the body 68. That circuit connects the heat transducers of the drop generators with suitable conditioned control signals from a controller 52, which is part of the inhaler control system 81. The control system 81 includes the controller 52 that is provided with a power supply 79 and operator switch 77. The controller is an integrated circuit that responds to the switch signal by directing to the head 72 controlled current pulses for firing the drop generators as required. It will be appreciated that the control system can be configured in any of a number of ways and, most preferably, integrated with the body of the inhaler.

[0056] The drop generator head 72 is preferably located at the mouthpiece 69 of the inhaler. The recess 61 or other mechanisms may be used for providing an air stream during inhalation so that the droplets become entrained in the air.

[0057] It will be appreciated that the control system 81 and arrangement of the drop generator head 72 (that is, so that the droplets produced by the head 72 are immediately propelled into the surrounding air) provides for both precise metering of the amount of droplets ejected and of the amount of liquid expelled, as well as the generation of suitably small droplets. That is, the expulsion of the liquid from the chamber need not be accompanied with other mechanisms for reducing the volume of ejected liquid to suitably small droplets.

[0058] Even though the foregoing description has focused on the production of droplets suitable for aerosol delivery of the droplets to the alveoli, it will be appreciated that such small droplets can be generated for other applications. The drop' generators of the present invention could be incorporated with supplies of liquids suitable for scent delivery, dispensing precisely controlled amounts of pesticides, paints, fuels, etc.

[0059] Thus, having here described preferred embodiments of the present invention, it is anticipated that other modifications may be made thereto within the scope of the invention by individuals skilled in the art. Thus, although preferred and alternative embodiments of the present invention have been described, it will be appreciated that the spirit and scope of the invention is not limited to those embodiments, but extend to the various modifications and equivalents as defined in the appended claims.

Claims

1. A drop generator (20), comprising:

   a substrate (40) having a heat transducer (35) carried on an upper surface (56) of the substrate, the heat transducer being a substantially planar member having an area;
   an orifice member (48) attached to the substrate and having an outer surface (49) through which is formed an orifice (25), the orifice member defining a chamber (33) that is adjacent to the heat transducer and is in fluid communication with the orifice and with an inlet (54) in the substrate for conducting liquid through the inlet and into the chamber;

   wherein a chamber thickness is a dimension extending from the upper surface to the outer surface; and

   wherein a ratio of the chamber thickness to the square root of the transducer area is less than about 0.75.

2. The drop generator (20) of claim 1 wherein the ratio is less than 0.50.

3. The drop generator (20) of claim 1 wherein the ratio is about 0.35.

4. The drop generator (20) of claim 1 wherein the orifice member (48) has at least two orifices (125) extending from the chamber (33) to open through the outer surface (49) of the orifice member (48) thereby to permit liquid to be propelled through the orifices from the chamber.

5. The drop generator (20) of claim 4 wherein the heat transducer (35) in the chamber (33) is a unitary member.

6. A method of generating droplets, comprising the steps of:

   providing a supply of liquid;
   filling chambers (33) with some of the liquid; and
   instantaneously heating the liquid in the chambers by an amount sufficient to produce a vapor bubble in each chamber for
   propelling from each chamber droplets (36) of the liquid wherein each droplet has a volume of less than 100 femtoliters.

7. The method of claim 6 including the step of propelling the liquid from each chamber (33) as a substantially single volume that separates into two or more droplets.

8. The method of claim 7 including the step of instantaneously heating the liquid so that the liquid in the chamber (33) is propelled with a single instance of heating the liquid.

9. The method of claim 7 further comprising the step of providing an orifice member (48) that has at least two orifices (125) extending from the chamber (33) to permit liquid to be propelled through the orifices from the chamber.

10. The method of claim 7 further comprising the step of providing a single orifice (25) through which substantially all of the liquid in the chamber (33) is propelled.

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(12) **United States Patent**
Fuchs et al.

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(45) **Date of Patent: Mar. 23, 2004**

(54) **DISPENSER FOR FLOWABLE MEDIA**

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(73) Assignee: **Ing. Erich Pfeiffer GmbH**, Radolfzell (DE)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

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(58) **Field of Search** 222/82, 83, 83.5, 222/326, 327, 321.6, 386

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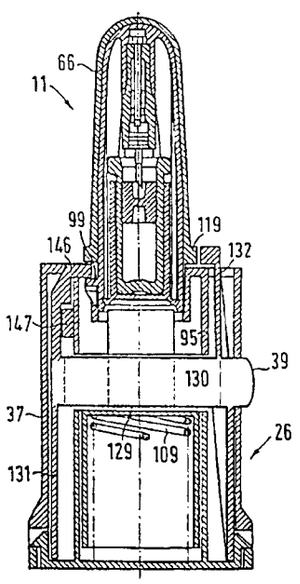
(57) **ABSTRACT**

The invention relates to a dispenser, especially a disposable atomizer **(25)**, with a dispenser unit **(11)**. Said unit contains a media container **(12)** which also forms the pump chamber and which is sealed by a piston-type stopper **(14)**. When activated, said piston-type stopper is punctured by a hollow needle **(16)**. The outlet nozzle **(20)** surrounds the dispenser unit to a large extent. The dispenser unit **(11)** can be introduced into an activating unit **(26)**. According to one configuration, this activating unit is pin-shaped with a loading chamber **(29)**. The dispenser unit is held in place by an activating push rod **(30)** which can be longitudinally displaced when activated by turning **(33)** and is prestressed by a spring **(36)**. The dispenser is activated by a trigger device **(39)**. The dispenser unit **(11)** can also be changed after use.

15 Claims, 15 Drawing Sheets



also FIG. **40**), on which is shaped a fork **147** which is wedge-shaped at its two free ends and which is shown in FIG. **39***a*. As shown in FIG. **39**, said fork **147** engages between the projection **95** of casing **37** and the locking lever **146** and presses the same outwards, so that the locking elements **99** are freed and the dispenser unit **11** can be removed. The projections **99** can correspond both to a bayonet and also simply to snap locking without turning into an operating position.

Following the release of the protective cap, which can only take place when the dispenser unit **11** has been inserted in the actuating unit **26**, the bottom wedge-shaped member drops freely downwards. It is then no longer possible to fit said dispenser unit on an actuating unit.

FIG. **40** shows a construction with a tear-up tongue on the protective cap **66**, but the arrangement of the actuating and release buttons **39** and **115** is the same as for FIG. **39**.

FIG. **43** shows an actuating unit **26** with manual actuation by means of an actuating pusher **56**, as shown in FIGS. **7** to **9**. It projects a relatively long way and on it can be placed a lid **148**, which contains a reserve holder **149** for two rechargeable replacement dispenser units **11**. They can be jammed in or can also be inserted by means of the screw-bayonet connection with propeller blade-like locking elements **99**. With the head of their protective caps **66** they engage in corresponding depressions in the actuating shoulder **44**, so that even in the case of violent movements they remain in position.

Thus, this constitutes a different construction to the reserve holder for "replacement cartridges" or their functional parts already shown in FIGS. **2** and **8**.

In the vicinity of the actuating shoulders a two-armed locking lever **150** is. shaped onto the casing **37** and as a result of whose manufacture it can pivot in the direction of the arrow **151**, i.e. counterclockwise. However, it is prevented from doing so by the flange **119** of the protective cap **66**, so that it rests with its lower barrier surface **152** on an inner projection **153** of the actuating pusher and prevents an actuation before the protective cap is removed. On removing the protective cap **66**, the locking lever **150** pivots counterclockwise into a position releasing actuation.

What is claimed is:

1. A dispenser for flowable media, for applying media to a person, comprising:

an exchangeable dispenser unit **(11)** operable for a limited number of application strokes, having

an outlet opening **(19)** in form of a spray nozzle,

at least one closing and opening element **(15, 16)** located between a media container **(12)** and the outlet opening **(19)** said opening element **(16)** being spaced inwardly from the outlet opening **(19)** and

an outlet channel located between the media container **(12)** and the spray nozzle **(19)**; and

said dispenser further comprising

an actuating unit **(26)** that is separable from the dispenser unit **(11)**, and that is reusable,

the actuating unit **(26)** having functional parts at least contributing to actuation of the dispenser unit **(11)**; and

wherein the dispenser unit **(11)** includes a wall apart from the media container that encloses the opening and closing elements to protect the medium within the dispenser from contamination.

2. The dispenser according to claim **1**, wherein the media container **(12)** is at least partly located within the outlet piece **(20)** containing the spray nozzle **(19)**.

3. A dispenser for flowable media, for applying media to a person, comprising:

an exchangeable dispenser unit **(11)** operable for a limited number of application strokes, having

an outlet opening **(19)** in form of a spray nozzle,

at least one closing and opening element **(15, 16)** located between a media container **(12)** and the outlet opening **(19)** said opening element **(16)** being spaced inwardly from the outlet opening **(19)**, and

an outlet channel located between the media container **(12)** and the spray nozzle **(19)**; and

said dispenser further comprising

an actuating unit **(26)** that is separable from the dispenser unit **(11)** and that is reusable,

the actuating unit **(26)** having functional parts at least contributing to actuation of the dispenser unit **(11)**; and

wherein the dispenser unit **(11)** includes a wall apart from the media container that, encloses the opening and closing elements to protect the medium within the dispenser from contamination, and

wherein the media container **(12)** also forms a pump cylinder of a thrust piston pump, and wherein a closing element of the media container **(12)** is formed by a piston-type stopper being pierceable by an opening element including a hollow needle **(16)**, and wherein a push rod **(18)** receives the hollow needle, the push rod having an end face **(24)** pressing onto the piston-type stopper **(14)** to perform a pump stroke, the push rod **(18)** being located in the outlet piece **(20)** containing the spray nozzle **(19)**.

4. The dispenser according to claim **3**, wherein a narrow sealing gap **(120)** is provided between a casing part **(95)** of the dispenser unit **(11)** and a reception sleeve **(40)** receiving the media container.

5. The dispenser according to claim **3**, wherein the actuating unit **(26)** has a charging chamber in which the dispenser unit **(11)** can be inserted.

6. The dispenser according to claim **3**, wherein the actuating unit comprises a tensionable and releasable actuating mechanism.

7. A dispenser for flowable media, for applying media to a person, comprising:

an exchangeable dispenser unit **(11)** operable for a limited number of application strokes, having

an outlet opening **(19)** in form of a spray nozzle,

at least one closing and opening element **(15, 16)** located between a media container **(12)** and the outlet opening **(19)**, and

an outlet channel located between the media container **(12)** and the spray nozzle **(19)**; and

said dispenser further comprising

an actuating unit **(26)** that is separable from the dispenser unit **(11)** and that is reusable,

the actuating unit **(26)** having functional parts at least contributing to actuation of the dispenser unit **(11)**; and

wherein the dispenser unit **(11)** encloses the opening and closing elements to protect the medium within the dispenser from contamination, and

further comprising actuating pressure point means for ensuring a minimum actuating force for the dispenser.

8. The dispenser according to claim **7**, wherein the actuating pressure point means are provided by destructible material bridges **(55)**.

9. A dispenser for flowable media, for applying media to a person, comprising:

an exchangeable dispenser unit **(11)** operable for a limited number of application strokes, having

an outlet opening **(19)** in form of a spray nozzle,

at least one closing and opening element **(15, 16)** located between a media container **(12)** and the outlet opening **(19)**, and

an outlet channel located between the media container (12) and the spray nozzle (19); and

said dispenser further comprising

an actuating unit (26) that is separable from the dispenser unit (11) and that is reusable,

the actuating unit (26) having functional parts at least contributing to actuation of the dispenser unit (11); and

wherein the dispenser unit (11) encloses the opening and closing elements to protect the medium within the dispenser from contamination, and

wherein the actuating unit (26) is shaped like a round cylinder, having one end face providing a recess with fixing means for the dispenser unit (11).

10. A dispenser for flowable media, for applying media to a person, comprising:

an exchangeable dispenser unit (11) operable for a limited number of application strokes, having

an outlet opening (19) in form of a spray nozzle,

at least one closing and opening element (15, 16) located between a media container (12) and the outlet opening (19), and

an outlet channel located between the media container (12) and the spray nozzle (19); and

said dispenser further comprising

an actuating unit (26) that is separable from the dispenser unit (11) and that is reusable,

the actuating unit (26) having functional parts at least contributing to actuation of the dispenser unit (11); and

wherein the dispenser unit (11) encloses the opening and closing elements to protect the medium within the dispenser from contamination, and

wherein the actuating unit comprises a tensionable and releasable actuating mechanism, the actuating mechanism contains a release mechanism having a shape--variable ring (130), which has a release shape (B) closer to a circle shape than a blocking oval shape (N).

11. A dispenser for flowable media, for applying media to a person, comprising:

an exchangeable dispenser unit (11) operable for a limited number of application strokes, having

an outlet opening (19) in form of a spray nozzle,

at least one closing and opening element (15, 16) located between a media container (12) and the outlet opening (19), and

an outlet channel located between the media container (12) and the spray nozzle (19); and

said dispenser further comprising

an actuating unit (26) that is separable from the dispenser unit (11) and that is reusable,

the actuating unit (26) having functional parts at least contributing to actuation of the dispenser unit (11); and

wherein the dispenser unit (11) encloses the opening and closing elements to protect the medium within the dispenser from contamination, and

further comprising actuation blocking means for preventing undesired actuation of the dispenser (25).

12. The dispenser according to claim 11, wherein the blocking means cooperate with means (88, 89, 132, 133, 150) dependent on proper insertion of the dispenser unit (11) in the actuating unit (26).

13. The dispenser according to claim 11, wherein the blocking means contain a locking element (132, 150) , which cooperates with the dispenser unit and with a release element (129).

14. The dispenser according to claim 11, wherein, for preventing actuation prior to the removal of a protective cap (66), the blocking means cooperate with a protective cap (66) for the dispenser unit (11).

15. A dispenser for flowable media, for applying media to a person, comprising:

an exchangeable dispenser unit (11) operable for a limited number of application strokes, having

an outlet opening (19) in form of a spray nozzle,

at least one closing and opening element (15, 16) located between a media container (12) and the outlet opening (19), and

an outlet channel located between the media container (12) and the spray nozzle (19); and

said dispenser further comprising

an actuating unit (26) that is separable from the dispenser unit (11) and that is reusable,

the actuating unit (26) having functional parts at least contributing to actuation of the dispenser unit (11); and

wherein the dispenser unit (11) encloses the opening and closing elements to protect the medium within the dispenser from contamination, and

further comprising a protective cap being prevented from being drawn off from the dispenser unit by locking means (85, 86) before the dispenser is ready to operate.

* * * * *

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(125)

United States Patent [19]

Phillips

[11] **3,818,908**

[45] **June 25, 1974**

[54] **MEDICAMENT DISPENSER**

[75] Inventor: **Robert E. Phillips**, Studio City, Calif.

[73] Assignee: **Riker Laboratories, Inc.**, Northridge, Calif.

[22] Filed: **Aug. 7, 1972**

[21] Appl. No.: **278,538**

[52] **U.S. Cl.** **128/173**, 222/193, 239/350, 128/208, 128/211

[51] **Int. Cl.** **A61m 11/00**

[58] **Field of Search** 128/173, 173.1, 194, 201, 128/211, 208, 266, 222, 185, 186; 239/350, 345–349, 355, 308, 318, 338; 222/193, 136, 402.2, 335, 383–385

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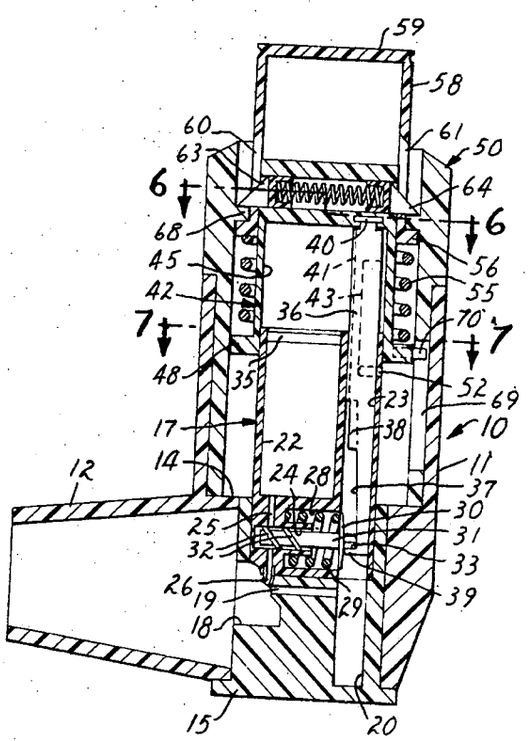
Primary Examiner—Richard A. Gaudet
Assistant Examiner—Lee S. Cohen
Attorney, Agent, or Firm—Alexander, Sell, Steldt & DeLaHunt

[57] **ABSTRACT**

A dispenser for dispensing inhalable medicaments which dispenser dispenses the liquid medicaments in a mist by nebulizing a metered amount of the liquid. The liquid is metered by a rotary piston pump and a piston and cylinder arrangement within the dispenser compresses a small amount of air when a release mechanism is triggered to carry the dispensed liquid such that the patients will inhale a mist.

9 Claims, 7 Drawing Figures



amount of the medicament is drawn into the cylinder **24** forward of the O ring **32.** As the shell **58** is lifted the detents **63** and **64** are forced inwardly by rib **68** engaging their beveled edges and then are forced outwardly again to seat on the upper side of the rib **68** in the cap **50.** Cam **39** again contacts the follower **33** to rotate the piston **31,** turning the O rings **32** to a position cutting off communication between the pump and the inlet **25.** The device is now positioned for a subsequent operation.

In an operative example, the air discharged from the passageway **19** to nebulize the liquid can be at pressures between 5 and 8 pounds per square inch at standard temperature and atmospheric pressure. The bore **45** of the shell **42** has a diameter of about 0.85 inch and it travels a total of 0.8 inch. The shell travels about 0.4 inch to release the spring and when released the pressure therein is about 8 pounds. The spring and the continued movement maintained by the operator then drives the shell **42.** The amount of liquid dispensed may be about 5, 6, or 7 microliters, depending on pump capacity.

For preferred operation, a predetermined amount of air under a predetermined amount of pressure is directed at the discharged liquid. The predetermined amount of liquid is introduced into the air stream when the air is at its peak pressure.

Having thus described the invention with respect to a preferred embodiment, it will be understood that certain modifications can be made without departing from the spirit of this invention.

What is claimed is:

1. A dispenser for medicaments such that metered amounts of the medicament will be discharged in a state to be orally received during inhalation, said dispenser comprising:

a housing formed with a discharge passageway,

a reservoir for a quantity of liquid disposed in said housing,

metering pump means having an inlet communicating with said reservoir and an outlet communicating with said passageway for dispensing under pressure metered amounts of liquid from said reservoir,

operator means for operating said metering pump means to dispense said liquid from said outlet under pressure,

air compressing means within said housing for placing a volume of air under pressure and for directing said air under pressure toward said outlet, and

mechanical actuating means for actuating said operator means and said air compressing means whereby a metered amount of liquid is dispensed from said outlet and struck by said compressed air to be discharged with said air as a spray.

2. A dispenser according to claim **1** comprising resettable release means connected between said housing and said air compressing means for releasing said mechanical actuating means upon an operator applying pressure to said release means.

3. A dispenser according to claim **1** wherein said air compressing means comprises:

a hollow cylinder and a mating piston member, said cylinder and piston member being interfitted within said housing and mounted for relative movement, and

a passageway leading from within said cylinder to a position adjacent said outlet.

4. A dispenser according to claim **3** wherein said mechanical actuating means comprises a helical compression spring disposed about the outer surface of said cylinder, said cylinder having a first position relative to said piston member wherein said compression spring is under compression and in which first position said cylinder is retained by said release means, and a second position relative to said piston wherein air has been driven from said cylinder by said spring compression being dissipated, and said operator means has actuated said metering pump means.

5. A dispenser according to claim **4** wherein said metering pump means is a rotary piston pump comprising means defining a cylindrical bore, a piston slidably received in said bore, spring means urging said piston out of said bore, passage means communicating with said bore to define said inlet and outlet and seal means on said piston for connecting the bore in fluid flow communication with said reservoir when said cylinder is in said first position and with said outlet when said cylinder is in said second position.

6. A dispenser according to claim **4** wherein resettable release means are provided for releasing said mechanical actuating means and comprises:

detent means supported by said cylinder,

shoulder means on said housing engageable by said detent means to hold said cylinder in said first position, and

manually actuatable means for compressing said compression spring with said cylinder in said first position and for unlocking said detent means and said shoulder means to allow movement of said cylinder to said second position.

7. A dispenser according to claim **1** wherein said metering pump means is a rotary piston pump comprising means defining a cylindrical bore, a piston slidably received in said bore, seal means on said piston connecting said bore with said inlet and then with said outlet upon operation of said actuating means, spring means urging said piston out of said bore, and passage means communicating with said bore to define said inlet and outlet.

8. A dispenser for an inhalation medicament comprising a tubular housing having a laterally projecting mouthpiece, a supply canister of medicament within said housing, means for metering a quantity of medicament for discharge upon actuation of an actuator on said dispenser, wherein the improvement comprises:

a rotary piston pump means for discharging a predetermined quantity of medicament from said canister and discharging the same from an outlet under pressure, and

means within said housing for providing a quantity of compressed air directed at said outlet and into said mouthpiece to carry said discharged medicament into said mouthpiece upon actuation of said actuator.

9. A dispenser according to claim **8** wherein said canister comprises:

a cylindrical shaped body member having an axially extending bore extending therethrough and a second bore forming a reservoir, said second bore extending toward one end, said body having a third bore extending generally diametrically and having

passageways connecting said third bore to said reservoir and to said one end, and

said rotary piston pump means includes a piston slidably fitted in said third bore, said piston having means affording selective communication of said third bore with said reservoir and said one end, and a spring positioned about said piston urging it from said bore.

* * * * *

United States Patent [19]

Hughes

[11] **Patent Number: 4,702,415**

[45] **Date of Patent: Oct. 27, 1987**

[54] **AEROSOL PRODUCING DEVICE**

[75] Inventor: **Nathaniel Hughes**, Palm Springs, Calif.

[73] Assignee: **Vortran Corporation**, Culver City, Calif.

[21] Appl. No.: **652,740**

[22] Filed: **Sep. 18, 1984**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 555,703, Nov. 28, 1983, Pat. No. 4,635,857.

[51] **Int. Cl.**[4] **A61M 11/06**

[52] **U.S. Cl.** **239/8**; 128/200.18; 128/200.21; 239/11; 239/338; 239/370; 239/426; 239/434; 239/589.1; 261/78.2; 261/DIG. 65

[58] **Field of Search** ..... 239/102, 338, 370, 590, 239/590.3, 590.5, DIG. 20, DIG. 23, 403, 426, 434, 8, 11, 461, 463, 589.1; 128/200.18, 200.21; DIG. 65, 78.2

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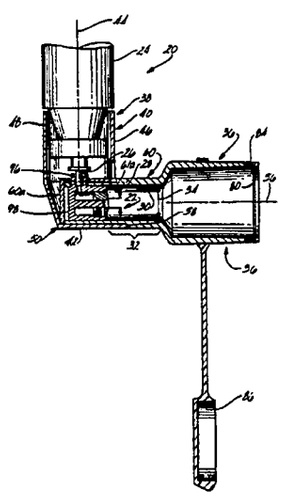
Primary Examiner—Andres Kashnikow
Assistant Examiner—Michael Forman
Attorney, Agent, or Firm—Christie, Parker & Hale

[57] **ABSTRACT**

An apparatus and method are disclosed for applying an active ingredient as an aerosol. A transducer (**22**) for creating an aerosol includes a propellant inlet (**96**) and a chamber defined by at least one chamber wall (**128**) confluent with the propellant inlet. A bluff body (**112**) is provided for creating at least one vortex (**152**) in the chamber when the propellant enters the propellant inlet in a supersonic flow condition. An orifice (**118, 146**) spaced apart from the bluff body and separated therefrom by the chamber wall is provided for creating an exiting vortex (**154**).

2 Claims, 15 Drawing Figures



The flow through the cylindrical apertures is substantially the same.

As the fluid exits the orifice **172**, a vacuum is produced at the outlet of tube **192** due to the supersonic and vortical flow of the exiting vortex. Additionally, the sub-atmospheric pressure region in the vortex serves to produce flow of the fluid in container **194** through the tube **192**. As the active ingredient leaves the tube **192**, the fluid is effectively atomized by the action of the exiting vortex. The atomization of the active ingredient is substantially the same due to the action of the vortex as the atomization with the transducers previously described.

The propellant canister **188** may be a unit dose canister such as that described above with respect to FIG. **1** or may be a continuous flow canister providing output whenever the inlet tube **190** is depressed with respect to canister **188**. In either case, the exiting vortex produced by the transducer **196** draws the active ingredient from container **194** as long as propellant is produced from canister **188**. During continuous operation of canister **188**, the active ingredient is drawn from flexible container **194** until fluid is no longer present in the container.

The manipulation of the resulting vortex may be carried out as desired. For example, the guide tube **196** may be provided with expansion chambers and resonant screens as discussed with respect to FIG. **1**. Alternatively, if the active ingredient is to be applied directly from the transducer, the guide tube **196** may be omitted.

FIG. **14** shows an alternative embodiment of transducer **186** and the inlet tube **192** wherein the inlet tube is placed external to the transducer **186** adjacent the outer rim of the diverging conical portion **174**. Substantially the same result can be obtained for atomizing the active ingredient with the inlet tube **192** located as shown in FIG. **14** as can be obtained with the arrangement provided in FIG. **13**. The function and operation of the arrangement shown in FIG. **14** is otherwise the same as that described with respect to FIG. **13**.

FIG. **15** shows an additional embodiment of transducer **186** and the inlet tube **192** wherein the inlet **192** has its terminal portion flush with the surface of conical portion **174**. The structure and function of the transducer is otherwise the same as described with respect to FIGS. **13** and **14**.

These transducers are particularly efficient at low liter flows of oxygen and are very much suited for general hospital use at these flows with the requisite advantages for low oxygen rate therapy cited earlier. This capability makes nebulizers built with these inventions uniquely operable with oxygen concentrators.

It should be noted that the above are preferred configurations but others are foreseeable. The described embodiments of the invention are only considered to be preferred and illustrative of the inventive concept; the scope of the invention is not to be restricted to such embodiments. Various and numerous other arrangements may be devised by one skilled in the art without departing from the spirit and scope of the invention.

I claim:

1. A process for creating an aerosol characterized by the steps of:

providing a propellant to an inlet of a transducer;

impacting the propellant on a bluff body to create at least one vortex;

feeding the at least one vortex to an aperture spaced apart from the bluff body;

producing a vortex through an orifice spaced apart from the bluff body and separated from the bluff body by a wall preventing flow of fluid along the bluff body to the orifice; and

incorporating an active ingredient into the propellant.

2. A transducer for creating an aerosol having an inlet and an outlet portions, the transducer characterized by:

a single inlet tube having a first central axis;

a transducer body having a second central axis and to which the tube is coupled and wherein the first central axis is normal to a plane containing the second central axis;

a bluff body extending from one end of the transducer body substantially to another end along the second central axis and comprising a groove in an end adjacent the other end of the transducer body extending from an interior surface portion of the bluff body to the end thereof; and

a cylindrical lens portion adapted to be positioned substantially within the other end of the transducer body and about the end of the bluff body, the lens portion comprising:

a first cylindrical aperture comprising an upstream portion and extending from an upstream portion of the lens portion to a downstream portion through the center of the lens portion for fitting the lens portion about the bluff body,

a first conically-shaped depression in the upstream portion converging downstream-wise to the upstream portion of the aperture,

a second conically-shaped depression in the downstream portion of the lens portion diverging downstream-wise from the dowstream portion of the aperture,

a second cylindrical aperture extending from the first depression toward the second depression, and

a third cylindrical aperture extending from the second cylindrical aperture to the first cylindrical aperture.

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REPUBLICA DE COLOMBIA

NOTARIA 33 DE BOGOTA D.C.

ESCRITURA PUBLICA NUMERO: 1 6 5 8

- - MIL SEISCIENTOS CINCUENTA Y OCHO - -

FECHA DE OTORGAMIENTO: CUATRO (4) DE JULIO - - - - - - - -

DEL AÑO DOS MIL DOS (2002). ----------

ACTO: ----------

1.- PODER ESPECIAL.----------

OTORGADO POR: LAFRANCOL S.A., con Nit. No. - - -

890.301.463-8 - - - - - -

a favor de: JOSE LUIS REYES VILLAMIZAR, con C.C.No.

79.152.473 de Usaquén - Bogotá.---------

DIANA BEATRIZ LOPEZ

NOTARIA TREINTA Y TRES (33) DE BOGOTA D.C.

EN LA CIUDAD DE BOGOTA, DISTRITO CAPITAL, DEPARTAMENTO DE CUNDINAMARCA, REPUBLICA DE COLOMBIA, ANTE MI, DIANA BEATRIZ LOPEZ, - - - - - - NOTARIA TREINTA Y TRES (33) - - - - - DE ESTE CIRCULO SE OTORGA LA ESCRITURA PUBLICA QUE SE CONSIGNA EN LOS SIGUIENTES TERMINOS:----------

COMPARECIO: JUAN MARIA RENDON, mayor de edad, vecino de Bogotá, D.C, identificado con la cédula de ciudadanía número 17.125.100 de - - - - - - Expedida en Bogotá - - - - - - - - - - Y manifestó:----------

PRIMERO: Que obra en su carácter de Representante Legal y en nombre y representación de LAFRANCOL S.A., sociedad comercial organizada y existente conforme a las leyes colombianas, con domicilio y sede principal en Cali - Valle, constituida mediante escritura pública número

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Copia Notaría Veinticinco del Círculo de Bogotá D.C. certifico que, previo cotejo especificado, la presente copia coincide exactamente con la copia auténtica que tuve a la vista. 30 DIC 2008 LILIANA CONSTANZA BAQUERO

De la Notaría

De fecha

Reformada en distintas oportunidades, según consta en el certificado expedido por la Cámara de Comercio de Cali - Valle.----------

SEGUNDO: Que en tal carácter, por este público instrumento, concede PODER ESPECIAL, PERO AMPLIO Y SUFICIENTE a **JOSE LUIS REYES VILLAMIZAR** mayor de edad, vecino de Bogotá, D.C, identificado con la cédula de ciudadanía número 79.152.473 de Usaquén, abogado en ejercicio, portador de la T.P.No. 446 55 del C.S. de la J., domiciliado en Bogotá, D.C, República de Colombia, con dirección en la carrera 17 No. 88-23, Oficina 205, de la misma ciudad, como su representante con poder especial, amplio y suficiente, para obtener la protección los derechos de propiedad industrial y de libre competencia de Lafrancol S.A., a cuyo efecto lo autorizo, par que nos represente ante cualesquiera entidad o persona, ejerza o no jurisdicción, especialmente ante las el orden administrativo, contencioso, administrativo y judicial, en todo lo concerniente a los siguientes asuntos:----------

a.- Obtención, formulación de oberservaciones y oposición a patentes de invención, modelos y dibujos industriales y el registro de licencias de uso de esos derechos.----------

b.- Las acciones de oposición, cancelación, nulidad, medidas cautelares, concesión de licencias y en general los procesos civiles, penales, administrativos o contencioso- adm[illegible] relacionados con estos derechosa [illegible] diferente naturaleza, acciones y [illegible]

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c.- Para que en todos los asuntos arriba determinados, tanto en los términos señalados por los artículos 42 y complementarios de la decisión 486 de la Comunidad Andina como del artículo 70 del C.P.C. pueda sustituir este mandato, transigir, conciliar, admitir los hechos del proceso, desistir, cancelar, recibir, renunciar y ratificar los actos de agentes oficiosos y ceder a título gratuito y/o oneroso, licenciar, inscribir contratos de cesión y de licencia, inscripción de prendas, levantamiento de prendas, inscribir derechos de retención y en general todos los asuntos que se deban tramitar ante la Superintendencia de Industria y Comercio.----------

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RESOLUCION No. 4188 del 28 de Diciembre del 2001

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C.C.No. 17.125.100 de Bogotá

LAFRANCOL S.A.

Nit. No. 890.301.463-8

TEL: 622-04-66.

ACEPTO :

JOSE LUIS REYES VILLAMIZAR

C.C. No. 79.152.473

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DIANA BEATRIZ LOPEZ

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Operacion : 03C291126002 PAGINA No. 1

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CERTIFICA:

NOMBRE:LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A.
DOMICILIO: CALI VALLE
DIRECCION COMERCIAL :---K 1 46 84
DIRECCION NOTIFICACION JUDICIAL:---K 1 46 84
CIUDAD:CALI
MATRICULA MERCANTIL NRO. 5233-4 FECHA MATRICULA : 02 DE OCTUBRE DE 1958
DIRECCION ELECTRONICA : esperanzacortes@lafrancol.net
AFILIADO

CERTIFICA:

NIT : 890301463-8

CERTIFICA:

QUE POR ESCRITURA NRO. 1434 DEL 29 DE SEPTIEMBRE DE 1958 NOTARIA CUARTA DE CALI , INSCRITA EN LA CAMARA DE COMERCIO EL 02 DE OCTUBRE DE 1958 BAJO EL NRO. 18319 DEL LIBRO IX , SE CONSTITUYO LA SOCIEDAD DENOMINADA LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A.

CERTIFICA:

REFORMAS

DOCUMENTO	FECHA.DOC	ORIGEN	FECHA.INS	NRO. INS LIBRO
E.P. 1104	30/06/1959	NOTARIA CUARTA DE CALI	07/07/1959	19467
E.P. 2309	26/12/1959	NOTARIA CUARTA DE CALI	29/12/1959	20089
E.P. 1725	24/07/1962	NOTARIA CUARTA DE CALI	26/07/1962	24528
E.P. 1824	31/07/1963	NOTARIA CUARTA DE CALI	14/08/1963	26360
E.P. 2422	25/10/1963	NOTARIA CUARTA DE CALI	28/10/1963	26717
E.P. 1720	16/09/1964	NOTARIA CUARTA DE CALI	22/09/1964	

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20081126 Hora Certificado 08:22:32

Operacion : 03C291126002 PAGINA No. 2

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28406				
E.P. 101	31/01/1966	NOTARIA CUARTA DE CALI		01/02/1966
31039				
E.P. 552	21/03/1968	NOTARIA CUARTA DE CALI		01/04/1968
35711				
E.P. 4964	12/12/1972	NOTARIA CUARTA DE CALI		16/01/1973
2975 IX				
E.P. 1956	30/05/1973	NOTARIA CUARTA DE CALI		13/06/1973
4337 IX				
E.P. 4964	12/12/1972	NOTARIA CUARTA DE CALI		28/11/1973
5994 IX				
E.P. 5579	12/11/1973	NOTARIA CUARTA DE CALI		28/11/1973
5995 IX				
E.P. 4406	30/09/1974	NOTARIA CUARTA DE CALI		28/11/1974
10887 IX				
E.P. 192	03/02/1978	NOTARIA CUARTA DE CALI		14/02/1978
25355 IX				
E.P. 3479	07/09/1979	NOTARIA CUARTA DE CALI		19/09/1979
34204 IX				
E.P. 4274	12/12/1984	NOTARIA NOVENA DE CALI		19/12/1984
73088 IX				
E.P. 1155	21/05/1985	NOTARIA SEPTIMA DE CALI		03/06/1985
76917 IX				
E.P. 1553	20/06/1986	NOTARIA SEPTIMA DE CALI		08/07/1986
85997 IX				
E.P. 1458	09/06/1987	NOTARIA SEPTIMA DE CALI		24/12/1987
3508 IX				
E.P. 7222	14/12/1988	NOTARIA TERCERA DE CALI		19/12/1988
13847 IX				
E.P. 4530	04/09/1989	NOTARIA TERCERA DE CALI		07/09/1989
21508 IX				
E.P. 3865	02/08/1990	NOTARIA TERCERA DE CALI		13/08/1990
31708 IX				
E.P. 8305	13/12/1995	NOTARIA TERCERA DE CALI		23/01/1996
557 IX				
E.P. 4559	16/11/1999	NOTARIA TERCERA DE CALI		26/11/1999
7911 IX				
E.P. 6.004	02/12/2004	NOTARIA TERCERA DE CALI		14/12/2004
13371 IX				
E.P. 6241	27/12/2006	NOTARIA TERCERA DE CALI		19/01/2007
625 IX				
E.P. 389	07/02/2008	NOTARIA TERCERA DE CALI		19/02/2008
1880 IX				

CERTIFICA:

VIGENCIA: 29 DE SEPTIEMBRE DEL A?O 2057

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CERTIFICA:

OBJETO SOCIAL. SE OCUPA EN: A) FABRICACION, DISTRIBUCION Y VENTA EN EL TERRITORIO DE LA REPUBLICA DE COLOMBIA O EN EL EXTRANJERO DE CUALESQUIERA TIPOS DE VACUNAS, PRODUCTOS QUIMICOS, FARMACEUTICOS ALIMENTICIOS FUNCIONALES, COSMETICOS Y FISOLOGICOS, REACTIVOS, ANTIBIOTICOS PARA USO HUMANO Y VETERINARIO, PRODUCTOS DIETETICOS, COLORANTES DE PERFUMERIA Y AFINES. B) LA REPRESENTACION DE CASAS FABRICANTES NACIONALES O EXTRANJERAS DE ESTOS MISMOS PRODUCTOS. C) FABRICACION, IMPORTACION, DISTRIBUCION Y VENTA DE CUALESQUIERA TIPOS DE PRODUCTOS VETERINARIOS. D) LA REALIZACION DE TODOS LOS ACTOS, CONTRATOS, CONVENIOS, DIRECTAMENTE RELACIONADOS CON LOS FINES ANTES INDICADOS. EN DESARROLLO DE SU OBJETO SOCIAL PODRA LA SOCIEDAD ADQUIRIR Y VENDER BIENES RAICES Y MUEBLES, DARLOS Y TOMARLOS EN ARRENDAMIENTO, GARANTIZAR CON HIPOTECA SOBRE LOS BIENES RAICES O CON PRENDA SOBRE LOS BIENES MUEBLES, OBLIGACIONES A CARGO DE LA SOCIEDAD; DAR Y RECIBIR A MUTUO COMERCIAL DINERO Y CELEBRAR LOS CONTRATOS COMERCIALES DE CAMBIO EN TODAS SUS MANIFESTACIONES, FUNDAR EMPRESAS QUE TENGAN LA MISMA FINALIDAD SOCIAL O ASOCIARSE CON ELLAS.

CERTIFICA:

ORGANOS DE DIRECCION Y ADMINISTRACION: 1) ASAMBLEA GENERAL DE ACCIONISTAS; 2) JUNTA DIRECTIVA; 3) GERENCIA GENERAL. TAMBIEN TENDRA UN REVISOR FISCAL.

ADMINISTRACION: LA ADMINISTRACION INMEDIATA DE LA SOCIEDAD, SU REPRESENTACION LEGAL Y LA GESTION DE LOS NEGOCIOS SOCIALES ESTARAN A CARGO DE UN GERENTE, DESIGNADO POR LA ASAMBLEA GENERAL DE ACCIONISTAS, PARA PERIODOS DE DE DOS (2) A?OS REELEGIBLE INDEFINIDAMENTE Y REMOVIBLE LIBREMENTE POR ELLA EN CUALQUIER TIEMPO.

PARAGRAFO PRIMERO. SUPLENTES: EL GERENTE Y REPRESENTANTE LEGAL TENDRA LOS SIGUIENTES SUPLENTES: PRIMERO, SEGUNDO Y TERCERO QUE LO REEMPLAZARAN EN LOS CASOS DE AUSENCIAS ACCIDENTAL, TEMPORAL Y ABSOLUTA CON LAS LIMITACIONES QUE MAS ADELANTE SE ESTABLECEN.

PARAGRAFO SEGUNDO. EL TERCER SUPLENTE DEL GERENTE GENERAL Y REPRESENTANTE LEGAL ESTARA LIMITADO EN SUS FUNCIONES A: COMPROMETER LOS NEGOCIOS SOCIALES EN CUANTIA NO SUPERIOR A CUATRO MIL DOSCIENTOS SALARIOS MINIMOS MENSUALES LEGALES VIGENTES (4.200 SMMLV); CELEBRAR CONTRATOS COMERCIALES DE COMPRAVENTA EN GENERAL YA SEA CON LA NACION (MINISTERIOS Y DEPARTAMENTOS ADMINISTRATIVOS), ENTIDADES DESCENTRALIZADAS (ESTABLECIMIENTOS PUBLICOS, EMPRESAS INDUSTRIALES Y COMERCIALES DEL ESTADO, SOCIEDADES DE ECONOMIA MIXTA), EMPRESAS SOCIALES CIVILES Y COMERCIALES, CUALQUIERA QUE SEA SU NATURALEZA CON FACULTADES PARA EXIGIR O SUSCRIBIR LOS DOCUMENTOS Y GARANTIAS NECESARIOS HASTA LA CUANTIA ANTES MENCIONADA.

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FUNCIONES DEL GERENTE: A) ... B) EJECUTAR Y HACER CUMPLIR LOS ACUERDOS Y DECISIONES DE LA ASAMBLEA GENERAL DE ACCIONISTAS Y DE LA JUNTA DIRECTIVA Y HACER USO DE LA RAZON SOCIAL. C) REPRESENTAR LEGALMENTE A LA SOCIEDAD CONFORME A LA LEY ANTE TODAS LAS AUTORIDADES CIVILES, JUDICIALES, MILITARES, SANITARIAS, DE POLICIA, ADUANALES, POSTALES, ETC. G) LLEVAR A CABO LA GESTION COMERCIAL Y FINANCIERA. H) TENDRA LA PLENA RESPONSABILIDAD DE LA ACCION ADMINISTRATIVA, LA COORDINACION Y LA SUPERVISION GENERAL DE LA SOCIEDAD, LAS CUALES CUMPLIRA CON ARREGLO A LAS NORMAS DE LOS ESTATUTOS.
EN EL EJERCICIO DE SUS FUNCIONES, EL GERENTE PUEDE: 1.- COMPARECER EN LOS JUICIOS, TRANSIGIR Y COMPROMETER LOS NEGOCIOS SOCIALES DE CUALQUIERA NATURALEZA QUE FUEREN, INTERPONER TODO GENERO DE RECURSOS Y CONSTITUIR APODERADOS QUE LO REPRESENTEN JUDICIAL O EXTRAJUDICIALMENTE. 2.- ENAJENAR A CUALQUIER TITULO Y COMPRAR BIENES MUEBLES, CELEBRAR CONTRATOS COMERCIALES DE COMPRA Y VENTA EN GENERAL YA SEA CON LA NACION (MINISTERIOS Y DEPARTAMENTOS ADMINISTRATIVOS), ENTIDADES DESCENTRALIZADAS (ESTABLECIMIENTOS PUBLICOS), EMPRESAS INDUSTRIALES Y COMERCIALES DEL ESTADO, SOCIEDADES DE ECONOMIA MIXTA), EMPRESAS O SOCIEDADES CIVILES Y COMERCIALES CUALQUIERA QUE SEA SU NATURALEZA Y SU CUANTIA, CON AMPLIAS FACULTADES QUE EXIGIR O SUSCRIBIR LOS DOCUMENTOS, Y GARANTIAS NECESARIAS. CONTRATAR PRESTAMOS CUALQUIERA QUE SEA SU CUANTIA, CELEBRAR EL CONTRATO COMERCIAL DE MUTUO EN TODAS SUS MANIFESTACIONES Y SUSCRIBIR LOS DOCUMENTOS Y COMPROMISOS RESPECTIVOS. HACER DEPOSITOS EN BANCOS Y AGENCIAS BANCARIAS, FIRMAR CHEQUES, LETRAS, PAGARES, GIROS, LIBRANZAS Y CUALQUIER OTRO DOCUMENTO, ASI COMO NEGOCIAR ESTOS INSTRUMENTOS, TENERLOS, COBRARLOS, PAGARLOS, DESCARGARLOS, ETC.

CERTIFICA:

DOCUMENTO: ACTA No. 99 DEL 14 DE MARZO DE 2002
ORIGEN: ASAMBLEA GENERAL DE ACCIONISTAS
INSCRIPCION: 09 DE SEPTIEMBRE DE 2002 No. 14675 DEL LIBRO IX

FUE(RON) NOMBRADO(S):

GERENTE GENERAL Y REPRESENTANTE LEGAL
JUAN MARIA RENDON GUTIERREZ
C.C.17125100

PRIMER SUPLENTE DEL GERENTE
ESTHER ISABEL VENTURA DE RENDON
C.C.38979831

SEGUNDO SUPLENTE DEL GERENTE
ROBERTO M. VENTURA CRISPINO
C.C.9086003

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PRESIDENTE
ESTHER ISABEL VENTURA DE RENDON
C.C.38979831

VICEPRESIDENTE
ROBERTO S. VENTURA PAULY
C.C.16697614

CERTIFICA:

DOCUMENTO: ACTA No. 105 DEL 09 DE NOVIEMBRE DE 2004
ORIGEN: ASAMBLEA DE ACCIONISTAS
INSCRIPCION: 17 DE FEBRERO DE 2005 No. 2032 DEL LIBRO IX

FUE(RON) NOMBRADO(S):

TERCER SUPLENTE DEL GERENTE
JUAN PABLO REYES VILLAMIZAR
C.C.80419709

CERTIFICA:

DOCUMENTO: ACTA No. 99 DEL 14 DE MARZO DE 2002
ORIGEN: ASAMBLEA GENERAL DE ACCIONISTAS
INSCRIPCION: 09 DE SEPTIEMBRE DE 2002 No. 14675 DEL LIBRO IX

DOCUMENTO: ACTA No. 105 DEL 09 DE NOVIEMBRE DE 2004
ORIGEN: ASAMBLEA DE ACCIONISTAS
INSCRIPCION: 17 DE FEBRERO DE 2005 No. 2031 DEL LIBRO IX

FUE(RON) NOMBRADO(S)

JUNTA DIRECTIVA

PRINCIPALES

PRIMER RENGLON
ESTHER ISABEL VENTURA DE RENDON
C.C.38979831

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SEGUNDO RENGLON
ROSA VICTORIA VENTURA DE VISBAL
C.C.38992048

TERCER RENGLON
JUAN PABLO REYES VILLAMIZAR
C.C.80419709

SUPLENTES

PRIMER RENGLON
JUAN MARIA RENDON GUTIERREZ
C.C.17125100

SEGUNDO RENGLON
ROBERTO M. VENTURA CRISPINO
C.C.9086003

TERCER RENGLON
ROBERTO S. VENTURA PAULY
C.C.16697614

CERTIFICA:

DOCUMENTO: ACTA No. 99 DEL 14 DE MARZO DE 2002
ORIGEN: ASAMBLEA GENERAL DE ACCIONISTAS
INSCRIPCION: 09 DE SEPTIEMBRE DE 2002 No. 14675 DEL LIBRO IX

FUE(RON) NOMBRADO(S):

REVISOR FISCAL
ALFREDO LOPEZ & CIA. LTDA
NIT.800026893-5

CERTIFICA:

DOCUMENTO: DOCUMENTO PRIVADO DEL 08 DE MAYO DE 2008
ORIGEN: ALFREDO LOPEZ & CIA LTDA
INSCRIPCION: 23 DE MAYO DE 2008 No. 5771 DEL LIBRO IX

FUE(RON) NOMBRADO(S):

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REVISOR FISCAL PRINCIPAL
ALFREDO LOPEZ CAMPO
C.C.8241912

REVISOR FISCAL SUPLENTE
ANDERSON DAVID RODRIGUEZ REYES
C.C.16916373

CERTIFICA:

CAPITAL AUTORIZADO: $7,500,000,000
NUMERO DE ACCIONES: 750,000,000
VALOR NOMINAL: $10
CAPITAL SUSCRITO: $6,000,000,000
NUMERO DE ACCIONES: 600,000,000
VALOR NOMINAL: $10
CAPITAL PAGADO: $6,000,000,000
NUMERO DE ACCIONES: 600,000,000
VALOR NOMINAL: $10

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO EL NRO.5234- 2 ESTABLECIMIENTO DE COMERCIO: LABORATORIO FRANCO COLOMBIANO LAFRANCOL
UBICADO EN: ---K 1 46 84 DE CALI
RENOVO : POR EL A?O 2008

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO EL NRO.369809- 2 ESTABLECIMIENTO DE COMERCIO: LABORATORIO FRANCO COLOMBIANO LAFRANCOL S A
UBICADO EN: --K 1 46A 70 DE CALI
FECHA MATRICULA : 29 DE ABRIL DE 1994
RENOVO : POR EL A?O 2008

CERTIFICA:

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QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO EL NRO.369810- 2 ESTABLECIMIENTO DE COMERCIO: LABORATORIO FRANCO COLOMBIANO LAFRANCOL S A
UBICADO EN: ---K 1A 46 A 32 DE CALI
FECHA MATRICULA : 29 DE ABRIL DE 1994
RENOVO : POR EL A?O 2008

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO EL NRO.734908- 2 ESTABLECIMIENTO DE COMERCIO: LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A
UBICADO EN: CRA. 1A NRO. 46A 28 DE CALI
FECHA MATRICULA : 28 DE MARZO DE 2008
RENOVO : POR EL A?O 2008

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO EL NRO.734911- 2 ESTABLECIMIENTO DE COMERCIO: LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A
UBICADO EN: CRA. 1B NRO. 46A 121 DE CALI
FECHA MATRICULA : 28 DE MARZO DE 2008

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO EL NRO.734913- 2 ESTABLECIMIENTO DE COMERCIO: LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A
UBICADO EN: CRA. 3 NRO. 47 25 DE CALI
FECHA MATRICULA : 28 DE MARZO DE 2008

CERTIFICA:

QUE LA SOCIEDAD EFECTUO LA RENOVACION DE SU MATRICULA MERCANTIL EL 28 DE MARZO DE 2008 .

CERTIFICA:

QUE NO FIGURAN OTRAS INSCRIPCIONES QUE MODIFIQUEN TOTAL O PARCIALMENTE EL

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76041973

136

CAMARA
DE COMERCIO DE BOGOTA

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20081126 Hora Certificado 08:22:32

Operacion : 03C291126002 PAGINA No. 9

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PRESENTE CERTIFICADO.
LOS ACTOS Y DOCUMENTOS REGISTRADOS QUEDAN EN FIRME CINCO (5) DIAS HABILES DESPUES DE LA FECHA DE SU INSCRIPCION, SIEMPRE Y CUANDO DENTRO DE DICHO TERMINO NO SEAN OBJETO DE RECURSOS EN LA VIA GUBERNATIVA.

DE CONFORMIDAD CON EL DECRETO 2150 DE 1.995 Y LA AUTORIZACION IMPARTIDA POR LA SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO LA FIRMA MECANICA QUE APARECE A CONTINUACION TIENE PLENA VALIDEZ PARA TODOS LOS EFECTOS LEGALES.
DADO EN CALI A LOS 26 DIAS DEL MES DE NOVIEMBRE DEL A?O 2008 HORA: 08:19:35

DIEGO FERNANDO OCAMPO GARCIA

73

(37)

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 101,582
FECHA : DICIEMBRE 30 DE 2008

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 07-055028- -00005-0000
Fecha 2008-12-30 17:20:10 Dep: 2020 NUEVACIONES
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 400 OPOSIOBSERVTER Folios: 73

C O N S I G N A C I O N

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
REYES Y REYES ABOGADOS	CONSIGNACION	BANCO DE BOGOTA	062754387	20257532	30/12/2008	948,000.00

C O N C E P T O

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-04 PRESENTACION DE OBSERVACIONES	12 MARCAS Y LEMAS COMERCIALES	266,000.00
		TOTAL :	$ 266,000.00

SON: DOSCIENTOS SESENTA Y SEIS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____