

AS. 98.573

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 05-079289- -00003-0000
Fec: 2006-11-07 16:34:13 Dep. 2020 NUECREACIONES
Tra. 11 PATENTE IYII
Evo: 378 FASE NACIONAL I
Act 538 PETICION Fotos: 2

Señores

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES**

E. S. D.

REF.: Expediente No. 05 079.289 - Solicitud de Patente FASE NACIONAL
Corresp. a la Solicitud Internacional PCT/US2004/003842.

A favor de **COLGATE-PALMOLIVE COMPANY**.

Titulada: **COMPOSICION ORAL QUE CONTIENE ENZIMAS CON ESTABILIDAD
MEJORADA.**

JUAN PABLO CADENA SARMIENTO, vecino de Bogotá, portador de la tarjeta Profesional No. 57492 del Consejo Superior de la Judicatura, obrando como apoderado de la Sociedad COLGATE-PALMOLIVE COMPANY, según documento de poder presentado en esa División, de acuerdo con el Artículo 44 de la Decisión 486 de la Comisión de la Comunidad Andina, me permito solicitar que se examine si la invención contenida en la solicitud en referencia es patentable.

De acuerdo con lo anterior, me permito allegar el recibo oficial de caja No. 06-49,407 por valor de \$388.000.

De la Señora Jefe atentamente,



JUAN PABLO CADENA SARMIENTO
C.C. No. 80.410.337 de Usaquén
T.P. No. 57492 del C.S.J.
Carrera 7 No. 71-21 Torre B Piso 4

Bogotá, 7 de noviembre de 2006

CHP:MEV:yb

133

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 05-079289- -00003-0000
Fec: 2006-11-07 16:34:13 Dep. 2020 NUECREACIONES
Tra. 11 PATENTEIYH
Eve: 378 FASENACIONALI
Act 538 PETICION Folios: 2

RECIBO OFICIAL DE CAJA : 06 - 49,407
FECHA : JUNIO 29 DE 2006

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	Nº. PAGO	FECHA PGO	Vr. PAGO
BRIGARD & CASTRO LTDA	CONSIGNACION	BANCO POPULAR	050-00110-6	55101158	29/06/2006	2,868,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	85 EXAMEN DE PATENTABILIDAD DE INVEN	388,000.00
		TOTAL :	\$ 388,000.00

M: TRESCIENTOS OCHENTA Y OCHO MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

134

134

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 05-79289

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCION**

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **564** DE

FECHA **31 DE MAYO DE 2006** EL TÉRMINO HÁBIL SEÑALADO POR LA LEY

EXPIRA EL **31 DE AGOSTO DE 2006**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____

NO X

PETITORIO

AS: 95.761



SUPERINDUSTRIA Y COMERCIO
 Radicación : 04122181 800000000 Folios: 64
 Fecha (AMD): 2004-12-03 17:02:04
 Trámite : 011 PCT-PATENT 379 FASE HACI 411 PRESENTA
 Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE

P C T

ENTRADA EN FASE NACIONAL

1

SOLICITUD DE:

☒ Patente de Invención.

☐ Patente de Modelo de Utilidad.

☐ Capítulo I.

☒ Capítulo II.

2

SOLICITANTE
(71)

Nombre: COLGATE - PALMOLIVE COMPANY

Dirección: 300 Park Avenue, New York, NY 10022,
 Estados Unidos de América
 Nacionalidad o Domicilio: Estados Unidos
 Lugar de Constitución: Estados Unidos
 Teléfono: Fax:
 E-mail

IDENTIFICACION

C.C. ☐ NIT ☐

C.E. ☐ Otro ☐

Cual _____

Número _____

3

REPRESENTANTE
O APODERADO

Nombre: JUAN PABLO CADENA SARMIENTO

Dirección: Cra. 7 No. 16-56 Piso 9

Teléfono: 380-2200 Fax: 380-2700
 E-mail:

IDENTIFICACION

C.C. ☒ NIT ☐

C.E. ☐ Otro ☐

Cual _____

Número 80.410.337 TP 57492

4

INVENTOR (ES)
(72)

Nombre: Lori H. Szeles, Xiaoyan Liu, Malcolm Williams, Teresa R. Carale M., Michael
 Prencipe, James G. Masters
 Dirección: 44 Watson Court, Howell, NJ 07731, US; 909 South Park Avenue, Highland
 Park, NJ 08904, US; 224 Hillside Avenue, Piscataway, NJ 08854, US; 23 Moran Avenue,
 Princeton, NJ 08542, US; 39 Spruce Street, Princeton Junction, NJ 08550, US; 1
 Stephen Court, Ringoes, NJ 08851, Estados Unidos de América (Respectivamente)
 Nacionalidad o Domicilio: Estados Unidos de América (Respectivamente)

5 PCT (86)

Solicitud Internacional No. PCT/US03/14569 Fecha 08-05-2003

Publicación Internacional No. WO 03/094879 A1 Fecha 20-11-2003

6

Título (54): DENTÍFRICO ANTIBACTERIAL QUE EXHIBE PROPIEDADES EN CONTRA DE LA
 PLACA Y PARA REFRESCAR EL ALIENTO MEJORADAS

7

Clasificación Internacional (51) A61K 7/28

8 Prioridad

SI ☒ NO ☐

(33) País de Origen

US

(32) Fecha

10-05-2002

(31) Número de Solicitud

10/143,388

9

Comprobante de pago No. 04-86-799

Fecha 03-12-2004

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

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
20 November 2003 (20.11.2003)

PCT

(10) International Publication Number
WO 03/094879 A1

(51) International Patent Classification: A61K 7/28, 7/22, 7/16

(21) International Application Number: PCT/US03/14569

(22) International Filing Date: 8 May 2003 (08.05.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
10/143,388 10 May 2002 (10.05.2002) US

(71) Applicant: COLGATE-PALMOLIVE COMPANY
[US/US]; 300 Park Avenue, New York, NY 10022 (US).

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

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

Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(I)) for all designations
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(III)) for all designations

Published:

- with international search report

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

(72) Inventors: SZELLES, Lori, E.; 44 Watson Court, Howell, NJ 07731 (US). LIU, Xinyan; 909 South Park Avenue, Highland Park, NJ 08904 (US). WILLIAMS, Malcolm; 224 Hillside Avenue, Piscataway, NJ 08854 (US). CARALE, M., Teresa, E.; 23 Moran Avenue, Princeton, NJ 08542 (US). PRENCIPE, Michael; 39 Spruce Street, Princeton Junction, NJ 08550 (US). MASTERS, James, G.; 1 Stephen Court, Ringoes, NJ 08851 (US).

(74) Agents: SHAPIRO, Paul et al.; Colgate-Palmolive Company, 909 River Road, P.O. Box 1343, Piscataway, NJ 08855-1343 (US).

(54) Title: ANTIBACTERIAL DENTIFRICE EXHIBITING ENHANCED ANTIPLAQUE AND BREATH FRESHENING PROPERTIES

(57) Abstract: An abrasive dentifrice composition which effects enhanced antiplaque and breath freshening properties which comprises an orally acceptable vehicle containing a combination of a safe and effective amount of an antibacterial agent and at least two enzyme ingredients.

WO 03/094879 A1

137
29 137

compuesto antibacterial. La entrega del compuesto antibacterial a la lengua permitirá un control efectivo del mal aliento.

Síntesis de la Invención

5

La presente invención abarca una composición dental que contiene un vehículo oralmente aceptable una combinación de un compuesto antibacterial, una enzima proteolítica por lo que la reducción superior de la acumulación de placa es lograda por medio de una reducción del mal olor mejorada.

Descripción de las Incorporaciones Preferidas

15

En la práctica de la presente invención la composición dental que contiene el agente antibacterial y los ingredientes de enzima se formula como una pasta usando un vehículo que contiene una cantidad segura y efectiva de compuestos de enzima y antibacteriales.

20

Los agentes antibacteriales catiónicos útiles en la práctica de la presente invención son muy conocidos en el arte e incluyen ambos los agentes no iónicos y catiónicos. Vea, por ejemplo, la sección sobre "Compuestos de Amonio Cuaternario y Relacionados" en el artículo sobre "Antisépticos y Desinfectantes" de la enciclopedia de Kira-Othmer de Tecnología

25

Química, segunda edición (volumen 2, páginas 632-635), incorporada aquí por referencia. Los compuestos antibacteriales catiónicos los cuales poseen la actividad antibacterial (por ejemplo son germicidas) son usados en contra de las bacterias y se han usado en las composiciones orales para contra atacar la formación de placa causada por las bacterias en la cavidad oral.

Entre los compuestos más comunes de éstos compuestos de amonio cuaternario antiplaca antibacteriales catiónicos está el cloruro de bencetonio, o el cloruro de diisobutilfenoxietoxietil dimetil bencilo amonio, y el cloruro de cetil piridinio. En una preparación dentífrica éste material es altamente efectivo para promover la higiene oral mediante el reducir la formación de una placa dental y el cálculo, el cual es generalmente acompañado por una reducción en las enfermedades periodontales.

Otros compuestos de amonio cuaternario antibacteriales catiónicos útiles en la práctica de la presente invención incluyen aquellos en los cuales uno o dos de los sustituyentes sobre el nitrógeno cuaternario tiene una longitud de cadena de carbón (típicamente grupo de alquilo) de algo de 8 a 20, típicamente de 10 a 18, átomos de carbono mientras que los sustituyentes restantes tienen un número inferior de átomos de carbono (típicamente un grupo de alquilo o bencilo), tal como de 1 a 7 átomos de carbono, típicamente grupos de metilo o etilo.

139
139

El bromuro de dodecil trimetil amonio, el cloruro de bencilo dimetil estearil amonio, el cloruro de cetil piridinio (CPC) y la 5-amino-1, 3-bis(2-etilhexilo)-5-metilo hexa hidropirimidina cuaternizada son agentes antibacteriales de amonio cuaternario
5 típicos.

El agente antibacterial está incluido en el dentífrico a una concentración de alrededor de 0,10 a alrededor de 1,5% por peso y preferiblemente de alrededor de 0,3 a alrededor de 1,2% por peso.

10

Abrasivos

Los abrasivos preferidos para usarse en la práctica de la presente invención incluyen materiales de sílice y particularmente geles de sílice y sílice amorfa precipitada
15 que tiene un valor de absorción de aceite de menos de 100 centímetros cúbicos/100 g de sílice y preferiblemente en el rango de desde alrededor de 45 centímetros cúbicos/100 g a menos de alrededor de 70 centímetros cúbicos/100 g de sílice. Estas
20 sílices son partículas coloidales que tienen un tamaño de partícula promedio que varía de desde alrededor de 3 micras a alrededor de 12 micras, y más preferiblemente de entre alrededor de 5 a alrededor de 10 micras y un rango de pH de desde 4 a 10 preferiblemente de 6 a 9 cuando se mide como una solución de 5%
25 por peso.

centímetros cúbicos/100 g.

Otros abrasivos los cuales pueden ser usados en la práctica de la presente invención incluyen sílices precipitadas que tienen un tamaño de partícula medio de hasta alrededor de 20 micras tal como Zeodent 115, comercializado por J. M. Huber Chemicals Division, de Havre de Grace, Maryland 21078, o Sylondent 783 comercializado por Davison Chemical Division de W. R. Grace & Company, metafosfato de sodio, metafosfato de potasio, fosfato tricalcio, fosfato dicalcio dihidratado, silicato de aluminio, alúmina calcinada, bentonita u otros materiales silicios o combinaciones de los mismos.

Los materiales abrasivos pueden ser usados individualmente como el único abrasivo para preparar la composición dental de la presente invención o en combinación con otros abrasivos dentífricos conocidos. La cantidad total del abrasivo presente en las composiciones dentífricas de la presente invención está a un nivel de desde alrededor de 5% a alrededor de 60% por peso, preferiblemente de desde alrededor de 10% a alrededor de 55% por peso cuando la composición dentífrica es una pasta dental.

Enzimas

25

Las enzimas útiles en la práctica de la presente

141
134
141

invención incluyen sustancias de proteína dentro de la clase de proteasas, las cuales rompen o hidrolizan las proteínas (proteasas). Estas enzimas proteolíticas son obtenidas de fuentes naturales o por la acción de microorganismos que tienen una fuente de nitrógeno y una fuente de carbón. Los ejemplos de las enzimas proteolíticas útiles en la práctica de la presente invención incluyen papaína, bromelaina, quimotripsina, ficín y alcalasa.

La papaína obtenida del látex lechoso del árbol de papaya es la enzima proteolítica preferida para usarse en la práctica de la presente invención y se incorpora en la composición para el cuidado oral de la presente invención en una cantidad de alrededor de 0,1 a alrededor de 10% por peso y preferiblemente de alrededor de 0,5 a alrededor de 5% por peso, tal papaína teniendo una actividad de 150 a 300 MCU por miligramo como se determinó por la prueba de ensayo de coagulo de leche de Biddle Sawyer Group (vea el diario de Biología Química, volumen 121, páginas 737-745).

Una enzima adicional la cual puede ser formulada en combinación con la enzima proteasa tal como la papaína es la glucoamilasa. La glucoamilasa es una glucoamilasa sacarificante de origen *Aspergillus niger* cultivada por fermentación. Esta enzima puede hidrolizar ambas las puntas de rama de alfa-D-1.6 glucosídico y las uniones alfa-1.4 glucosídicas de oligosacaridos glucosil. El producto de la invención comprende

alrededor de 0,001 a 2% de la carbohidrasa y preferiblemente
alrededor de 0,01 a 0,55% por peso. Las carbohidrasas
adicionales útiles de acuerdo con ésta invención son
glucoamilasa, alfa y beta-amilasa, dextranasa y mutanasa.

5

Otras enzimas las cuales pueden ser usadas en la
práctica de la presente invención incluyen otras carbohidrasas
tal como alfa-amilasa, beta-amilasa, dextranasa y mutanasa y
lipasas tal como lipasa de planta, lipasa gástrica, lipasa
10 pancreática, pectinasa, tannasa lisozima y proteasas serina.

La enzima lipasa es derivada de una sepa selecta
de *Aspergillus niger*, que exhibe desdoblamiento al azar de las
1,3 posiciones de grasas y aceites. La enzima tiene una
15 actividad lipolítica máxima a un pH de 5,0 a 7,0 cuando se
ensaya con aceite de oliva. La enzima tiene una actividad
medida de 120.000 unidades lipasa por gramo. La lipasa puede
ser incluida a la composición dentífrica a una concentración de
alrededor de 0,010 a alrededor de 5,5% por pes y
20 preferiblemente de alrededor de 0,02 a alrededor de 0,10% por
peso.

La presencia de enzima tannasa puede además ser
benéfica para facilitar el rompimiento de la mancha extrínseca.
25 Las enzimas tannasa se han purificado de *Aspergillus niger* y de
Aspergillus allianceus y son útiles en la hidrólisis de taninos,

conocidos como que dec loran la superficie de los dientes.

Otras enzimas adecuadas las cuales pueden comprender la presente invención incluyen lisozima, derivada de clara de huevo, la cual contiene una cadena de polipéptido única entrecruzada por cuatro uniones de disulfuro que tienen un peso molecular de 14.600 daltons. La enzima puede exhibir propiedades antibacteriales mediante el facilitar la hidrólisis de las paredes de célula bacterial desdoblando la unión glicosídica entre el carbón número 1 de N-ácido acetilmurámico y el carbón número 4 de N-acetil-D-glucosamina, el cual en vivo, éstos dos carbohidratos son polimerizados para formar el polisacarido de pared de célula. Adicionalmente, la pectinasa, una enzima que está presente en la mayoría de las plantas facilitan la hidrólisis de la pectina polisacarida en azúcares y el ácido galacturónico.

Vehículo del Dentífrico

El vehículo de dentífrico oralmente aceptable usado para preparar la composición dentífrica comprende una fase de agua, que contiene un humectante ahí. El humectante es preferiblemente glicerina, sorbitol, xilitol, y/o propilenglicol de peso molecular en el rango de 200 a 1.000; pero otros humectantes y mezclas de los mismos también pueden ser empleados. La concentración humectante típicamente hace un

total de alrededor de 5 a alrededor de 70% por peso de la composición oral.

La referencia aquí a sorbitol se refiere a un material típicamente disponible comercialmente como una solución acuosa de 70%. El agua está presente típicamente en una cantidad de por lo menos de alrededor de 10% por peso, y generalmente de alrededor de 15 a 30% por peso de la composición oral. El agua empleada en la preparación de pastas dentales comercialmente adecuadas debe preferiblemente ser deionizada y estar libre de impurezas orgánicas. Estas cantidades de agua incluyen el agua libre la cual es agregada más aquella la cual es introducida con otros materiales tal como con sorbitol.

Las composiciones dentífricas de la presente invención pueden contener una variedad de ingredientes dentífricos opcionales. Como se describe abajo, tales ingredientes opcionales pueden incluir, pero no se limitan a agentes engrosadores, surfactantes, una fuente de iones de fluoruro, un policarboxilato aniónico sintético, una agente saborizante, agentes en contra del sarro y colorantes.

Agentes Espesadores

Los espesadores usados en las composiciones de la presente invención incluyen gomas naturales y sintéticas y

38
145

coloides. No todos los espesadores de polímero que ocurren naturalmente (tales como celulosa o carragenina) son compatibles con los ingredientes del dentífrico (específicamente las enzimas) de las composiciones de dentífrico cuando se formulan en la presencia de enzimas proteolíticas. Los espesadores compatibles con las enzimas proteolíticas incluyen goma xantano, poliglicoles de pesos moleculares variables vendidos bajo la marca Polyox, y polivinilpirrolidona. Los espesadores inorgánicos compatibles incluyen losa compuestos de sílice amorfa los cuales funcionan como agentes espesadores e incluyen compuestos de sílices coloidales disponibles bajo la designación de comercio Cab-o-sil fabricados por Cabot Corporation y distribuidos por FENAPE Chemical, de Bound Brook, Nueva Jersey; Zeodent 165 de J. M. Huber Chemicals Division, de Havre de Grace, Maryland 21078; y Sylodent 15, disponible de Davison Chemical Division de W. R. Grace Corporation, de Baltimore, MD 21203. Otros espesadores inorgánicos incluyen arcillas naturales y sintéticas, silicato de magnesio litio (saponita) y silicato de aluminio magnesio (Veegum).

20

El agente espesador está presente en la composición dentífrica en cantidades de alrededor de 0,1 a alrededor de 10% por peso, preferiblemente de alrededor de 0,5 a alrededor de 4,0% por peso.

25

Surfactantes

146
146

$K_2H_2P_2O_7$ polifosfatos de cadena larga tal como hexametafosfato sódico y fosfatos cíclicos tal como trimetafosfato sódico. Estos agentes en contra del sarro sin incluidos en la composición dentífrica a una concentración de alrededor de 1 a alrededor de 5 5% por peso.

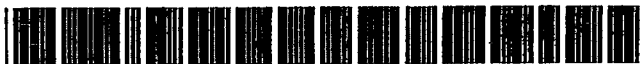
Agentes Estabilizadores de Enzima

La composición dentífrica de la presente invención también puede contener ingredientes los cuales estabilizan las enzimas en un ambiente de dentífrico. Estos estabilizadores protegen la enzima de la inactivación por las impurezas de metal quelatante presentes en la composición dentífrica las cuales tienen la propensión a desnaturalizar el sitio activo de la enzima mediante el proteger la enzima de la oxidación. Los agentes quelatantes incluyen, ácido etilendiamina tetraacético (EDTA) y gluconato de sodio a concentraciones de entre 0.01 y 1%, preferiblemente de entre 0,1 y 0,5%. Los agentes estabilizadores de la enzima en contra de la oxidación incluyen bisulfito de sodio, galatas de metal, estanato de sodio y ácido ascórbico a concentraciones de entre alrededor de 0,03 y alrededor de 2,0%, preferiblemente de entre alrededor de 0,1 y alrededor de 0,75%.

25

Policarboxilato Aniónico

147
D447



US005624906A

United States Patent [19]
Vermeer

[11] **Patent Number:** **5,624,906**
[45] **Date of Patent:** **Apr. 29, 1997**

[54] **ORAL HYGIENE COMPOSITIONS
COMPRISING HETEROATOM CONTAINING
ALKYL ALDONAMIDE COMPOUNDS**

4,342,706	8/1982	Conner et al.	260/501.15
4,973,473	11/1990	Schneider et al.	424/63
5,102,654	4/1992	Castrogiovanni et al.	424/61
5,310,542	5/1994	Au et al.	424/52

[75] **Inventor:** Robert Vermeer, Nutley, N.J. -

[73] **Assignee:** Lever Brothers Company, Division of
Conopco, Inc., New York, N.Y.

[21] **Appl. No.:** 351,930

[22] **Filed:** Dec. 8, 1994

[51] **Int. Cl.⁶** A61K 7/16; A61K 31/70;
C07H 15/02

[52] **U.S. Cl.** 514/23; 514/53; 514/54;
514/62; 514/835; 514/944; 514/945; 514/951;
514/960; 536/4.1; 536/18.5; 536/18.7; 536/29.1;
536/123.1; 536/123.13

[58] **Field of Search** 514/23, 25, 53,
514/54, 62, 835, 944, 945, 951, 960; 536/4.1,
18.5, 123.1, 123.13, 18.7, 29.1

[56] **References Cited**

U.S. PATENT DOCUMENTS

2,776,951 1/1957 Melamed 260/78.3

FOREIGN PATENT DOCUMENTS

580453	1/1926	European Pat. Off.
550278	7/1993	European Pat. Off.
550106	7/1993	European Pat. Off.
551675	7/1993	European Pat. Off.
550281	7/1993	European Pat. Off.
3148047	6/1983	Germany
04152337	5/1992	Japan

Primary Examiner—John Kight
Assistant Examiner—Howard C. Lee
Attorney, Agent, or Firm—Ronald A. Koatz

[57] **ABSTRACT**

The present invention is related to new oral hygiene compositions that have improved foam, viscosity, clarity and good taste due to the inclusion of a new type of alkyl aldonamide compound, specifically heteroatom containing alkyl aldonamide compounds.

24 Claims, No Drawings

ORAL HYGIENE COMPOSITIONS COMPRISING HETEROATOM CONTAINING ALKYL ALDONAMIDE COMPOUNDS

TECHNICAL FIELD

The present invention is related to new oral hygiene compositions that have improved foam, viscosity, clarity and good taste due to the inclusion of a new type of alkyl aldonamide compound, specifically heteroatom containing alkyl aldonamide compounds.

BACKGROUND OF THE INVENTION

Oral hygiene compositions of the present invention are preparations that cleanse, refresh and deodorize the accessible surfaces of the mouth and teeth while providing a physiologically acceptable, stable clear liquid or gel composition that foams copiously and tastes well. Such compositions may be prepared in aerosol, liquid, gel, cream, paste, granular, tablet or powdered form. Oral hygiene compositions of the present invention include mouthwashes, pre-brushing dental rinses, post-brushing dental rinses or dental sprays as well as dental creams, toothpastes, toothpaste gels, toothpowders, dental cleansers, dental flosses, chewing gums, lozenges and other oral delivery vehicles.

Mouthwashes are generally liquid preparations specifically designed to cleanse and refresh the mouth. Many early mouthwashes usually comprise ingredients that only serve to coverup oral mal odor and so this has prompted a need for a new generation of rinses containing ingredients that provide efficacious action against problems associated in the oral cavity such as mal odor, caries, gum disorders and infections while providing a physiologically acceptable, stable clear compositions that foams copiously and tastes well.

There is a wide choice of conventional ingredients and components available for mouthwash/dental rinse compositions depending upon the ultimate end purpose sought from the preparation. This end purpose serves as a basis of classifying various mouthwashes into six specific categories: cosmetic, astringent, buffered, deodorizing, therapeutic and antibacterial.

Cosmetic mouthwashes usually contain water, alcohol, flavor and color. They may also contain surface-active agents (surfactants) for the purpose of assisting in the solubilization of certain flavor components as well as aiding in the irrigation and cleansing of the mouth and teeth. Cosmetic mouthwashes can be considered as "flavored water" formulations.

Astringent mouthwashes provide a direct effect on the oral mucosa and also provide a means for flocculating and precipitating proteinaceous material so that it may be more readily removed by flushing.

Buffered mouthwashes may be helpful in reducing stringy saliva or reducing mucinous deposits by dispersion of protein based on the pH of the rinse (preferably at alkaline pH—s).

Deodorizing mouthwashes depend heavily upon perfume to mask mal odor, however, some may depend upon antibacterial agents or other agents for their effect.

Therapeutic mouthwashes are formulated for the purpose of relieving infection, preventing dental caries, or mitigating some other pathological condition that may be associated with the mouth, teeth or throat.

Finally, antibacterial (antiseptic) mouthwashes are compositions which are efficacious against bacteria found in the

mouth and have the primary purpose of reducing or removing bacteria that are usually present in large numbers in the oral cavity.

It should be noted that the mouthwash and dental rinse compositions of the invention could be cosmetic, astringent, buffered, deodorizing, therapeutic, antibacterial or mixtures thereof. A single product could conceivably be antiseptic and astringent or be buffered at an optimum pH with an antibacterial agent or produced in concentrated form and offered for therapy of a specific condition.

It is well known that the mal odorous elements of mouth aroma are generated by bacteria arising from dental plaque, decaying food particles and salivary stagnation. Additionally, these microbes can present a source of infection and are believed by some investigators to be related at least in part to such problems as caries and periodontal disease. It has been suggested that certain germicidal and bacterial agents exert their antimicrobial effect by destroying or inhibiting oral bacteria. Attempts to improve efficacy against oral real odor and other oral problems recently has resulted in increased stress on the importance of bacterial effectiveness. The compounds, however, that seem to provide efficacy, at least at levels where bactericidal activity can be demonstrated, contribute significantly to flavor (taste), foam, clarity and irritably problems. Lacking physiological acceptance, these products have proved unacceptable to many consumers for a number of reasons. For one thing, certain germicidal or bacterial agents have either a disagreeable taste, or they are significantly effective only at levels where they cannot be effectively masked by flavorants. Still others are incompatible with other ingredients or have an undesirable sensitization potential. Therefore, there is a definite need in the art for mouthwash compositions that cleanse, refresh and deodorize accessible surfaces of the oral cavity while providing a physiologically acceptable, stable, clear liquid that foams copiously and tastes well. It has now been found that the inclusion of a heteroatom containing alkyl aldonamide compound in a mouthwash composition of the invention, surprisingly provides improved foam, viscosity, clarity and flavor characteristics. These findings are quite unexpected and have not been recognized or appreciated in the art.

Dentifrice or toothpaste compositions are generally gel or paste preparations that are designed to loosen and remove plaque in conjunction with a regular toothbrushing regimen whereas dental rinses are liquid preparations specifically designed to loosen and remove plaque before or after a regular toothbrushing regimen. Dental plaque is present to some degree, in the form of a film, on virtually all dental surfaces. It is a byproduct of microbial growth, and comprises a dense microbial layer consisting of a mass of microorganisms embedded in a polysaccharide matrix. The microorganisms present in plaque are mainly coccoidal organisms, particularly in early plaque, which, in the mouths of some persons can change to filamentous organisms after a few days. Plaque itself adheres firmly to dental surfaces and is removed only with difficulty even through a rigorous brushing regimen. Moreover, plaque rapidly reforms on the tooth surface after it is removed. Plaque may form on any part of the tooth surface, and is found particularly at the gingival margin, in cracks in the enamel, and on the surface of dental calculus. The danger associated with the formation of plaque on the teeth lies in the tendency of plaque to build up and eventually produce gingivitis, periodontitis and other types of periodontal disease, as well as dental caries and dental calculus. More specifically, dental plaque is a precursor to the formation of the hard crystalline buildup on

148
148

5,624,906

15

N-gluconyl alkyltri(oxyethyl) α -aminobutyrate
N-gluconyl alkyl(oxyethyl) sarcosinate
N-gluconyl alkyl-di(oxyethyl) sarcosinate
N-gluconyl alkyltri(oxyethyl) sarcosinate
N-gluconyl alkyltri(oxyethyl) leucinate
N-lactobionyl alkyl-di(oxyethyl) glycinate
N-lactobionyl alkyltri(oxyethyl) alaninate
N-lactobionyl alkyltetra(oxyethyl) β -alaninate
N-lactobionyl alkyl-di(oxyethyl) N-methylalaninate
N-lactobionyl alkyltri(oxyethyl) α -aminobutyrate
N-lactobionyl alkyltri(oxyethyl) α -aminoisobutyrate
N-lactobionyl alkyltri(oxyethyl) ϵ -aminocaproate
N-lactobionyl alkyl-di(oxyethyl) sarcosinate
N-lactobionyl alkyltri(oxyethyl) leucinate
N-glucoheptonyl alkyl(oxyethyl) glycinate
N-maltobionyl alkyl(oxyethyl) glycinate
N-cellobionyl alkyl(oxyethyl) glycinate
alkyloxypopyl D-gluconamide monooxyethylene ether
alkyloxypopyl D-gluconamide dioxyethylene ether
alkyloxypopyl D-gluconamide trioxyethylene ether
alkyloxypopyl D-gluconamide tetraoxyethylene ether
alkyloxypopyl D-gluconamide pentaoxyethylene ether
alkyloxypopyl D-gluconamide hexaoxyethylene ether
alkyloxypopyl D-gluconamide heptaoxyethylene ether
alkyloxypopyl D-gluconamide octaoxyethylene ether
alkyloxypopyl D-gluconamide nonaoxyethylene ether
alkyloxypopyl D-gluconamide decaoxyethylene ether
alkyloxypopyl D-gluconamide trioxypropylene ether
alkyloxypopyl D-gluconamide oxyethylenedioxypropylene ether
alkyloxyethyl D-gluconamide dioxyethylenetrioxypropylene ether
alkyloxyethyl D-gluconamide trioxypropylenedioxyethylene ether
alkyloxypopyl D-lactobionamide monooxyethylene ether
alkyloxypopyl D-lactobionamide dioxyethylene ether
alkyloxypopyl D-lactobionamide trioxyethylene ether
alkyloxypopyl D-lactobionamide tetraoxyethylene ether
alkyloxypopyl D-maltobionamide dioxyethylene ether
alkyloxypopyl D-maltobionamide pentaoxypropylene ether
alkyloxypopyl D-maltobionamide decaoxypropylene ether

Wherein the alkyl group contains from about 1 to about 28 carbon atoms, preferably from about 7 to about 24 carbon atoms and even more preferably from about 8 to about 22 carbon atoms.

The A group is preferably hydrogen, although it may be a hydroxy C_1 - C_4 alkyl group or a C_1 to C_{18} straight or branched chain, saturated or unsaturated hydrocarbon radical. The A group may also be interrupted by a heteroatom and may have the same structure as the group attached to the nitrogen atom.

If the A or Rhd 12group is an aliphatic radical, suitable examples include methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, hexadecyl, heptadecyl, octadecyl, 65 coco, soya, tallow, tall oil, castor, corn, cottonseed, palm, rapeseed, safflower, sesame, sunflower, fish oil, allyl,

16

octenyl, nonenyl, decenyl, undecenyl, dodecenyl, tridecenyl, tetradecenyl, pentadecenyl, hexadecenyl, heptadecenyl, octadecenyl (oleyl), linoleyl and linolenyl.

If the A or R_{12} group is interrupted by an aromatic group, the aromatic radical may be for example, benzyl or aniline. Cycloaliphatic radicals are exemplified but are not limited to cyclopentyl and cyclohexyl. Suitable mixed aromatic aliphatic radicals are exemplified by benzylpropyl, phenylethyl, phenoxyethyl and vinylbenzyl.

The G group may be hydrogen or an attached mono-, di-, oligo-, polysaccharide or mixtures thereof. Examples of suitable saccharides that can be oxidized to sugar acids $[GOCH_2(CHOG)_nCOOH]$ include but are not limited to, erythrose, threose, ribose, arabinose, xylose, lyxose, allose, 15 altrose, idose, talose, glucose, galactose, mannose, gulose, fructose, sorbose, sucrose, isomaltose, isomalt, isomaltulose (palatinose), trehalulose, 3-ketosucrose, leucrose, lactulose, gentiobiose, maltose, lactose, melibiose, cellobiose, triglucose, tetraglucose, starch and cellulose.

When an amino group is present it may be convened to the corresponding salt by reaction with, for example an organic or inorganic acid such as hydrochloric acid, sulfuric acid, phosphoric acid, boric acid, oxalic acid, malonic acid, glutaric acid, adipic acid, sebacic acid, tricarballic acid, 25 butanetetra-carboxylic acid, itaconic acid, maleic acid, malic acid, fumaric acid, citraconic acid, glutaconic acid, bis (hydroxymethyl)propionic acid, tartaric acid, citric acid, formic acid, lactic acid, acetic acid, benzoic acid, methane-sulfonic acid, ethanesulfonic acid, toluenesulfonic acid and mixtures thereof or by reaction with, for example an alkylating agent such as chloromethane, dimethyl sulfate, diethyl sulfate and benzyl chloride.

The heteroatom containing alkyl aldnamide compounds of the present invention can also be ethoxylated, propoxylated or butoxylated with ethylene oxide, propylene oxide, 35 butylene oxide or mixtures thereof to give a series of polyoxy ether sugar surfactants.

Typical levels of heteroatom containing alkyl aldnamide compound are from about 0.01% to about 15%, preferably 40 from about 0.02% to about 13%, even more preferably from about 0.03% to about 10% by weight of the composition.

The mouthwash compositions of the invention are preparations that are intended to cleanse, refresh and deodorize the oral cavity. The dental rinse compositions of the invention 45 are intended to loosen plaque present on dental surfaces and render it more amenable to removal during brushing with a conventional dentifrice.

Both the mouthwash and dental rinse compositions are preferably liquids based predominantly on water. However, it is also possible to prepare the mouthwash and dental rinse compositions of the invention in tablet, granular, powder or concentrated liquid form which are diluted with water upon use. The concentrates offer the advantage of economy of manufacture, shipping and storage, but the traditional liquid 55 form has gained greater consumer acceptance.

The dentifrice or toothpaste compositions of the invention are intended for use with a toothbrush for the purpose of cleaning the accessible surfaces of the teeth. The dentifrice compositions of the invention may be prepared in paste, gel, powder and to a lesser extent in liquid and block forms. Secondary effects of the dentifrice compositions of the invention are a reduction in the incidence of dental decay, an improvement in the maintenance of gingival health and a reduction in offensive mouth odors.

There are a wide variety of ingredients that can be used in oral hygiene compositions depending on the characteristics and end purpose sought. Such ingredients are well known to

those skilled in the art and include, but are not limited to abrasive polishing agents, humectants, alcohols, binding/thickening agents, cosurfactants, astringents, anti-plaque agents, anti-calculus agents, antibacterial agents, ph-buffering salts, alkali metal halides (salts), flavorants, sweeteners, fluorides, colorants and optional ingredients (auxiliary agents).

The individual ingredients have to fulfill, in part, wholly different functions while at the same time each ingredient must complement and increase the effect of other substances. This has always been a difficult challenge to meet and finding the right combination of ingredients for improved foam, viscosity, clarity and flavor characteristics is a significant achievement.

COMPOSITIONS

The essential and optional ingredients of the present invention are given in the following paragraphs.

Abrasive Polishing Agents

Examples of abrasive polishing agents (body agents) useful in the dentifrice compositions of the present invention which function to remove debris and residual stains from the teeth as well as to polish the tooth surface include calcium carbonate, precipitated calcium carbonate, light calcium carbonate, medium calcium carbonate, dense calcium carbonate, extra dense calcium carbonate, sodium carbonate, sodium bicarbonate (baking soda), potassium carbonate, potassium bicarbonate, anhydrous calcium phosphate, dicalcium phosphate, dibasic calcium phosphate dihydrate, tribasic calcium phosphate, sodium phosphate, potassium phosphate, calcium pyrophosphate, insoluble sodium metaphosphate, disodium orthophosphate, dibasic sodium phosphate, magnesium hydroxide, magnesium carbonate, magnesium silicate, magnesium trisilicate, trimagnesium phosphate, monomagnesium phosphate, magnesium oxide, stannic oxide, zinc oxide, chalk, extra light chalk, light chalk, medium chalk, coarse chalk, bentonite, flour of pumice, α -alumina trihydrate, levigated alumina, hydrated alumina, alumina aerogel, gelatinous alumina, aluminum silicate, calcined aluminum silicate, zirconium silicate, hydroxyapatite, crosslinked urea-formaldehyde resin, crosslinked melamine-formaldehyde resin, polymethacrylate, polymethylmethacrylate, polystyrene, powdered polyethylene, silica gel (hydrated silica), dehydrated silica gel (silica), silica precipitates, silica xerogel, silica hydrogels, silica pyrogel, silica aerogel and mixtures thereof. The average particle size of an abrasive polishing agent is from about 1 μ m to about 20 μ m, preferably from about 3 μ m to about 12 μ m. Preferred abrasive polishing agents include the silicas, sodium bicarbonate (baking soda), sodium carbonate, dicalcium phosphate, dibasic calcium phosphate dihydrate, tribasic calcium phosphate, sodium phosphate, calcium carbonate, α -alumina trihydrate and mixtures thereof. Most highly preferred abrasive polishing agents are hydrated silica and sodium bicarbonate. Typical levels of abrasive polishing agents are from about 0% to about 65% by weight of the composition.

Humectants

Examples of humectants useful in the present invention which serve to add body or mouth feel to a mouthwash or dental rinse composition and retain moisture in a dentifrice composition include polyethylene glycol-14 (PEG-14), polyethylene glycol-18 (PEG-18), polyethylene glycol-55 (PEG-55), polyethylene glycol-100 (PEG-100), polyethyl-

ene glycol-135 (PEG-135), polyethylene glycol-180 (PEG-180), polyethylene glycol-200 (PEG-4), polyethylene glycol-240 (PEG-240), polyethylene glycol-300 (PEG-6), polyethylene glycol-400 (PEG-8), polyethylene glycol-450 (PEG-9), polyethylene glycol-500 (PEG-10), polyethylene glycol-600 (PEG-12), polyethylene glycol-1540 (PEG-32), polyethylene glycol-2000 (PEG-40 or PEG-2M), polyethylene glycol-3000 (PEG-60), polyethylene glycol-4000 (PEG-75), polyethylene glycol-6000 (PEG-150), polyethylene glycol-9000 (PEG-9M or PEG-200), polyethylene glycol-20,000 (PEG-20M or PEG-350), polyethylene glycol-600,000 (PEG-14M), propylene glycol (PG), glycerol (glycerin), erythritol, xylitol, sorbitol, mannitol, lactitol, hydrogenated starch hydrolyzates and mixtures thereof. In addition, humectants help prevent microbial deterioration during storage of oral hygiene composition, assist in maintaining phase stability and provide a means to formulate a transparent or translucent dentifrice. Preferred humectants are PEG-6, PEG-8, PEG-12, PEG-32, glycerin, sorbitol, hydrogenated starch hydrolyzates and mixtures thereof. Most highly preferred humectants are glycerin, sorbitol, hydrogenated starch hydrolyzates and mixtures thereof as described in U.S. Pat. No. 4,435,380 which is incorporated herein by reference. Typical levels of humectant are from about 0% to about 80% by weight of a composition.

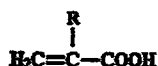
Alcohols

Examples of alcohols useful in the present invention which serve as a partial fluid base include denatured ethanol SD37, denatured ethanol SD37A, denatured ethanol SD38B (SD alcohol 38B) and denatured ethanol SD38A through F. Ethanol is added to enhance flavor impact, provide bite and freshness, help solubilize flavor, and contribute to cleansing action and antibacterial activity by surface tension reduction. In addition, ethanol may also serve as a mild astringent by virtue of its water binding and protein denaturing properties. A preferred alcohol is SD alcohol 38. Typical levels of alcohol are from about 0% to about 45% by weight of the composition.

Binders/Thickeners

Examples of binders/thickeners (stabilizing agents) useful in the dentifrice compositions of the present invention which provide gelatinous structure, paste firmness, mouth feel benefits and stabilize the toothpaste mass against liquid phase separation include starch, glycerite of starch, gum karaya (sterculia gum), gum tragacanth, gum arabic, gum ghatti, gum acacia, locust bean gum, xanthan gum, guar gum, veegum, irish moss extract (chondrus extract), irish moss (carrageenan), sodium alginate, agar-agar, pectin, gelatin, cellulose, cellulose gum, carboxymethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxymethyl carboxymethyl cellulose, hydroxymethyl carboxypropyl cellulose, methyl cellulose, ethyl cellulose, sulfated cellulose, polyacrylate, polyvinylpyrrolidone (PVP), silicate clays, silica precipitates, silica aerogels, pyrogenic silicas, colloidal magnesium aluminum silicate and mixtures thereof. Preferred binders/thickeners are those which are hydrophilic colloids that disperse as well as absorb water to form a viscous liquid phase, such as the silicas, carrageenan, hydroxyethyl cellulose, cellulose gum, xanthan gum, veegum, polyacrylates and mixtures thereof. Most highly preferred binders/thickeners are cellulose gum and xanthan gum. Typical levels of binders/thickeners are from about 0% to about 30% by weight of a composition.

non-astringent anti-plaque and/or anti-calculus agents are the carboxylate polymers particularly the carboxyvinyl polymers (polyacrylic acid copolymers) sold under the trade name carbopol by BF Goodrich Company. These materials have also been taught in the art as binders or cothickeners. Specific examples of carboxyvinyl polymers include carbopol 907, carbopol 910 (having a molecular weight of about 750,000), carbopol 934 (having a molecular weight of about 3,000,000), carbopol 934P, carbopol 940 (having a molecular weight of about 4,000,000), carbopol 941 (having a molecular weight of about 1,250,000), carbopol 954, carbopol 956, carbopol 980, carbopol 981, carbopol 984, carbopol 1342 and mixtures thereof. The CIPA adopted name for this class of compound is carbomer. Preferred polycarboxylate polymers include the non-linear, water-dispersible, polyacrylic acid cross-linked with a polyalkenyl polyether and having a molecular weight of from about 750,000 to about 10,000,000. Examples of preferred monomeric unsaturated carboxylic acids used in producing carboxyvinyl polymers of the invention include monomeric, α,β -monoolefinically lower aliphatic carboxylic acids such as the monomeric monoolefinic acrylic acids of the structure



wherein R is a substituent selected from the group consisting of hydrogen and lower alkyl groups.

The carbopols consist essentially of a colloiddally water-soluble polymer of acrylic acid crosslinked with about 0.5% to about 2.0% of a cross-linking agent selected from the class consisting of polyallyl pentaerythritol and polyallyl sucrose (polyalkenyl polyethers). Highly preferred carboxyvinyl polymers include carbopol 934, carbopol 940, carbopol 941, carbopol 956 and mixtures thereof.

Additional polycarboxylate polymers useful in the present invention are Sokolan PHC-25, a polyacrylic acid available from BASF Corporation, and Gantrez, a poly(methyl vinyl ether/maleic acid) interpolymers available from GAF Corp. Typical levels of anionic polymer are from about 0% to about 8% by weight of the composition.

Still, further examples of addition non-astringent anti-plaque and/or anti-calculus agents include the soluble pyrophosphate salts such as sodium trihydrogen pyrophosphate, disodium dihydrogen pyrophosphate, trisodium hydrogen pyrophosphate, trisodium hydrogen pyrophosphate monohydrate, trisodium hydrogen pyrophosphate nonahydrate, tetrasodium pyrophosphate, tetrasodium pyrophosphate decahydrate, potassium trihydrogen pyrophosphate, dipotassium dihydrogen pyrophosphate, tripotassium hydrogen pyrophosphate, tetrapotassium pyrophosphate, diammonium dihydrogen pyrophosphate, triammonium hydrogen pyrophosphate, triammonium hydrogen pyrophosphate monohydrate, calcium dihydrogen pyrophosphate, calcium pyrophosphate, tetraaluminium pyrophosphate and mixtures thereof. These compounds are more fully disclosed in U.S. Pat. Nos. 4,515,772, 4,515,772 and 4,627,977 all of which are incorporated herein by reference. Preferred soluble pyrophosphate salts are sodium trihydrogen pyrophosphate, disodium dihydrogen pyrophosphate, tetrasodium pyrophosphate, tetrapotassium pyrophosphate and mixtures thereof. Typical levels of soluble pyrophosphate salt are from about 0% to about 8% by weight of the composition.

Antibacterial Agents

Examples of antibacterial agents useful in the present invention which are known to be active against a wide

variety of microorganisms at levels below those known to be harmful include phenolic compounds such as betanaphthol, chlorothymol, thymol, anethole, eucalyptol, carvacrol, menthol, phenol, amylphenol, hexylphenol, heptylphenol, octylphenol, hexylresorcinol, hexachlorophene [2,2-methylene bis(3,4,6-trichlorophenol)], chlorhexidine [1,1'-hexamethylene bis(5-p-chlorophenyl)biguanide)], chlorhexidine diacetate, chlorhexidine dihydrochloride, chlorhexidine digluconate, chlorhexidine diactobionate, chlorhexidine dimaltobionate and methyl salicylate; quaternary ammonium salt compounds such as morpholinium tetradecylsulfate, laurylpyridinium chloride, myristylpyridinium chloride, cetylpyridinium fluoride, cetylpyridinium chloride, cetylpyridinium bromide, cetylpyridinium iodide, stearylpyridinium chloride, dodecyltrimethylammonium chloride, tetradecyltrimethylammonium chloride, hexadecyltrimethylammonium bromide, C_{12} - C_{16} benzyltrimethylammonium chloride (benzethonium chloride), phenoxyethyl dodecyltrimethylammonium bromide (domiphen bromide), triclobisonium chloride; as well as benzoic acid, sodium benzoate, potassium benzoate boric acid, tyrothricin, gramicidin, sanguinarine chloride and -mixtures thereof. Preferred antibacterial agents include thymol, anethole, eucalyptol, menthol, cetylpyridinium chloride, benzoic acid, sodium benzoate, boric acid, domiphen bromide and chlorhexidine gluconate. Most highly preferred antibacterial agents are cetylpyridinium chloride, benzoic acid, sodium benzoate and domiphen bromide. Typical levels of antibacterial agent are from about 0% to about 5% by weight of the composition.

pH-Buffering Salts

Additionally, the oral hygiene compositions of the invention may contain a buffering salt pair to control the pH of the final product. The composition of the salt pair is highly variable and one skilled in the art can with simple experimentation arrive at various salt pairs that will be functional and that will not detract from the overall compositions. Generally, the salt pair should be capable of buffering the mouthwash to a pH of between about 3 and about 8 and should be present at a level of about 0.01% to about 5% by weight of the composition. The preferred salt pair is a mixture of sodium acetate and acetic acid. When employing this mixture, the ratio of the sodium acetate to the acetic acid can vary widely so long as the resultant ratio is capable of producing a pH within the desired range. Preferably, however, the ratio of sodium acetate to acetic acid is about 3:2.

Alkali Metal Halides (Salts)

Examples of alkali metal halides (salts) useful in the present invention include sodium chloride, potassium chloride, potassium iodide, ammonium chloride, chromium chloride, calcium chloride, magnesium chloride, sodium sulfate, potassium sulfate, magnesium sulfate, nickelous sulfate, sodium metavanadate and sodium selenate. Preferred alkali metal halides are sodium chloride, potassium chloride and mixtures thereof. The alkali metal halide salt compounds serve as an electrolyte and contributes to the overall flavor. Typical levels of alkali metal halide salt are from about 0% to about 5% by weight of the composition.

Flavorant

Examples of essential flavorant oils useful in the present invention include oils of anise, fennel, orris, caraway, clove, coriander, pimento, eucalyptus, eucalyptol, eugenol.

nutmeg, thyme, peppermint, spearmint, wintergreen, cinnamon, cinnamon-mint, menthol, sassafras, anethole and mixtures thereof. Flavorant oils are added mainly to provide good flavor and favorable taste, however, some flavorant oils also provide antibacterial action. Preferred class of flavorant oil are peppermint, spearmint, wintergreen and mixtures thereof. Peppermint oil consists of a mixture of menthol, α -pinene, β -pinene, limonene, cineol, ethylamylcarbinol, methyl acetate, menthone, isomenthone, menthofuran, neomenthol, isomenthol and piperitone. Spearmint oil consists of a mixture of α -pinene, α -phellandrene, limonene, octyl alcohol, dehydrocarveol, dipenlene cineol and carvene. Wintergreen oil consists mainly of methyl salicylate (wintergreen oil has been largely replaced with synthetic methyl salicylate). It should be noted that the specific choice of flavor is made on the basis that this class of flavor is highly desirable to the consuming public as representing and furnishing a fresh mouth feel as well as providing excellent persistent flavor notes effective for residual odor masking. The flavorant is characterized by containing major portions of menthol, carvene and methyl salicylate. Both natural and synthetic oils along with various flavor modifiers which give a distinctive note may be employed. Preferred flavor oils are peppermint, spearmint, wintergreen (as synthetic methyl salicylate) and mixtures thereof. Typical levels of flavorant oil are from about 0.01% to about 4% by weight of the composition.

Sweeteners

Examples of sweeteners useful in the present invention which may be employed to round out the overall taste of the product include saccharin (as sodium, potassium or calcium saccharin), cyclamate (as sodium, potassium or calcium cyclamate), ASPARTAME®, acesulfame-K, thaumatin, neohesperidin dihydrochalcone, ammoniated glycyrrhizin, dextrose, levulose, sucrose, D-tryptophan, miraculin, NUTRASWEET, mannose, glucose, α -D-glucose, β -D-glucose, lactose, galactose and mixtures thereof. Both artificial and natural sweeteners may be used to add further sweetness than that provided by the essential flavoring oils. A preferred sweetener is the potassium or sodium salts of saccharin. Typical levels of sweetener are from about 0.01% to about 4% by weight of the composition.

Fluorides

Examples of fluorides useful in the present invention which serve to prevent dental caries include sodium fluoride, potassium fluoride, calcium fluoride, zinc fluoride, stannous fluoride, zinc ammonium fluoride, sodium monofluorophosphate, potassium monofluorophosphate, laurylamine hydrofluoride, diethylaminoethyl octylamide hydrofluoride, 1-ethanol-2-hexadecylimidazoline dihydrofluoride, dodecyltrimethylammonium fluoride, tetraethylammonium fluoride, didecyl dimethylammonium fluoride, cetylpyridinium fluoride, dilaurylmorpholinium fluoride, N-carboxymethyl-N-dodecyl diethylammonium fluoride, sarcosine stannous fluoride, glycine potassium fluoride, glycine hydrofluoride, sodium monofluorophosphate and mixtures thereof. Preferred fluorides are sodium fluoride, potassium fluoride, sodium monofluorophosphate, potassium monofluorophosphate, stannous fluoride and mixtures thereof. Most highly preferred fluorides are sodium fluoride, sodium monofluorophosphate and mixtures thereof. Typical levels of fluoride are from about 0% to about 5% by weight of the composition.

Colorants

Examples of colorants (dyes) useful in the present invention include D&C blue #1, D&C blue #4, D&C brown #1, D&C green #5 through #8, D&C orange #4 through #11, D&C yellow #2 through #11, D&C red #6 through #40, FD&C blue #1, FD&C blue #2, FD&C blue #4, FD&C red #3, FD&C red #4, FD&C red #33, FD&C red #40, FD&C yellow #5, FD&C yellow #6, FD&C yellow #10, FD&C orange #4, FD&C green #3, carmine and mixtures thereof. Preferred colorants are FD&C blue #1, FD&C green #3, FD&C yellow #10 and mixtures thereof. Typical levels of colorant are from about 0% to about 2% by weight of the composition.

Water

Water is the last essential component of the present invention and forms the remainder of the composition. When water is employed in the oral hygiene compositions of the present invention, it should be deionized and free of organic impurities. Water is generally present from about 1% to about 95%, preferably from about 45% to about 90%.

Optional Ingredients (Auxiliary Agents)

The oral hygiene compositions of the present invention can contain a variety of less essential optional ingredients (auxiliary agents) suitable for rendering such compositions more acceptable. Such ingredients are well known to those skilled in the art and include, but are not limited to, desensitizing agents, healing agents, other preventive caries agents, chelating/sequestering agents, vitamins, amino acids, proteins, other anti-plaque/anti-calculus agents, opacifiers, antibiotics, anti-enzymes, enzymes, pH control agents, oxidizing agents, antioxidants, whitening agents and preservatives/antimicrobial agents. These ingredients, when used, are added at their usual levels, each generally up to about 8% by weight of the composition and usually totaling up to about 0.05% to about 30% by weight of the composition.

Examples of desensitizing agents (anti-inflammatory agents) useful in the present invention which serve to reduce and alleviate dentinal or cervical hypersensitivity that may be experienced by some individuals after tooth root surfaces are exposed by gingival recession or after periodontal treatments include bisabolol, tribasic sodium citrate, dibasic sodium citrate, monobasic sodium citrate, sodium silicofluoride, potassium nitrate, sodium nitrate, silver nitrate, zinc nitrate, calcium nitrate, calcium hydroxide, strontium chloride hexahydrate, (papain), formaldehyde, sodium fluoride, sodium monofluorophosphate and mixtures thereof. Preferred desensitizing agents are nitrate salts, strontium chloride, citrate salts, bisabolol and mixtures thereof. Most highly preferred desensitizing agents are sodium nitrate, potassium nitrate, calcium nitrate, strontium chloride hexahydrate and mixtures thereof. Typical levels of desensitizing agent are from about 0% to about 8% by weight of the composition.

Examples of healing agents useful in the present invention that have wound healing analgesic properties and provide a smoothing effect to gums that may be irritated after brushing include allantoin (glyoxyl diuride), allantoin acetyl methionine, allantoin galacturonic acid, allantoin polygalacturonic acid, allantoin glucuronic acid, allantoin ascorbate, allantoin biotin, allantoin calcium pantothenate, allantoin glycyrrhetic acid, allantoin p-aminobenzoic acid (allantoin PABA), sodium salicylate, potassium salicylate, calcium

salicylate and mixtures thereof. Typical levels of healing agent are from about 0% to about 8% by weight of the composition.

Examples of other preventive caries agents useful in the present invention which prevent tooth decay include C₁-C₃₁ D-lactobionamide, urea, urease, dibasic ammonium phosphate, ammonia, magnesium chlorophyllin, sodium copper chlorophyllin and mixtures thereof. Typical levels of other preventive caries agent and from about 0% to about 7% by weight of the composition.

Examples of chelating or sequestering agents (builders) useful in the present invention which enhances or builds the cleaning efficiency of surfactants by inactivating water hardness minerals include the sodium, potassium and ammonium salts of diphosphoric acid, triphosphoric acid, pyrophosphoric acid, orthophosphoric acid, hexametaphosphoric acid, 1-hydroxyethane-1,1-phosphonic acid, diethylenetriamine penta(methylene diphosphonic acid), ethylenediamine tetraacetic acid (EDTA), diethylenetriamine pentaacetic acid (DTPA), N-(hydroxyethyl) ethylenediamine triacetic acid (HEDTA), propylene-diamine tetraacetic acid (PDTA), nitrilotriacetic acid (NTA), mellitic acid, 1,2,3,4-cyclopentane tetracarboxylic acid, succinic acid, lauryl succinic acid, oxydisuccinic acid (ODS), carboxymethylxysuccinic acid, citric acid, lactic acid, tartaric acid, O-carboxymethyltartronic acid, polyacrylic acid, poly(α -hydroxyacrylic acid), poly(tetramethylene-1,2-dicarboxylic acid), poly(4-methoxytetramethylene-1,2-dicarboxylic acid), acrylic acid/maleic acid copolymer (polycarboxylate), acrylic acid/allyl alcohol copolymer (polycarboxylate), pyrrolidone carboxylic acid (PCA), gluconic acid, glucoheptonic acid, lactobionic acid, maltobionic acid and mixtures thereof. Builders soften water by sequestration, precipitation, or ion exchange. Most builders provide a desirable level of alkalinity, which aids in cleaning dispersion and neutralization of mouth acid and bacteria. Preferred builders are the sodium, potassium and ammonium salts of ethylenediamine tetraacetic acid, diethylenetriamine pentaacetic acid and citric acid. Typical levels of chelating or sequestering agent useful for complexing hard ions such as calcium and magnesium are from about 0% to about 6% by weight of the composition.

Examples of vitamins useful in the present invention include vitamin A (as retinyl acetate, propionate or palmitate) vitamin B₁ (as thiamine mononitrate), vitamin B₂ (as riboflavin), vitamin B₃ (as pantothenic acid), vitamin B₆ (as pyridoxane hydrochloride, dioctenoate, dilaurate, dipalmitate or tripalmitate), vitamin B₁₂ (as cyanocobalamin), vitamin B₁₅ (as pangamic acid), vitamin C (as ascorbic acid), vitamin D₂ (as ergocalciferol), vitamin D₃ (as cholecalciferol), vitamin E (as dl- α -tocopherol acetate, linoleate or nicotinate), vitamin F (as glyceryl linoleate and glyceryl linolenate), vitamin K₁ (as phytonadione), vitamin K₃ (as menadione), paba (p-aminobenzoic acid), choline, folic acid, niacinamide, niacin, biotin, retinol, inositol and mixtures thereof. Preferred vitamins are vitamin A, vitamin B₂, vitamin C, vitamin D₂ and vitamin E. Typical levels of vitamin are from about 0% to about 5% by weight of the composition.

Examples of amino acids useful in the present invention include alanine, β -alanine, N-methylalanine, N-phenylalanine, α -aminoisobutyric acid, α -aminobutyric acid, α -aminocaproic acid, α -aminocaproic acid, glycine, N-ethylglycine, N-propylglycine, N-butylglycine, leucine, methionine, sarcosine, serine, norvaline, tryptophan, lysine, aspartic acid, glutamic acid, iminodiacetic acid, keratin amino acids and mixtures thereof. The sodium, potassium, ammo-

nium or calcium salts of amino acids are useful as well and may be preferred in certain instances. Typical levels of amino acid are from about 0% to about 5% by weight of the composition.

Examples of proteins useful in the present invention include hydrolyzed casein, hydrolyzed collagen (hydrolyzed animal protein), hydrolyzed corn protein, hydrolyzed glycosaminoglycans, hydrolyzed keratin (keratin protein), hydrolyzed milk protein, hydrolyzed pea protein, hydrolyzed potato protein, hydrolyzed rice protein, hydrolyzed soy protein, hydrolyzed vegetable protein, hydrolyzed wheat gluten, hydrolyzed wheat protein, hydrolyzed yeast protein and mixtures thereof. The sodium, potassium, ammonium or calcium salts of proteins are useful as well and may be preferred in certain instances. Preferred proteins are hydrolyzed milk protein and hydrolyzed soy protein. Typical levels of protein are from about 0% to about 5% by weight of the composition.

Examples of other anti-plaque/anti-calculus agents useful in the present invention include C₁-C₂₁ D-lactobionamide, sodium phytate, folic acid, fatty acids such as nonanoic acid, peptides, stannous phosphate salts, copper phosphate salts, strontium phosphate salts, magnesium phosphate salts, inorganic phosphate salts, organic phosphate salts, chlorhexidine salt derivatives and stannous fluoride. The chlorhexidine salt derivatives are particularly useful as anti-plaque/antibacterial agents as described in U.S. Pat. Nos. 3,923,002, 3,937,807 and in Belgian Patent Nos. 0,843,244, 0,844,764 all of which are incorporated herein by reference. Typical levels of other anti-plaque/anti-calculus agents are from about 0% to about 5% by weight of the composition.

Examples of opacifiers and pearlescent agents useful in the present invention which provide a soft, silvery and pearly luster to hair care compositions include hexadecanol, octadecanol, tallow alcohol, oleyl alcohol, ethylene glycol monostearate, ethylene glycol distearate, diethylene glycol distearate, triethylene glycol distearate, glycerol mono/distearate, PEG 400 stearate, PEG 600 oleate, PEG-4 to PEG 150 laurate/dilaurate, PEG 4 to PEG 150 stearate/distearate, PEG-4 to PEG 150 oleate/dioleate, coco gluconamide, tallow gluconamide, dodecyl gluconamide hexadecyl gluconamide, octadecyl gluconamide, coco glucoheptonamide, tallow lactobionamide, octadecyl lactobionamide, tallow maltobionamide, bismuthoxychloride, spermaceti, magnesium silicate, calcium silicate, guanidine, zinc oxide titanium dioxide (anatase form or rutile form), titanium dioxide coated mica and coloured pigments coated mica and as well as the zinc, calcium and magnesium salts of fatty acids such as myristic acid, palmitic acid, stearic acid, behenic acid, coconut fatty acid. Preferred are the non-heteroatom containing alkyl aldonamides and the ethylene glycol esters such as ethylene glycol monostearate and distearate. Typical levels of opacifiers or pearlescent agent are from about 0% to about 5% by weight of the composition.

Examples of antibiotics useful in the present invention which function as a means of controlling plaque, caries, calculus and periodontal disease include penicillin, neomycin, erythromycin, tyrothricin, chlorotetracycline, vancomycin, alexidine, octenidine and mixtures thereof. Preferred antibiotics are neomycin, alexidine and mixtures thereof. Typical levels of antibiotic are from about 0% to about 3% by weight of the composition.

Examples of anti-enzymes (enzyme inhibitors) useful in the present invention include penicillin, anionic surfactants such as sodium N-lauroyl sarcosinate and sodium

150
156

dodecylbenzenesulfonate, sodium dehydroacetate and mixtures thereof. Anti-enzymes prevent dental caries by inhibiting acid producing enzymes that convert sugars into acids which are corrosive to teeth. Typical levels of anti-enzyme are from about 0% to about 3% by weight of the composition.

Examples of enzymes useful in the present invention which disrupt or interfere with plaque/calculus formation and bacterial adhesion to the tooth surface thereby prevent dental caries include glucose oxidase, galactose oxidase, lactose peroxidase, lactoferrin, lysozyme, proteolytic enzymes, pancreatic enzymes, bacterial enzymes such as bacillus subtilis, lipolytic enzymes and dextranases such as those from penicillin funiculosium and mixtures thereof.

Typical levels of enzyme are from about 0% to about 3% by weight of the composition.

Examples of pH-control agents useful in the present invention include citric acid, tartaric acid, lactic acid, gluconic acid, lactobionic acid, glycolic acid, propionic acid, succinic acid, hydrochloric acid, phosphoric acid, nitric acid, sulfuric acid, formic acid, boric acid, acetic acid, benzoic acid, palmitic acid, stearic acid, sodium hydroxide, sodium carbonate, sodium bicarbonate, potassium hydroxide, potassium carbonate, potassium bicarbonate and mixtures thereof. The amount of pH-control agent used will be that which is sufficient to provide the desired pH. The pH of the present compositions may be in the range of about 3 to about 9 preferably from about 4 to about 8. The amount of pH-adjusting agent used will be that which is sufficient to provide the desired pH, typically from about 0.01% to about 3% by weight of the composition.

Examples of oxidizing agents useful in the present invention which disrupt bacterial adhesion to the tooth surface and prevent dental caries as well as assist in providing a clean refreshing feeling include sodium chlorate, potassium chlorate, sodium perborate, potassium perborate, sodium percarbonate, potassium percarbonate, urea peroxide, calcium peroxide, magnesium oxide and hydrogen peroxide. A preferred oxidizing agent is calcium peroxide and hydrogen peroxide. Methods and systems for stabilizing hydrogen peroxide in oral hygiene compositions are well known in the art and are described in U.S. Pat. Nos. 4,980,154, 4,687,663, 5,020,694, 5,038,963, 5,059,417 and Des. 0,315,496 all of which are incorporated herein by reference. Typical levels of oxidizing agent are from 0% to about 5% by weight of the composition.

Examples of antioxidants useful in the present invention include propyl gallate, butylated hydroxyanisole (BHA), toluhydroquinone (THQ) sold as Tenox PG, Tenox BHA and Tenox THQ by Eastman Chemical Products Inc., and butylated hydroxytoluene (BHT) sold as Sustane BHT by UOP Process Division. Typical levels of antioxidant used to prevent oxidation of air sensitive ingredients which assist in preventing color and odor formation are from about 0% to about 3% by weight of the composition.

An example of a preferred whitening agent which functions to whiten teeth is titanium dioxide. Typical levels of whitening agent is from about 0% to about 5% by weight of the composition.

Examples of preservatives or antimicrobial agents that function as bactericides and/or fungicides useful in the present invention include glutaraldehyde, formaldehyde, paraformaldehyde, glyoxal, benzoic acid, sodium benzoate, potassium benzoate, sodium methyl p-hydroxybenzoate, salicylic acid, sorbic acid, dehydroacetic acid, benzyl alcohol, ethanol, 2-phenoxyethanol, chlorohexidine

hydrochloride, dichlorophene (2,2'-dihydroxy-5,5'-dichlorodiphenyl methane)triclosan, chloroacetamide, p-chloro-m-xlenol, 1-(3-chloroallyl)-3,5,7-triaza-1-azoniaadamantane chloride, methyl paraben, propyl paraben, butyl paraben, benzyl paraben, imidazolidinyl urea, diazolidinyl urea, monomethylol dimethyl hydantoin (MDM hydantoin), dimethylol dimethyl hydantoin (DMDM hydantoin), iodopropyl nyl butylcarbamate, 2-bromo-2-nitropropane-1,3-diol, 2-octyl-4-isothiazolin-3-one, 5-chloro-2-methyl-4-isothiazolin-3-one (methylchloroisothiazoline), 2-methyl-4-isothiazolin-3-one (methylisothiazoline) and dicocodimethylammonium chloride. Preferred preservatives are the alkyl parabens, benzoic acid and their salts. Typical levels of preservative used to control bacterial action are from about 0% to about 2% by weight of the composition.

Many additional optional ingredients that are useful in the present invention are described in McCutcheon's, Detergents and Emulsifiers (Vol 1), McCutcheon's, Functional Materials (Vol 2), 1992 Annual Edition, published by McCutcheon's MC Publishing Co., and Foods Chemicals Index, 1981 Third Edition, published by National Academy Press as well as the CTFA (Cosmetic, Toiletory and Fragrance Association) 1992 International Buyers Guide, published by CTFA Publications and OPD 1993 Chemical Buyers Directory 80th Annual Edition, published by Schnell Publishing Co. which are all incorporated herein by reference.

According to the present invention an oral hygiene composition comprises the following ingredients:

(a) from about 0.01% to about 15% by weight of the composition is a heteroatom containing alkyl aldonamide compound:

(b) from about 0% to about 65% by weight of the composition is an abrasive polishing agent;

(c) from about 0% to about 80% by weight of the composition is a humectant;

(d) from about 0% to about 45% by weight of the composition is ethanol;

(e) from about 0% to about 30% by weight of the composition is a binder/cothickener;

(f) from about 0% to about 30% by weight of the composition is a cosurfactant;

(g) from about 0% to about 8% by weight of the composition is an astringent;

(h) from about 0% to about 8% by weight of the composition is an anti-plaque agent;

(i) from about 0% to about 8% by weight of the composition is an anticalculus agent;

(j) from about 0% to about 5% by weight of the composition is an antibacterial agent;

(k) from about 0% to about 5% by weight of the composition is a buffering salt pair;

(l) from about 0% to about 5% by weight of the composition is an alkali metal halide (salt);

(m) from about 0.01% to about 4% by weight of the composition is an essential flavor oil;

(n) from about 0.01% to about 4% by weight of the composition is a sweetening agent;

(o) from about 0% to about 5% by weight of the composition is a fluoride source;

(p) from about 0% to about 2% by weight of the composition is a colorant;

(q) from about 0% to about 8% by weight of the composition is a desensitizing agent;

(r) from about 0% to about 8% by weight of the composition is a healing agent;

(s) from about 0% to about 6% by weight of the composition is a chelating/sequestering agent;

(t) from about 0% to about 5% by weight of the composition is a vitamin;

(u) from about 0% to about 5% by weight of the composition is an amino acid;

(v) from about 0% to about 5% by weight of the composition is a protein;

(w) from about 0% to about 5% by weight of the composition is an opacifier;

(x) from about 0% to about 3% by weight of the composition is an antibiotic;

(y) from about 0% to about 3% by weight of the composition is an antienzyme;

(z) from about 0% to about 3% by weight of the composition is an enzyme;

(aa) from about 0.01% to about 3% by weight of the composition is a pH control agent;

(bb) from about 0% to about 5% by weight of the composition is an oxidizing agent;

(cc) from about 0% to about 3% by weight of the composition is an antioxidant;

(dd) from about 0% to about 5% by weight of the composition is a whitening agent;

(ee) from about 0% to about 2% by weight of the composition is a preservative/antimicrobial agent; and

(ff) the remainder is water.

In a more narrow aspect of the present invention an oral hygiene composition comprises the following ingredients:

(a) from about 0.02% to about 13% by weight of the composition is a heteroatom containing alkyl aldnamide compound;

(b) from about 0% to about 55% by weight of the composition is an abrasive polishing agent;

(c) from about 0% to about 75% by weight of the composition is a humectant;

(d) from about 0% to about 40% by weight of the composition is ethanol;

(e) from about 0% to about 25% by weight of the composition is a binder/cothickener;

(f) from about 0.01% to about 28% by weight of the composition is a cosurfactant;

(g) from about 0% to about 6% by weight of the composition is an astringent;

(h) from about 0% to about 6% by weight of the composition is an anti-plaque agent;

(i) from about 0% to about 6% by weight of the composition is an anticalculus agent;

(j) from about 0% to about 4% by weight of the composition is an antibacterial agent;

(k) from about 0% to about 4% by weight of the composition is a buffering salt pair;

(l) from about 0% to about 4% by weight of the composition is an alkali metal halide (salt);

(m) from about 0.02% to about 3% by weight of the composition is an essential flavor oil;

(n) from about 0.02% to about 3% by weight of the composition is a sweetening agent;

(o) from about 0% to about 4% by weight of the composition is a fluoride source;

(p) from about 0% to about 1.5% by weight of the composition is a colorant;

(q) from about 0% to about 7% by weight of the composition is a desensitizing agent;

(r) from about 0% to about 6% by weight of the composition is a healing agent;

(s) from about 0% to about 4% by weight of the composition is a chelating/sequestering agent;

(t) from about 0% to about 4% by weight of the composition is a vitamin;

(u) from about 0% to about 4% by weight of the composition is an amino acid;

(v) from about 0% to about 4% by weight of the composition is a protein;

(w) from about 0% to about 4% by weight of the composition is an opacifier;

(x) from about 0% to about 2% by weight of the composition is an antibiotic;

(y) from about 0% to about 2% by weight of the composition is an antienzyme;

(z) from about 0% to about 2% by weight of the composition is an enzyme;

(aa) from about 0.02% to about 2% by weight of the composition is a pH control agent;

(bb) from about 0% to about 4% by weight of the composition is an oxidizing agent;

(cc) from about 0% to about 2% by weight of the composition is an antioxidant;

(dd) from about 0% to about 4% by weight of the composition is a whitening agent;

(ee) from about 0% to about 1% by weight of the composition is a preservative/antimicrobial agent; and

(ff) the remainder is water.

In an even more narrow aspect of the present invention an oral hygiene composition comprises the following ingredients:

(a) from about 0.03% to about 10% by weight of the composition is a heteroatom containing alkyl aldnamide compound;

(b) from about 0% to about 50% by weight of the composition is an abrasive polishing agent;

(c) from about 0% to about 70% by weight of the composition is a humectant;

(d) from about 0% to about 35% by weight of the composition is ethanol;

(e) from about 0% to about 20% by weight of the composition is a binder/cothickener;

(f) from about 0.02% to about 25% by weight of the composition is a cosurfactant;

(g) from about 0% to about 4% by weight of the composition is an astringent;

(h) from about 0% to about 4% by weight of the composition is an anti-plaque agent;

(i) from about 0% to about 4% by weight of the composition is an anticalculus agent;

(j) from about 0% to about 3% by weight of the composition is an antibacterial agent;

(k) from about 0% to about 3% by weight of the composition is a buffering salt pair;

(l) from about 0% to about 3% by weight of the composition is an alkali metal halide (salt);

(m) from about 0.03% to about 2% by weight of the composition is an essential flavor oil;

(n) from about 0.03% to about 2% by weight of the composition is a sweetening agent;

(o) from about 0% to about 3% by weight of the composition is a fluoride source;

(p) from about 0% to about 1% by weight of the composition is a colorant;

(q) from about 0.05% to about 30% by weight of the composition is an optional ingredient(s); and

(r) the remainder is water.

Method of Manufacture

Aldonic acids, aldobionic acids and their lactones are prepared by microbial fermentation, chemical oxidation or enzymatic oxidation of sugars. (See for example, EP 142,725 (1985) to Saito, et al.; EP 232,202 (1986) and EP 233,816 (1987) to Fuertes et al.; JP 62/269728 (1987) to Kimura, et al.; Biotechnology Letters 6:487 (1984) to Chang, et al.; Biotechnology Letters 9:252 (1987) to Burdick, et al.; German Pat. No. 2,911,192 (1980) and U.S. Pat. No. 4,460,686 (1984) to Hartmeier and Appl. Microbiol. Biotechnol. 21:356 (1985) to Seiskari, et al. all of which are incorporated herein by reference). Examples of aldonic acids, aldobionic acids and their lactones suitable for the preparation of heteroatom containing alkyl aldonaide compounds include but are not limited to threonic acid, arabinonic acid, lyxonic acid, allonic acid, altronic acid, idonic acid, talonic acid, gluconic acid, galactonic acid, mannonic acid, lactobionic acid, maltobionic acid, cellobionic acid, gentiobionic acid, melibionic acid, glucopyranosyl-(1-5)-arabinonic acid, erythronolactone, ribonolactone, xylonolactone, gluconolactone, galactonolactone, mannonolactone, gulonolactone, glucoheptonolactone, lactobionolactone and maltobionolactone.

Heteroatom containing alkyl aldonaide compounds of the invention are prepared by reaction of the appropriate heteroatom containing amine with an aldonic acid or aldobionic acid (preferably with the corresponding aldonaide or aldobionolactone) in an organic solvent (such as methanol) with or without an acid catalyst (such as methanesulfonic acid) at about 0° C. to about 90° C., preferably at about 20° C. to about 70° C., even more preferably at about 30° C., to about 60° C.

Heteroatom containing alkyl aldonaide salt, compounds of the invention are prepared by reaction of an alkylaminoalkyl aldonaide or aldobionamide compound with an organic or inorganic acid in water or organic solvent at about 0° C. to about 100° C., preferably at about 20° C. to about 70° C., even more preferably at about 25° C. to about 55° C.

All raw materials such as D-gluconic acid, D-gluconolactone, D-lactobionic acid, D-lactobionolactone, alkylloxypyrrolamine, alkylaminopropylamine and alkylloxypyrrolaminopropylamine are available in bulk and the end products are easily prepared by the commercially feasible process described above.

The dental rinse and mouthwash compositions of the present invention can be prepared by adding the appropriate amount of water and admixing the active ingredients with appropriate stirring at about 18° C. to about 100° C., preferably from about 20° C. to about 80° C., even more preferably from about 22° C. to about 70° C. Ingredients may be added as a main mix, partial mix or as a premix, the ingredients may be mixed in any order. All temperature sensitive components are added after the composition has cooled to a temperature of from about 18° C. to about 38° C.

after which the composition is stirred until homogeneous and discharged. Ingredients that are poorly soluble in the composition matrix can be predispersed in the alcohol or surfactant system which are later added to the composition.

Optionally, the dental rinse and mouthwash compositions of the present invention can be filtered through a 1-4 µm filter to provide a sparkling clear stable product. Commercial quantities of the dental rinse and mouthwash compositions of the present invention can be easily prepared in a dairy type stainless steel, tygon or glass lined kettle equipped with a provision for agitation, heating and cooling. Processing may be continuous or batch wise, however cost savings may be further increased through continuous processing by virtue of economy of scale.

The dentifrice compositions of the present invention can be prepared by adding the appropriate amount of water or humectant and admixing the active ingredients with appropriate stirring at about 18° C. to about 100° C., preferably from about 20° C. to about 80° C., even more preferably from about 22° C. to about 70° C. Ingredients may be added as a main mix, partial mix or as a premix. All temperature sensitive components are added after the composition has cooled from about 18° C. to about 38° C. after which the composition is stirred until homogeneous and discharged. Ingredients that are poorly soluble in the composition matrix can be predispersed in the surfactant system which are later added to the composition. Additionally, the dentifrice compositions of the present invention can be made free of air by pulling a carefully regulated vacuum to provide a smooth homogenous stable product. Commercial quantities of the dentifrice compositions of the present invention can be easily prepared in a dairy type stainless steel, tygon or glass lined kettle equipped with a provision for agitation, vacuum heating and cooling. Processing may be continuous or batch wise, however cost savings may be further increased through continuous processing by virtue of economy of scale.

Oral Hygiene Types and Form

Oral Hygiene compositions are available in a variety of types and forms. A classification according to product type includes, but is not limited to mouthwashes, pre-brushing dental rinses, post-brushing dental rinses, dental sprays, dental creams, toothpastes, toothpaste gels, toothpowders, dental cleansers, dental flosses, chewing gums, lozenges and the like. Preferred are the mouthwashes, pre-brushing dental rinses, post-brushing dental rinses, toothpastes and toothpaste gels.

A classification according to product form would consist of aerosol, liquid, gel, cream, paste, granular, tablet or powdered form. Preferred product form for mouthwashes, pre-brushing dental rinses and postbrushing dental rinses of the invention is liquid form. Preferred product form for denaces (toothpastes) of the invention is gel or paste form.

Industrial Application and Use

The heteroatom containing alkyl aldonaide compounds of the invention are useful as surfactants that may be used alone or in combination with other surfactants to provide improved foam, viscosity, clarity and conditioning characteristics. More specifically, the heteroatom containing alkyl aldonaide compounds of the invention are useful as foam stabilizing agents, thickening agents, solubilizing agents and antimicrobial agents. In addition, it has been found that the heteroatom containing alkyl aldonaide compounds of the invention are also useful as gelling agents, foam boosting

151A

D3 152 152



US005814304A

United States Patent [19]
Wong et al.

[11] **Patent Number:** **5,814,304**
[45] **Date of Patent:** **Sep. 29, 1998**

[54] **STABLE AQUEOUS ABRASIVE PEROXIDE TOOTH WHITENING DENTIFRICE**
[75] **Inventors:** Michael Wong, North Brunswick;
Michael Prencipe, West Windsor;
Kedar N. Rustogi, Kendall Park, all of N.J.
[73] **Assignee:** Colgate Palmolive Company, New York, N.Y.
[21] **Appl. No.:** 891,010
[22] **Filed:** Jul. 10, 1997

2,027,838	1/1936	Reichert	23/251
2,904,517	9/1959	Baker	252/397
3,114,606	12/1963	Meeker	23/207.5
3,333,925	8/1967	Young	23/207.5
3,607,053	9/1971	Reilly	23/207.5
3,811,833	5/1974	Stalter	8/111
3,864,271	2/1975	Stalter	252/99
4,320,102	3/1982	Dalton et al.	423/273
5,565,190	10/1996	Santalucia et al.	424/53
5,599,525	2/1997	Hsu et al.	424/53
5,599,527	2/1997	Hsu et al.	424/53
5,614,174	3/1997	Hsu et al.	424/53
5,648,064	7/1997	Gaffar et al.	424/53
5,683,680	11/1997	Santalucia et al.	424/53
5,690,913	11/1997	Hsu et al.	424/53
5,698,182	12/1997	Prencipe et al.	424/53

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 692,841, Aug. 2, 1996.
[51] **Int. Cl.⁶** A61K 7/16; A61K 7/20; A61K 33/40
[52] **U.S. Cl.** 424/53; 424/49; 424/63; 424/616
[58] **Field of Search** 424/49-58

References Cited

U.S. PATENT DOCUMENTS

1,958,204 5/1934 Reichert 23/251

Primary Examiner—Shep K. Rose
Attorney, Agent, or Firm—Paul Shapiro

[57] **ABSTRACT**

An aqueous abrasive whitening composition containing a peroxide whitening compound which is chemically and physically stable and exhibits heightened and rapid whitening of teeth and stain removal which comprises a combination of water, calcined alumina abrasive and a peroxide compound.

14 Claims, No Drawings

STABLE AQUEOUS ABRASIVE PEROXIDE TOOTH WHITENING DENTIFRICE

This application is a continuation-in-part of copending application Ser. No. 08/692,841 filed Aug. 2, 1996.

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates generally to peroxide containing preparations for whitening human teeth, and more particularly, to a stable peroxide dentifrice composition which when applied onto the surface of teeth acts to both whiten and remove stain from teeth.

2. The Prior Art

A tooth is comprised of an inner dentin layer and an outer hard enamel layer that is the protective layer of the tooth. The enamel layer of a tooth is naturally an opaque white or slightly off-white color. It is this enamel layer that can become stained or discolored. The enamel layer of a tooth is composed of hydroxyapatite mineral crystals that create a somewhat porous surface. It is believed that this porous nature of the enamel layer is what allows staining agents and discoloring substances to permeate the enamel and discolor the tooth.

Many substances that a person confronts or comes in contact with on a daily basis can "stain" or reduce the "whiteness" of one's teeth. In particular, the foods, tobacco products and fluids such as tea and coffee that one consumes tend to stain one's teeth. These products or substances tend to accumulate on the enamel layer of the tooth and form a film over the teeth. These staining and discoloring substances can then permeate the enamel layer. This problem occurs gradually over many years, but imparts a noticeable discoloration of the enamel of one's teeth.

There are available in the marketplace non-abrasive gel compositions for home use which contain 1-3% by weight concentrations of hydrogen peroxide or urea peroxide and when brushed on the teeth effect whitening and removal of stains.

A drawback to the use of these peroxide based whitening gels is the tendency of the peroxide component to decompose within a relatively short period of time following manufacture with concomitant loss of all or a substantial amount of the available oxygen thereby limiting the efficacy of these products as teeth whitening compositions. Peroxy compounds such as hydrogen peroxide are notoriously unstable with respect to maintenance of peroxide level and have been found to be difficult to formulate into aqueous gels or pastes which will have an adequate shelf-life and yet will readily liberate oxygen when applied to teeth. Therefore, the prior art, for example U.S. Pat. No. 4,988,450 and U.S. Pat. No. 3,657,413, in formulating oxygen liberating compositions for the whitening of teeth, utilize anhydrous powders or water-free pastes or gels which must be protected against chemical interaction. A drawback to the use of such anhydrous products is that, due to the absence of water, application of the product tends to desiccate oral tissue which leads to irritation and tissue damage. Further, due to the absence of water in the formulation of the anhydrous product, the product exhibits poor, often unacceptable rheological properties due to inadequate hydration of the gelling agents added to thicken the product.

Dentifrice whitening products formulated with peroxy compounds normally do not contain abrasive polishing agents as such materials activate the rapid decomposition of

the peroxy compounds whereby the oxygen whitening agent is prematurely released. The gas evolution is especially undesirable as such gas evolution can cause swelling and/or bursting of tubes containing the dentifrice product. Capped tubes filled with dentifrice products containing peroxide compounds and silica abrasives have been known to explode within one day after filling. U.S. Pat. No. 5,256,402 discloses that when alumina abrasives are substituted for silica, the filled product is pocketed with gas bubbles within days of filling.

A drawback to the use of whitening products which are formulated without abrasives is that, in addition to the stability problem, the products are not effective in stain removal. Thus the abrasive or polishing agent incorporated in a dentifrice acts to debride and physically scrub the external surface of teeth. This scrubbing action removes filmy bacterial and plaque layers as well as some of the stains and discoloring pigments that are found on teeth that cause the undesired discoloration. These abrasive agents also microabrade the tooth so as to polish the teeth to give the enamel a more lustrous appearance and a higher optical sheen. This micro abrasion action enhances the scrubbed teeth's ability to reflect white light and thereby appear brighter.

The aqueous abrasive toothpaste composition disclosed in U.S. Pat. No. 5,256,402 contains a urea or hydrogen peroxide compound an alkali pyrophosphate salt and a calcium pyrophosphate abrasive which is stable with respect to active oxygen level. A drawback to the abrasive peroxide oral composition disclosed in U.S. Pat. No. 5,256,402 is that although the peroxide compound is stable, additional stability is required when the product is subjected to extended storage periods at abnormally high temperatures.

In copending patent application Ser. No. 08/692,841 filed Aug. 2, 1996 there is disclosed an aqueous abrasive provide dentifrice composition which is physically and chemically stable and effects rapid whitening of teeth and stain removal which contains a dicalcium phosphate abrasive, a peroxide compound, a humectant containing a polyethylene glycol, a metal ion complexing agent, an antioxidant compound and a polyoxyethylene-polyoxypropylene block copolymer gelling agent, the pH of the dentifrice being buffered in the range of about 5.8 to about 7.2.

Although the aqueous abrasive peroxide dentifrice composition of copending application Ser. No. 08/692,841 is effective in whitening teeth, the art continuously seeks dentifrice compositions of greater whitening efficacy and stability.

SUMMARY OF THE INVENTION

In accordance with the present invention, it has now been found that an aqueous abrasive peroxide dentifrice composition which is physically and chemically stable and effects rapid whitening of teeth and stain removal is obtained using a calcined alumina abrasive, a peroxide compound, and a stabilizer compound.

The stability of the dentifrice composition of the present invention is unexpected, for as previously discussed, the prior art (U.S. Pat. No. 5,256,402) understood that dentifrices containing peroxy compounds and alumina abrasives have poor stability.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

It is critical to the practice of the present invention that the form of alumina used as the abrasive in the dentifrice

compositions of the present invention be calcined alumina, a form of alumina produced by calcination of aluminum hydroxide into $\alpha\text{-Al}_2\text{O}_3$ which is thermodynamically stable at temperatures above 1200° C. Calcined alumina abrasives are available commercially. A preferred calcined alumina abrasive is sold by Alcan Chemicals under the designation Baco Aluminum Oxide.

The calcined alumina abrasive is incorporated in the whitening composition of the present invention at a concentration of about 1 to 30% by weight and preferably about 5 to about 10% by weight.

The peroxide component of the composition of the invention is included in an amount sufficient to allow release of sufficient oxygen during brushing of teeth to effect whitening thereof. Typically, the peroxide compound can be employed in the composition of the present invention in amounts so that at least about 0.5% of the composition comprises a peroxide. Preferably, the peroxide comprises from about 0.5 to about 10% by weight of the composition. More preferably, the peroxide comprises from about 0.75 to about 5% by weight of the composition. Examples of suitable peroxide compounds used to prepare the compositions of the present invention include metal peroxides such as calcium peroxide, hydrogen peroxide and organic peroxides including urea peroxide, glyceryl peroxide, benzoyl peroxide and the like. A preferred peroxide compound is hydrogen peroxide.

The peroxide and calcined alumina abrasive used to prepare the whitening composition of the present invention are dissolved or suspended in a vehicle comprised of water and a humectant such as a polyethylene glycol and glycerin. Water constitutes about 7 to about 40% by weight of the whitening composition of the present invention and preferably about 20 to about 30% by weight.

Illustrative of polyethylene glycols useful in the practice of the present invention include polyethylene glycols known by the trademark Carbowax which are nonionic polymers of ethylene oxide having the general formula: $\text{HOCH}_2(\text{CH}_2\text{OCH}_2)_n\text{CH}_2\text{OH}$ wherein n represents the average number of oxyethylene groups. The Carbowax polyethylene glycols are designated by a number such as 400, 600, 800, 1000, 2000 which represents the average molecular weight. The molecular weight range of the polyethylene glycols used herein is about 200 to about 2000 and preferably about 600 hereinafter referred to as PEG 600.

The polyethylene glycol component included in the composition of the present invention constitutes about 10 to about 30% by weight of the whitening composition and preferably about 15 to about 20% by weight.

Glycerin may be included in the whitening composition of the present invention in the range from 0 to about 10% by weight of the whitening composition. Concentrations of glycerin substantially in excess of 10% by weight have been found to cause physical destabilization (liquefaction) of the composition and therefore such excess should be avoided.

Gelling agents are included in the abrasive peroxide compositions of the present invention in amounts from about 10% to about 25% by weight of the composition and preferably about 12 to about 20% by weight. Examples of suitable gelling agents include polyoxyethylene polyoxypropylene block copolymers having the formula $\text{HO}(\text{C}_2\text{H}_4\text{O})_b(\text{C}_3\text{H}_6\text{O})_a(\text{C}_2\text{H}_4\text{O})_b\text{H}$ wherein a is an integer such that the hydrophobic base represented by $(\text{C}_3\text{H}_6\text{O})_a$ has a molecular weight of about 2750 to 4000, b is an integer such that the hydrophilic portion represented by $(\text{C}_2\text{H}_4\text{O})$ constitutes about 70-80% by weight of the copolymer. Block copoly-

mers of this composition are available commercially under the trademark Pluronic F type.

Pluronic F127, which has a molecular weight of range of about 9000 to about 14000 and contains 70% of the hydrophilic polyoxyethylene moiety is preferred for use as a gelling agent in the practice of the present invention.

Other examples of gelling agents which may be employed are the well-known carboxy vinyl polymers of extremely high molecular weight sold under the trade name Carbopol by the B.F. Goodrich Chemical Company as well as carboxypolymethylene polymers which comprise a major portion of one or more alpha, beta-olefinically unsaturated carboxylic acids, and a minor portion of a polyalkenyl polyether or a polyol, i.e., a copolymer or acrylic acid cross-linked with from about 0.75% to 1.5% of polyallyl sucrose.

The presence of metal ion chelating agents and antioxidants (oxygen scavengers) stabilizer compounds in the dentifrice compositions of the present invention contribute to the chemical stability of the abrasive peroxide composition. Examples of suitable metal ion chelating agents include alkali metal stannates such as sodium and potassium stannate, ethylenediaminetetracetic acid and its salts. Examples of antioxidants useful in the practice of the present invention include butylated hydroxy toluene (BHT), nordihydroguaiaretic acid, propyl gallate and trihydroxybutyphenone. The metal ion chelating agents are incorporated in the compositions of the present invention at a concentration of about 0.01 to about 1% by weight and the antioxidant is incorporated at a concentration of about 0.05 to about 0.20% by weight and preferably about 0.02 to about 0.05% by weight.

In preparing the abrasive peroxide compositions of the present invention, the pH of the composition is adjusted to a range between about 3.0 and about 8 and preferably about between about 5 and about 7.

Pyrophosphate salts having anti-tartar efficacy such as dialkali or tetra-alkali metal pyrophosphate salts such as $\text{Na}_4\text{P}_2\text{O}_7$ (TSPP), $\text{K}_4\text{P}_2\text{O}_7$, $\text{Na}_2\text{K}_2\text{P}_2\text{O}_7$, $\text{Na}_2\text{H}_2\text{P}_2\text{O}_7$ (SAPP), and $\text{K}_2\text{H}_2\text{P}_2\text{O}_7$, may be included in the composition of the present invention at a concentration of about 0.5 to about 8.0% by weight and preferably about 1.5 to 3.5% by weight. In addition to their antitartar efficacy, pyrophosphate salts serve a dual function as supplementary metal ion complexing agents.

Fluoride salts having anti-caries efficacy may also be incorporated in the dentifrice of the present invention and are characterized by their ability to release fluoride ions in water, for example, sodium fluoride, potassium fluoride, sodium fluorosilicate, ammonium fluorosilicate and sodium monofluorophosphate (NaMFP). It is preferable to employ a fluoride salt to release about 10-1500 ppm of fluoride ion.

A surfactant is also included in the whitening composition of the present invention and serves as a solubilizing, dispersing, emulsifying and wetting agent and is especially effective in solubilizing the flavor ingredient present. Surfactants which may be used in the practice of the present invention include cationic surfactants, anionic surfactants such as sodium laurylsulfate and sodium laurylsulfoacetate, ampholytic and amphoteric surfactants like cocoamidopropyl betaine.

The flavor ingredient constitutes about 0.5-5.0% by weight of the dentifrice composition of the present invention. Suitable flavoring constituents are flavoring oils, e.g., oils of spearmint, peppermint, wintergreen, menthol, cineole, limonene, menthone and menthyl acetate.

A sweetening material is preferably also employed as a complement to the flavoring material. Suitable sweetening agents are water soluble and include sodium saccharin, sodium cyclamate, xylitol, aspartame and the like, in concentrations of about 0.01 to 1.0% by weight. Sodium saccharin is preferred.

To prepare the whitening compositions of the present invention, water soluble salts such as sodium saccharin and sodium monofluorophosphate (NaMFP) are dissolved in an aqueous vehicle containing a humectant such as PEG 600 and glycerin. The vehicle is heated to a temperature of about 130°-170° C., followed by the addition of a polyoxyethylene-polyoxypropylene block copolymer gelling agent and the ingredients are mixed until a gel phase is formed. An abrasive compound such as calcium pyrophosphate is added to the gel and mixed to form a paste. The paste when formed is cooled to about 90°-130° F., preferably about 100° F. A metal ion chelating agent, antioxidant, buffering agent and peroxide compound are then added to the paste and the ingredients mixed to obtain an homogeneous mixture. The flavor and surfactant, are then added to the mixture to obtain a finished tooth whitening paste of the present invention.

It has been determined that when pyrophosphate salts are used in the manufacture of the whitening compositions of the present invention, attempts to dissolve such salts in the aqueous vehicle at temperatures in excess of 130° F. should be avoided as such temperature conditions bring into solution levels of pyrophosphate salt in excess of the solubility capacity of the salt thereby creating a supersaturated condition with respect to the excess salt. During storage at lower, ambient temperatures, the excess pyrophosphate salt crystallizes out from the whitening composition matrix forming insoluble solid matter which is cosmetically unacceptable and may have the further disadvantage of promoting chemical instability.

It is therefore preferred in the practice of the present invention, that when pyrophosphate salts are to be included in the whitening formulation that during the manufacture of the whitening composition any pyrophosphate salt added to the composition is premixed in the humectant and the premixture added to the composition matrix at a temperature no higher than 100° F.

The following example further illustrates the present invention, but it is understood that the invention is not limited thereto. All amounts and proportions referred to herein and in the appended claims are by weight unless otherwise indicated.

EXAMPLE I

A whitening abrasive peroxide of the present invention containing calcined alumina designated "Composition A" was prepared. For purposes of comparison, a comparative whitening peroxide dentifrice (Composition B) was prepared in the same manner as Composition A except calcined alumina was not present as an abrasive. The ingredients of Compositions A and B are recorded in Table I below.

TABLE I

COMPOSITIONS A-B		
Ingredients	Composition A (Weight %)	Composition B (Weight %)
Water	24.28	25.64
PEG 600	17.42	17.42
Glycerin	7.42	7.42
TSPP	2.00	2.00

TABLE I-continued

COMPOSITIONS A-B		
Ingredients	Composition A (Weight %)	Composition B (Weight %)
Pluronic F-127	15.00	15.00
Calcined Alumina	10	0
Calcium Pyrophosphate	15.00	25.00
Na MFP	0.76	0.76
Saccharin	0.50	0.50
Phosphoric Acid	1.000	0.50
H ₂ O ₂ (35%) containing sodium stannate	4.29	3.43
Flavor	1.50	1.50
BHT	0.03	0.03
SLS	0.80	0.8
pH	7.02	6.70

Compositions A and B were prepared by dispersing TSPP in a mixture of PEG 600 and glycerin and heating to 130° F. while stirring. Water was added to the mixture and the ingredients mixed for about 5 minutes. Saccharin and sodium monofluorophosphate (Na MFP) were added and the resultant mixture stirred for 10 minutes, followed by the addition of Pluronic F127 and stirring at 130° F., for 20 minutes. The mixture was then deaerated for 5 minutes and calcium pyrophosphate was added and the resulting paste mixed for 15 minutes at high speed under vacuum. Potassium stannate premixed with H₂O₂ was added to the paste which was further mixed for 10 minutes under vacuum at high speed. BHT premixed with flavor oil was then added to the paste and mixed under vacuum for 5 minutes. Sodium lauryl sulfate (SLS) was then added under vacuum for 5 minutes at low speed. When necessary, phosphoric acid was added to adjust the pH of the composition to the desired level.

The chemical stability of Compositions A and B was determined by initially analyzing the compositions for active oxygen (AO) and then storing the composition for a 6 week period at elevated temperatures 105° F., 120° F. and again analyzing the dentifrice for AO.

The results of these analyses are summarized in Table II below.

TABLE II

Composition Stability						
Composition	AO % Initial		AO % 6 weeks @		AO % Recovery	
	105° F.	120° F.	105° F.	120° F.	105° F.	120° F.
A	1.49	1.49	1.40	1.31	94.0	87.9
B	1.19	1.19	1.06	1.01	89.0	84.9

The data recorded in Table II indicate that the stability of the peroxide dentifrices of the present invention (Composition A) containing a calcined alumina abrasive is 94% after 6 weeks at 105° F. and greater than 87% after 6 weeks at 120° F. indicating that the dentifrice composition is relatively stable and even has a higher stability than a similar dentifrice (Composition B) in which calcined alumina is absent.

To test the whitening efficacy of Composition A, bovine teeth were stained by intermittent exposure of the bovine teeth to a staining broth containing finely ground instant coffee, instant tea, gastric mucin, trypticase, soy broth, and Sarcina lutea turtox (a chromogenic microorganism) throughout a four day period. Stained bovine teeth specimens selected for the test showed the same amount of discoloration. The selected specimens were then brushed



US 20020015697A1

(19) **United States**

(12) **Patent Application Publication**
Beckman et al.

(10) **Pub. No.: US 2002/0015697 A1**

(43) **Pub. Date: Feb. 7, 2002**

(54) **BIOCIDAL METHODS AND COMPOSITIONS**

(76) **Inventors:** Kenneth Beckman, Alameda, CA (US);
John L. Grimsich, Berkeley, CA (US);
Christopher Hawk, Pittsburg, CA
(US); Frank Swenson, Alameda, CA
(US); David Tyler, Alameda, CA (US)

Correspondence Address:

LAW OFFICES OF JONATHAN ALAN QUINE
P O BOX 458
ALAMEDA, CA 94501

(21) **Appl. No.: 09/804,694**

(22) **Filed: Mar. 14, 2001**

Related U.S. Application Data

(63) **Non-provisional of provisional application No.**
60/188,981, filed on Mar. 13, 2000. Non-provisional
of provisional application No. 60/188,995, filed on

Mar. 13, 2000. Non-provisional of provisional appli-
cation No. 60/188,783, filed on Mar. 13, 2000. Non-
provisional of provisional application No. 60/220,
618, filed on Jul. 25, 2000.

Publication Classification

(51) **Int. Cl.⁷** **A61K 38/44; A61K 33/26;**
A61K 31/715; A61L 9/00
(52) **U.S. Cl.** **424/94.4; 514/54; 424/646;**
422/30

(57) **ABSTRACT**

Methods, compositions, and kits for reducing a microbial
population on a surface are provided. The microbial popu-
lations which can be treated using the methods, composi-
tions, and kits of the present invention include prokaryotic,
viral, and protozoan populations. The methods, composi-
tions, and kits of the present invention have a number of uses
in the fields of food production and medicine.

[0073] An example of the type of considerations that will result in the selection of high concentrations (in concert with shorter exposures) versus low concentrations (and longer exposures) is the processing of poultry. In this process, birds are hung on shackles and move along a conveyor through the factory. The transit time generally involves less than 15 minutes from the time of slaughter to the time that carcasses are deposited into a chiller water bath, in which they spend roughly 45 minutes before final packaging. There are numerous points in the processing plant at which the stress inducers may be applied. To give just two contrasting examples, stress inducers can be applied early on in the plant at the time of defeathering, a point in the process at which spreading of microbes is most likely. Stress inducers can also (or alternatively) be included in chiller water itself, as is currently the case with chlorine. Defeathering is a rapid process; birds pass through the device in a matter of 15-30 seconds or so, and is followed by many other processing steps, including numerous water rinses, before the carcasses are deposited in a water chiller. In contrast, the chiller bath is a long treatment, and is the final rinse for the carcasses, which are then immediately packaged; as a consequence, residue from the chiller itself ultimately ends up in packaged products. Therefore, high concentrations of iron or copper (e.g. 100 mM Fe^{2+} , for example) may be preferable during the brief defeathering procedure, since these high concentrations will later be removed by rinsing, and since high concentrations will have a greater effect during such a short period of treatment. In contrast, far lower concentrations (10 μM or lower) may be preferable during a long chiller bath exposure, since in this case the solution may end up on the final product, where high concentrations may result in staining or a metallic taste. Therefore, specific embodiments include all those treatments, which are determined empirically by the use of high-throughput methods such as those disclosed herein, in which either rapid exposures to iron- and/or copper- based composition or low concentrations or such compositions are found to be effective in decontaminating said food items.

[0074] Buffered acidic solutions, such as may be achieved with weak organic acids such as acetic, citric, tartaric, or mandelic, are optionally used to prepare the transition metal preparation, since the solubility of iron and copper are increased at acidic pH, and since an acidic pH can also function as a stress inducer. The exact pH and acid used will depend to some extent on the suitability of acid conditions to the application in question. A large number of ligands are also known, to those skilled in the art, for the solubilization of iron, e.g. citrate, fumarate. It may also be particularly useful for solutions to be hypo-osmotic (e.g. prepared in pure water), since it is disclosed here that iron or copper overload sensitizes microbial cells to the stress of hypo-osmotic shock. Since reduced iron and copper in solution are subject to oxidation and subsequent precipitation, compositions requiring the reduced form of the transition metals preferably include powdered preparations that are stored in dry form and solubilized immediately prior to use.

[0075] Many food products possess complex surfaces involving barriers of grease, oils, or waxes under which pathogenic bacteria may be sequestered. These complex surfaces can also interfere with the contact of transition metal and/or stress inducer solutions with target microbes. Consequently, formulations for use in the methods of the present invention optionally include one or more

solvents, soaps, emulsions, detergents, foaming agents, or other means known to those skilled in the art for breaking down hydrophobic films. Optionally, physical methods such as the use of high-pressure sprays, sonication, or heated solutions are used to reduce and/or permeabilize water-impermeable layers. Contaminating bacteria are also often found in crevices and pores on foods, which can be an obstacle to the delivery of disinfectant compositions. Hence techniques for delivering formulations to such pores and crevices (e.g., high-pressure sprays, sonication, surfactants, and other means known to those skilled in the art) are optionally employed in the methods of the present invention.

[0076] Although the ingestion of moderate amounts of copper and large amounts of iron over an extended period of time may result in health problems in humans, the residues on food from the disclosed compositions and methods pose no health risk to consumers. Indeed, both iron and copper are essential for human health, and the average American typically consumes milligram quantities of iron and copper each day in food and/or dietary supplements. The safety of iron is particularly evident, since the U.S. recommended daily allowance is 18 mg (and human infant formula is routinely supplemented with even larger amounts of the element). In preferred embodiments of the present invention, the amount of iron remaining on treated surfaces of decontaminated foods will generally be far lower than the amount of iron or copper in the food itself. It is therefore not essential to remove iron or copper residues from decontaminated foods prior to packaging. However, since the residual iron may impart an unpleasant flavor, or may leave a yellow, brown, or black colored deposit upon the treated surface, the iron preparation can optionally be removed prior to packaging or consumption.

[0077] Medical and Veterinary Applications

[0078] In one embodiment of the present invention, the surface to be reduced in microbial population includes a living tissue (e.g., a plurality of host cells). The plurality of host cells includes an intact surface, such as an epidermal surface (e.g., the skin of a patient or the teat of a dairy cow), as well as damaged tissues, such as a wound, an abrasion, a burn and the like. Other living tissues include, but are not limited to, the surfaces lining an oral cavity, a vaginal cavity, an intestinal tract, and the like (e.g., mucosal surfaces). Host cells have specific systems to manage exposure to changes in transition metals in the environment. For example, in higher organisms such as man, iron and other transition metals are present in a bound, or "protected," form (either in carrier/storage proteins such as ferritin, lactoferrin and transferrin, or in the active site of redox proteins such as catalase), and as such are not capable of catalyzing destructive reactions and generally wreaking havoc in the cell. However, bacteria and other microbes do not have mechanisms for dealing with excess transition metals. The methods of the present invention take advantage of the ability of the plurality of host cells (for example, a skin surface of a human) to manage "transition metal overload" better than microbial cells.

[0079] The skin is the first line of defense in protecting one's body from microbial infection. The outermost surface of the skin is comprised of squamous epithelial cells, which are continuously being removed (sloughed off) as new cell growth occurs. Damaged skin (e.g., a wound, an abrasion, a

bum, or a damaged region of tissue) provides a portal through which invading microbes can potentially enter. The methods and compositions of the present invention can be used to reduce the populations of microbes in these regions, thus reducing the possibility of infection.

[0080] Disinfectants commonly used for the cleaning of epidermal surfaces and/or damaged tissues such as wounds are typically non-selective. While effective, iodine, hydrogen peroxide, soap, and other disinfectants often destroy host cells along with pathogens. Multicellular organisms (such as humans) can tolerate the killing of a certain percentage of "host cells" in a wound, which is preferable to the unchecked growth of bacterial pathogens. However, since the ultimate defense of the host against infection is due to its immune system, the destruction of immune cells along with bacteria is less than an ideal solution.

[0081] The use of antibiotic-containing creams, which selectively target microbial processes and kill susceptible cells but generally are benign to the host at doses to which susceptible bacteria are sensitive has become a common first aid technique. Antibiotics, such as are ingested by humans with systemic infections, or spread topically across areas to be treated, typically work by targeting metabolic processes which are unique to bacteria, and are therefore innocuous to host cells. Antibiotics are hence distinct from disinfectants (antiseptics), both because antibiotics are generally harmless to the host, and because they target a single or a small number of metabolic processes. However, antibiotic-resistant strains of bacteria arise which overcome the specific modes of action of antibiotics. In other words, the strength of antibiotics—that they target particular and unique bacterial molecules—is also a weakness, since mutation of the genes encoding antibiotic targets may render a bacterium capable of overcoming the antibiotics. In this regard, the strength of disinfectants such as hydrogen peroxide is that they attack a broad-spectrum of molecules and thereby defy attempts by pathogens to evolve resistance.

[0082] The present invention provides methods for reducing a microbial population on a living tissue. The methods include the steps of a) providing a composition of free iron; b) providing a stress inducer (optionally, a non-oxidant stress inducer); and c) bringing the living tissue into contact with the free iron and the stress inducer, thereby reducing the microbial population on the living tissue. These methods have the advantage of selectively harming the microbial cells while not interfering with host cell growth (similar to an antibiotic) while retaining the ability to affect more than one type of microbe (similar to a disinfectant), thus providing novel mechanism to reduce the population of microbes on a living tissue.

[0083] Any number of transition metals can be employed in the methods of the present invention, but a particularly preferred transition metal is iron. The transition metal (or combination of transition metals) is provided, for example, as a salt, an organic complex, or a combination thereof. Exemplary salts and/or organic complexes include, but are not limited to, acetate, ammonium citrate, ammonium oxalate, ammonium sulfate, bromide, chloride, citrate, fluoride, fumarate, hydroxide, iodide, nitrate, oxide, phosphate, pyrophosphate, sulfate, and tartrate. The metal salt and/or organic complex can be prepared in water, or it can be prepared in a formulation (e.g., a buffer) suitable for the

intended use. Optionally, the iron formulation is prepared in water or a hypo-osmotic saline solution.

[0084] The transition metal can also be combined with one or more oxidant or non-oxidant stress inducers. Preferred stress inducers for use in the methods of treating a living tissue include, but are not limited to, halides (e.g., iodine), organic solvents such as ethanol, the oxidant stress inducer H_2O_2 , and the non-oxidant stress inducers lysozyme (and other lytic enzymes), polysaccharides (e.g., chitin, chitosan), soap, detergent, and other surfactants. Optionally, other stress inducers, such as physical disinfectants (e.g., osmotic shock), can also be employed, either as the primary stress inducer or in conjunction with an additional stress inducer.

[0085] The surfaces can be treated, for example, prior to contact with a living tissue (e.g., before milking a cow), prior to an invasive process (e.g., before a surgical procedure), or after the living tissue has been damaged (e.g., as part of a treatment regime for a wound). Contacting the living tissue with the free iron and stress inducer can be accomplished by any of a number of techniques as described previously, including spraying and dipping. Alternatively, the free iron and stress inducer can be applied to a matrix or other medium for transporting and/or retaining the preparation against the surface to be treated. For example, the preparation can be applied to a mop, a sponge, a cloth, a bandage, a gauze, or other material to be placed against a wound. One of skill in the art would note that the sponges or gauzes used for such a medical application differ in their synthesis and chemical composition from a sponge or cloth used for another, non-medical application (such as cleaning a countertop).

[0086] A range of concentrations of free iron can be employed in the methods for reducing a microbial population on a living tissue. For example, the free iron can be provided at a concentration as low as about $0.1 \mu M$ to as high as about $1 M$ free iron. Optionally, the concentration of free iron is between about $0.1 \mu M$ and about $100 mM$ free iron, preferably about $1 \mu M$ to $10 \mu M$ free iron. The living tissue to be treated is exposed to the free iron and/or stress inducer for a length of time sufficient to decrease the microbial population. This sufficient length of time is easily determined by one practicing the methods of the present invention. For example, the living tissue can be exposed for as short a time period as 5 seconds, or the amount of time that it would take to swipe a skin surface or a cow teat with a preparation of the free iron. Alternatively, the free iron can be applied to the living tissue and left there (i.e., not specifically removed or washed away after treatment of the surface). Times of exposure between these two extremes are also contemplated in the methods of the present invention, as described in greater detail in previous sections. The free iron and the stress inducer can be coadministered, or they can be applied to the surface sequentially. Optionally, the free iron can be applied first, and subsequently removed prior to bringing the surface into contact with the stress inducer. In this embodiment, for example, approximately 50%, 75%, 90%, 95%, 98%, 99%, 99.5%, or substantially all of the free iron is optionally removed. The optimum concentrations and exposure durations can be determined empirically for the living tissue to be treated (e.g., taking into account the type of living tissue, physical characteristics of the surface (e.g., whether it is damaged, extent of damage), and extent of exposure the living tissue can withstand).

156
~~156~~

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C.,

Abogado
JUAN PABLO CADENA SARMIENTO

ASUNTO	Radicación	05079289
	Trámite	002
	Evento	001
	Actuación	430
	Oficio	
	Folios	029 9914

Patente de Invención	☒	Patente de Modelo de Utilidad	☐
Vía Nacional	☐		
Vía PCT (fase nacional)	☒	Cap. I	☒
		Cap. II	☐

No. Sol. Internacional	PCT/US2004/003842
Fecha de Presentación Internal.	11-02-2004

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

Documentos estudiados

<u>Descripción:</u>	Folios: 35 a 60	(como se radicó inicialmente)
<u>Reivindicaciones:</u>	Folios: 61 a 63	(como se radicó inicialmente)
<u>Prioridad:</u>	Folios 1 (11-02-2003, US10/364,241).	

Objeto de la invención

- Título de la solicitud: COMPOSICIÓN ORAL QUE CONTIENE ENZIMAS CON ESTABILIDAD MEJORADA.

El objeto de la presente solicitud de patente de invención consiste en:

Una composición para el cuidado oral con propiedades mejoradas en términos de higiene oral y contra la placa.

Reivindicaciones 1-16 : Una composición para el cuidado oral con estabilidad mejorada y efectividad contra la placa que incluye un vehículo oralmente aceptable que contiene :

- Una enzima.
- Cloruro de cetilpiridinio
- Un agente reductor.

Reivindicaciones 17-32: Un método para lograr una mejor estabilidad de una composición oral que contiene enzimas, el cual consiste en preparar una composición conformada por un vehículo oralmente aceptable que contiene:

- Una enzima.
- Cloruro de cetilpiridinio.
- Un agente reductor
- y luego aplicar la composición a la cavidad oral.

Reivindicaciones 33-37: Un método para la preparación de una composición acuosa para el cuidado oral que contiene un compuesto enzimático estable, el cual consiste en :

- Primero disolver la enzima en una solución acuosa de cloruro de cetilpiridinio y un agente reductor.
- ó en preparar una premezcla y luego agregar la mencionada premezcla al vehículo de la composición para el cuidado oral.

El problema planteado en esta solicitud es la necesidad de proporcionar una composición oral con una mayor estabilidad y efectividad contra la placa.

Para solucionar este problema técnico la solicitud en estudio proporciona una composición oral que contiene cloruro de cetilpiridinio , un agente reductor y enzimas.

El objeto de la invención definido anteriormente se clasificó de acuerdo con la Clasificación Internacional de Patentes (IPC): A61K7/16; A61K7/22, A61K7/28.

De la solicitud de Patente

Reivindicaciones (artículo 30 D 486)

El método de la reivindicación 17 y sus dependientes 18-32 no es claro ya que se reivindica un " método para lograr una mejor estabilidad" por la manera como se prepara la composición. Sin embargo no es correcto reclamar de esta manera ya que el lograr una mejor estabilidad es el resultado que se espera alcanzar con la preparación de las composiciones que se reclaman en la actual solicitud.

Determinación del Estado de la Técnica

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es 11-02- 2003, se consultaron las bases de datos y los archivos con que cuenta la entidad con fecha de publicación anterior y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

N°	Documento	Título	Fecha de Publicación
D1	CO 04122181	DENTRIFICO ANTIBACTERIAL QUE EXHIBE PROPIEDADES EN CONTRA DE LA PLACA Y PARA REFRESCAR EL ALIENTO MEJORADAS	03-12-2004*
D2	US5624906	ORAL HYGIENE COMPOSITIONS COMPRISING HETEROATOM CONTAINING ALKYL ALDONAMIDE COMPOUNDS.	29-04-1997
D3	US5814304	STABLE AQUEOUS ABRASIVE PEROXIDE TOOTH WHITENING DENTRIFIQUE	29-09-1998
D4	US2002/0015697	BIOCIDAL METHODS AND COMPOSITIONS	07-02-2002

* Corresponde a la fecha de presentación en fase nacional con fecha de prioridad del 10-05-2002

Análisis de patentabilidad (artículo 14 D486)

Novedad (artículo 16 D486)

Respecto a la solicitud en estudio:

La reivindicación 1 dice : Una composición para el cuidado oral con estabilidad mejorada y efectividad contra la placa que incluye un vehículo oralmente aceptable que contiene :

- Una enzima.
- Cloruro de cetilpiridinio
- Un agente reductor.

La reivindicación 17 dice : Un método para lograr una mejor estabilidad de una composición oral que contiene enzimas, el cual consiste en preparar una composición conformada por un vehículo oralmente aceptable que contiene:

- Una enzima.
- Cloruro de cetilpiridinio.
- Un agente reductor
- y luego aplicar la composición a la cavidad oral.

Respecto al Estado de la Técnica:

D1 divulga composiciones dentríficas antibacteriales que exhibe propiedades en contra de la placa y para refrescar el aliento, que contienen una enzima, cloruro de cetilpiridinio y un agente reductor.

Las características **esenciales** de la composición de la reivindicación 1 y del método para lograr una mejor estabilidad de la composición oral de la reivindicación 17 ,habían sido divulgadas previamente en D1, es decir: Una enzima la papaína, la glucoamilasa(Folio141 , página 9, línea 9 y línea 22) , cloruro de cetilpiridinio (como un agente antibacterial, Ver folio 138, página 5, líneas11-12) y un agente reductor (gluconato de sodio, Bisulfito de sodio, galatas de metal, estanato de sodio y ácido ascórbico (Folio 146 , página 16,líneas 16-21). Por lo cual la reivindicación no es nueva.

Adicionalmente :

La concentración del agente antibacterial se encuentra entre el 0.1 al 1.5 % y preferiblemente de 0.3 a 1.2% por peso. (Ver folio 139, página 6, líneas 6-9)

La papaína es incluida en una concentración del 0.1 al 10% en peso , más preferiblemente de alrededor del 0.5 a alrededor del 5% en peso. (Ver folio 141, página 9, líneas 13-14)

La glucoamilasa es incluida en una concentración del 0.001% al 2% en peso , más preferiblemente del 0.01 al 0.55 % por peso. (Ver folio 142, página 10, líneas 1-2).

El agente reductor como el gluconato de sodio se encuentra entre el 0.01 y el 1% , más preferiblemente ente el 0.1 al 0.5 % y Bisulfito de sodio, galatas de metal, estanato de sodio y ácido ascórbico se encuentran entre el 0.03 y 2.0 % más preferiblemente entre el 0.1 y 0.75 % (Ver folio 146, página 16, líneas 17-23)

Entre los agentes espesantes así como celulosas son incorporadas en la composición dentrífica . (Ver folio 144, página 12, líneas 25-26 y folio 145, página 13, líneas 1-2) .

Por lo tanto las reivindicaciones dependientes 2 – 7, 10-11, 13 y las reivindicaciones 18-23, 26-27, 29 no mencionan alguna característica que haga nueva a la composición de la reivindicación 1 y el método de la reivindicación 17 , por lo cual se considera que no son nuevas.

D2 enseña composiciones para higiene oral dentro de las que incluye, dentríficos y enjuagues bucales. Dichas composiciones comprenden una enzima, cetilpiridinio cloruro y un agente reductor.

Las características **esenciales** de la composición de la reivindicación 1 y del método para lograr una mejor estabilidad de la composición oral de la reivindicación 17 , habían sido divulgadas previamente en D1, es decir: Una enzima la papaína, (Folio 149A , columna, 38, línea 50) , cloruro de cetilpiridinio (como un agente antibacterial, Ver folio 149 , columna 36 , línea 24) y un agente reductor (como EDTA , BHT, vitamina E , ácido ascórbico, Folio 150, columna 39, líneas 18-19, 25, 51-52; Folio 150 A , columna 41, líneas 51-52). Por lo cual la reivindicación no es nueva.

Adicionalmente :

La concentración del agente antibacterial se encuentra entre el 0 al 5 % . (Ver folio 149, columna 36, líneas 28-30) .

Las enzimas se encuentran en una concentración del 0 al 3% en peso (Ver folio 150A, columna 41, líneas 15-16)

El agente reductor como el EDTA se encuentra entre el 0% y el 6% (Ver folio 150, columna 39, líneas 41-42).

Entre los agentes espesantes se encuentra la carboximetilcelulosa (Ver folio 148A , columna 18, línea 55)

El agua se encuentra entre el 0-95% y más preferiblemente entre el 45% y el 90% (Ver folio 149A, columna 38, líneas 16-22)

Por lo tanto las reivindicaciones dependientes 2 – 4, 7, 10-16 y las reivindicaciones 18-20, 26-32 no mencionan alguna característica que haga nueva a la composición de la reivindicación 1 y el método de la reivindicación 17, por lo cual se considera que no son nuevas.

La reivindicación 33 dice: "Un método para la preparación de una composición acuosa para el cuidado oral que contiene un compuesto enzimático estable, el cual consiste en:

- Primero disolver la enzima en una solución acuosa de cloruro de cetilpiridinio y un agente reductor.
- ó en preparar una premezcla y luego agregar la mencionada premezcla al vehículo de la composición para el cuidado oral.

D2 enseña que los ingredientes activos pueden ser añadidos como una premezcla al agua (vehículo).

Por lo tanto las características técnicas esenciales del método de la reivindicación 33 ya eran conocidas en D2 (Ver folio 151A, columna 45, líneas 58-65) por lo cual la reivindicación no es nueva.

Las reivindicaciones dependientes 34-37 no mencionan alguna característica que hagan nuevo el método de la reivindicación 33, por lo cual se considera que no son nuevas.

Nivel inventivo (artículo 18 D486)

La reivindicación 8 dice: "La composición de la reivindicación 1, donde el agente reductor es estanato de potasio.

La reivindicación 24 dice: "El método de la reivindicación 17, donde el agente reductor es estanato de potasio".

El documento del estado de la técnica más cercano es D2

La solicitud se diferencia de D2 en el agente reductor utilizado.

El Efecto Técnico que logra la diferencia es proporcionar una composición oral con una mayor estabilidad y efectividad contra la placa.

El Problema Técnico Objetivo de esta solicitud es proporcionar una composición antiplaca con estabilidad mejorada alternativa.

D3 divulga una composición de un dentífrico acuoso estable que comprende agentes quelantes. Entre los agentes quelantes se incluyen el estanato de sodio y potasio (Ver folio 153, columna 4, líneas 21-23)

Para el experto en la materia en vista del Estado de la Técnica en su totalidad, es decir en vista de D2 y D3, hubiera sugerido sin mucho esfuerzo de su parte modificar los agentes reductores divulgados en D2 por los agentes quelantes divulgados en D3 con el fin de mejorar la estabilidad de la enzima y así obtener la

composición de oral reclamada.

De manera que la solución propuesta al problema técnico planteado en esta solicitud en la reivindicación 8 y 24, es obvia y no tiene Nivel Inventivo.

La reivindicación 9 dice: “La composición de la reivindicación 1 , donde el agente reductor es sulfato de amonio”.

La reivindicación 25 dice : “El método de la reivindicación 17 , donde el agente reductor es sulfato de amonio”.

El documento del estado de la técnica más cercano es D2

La solicitud se diferencia de D2 en el agente reductor utilizado.

El Efecto Técnico que logra la diferencia es proporcionar una composición oral con una mayor estabilidad y efectividad contra la placa.

El Problema Técnico Objetivo de esta solicitud es proporcionar una composición antiplaca con estabilidad mejorada alternativa.

D4 enseña composiciones orales que contienen agentes secuestrantes de metales .
Entre ellos se encuentran el sulfato de amonio (Ver folio 155, página 9, párrafo [0083].

Para el experto en la materia en vista del Estado de la Técnica en su totalidad, es decir en vista de D2 y D4, hubiera sugerido sin mucho esfuerzo de su parte modificar los agentes reductores divulgados en D2 por el sulfato de amonio divulgado en D4 con el fin de mejorar la estabilidad de la enzima y así obtener la composición de oral reclamada.

De manera que la solución propuesta al problema técnico planteado en esta solicitud en la reivindicación 9 y 25, es obvia y no tiene Nivel Inventivo.

Conclusión:

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

Nº	Documento Nº	Reivindicaciones afectadas	Requisito que afecta
D1	CO 04122181	1 – 7,10-11,13,17-23,26-27,29	Novedad
D2	US5624906	1-4,7,10-20,26-37 8-9,24-25	Novedad Nivel inventivo
D3	US5814304	8,24	Nivel inventivo
D4	US2002/0015697	9,25	Nivel inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.

ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha
22 ABO. 2009

Dr.

CONCEPTO TÉCNICO No. 2783	EXAMINADOR TÉCNICO Código No. 202075
-------------------------------------	--