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Señora

JEFE DE DIVISIÓN DE NUEVAS CREACIONES

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

E. S. D.

REF: Expediente No. 04 098 267 – solicitud de patente de invención a favor
de COLGATE-PALMOLIVE COMPANY

Respuesta a oficio No. 875 del 25 de enero de 2008

JUAN PABLO CADENA SARMIENTO, portador de la tarjeta profesional No. 57.492 del C.S.J., obrando como apoderado de la sociedad COLGATE-PALMOLIVE COMPANY según lo acredita el documento de poder presentado en esa División, me permito dar respuesta a las observaciones de carácter técnico y jurídico, relacionadas con la patentabilidad, para la concesión de la patente de acuerdo con la Decisión 486 según el concepto técnico No. 0035 notificado por fijación en lista de fecha 25 de enero de 2008.

En cuanto a las objeciones señaladas por el señor examinador frente a la descripción de la presente solicitud, se le remite al "Breve Sumario de la Invención". En la parte final de dicha sección, la solicitud claramente describe como se realizaron pruebas comparativas frente a un control conocido en el arte, demostrando la eficiencia de los compuestos allí reivindicados y la sinergia que se logra al combinar iones de zinc y iononas con cloruro de cetilpiridinio. Así las cosas, la objeción no es procedente puesto que claramente se demuestra el efecto inesperado de la presente solicitud frente a composiciones reveladas previamente.

En atención a la objeciones del señor examinador se presenta un nuevo capítulo reivindicatorio con 1 - 13 reivindicaciones, las cuales no adicionan materia nueva ni extienden el alcance de la solicitud como se presentó originalmente, y reemplazan completamente el capítulo reivindicatorio presentado anteriormente. En dicho capítulo reivindicatorio se han eliminado las reivindicaciones 14 y 15 por ser reivindicaciones de uso, acatando lo solicitado por el señor examinador. Así mismo, en la reivindicación 6 del capítulo reivindicatorio original se ha precisado la definición de la ionona, aclarando que la ionona mencionada es una irona. Por lo tanto, se ha hecho la debida modificación en busca de precisar la definición de la ionona, acatando lo solicitado por el señor examinador. Por otro lado, la reivindicación 4 ha sido incorporada a la reivindicación 1 para resaltar la adición de la cetona de terpeno de ionona como un elemento esencial de la presente solicitud que le proporciona su efecto inesperado e inventivo. Igualmente, acatando lo solicitado por el señor examinador, la reivindicación 13 ha sido modificada para así reivindicar la composición en su su presentación final.

Con referencia a las objeciones expuestas por el señor examinador respecto a la novedad y al nivel inventivo de la presente invención, nos permitimos presentar los siguientes argumentos:

El señor examinador cita que la anterioridad WO 90/15592 (D1) y WO 00/51559 (D2), afectan la novedad de la presente invención. Así mismo, cita la anterioridad US 4,659,214 (D3) la cual, en su concepto, afecta la altura inventiva de la solicitud en estudio. Con respecto a las objeciones señaladas frente a la novedad de la presente solicitud cabe resaltar que en ninguno de los documentos mencionados se revela la combinación de la cetona de terpeno de ionona con cloruro de cetilpiridinio y iones de zinc para formar un enjuague bucal antimicrobiano que controla el mal aliento superior a lo conocido en el arte, como se demuestra en los estudios comparativos en el capítulo descriptivo. Claramente, D1 y D2 se limitan a revelar composiciones que comprenden sales o iones de zinc con cetilpiridinio y en ningún momento

112

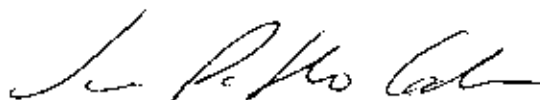
contemplan combinar dichos componentes con cetonas de terpeno de ionona o de irona para así obtener una sinergia de componentes que proporcionan un efecto antibacteriano, contra el mal aliento, inesperado y superior frente al arte conocido. Por otro lado, D3 se limita a revelar sales de zinc combinadas con cetona de terpeno de ionona; en dicho documento no se contempla la posibilidad de utilizar el cloruro de cetilpiridinio en combinación con los componentes mencionados para obtener la composición reclamada en la presente solicitud. Así las cosas, está claro que ninguno de D1, D2 o D3 revelan la composición reclamada en la presente solicitud, por lo cual la misma es claramente novedosa frente a lo conocido en el arte.

En cuanto a la altura inventiva objetada por el señor examinador, el solicitante se permite presentar los siguientes argumentos. Esta claro que el análisis realizado por el señor examinador se lleva a cabo en retrospectiva, sin considerar que nada en las anterioridades citadas sugiere al experto medio en la materia el combinar una cetona de terpeno de ionona con cloruro de cetilpiridinio y compuestos de zinc puesto que no habría manera de predecir la sinergia antibacteriana -el efecto inesperado- obtenida con esta combinación sin realizar los debidos estudios comparativos frente a composiciones conocidas. No existe motivación en D1, D2 o D3 para que el experto en la materia tome lo revelado en dichas anterioridades, anticipando que existe un potencial de mejorar los enjuagues bucales conocidos en el arte, y lleve a cabo la combinación de componentes revelada en la presente solicitud, realizando los debidos estudios y llegando a una composición antibacteriana superior a los enjuagues bucales conocidos que comprenden los compuestos mencionados en distintas combinaciones. En efecto, se debe reconocer la actividad inventiva del solicitante al llevar a cabo dichos estudios comparativos, descritos detalladamente en la presente solicitud; dado los resultados favorables de dichos estudios, el inventor está en todo su derecho de reivindicar la composición allí descrita, la cual deber ser tendiente a obtener privilegio de patente de invención.

En vista de lo anterior, respetuosamente solicitamos el retiro de las objeciones a la presente solicitud, sobre la base del nuevo capítulo reivindicatorio y los argumentos presentados ya que, en opinión del solicitante, la presente invención cumple con los requisitos de claridad así como los de novedad, altura inventiva y aplicabilidad industrial de la Decisión 486.

De la Señora Jefe,

Atentamente,



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Bogotá, abril 18 de 2008

MEV/JCN

anexos

5
114

REIVINDICACIONES

Reivindicamos:

1. Una composición oral sinérgica que controla el olor del aliento de compuestos volátiles de azufre, que comprende un compuesto de zinc atóxico y cloruro de cetilpiridinio, siendo la proporción de iones de zinc a cloruro de cetilpiridinio de 1.000:1 a 2:1 en peso, y cetona de terpeno de ionona, estando presente compuesto de zinc en la cantidad de 0.01 a 5% en peso, estando presente dicho cloruro de cetilpiridinio en una cantidad de de 0.0005 a 3% en peso y estando presente dicha cetona de ionona en una cantidad de 0.0005% a 2% en peso.
2. Una composición oral como en la reivindicación 1 en donde dicho compuesto de zinc está presente en una cantidad de de 0.02 a 2% en peso de compuesto de zinc, y el cloruro de cetilpiridinio está presente en cantidades de de 0.001 a 1% en peso.
3. Una composición oral como en la reivindicación 2 en donde dicho compuesto de zinc se selecciona del grupo conformado por cloruro de zinc y acetato de zinc.
4. Una composición oral como en la reivindicación 1 en donde dicho compuesto de zinc está presente en una cantidad de 0.02 a 2% en peso; dicho cloruro de cetilpiridinio está presente en una cantidad de 0.001 a 1 % en peso y dicha ionona está presente en una cantidad de 0.001 a 1% en peso.
5. Una composición oral como en la reivindicación 1 en donde dicha cetona de terpeno de ionona se selecciona del grupo conformado por alfa-ionona, beta-ionona, gamma-ionona, dihidro-ionona, alfa-metilionona e irona.

115

6. Una composición oral como se reivindica en la reivindicación 5 en donde dicha ionona de terpeno de cetona es alfa-ionona.
7. Una composición oral como se reivindica en la reivindicación 1 en donde dicho compuesto de zinc se selecciona del grupo conformado por cloruro de zinc y acetato de zinc.
8. Una composición oral como se reivindica en la reivindicación 4 en donde dicho compuesto es cloruro de zinc.
9. Una composición oral como se reivindica en la reivindicación 1 en donde dicha composición comprende una porción líquida, que comprende agua y humectante, y una porción sólida que comprende un agente gelificante y dicha composición oral es un dentífrico.
10. Una composición oral como en la reivindicación 1 en donde dichos derivados de terpeno de cetona de ionona están presentes en un componente de un aceite saborizante en cantidades de 0.5 a 1% en peso de dicho aceite saborizante.
11. Una composición oral como en la reivindicación 10 en donde dicho aceite saborizante es aceite de hierbabuena, el cual aceite de hierbabuena está presente en dicha composición oral en cantidades de 0.005 a 2% en peso.
12. Una composición oral como en la reivindicación 1 en donde dicha composición comprende composiciones de alcohol acuoso, en donde dicho alcohol es un alcohol alifático inferior, atóxico.
13. Una composición oral como en la reivindicación 1 la cual es un enjuague bucal o aerosol bucal.

1161
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : A61K 7/22	A1	(11) International Publication Number: WO 90/15594 (43) International Publication Date: 27 December 1990 (27.12.90)
(21) International Application Number: PCT/AU90/00255 (22) International Filing Date: 12 June 1990 (12.06.90) (30) Priority data: PJ 4645 12 June 1989 (12.06.89) AU (71)(72) Applicant and Inventor: SHANAHAN, Patrick, John [AU/AU]; 5/12 Victoria Avenue, Claremont, W.A. 6010 (AU). (74) Agents: SLATTERY, John, Michael et al.; Davies & Collis- on, 1 Little Collins Street, Melbourne, VIC 3000 (AU).		(81) Designated States: AT (European patent), AU, BE (European patent), CA, CH (European patent), DE (European patent)*, DK (European patent), ES (European patent), FR (European patent), GB (European patent), I (European patent), JP, LU (European patent), NL (European patent), SE (European patent), US. Published <i>With international search report.</i>
(54) Title: ANTI-PLAQUE DENTIFRICE (57) Abstract A non-abrasive dentifrice gel comprises an effective antibacterial amount of a combination of a zinc salt such as zinc chloride and a quaternary ammonium compound such as cetylpyridinium chloride, and a gelling agent.		

117

The zinc salts which may be used in the gel composition of this invention include any water soluble zinc salt such as zinc chloride, zinc acetate, zinc sulphate, and the like. Other less soluble zinc salts such as zinc fluoride and zinc citrate may also be used. Preferably, the zinc salt is zinc chloride. The zinc salt may be included in the gel composition in an amount of from about 0.1 to 5% by weight. Preferably, zinc chloride is added in an amount of from 0.2 to 0.25% by weight, more preferably an amount of about 0.22% by weight.

Suitable quaternary ammonium compounds for inclusion in the gel composition of the present invention include (C₈-18) alkyl pyridinium chlorides and (C₈-18) alkyl pyridinium bromides. Particularly preferred is cetyl pyridinium chloride (CPC). The quaternary ammonium compound may be incorporated in the gel composition in amounts in the range of 0.01 to 0.5% by weight. Preferably, the gel composition includes CPC in an amount of 0.01 to 0.1% by weight, more preferably an amount of about 0.05% by weight.

The gel composition of this invention also includes a gelling agent. Preferably, this gelling agent is a non-ionic gelling or thickening agent such as the natural or synthetic gums including hydroxyethyl cellulose, hydroxymethyl cellulose, and the like. The gelling agent may be used in amounts in the range of 0.5 to 5% by weight. Preferably, the gelling agent is hydroxyethyl cellulose in an amount of 2 to 4% by weight, more preferably an amount of about 2.5 to 3% by weight.

The gel composition may also include suitable fluoride-providing compounds including, by way of example, soluble inorganic fluoride salts such as sodium or potassium fluoride and sodium monofluorophosphate.

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

118 117

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : A61K 7/16, 7/22	A1	(11) International Publication Number: WO 00/51559 (43) International Publication Date: 8 September 2000 (08.09.00)
(21) International Application Number: PCT/NO99/00346 (22) International Filing Date: 16 November 1999 (16.11.99) (30) Priority Data: 19990975 1 March 1999 (01.03.99) NO (71) Applicant (for all designated States except US): ORIX AS [NO/NO]; Caroline Overlands Vei 12a, N-1356 Bekkestua (NO). (72) Inventor, and (75) Inventor/Applicant (for US only): RÖLLA, Gunnar [NO/NO]; Bygdøy Allé 56a, N-0265 Oslo (NO). (74) Agent: GÖRBITZ, Johan, H.; Bryn & Aarflot AS, P.O. Box 449 Sentrum, N-0104 Oslo (NO).		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: ORAL COMPOSITION FOR INHIBITING ORAL MALODOR (57) Abstract Oral composition for inhibiting oral malodor, containing an antibacterial agent and a zinc compound, in the form of a mouthwash containing 0.005–0.05 % w/v of an antibacterial agent selected from bis-guanides and quaternary ammonium compounds, and 0.05–0.5 % w/v of zinc acetate.		

Oral composition for inhibiting oral malodor.

119

The present invention relates to an oral composition which is effective against halitosis (oral malodor, foetor ex ore). Said composition is effective by eliminating or reducing the production of volatile sulfur compounds (VSCs) in the oral cavity. It is well established that in the majority of cases of halitosis this originates from the oral cavity and not from the stomach, as frequently believed by the public.

Bacteria located in the crypts at the back of the tongue and in periodontal pockets produce VSCs, mainly hydrogen sulfide (HS) and methyl mercaptan (MM). The bacteria produce these by proteolytic, anaerobic metabolism, and they have an extremely unpleasant odor even in very low concentrations. The VSCs are able to penetrate epithelium and have pathogenic potentials by damaging cells of the underlying tissues and also affect their metabolism. It has been suggested that the VSCs produced by bacteria in periodontal pockets may well be an important factor in the development of periodontal disease. MM appears to have a higher pathogenic potential than HS and has also a more offensive odor.

The most important substrate for HS production in the oral cavity appears to be cysteine. HS forms immediately upon rinsing the mouth with an aqueous solution of this amino acid (see example 2). Methionine is a major substrate for MM formation, although this compound is not as rapidly formed in the oral cavity as hydrogen sulfide.

~~It is known that zinc ions reduce the VSC production in the oral cavity.~~
The mechanism involved presumably involves a reaction between zinc and sulfur whereby non-volatile sulfides are formed and thus inhibit the transformation of sulfur containing substrates to VSCs. Zinc furthermore possesses a certain antibacterial activity and this metal ion is known to be able to inhibit plaque formation and reduce acid formation in dental plaque. The zinc salts usually used for such purposes are the chloride, the sulfate and the citrate. However, aqueous solutions of the two former salts have low pH and are thus, not necessarily suited for oral use whereas solutions of zinc citrate contain complexes of zinc and citrate and very few free zinc ions.

119
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The problem of getting zinc in a suitable form is the issue of US patent No. 4,289,753 and UK Patent Application No. 2,052,978. In the former the zinc compound used is an ammonium or alkali metal citrate. It is also stated in this patent that this zinc compound may be used in combination with antibacterial agents such as cetylpyridinium chloride.

The above UK Patent Application discloses an oral composition in which the pH of a zinc-containing solution is adjusted to 4.5 or 8 by means of glycine. The zinc is generally present as zinc chloride.

Antibacterial agents such as cationic bis-biguanides and quaternary ammonium compounds, have been widely used in preventive dentistry as inhibitors of plaque formation and of development of gingivitis. The bis-biguanide chlorhexidine is frequently used for this purpose, usually as an aqueous solution of 0.2% of its gluconate salt, and is applied as a mouthrinse twice daily. Such concentration and frequency are necessary to obtain consistent clinical plaque inhibition. However, chlorhexidine in these concentrations has a bitter taste and causes dental stain. Chlorhexidine forms salts of low solubility with chloride, sulfate and citrate and is thus not compatible with zinc containing these anions.

The other cationic antibacterial agents which inhibit plaque formation, for example cetylpyridinium chloride or benzalkonium chloride, have less clinical effect, but show a less pronounced tendency to cause dental stain. The cationic antibacterial agents mentioned above are able to inhibit VSC formation in the oral cavity, but relatively high concentrations are needed (see Example 1).

It has now unexpectedly been found that anti-VSC effect of zinc ions is mainly directed against hydrogen sulfide production and to a far lesser extent against the production of methyl mercaptan (see Example 1, Fig. 2). The VSC species with highest pathogenic potential and the most unpleasant odor i.e. MM, is thus incompletely eliminated by zinc ions.

This selective effect on HS by zinc can presumably be explained by the fact that cysteine (which is major substrate for HS formation) has an exposed -SH group, which will react readily with zinc ions, whereas methionine (which is a substrate for MM formation) has no such group. When hydrogen sulfide is dissolved in water (or saliva) HS- and S-- are formed (together with two protons), and both these sulfur containing intermediates react rapidly with zinc ions to form insoluble sulfides.

120
174

It was furthermore unexpectedly found that when a combination of zinc ions and very low concentrations of certain cationic antibacterial agents were used, the combinations inhibited both HS and MM formation. The effect of the combinations is synergistic (Example 1, table 1). The combinations of zinc and low concentrations of antibacterial agent caused a much higher inhibition of VSCs than any of the individual agents alone. The concentration of an antibacterial agent used in this way against oral malodor was markedly lower than the concentrations needed to obtain plaque inhibition or reduced acid formation in plaque (1/10 or less).

The importance of this invention resides in the fact that it allows the use of very low concentrations of antibacterial agents, i.e. concentrations where their undesired side effects are avoided. The contribution of the antibacterial agent is probably mainly to inhibit MM formation, but synergistic effect with zinc against HS was also observed, although not to the same degree as against MM. The concentration of zinc can also be kept lower than when zinc is used alone, for the same reason. Zinc has a metallic taste which is concentration dependent.

The use of combinations of zinc acetate and chlorhexidine is described in DE 30001575 A1. However, the purpose is to avoid discoloration of teeth by chlorhexidine. In US patent No. 4,522,806 an anti-plaque effect of the combination of chlorhexidine and zinc acetate is mentioned (page 5, first paragraph). The combination was found to be numerically better than chlorhexidine alone, but the difference was not statistically significant.

In US patent 5,906,811 a combination of zinc acetate and benzalkoniumchloride is mentioned as an ingredient in tooth-pastes. The main purpose is to avoid damage from free radical species on the oropharyngeal cavity of tobacco smokers, including secondary smokers.

The present invention provides an oral composition for inhibiting oral malodor, comprising an antibacterial agent and a zinc compound. The composition is in the form of a mouth wash containing 0.005 - 0.05% w/v of an antibacterial agent selected from bis-biguanides and quaternary ammonium compounds, and 0.05 - 0.5% w/v zinc acetate.

When zinc acetate is used together with an antibacterial agent selected from the bis-biguanides or quaternary ammonium compounds, the effect appears to be synergistic, as mentioned above. This means that by using such a

combination, the amount of both (i.e. zinc acetate and anti-bacterial agent) may be kept very low. By using such low amounts the bitterness of the taste and the tendency to cause dental stain will both be avoided.

A major benefit of this invention is that it allows the use of much lower concentrations of antibacterials in compositions specially designed to inhibit oral malodor, than in ordinary products intended for anti-plaque and anti-gingivitis purposes.

The low concentrations of the antibacterial agent is favorable both from an economical and toxicological point of view. The presence of zinc in itself reduces the tendency to cause dental stain, because zinc sulfide is white or gray, whereas the other metal sulfides which form on teeth are black, brown or yellow.

As mentioned above it is a great advantage that the concentrations of the two ingredients, in particular the concentration of the antibacterial agent, can be kept very low. This is particularly easy to control in a mouthrinse where the concentrations of said active ingredients can be readily adjusted to the desired value. According to a particularly preferred embodiment the oral composition of the invention is in the form of a mouthrinse containing from 0.01% to 0.025% w/v of the antibacterials and 0.1% to 0.3% w/v of zinc acetate.

As mentioned above, a preferred antibacterial agent is chlorhexidine or a salt thereof, in particular the acetate or the gluconate salts. Preferred quaternary ammonium compounds are cetyl pyridinium chloride or benzalkonium chloride.

According to another embodiment of the invention a composition comprising an antibacterial agent selected from the bis-biguanides and the quaternary ammonium compounds, ~~and zinc acetate~~, is used for the preparation of an oral composition in particular in a mouthrinse, for inhibiting oral malodor.

In a further embodiment of the invention a composition containing an antibacterial agent selected from bis-biguanides an quaternary ammonium compounds, and zinc acetate, is used for the treatment of oral malodor. In the use indicated above, the amounts of the components should be as described above in connection with the oral composition.

127

Example 1

In vitro experiments were performed to test the VSC-inhibiting potential of different combinations of zinc acetate and cationic antibacterial agents.

5 To a 1 ml sample of freshly collected human saliva in a test tube was added 10 microliter of the solutions (mouthrinses) described below. The test tubes were closed with a stopper and incubated overnight at 37°C. A control tube which contained only saliva served as a control. It is well known that large amounts of VSCs are formed in a test tube during the latter conditions, the
10 bacteria breaking down the salivary proteins and forming VSCs from cysteine and methionine. The VSCs in the gas phase above the incubated saliva, were measured by gas chromatography in a Shimadzu 14B instrument, and hydrogen sulfide, methyl mercaptan and di-methyl sulfide were used as standard.

The solutions to be tested were: 0,3% zinc acetate, 0.025%
15 chlorhexidine, 0.025% cetylpyridinium chloride and 0.025% benzalkonium chlorides. Subsequently the zinc acetate was combined with each of the individual antibacterial agents. All the experiments described in this paragraph were performed on the same day under identical conditions. The concentrations chosen were based on experience from pilot experiments with different
20 concentrations of the zinc and antibacterial agents. The results can be seen from the chromatograms in figures 1-8, and from table 1 below.

The experiments showed that the control contained very high amounts of both hydrogen sulfide (HS) and methyl mercaptan (MM), whereas the samples which contained zinc had low amounts of both HS and MM. It was, however,
25 found that the zinc acetate reduced the amount of HS much more than the amount of MM. This effect was seen in many experiments with saliva from different subjects.

Addition of chlorhexidine had a clear effect on both HS and MM in the same order of magnitude as zinc acetate. The other antibacterials were
30 effective, but much less so than chlorhexidine or zinc. However, when combinations of zinc acetate and the different antibacterials were tested, a clear further reduction in VSCs was observed, both for HS and MM. It can be seen that chlorhexidine was not better than the other antibacterials in these experiments.

124

An examination was conducted to investigate whether the effect of the combinations of zinc acetate and the individual antibacterial agents represented a synergistic effect. This was performed according to the method of Behrenbaum (J. Inf. Dis. 137:122-130, 1978). The fractional inhibitory concentrations (the FIC index) was calculated based on the amounts (AUC) of hydrogen sulfide and methyl mercaptan formed under different conditions. A low AUC thus indicates presence of a strong inhibitor. The FIC index was calculated from the following formula: $(A+B)/A + (A+B)/B$, where A+B represents the combinations of zinc and antibacterial agent, whereas A and B alone represent the individual agents.

If the FIC index is below 1 (<1) a synergistic effect is established. If the index is like 1 ($=1$) an additional effect between A and B is seen, whereas an index above 1 (>1) indicates an antagonistic effect. The FIC index of the different combinations is seen in Table 1. All the different combinations had synergistic effect against both HS and MM, but the effect was far stronger against MM, presumably because zinc acetate had a weaker effect against MM (table 1).

Table 1

The table contains the AUC values (amounts of VSCs) from fig. 1-8 and the FIC index* for the combinations of zinc and the individual antibacterial agents.

Fig.	Agents tested	HS	FIC index	MM	FIC index
1	Control	>27 mill		>41 mill	
2	Zinc Ac. 0.3%	150 000		4 mill	
3	CHX 0.025%	443 000		355 000	
4	CPC 0.025%	5.2 mill		6.89 mill	
5	Benzalk 0.025%	1.4 mill		1.7 mill	
6	Zinc Ac 0.3%+CHX 0.025%	82 000	0.73	34 000	0.1
7	Zinc Ac 0.3%+Benzalk. 0.025%	47 000	0.33	13 000	0.01
8	Zinc Ac 0.3%+CPC 0.025%	37 000	0.24	1 000	0.00

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AUC - area under curve

Ac - acetate

CHX - chlorhexidine acetate

Benzalk. - benzalkonium chloride

5 CPC; cetylpyridinium chloride

*A FIC index below 1 (<1) indicates a synergistic effect

HS - hydrogen sulfide

MM - methylmercaptane

10 Example 2

It has been shown that aqueous mouthrinses with 6 mM cysteine give an immediate, steep rise in VSC formation in the oral cavity. The effect can be used as a test system by observing the effect of a cysteine rinse when a prerinse with an inhibitor of oral VSC formation is performed (for instance with zinc solutions).
15 This system is described in US patent No. 5,833,955 of Kleinberg et al. (1998). By subsequent cysteine rinses each hour after for instance a zinc solution, it can be shown how long the inhibitor is effective. In the following it was shown that with 0.3% of zinc acetate and 0.025% of each of the antibacterial agents
20 chlorhexidine and cetylpyridinium chloride was effective for more than 5 hours. The experimental design described is presumably severe, and it seems likely that under "normal" conditions where no cysteine is introduced in the mouth, the duration of the effect would be expected to last considerably longer than the present results indicate. A limitation of the model is that only hydrogen sulfide is
25 formed by the test subjects upon cysteine rinses. This is clearly shown when the mouth air is analyzed by gas chromatography, as in the present study. If the frequently used Halimeter is employed for measurement, this limitation is not obvious because the Halimeter operates by chemical sensors which cannot differentiate between hydrogen sulfide and methyl mercaptan. The present
30 experiments thus show the inhibiting effect of the inhibitors on hydrogen sulfide only. However, in combination with the experiments in Example 1 (which examined the effect of the combinations on methyl mercaptan as well) the present experiments are judged to provide valid data.

126

In the present experiments the test subject rinsed with 5 ml of a 6 mM cysteine solution and the VSC in the mouth air was examined after the mouth had been kept closed for 90 sec. The subject then rinsed with a VSC inhibitor (i.e. combinations of zinc acetate and the respective antibacterial agents). After one hour the subject again rinsed with cysteine. Any reduction in VSC (i.e. hydrogen sulfide) from the original values was assumed to be caused by the inhibitor. Cysteine rinses were performed each hour for 5 hours to establish the duration of the inhibiting effect. The results of these tests are shown in the chromatograms in figures 9 and 10. Fig. 9 shows the normal hydrogen sulfide production by the test subject in the morning after a rinse with cysteine, which is 10 mill AUC. After a rinse with the combination of 0.3% zinc acetate and 0.025% of chlorhexidine acetate and a further rinse with cysteine one hour later the HS value was only 32 000 (fig. 9a), after a further hour it was 500 000 (fig. 9b), then 270 000 (fig. 9c), 1.7 mill (fig. 9d) and 1.7 mill (fig. 9e). The combination thus reduced the hydrogen sulfide production in the mouth by cysteine with more than 80% five hours after a single rinse with the combination described above.

In a similar experiment with the combination of 0.3% zinc acetate and 0.025% cetylpyridinium chloride was tested. The normal value after the cysteine rinse was 11 mill AUC of hydrogen sulfide (fig. 10). After a rinse with the combination and a cysteine rinse one hour later the HS value was as low as 22 000 (fig. 10a). After two hours it was 67 000 (fig. 10b), after three hours 315 000 (fig. 10c), four hours 275 000 (fig. 10d) and five hours 47 000 (fig. 10e).

It can be concluded that the combinations of zinc acetate and the two tested antibacterials had a very strong and long lasting effect, and that chlorhexidine was not better than cetylpyridinium chloride in combination with zinc. It is probably safe to conclude that a mouthrinse of this type would inhibit oral malodor for eight hours or more under normal conditions.

It was furthermore evident from additional experiments with the individual agents in the present experimental model, that the anti-VSC effect of the individual antibacterial agents was markedly inferior to the effect of the combinations. Synergistic effects of combinations of zinc acetate and the antibacterial agents were thus demonstrated also in the vivo model, which included hydrogen sulfide only (results not shown).

United States Patent [19]

Niles et al.

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[45] Date of Patent: Aug. 25, 1987

[54] COMPOSITION TO COUNTER BREATH ODOR

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[21] Appl. No.: 836,671

[22] Filed: Mar. 10, 1986

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 723,786, Apr. 16, 1985, abandoned.

[51] Int. Cl.⁴ A61K 7/16; A61K 7/26

[52] U.S. Cl. 424/49; 424/58; 424/145; 514/900; 514/901

[58] Field of Search 424/48-58; 426/538

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[57] ABSTRACT

A novel composition to counter by preventing and controlling breath odor containing as the essential agents, a salt which provides zinc ions, and an ionone ketone terpene derivative.

12 Claims, No Drawings

COMPOSITION TO COUNTER BREATH ODOR

This application is a continuation in part of application Ser. No. 723,786, filed Apr. 16, 1985, now abandoned.

This invention relates to novel oral formulations comprising a combination of a salt which provides zinc ions and an ionone ketone derivative as an effective material against breath odor.

The prior art is replete with oral compositions containing zinc salts such as zinc chloride, zinc iodide, zinc fluoride, zinc phenol sulfonate and the like as antiseptic agents, and correctives of oral conditions such as pyorrhea. Zinc chloride has commonly been used in oral formulations for its astringency properties. Zinc phenol sulfonate has been utilized in the prior art dentifrice compositions as an anti-plaque and anti-calculus agent as well as an odor inhibitor of fermentation and putrefaction which occurs in the oral cavity. Compositions in which these soluble zinc salts have been used have had the disadvantages such as leaving an unpleasant astringent taste in the mouth and/or having short-lived efficacy against plaque, and as an odor inhibitor.

Sparingly soluble zinc salts such as zinc citrate have been used in dentifrice formulations to prolong the anti-calculus and anti-plaque effectiveness of the zinc ions due to the slow dissolution of the zinc salts in the saliva.

The reaction product of a zinc compound and polymer has been described in U.S. Pat. No. 4,138,477 as a compound which effectively controls mouth odor. Such control can last a few hours, but generally not overnight.

The use of a zinc complex of a specified diketone as an agent for combating tartar and tooth discoloration is also known, as set forth in German Pat. No. 2,229,466. Thus, it is apparent that zinc compounds are generally known to have deodorizing properties as well as other properties desirable in oral hygiene.

Reodorant terpenes have been described in British Pat. No. 1,311,060. Such terpenes include the ketone terpenes, alpha-ionone and beta-ionone.

It is an object of this invention to provide a synergistic improvement in countering breath odor by incorporating into an oral composition a material comprising a compound which provides zinc ions and ionone.

Another object of instant invention is to provide an oral composition which is synergistically effective in countering breath odor over a prolonged period of time.

In accordance with certain of its aspects, the invention relates to an oral composition consisting essentially of a non-toxic zinc salt in amount which provides at least about 0.01 mg of zinc ions in 1 ml of water and an ionone ketone terpene derivative, the ratio of zinc ions to said ionone ketone terpene derivative being about 1,000:1 to 5:1 by weight.

The zinc compounds that provide zinc ions for use in combination with ionone may be any physiologically acceptable zinc salt including the water soluble (including sparingly water soluble) organic and inorganic zinc salts which provide at least about 0.01 mg of zinc ions per ml of water. The water-soluble zinc salts (at least 1% soluble) are preferred, especially the zinc halides and zinc acetate. Among sparingly soluble zinc salts, zinc citrate is preferred. Examples of suitable zinc salts that may be employed include:

zinc acetate	zinc fluoride
zinc ammonium sulfate	zinc formate
zinc bromide	zinc iodide
zinc chloride	zinc nitrate
zinc chromate	zinc phenol sulfonate
zinc citrate	zinc salicylate
zinc dithionite	zinc sulfate
zinc fluosilicate	zinc gluconate
zinc tartrate	zinc succinate
	zinc glycerophosphate

Other zinc salts disclosed in U.S. Pat. No. 4,138,477 having a solubility of at least about 0.01 mg of zinc ions per ml of water are incorporated herein by reference.

The zinc salt is present in amounts which provides about 0.01-5% by weight of zinc ions and preferably about 0.02-1% of zinc ions by weight in the oral composition.

The solubility of the zinc salt to provide zinc ions appears to be a factor in the activity against odor formation. However, the effect is synergistically improved when an ionone terpene ketone is present.

Ionone is a ketone terpene derivative containing one ketonic carbonyl group. The basic ionone formula is $(CH_3)_3C_6H_6CH=CHCOCH_3$. It is available as alpha-ionone (b.p. 120° C.) and beta-ionone (b.p. 135°), both of which are colorless liquids and slightly soluble in water. It is employed in oral compositions in amounts such that the ratio of zinc ions to ionone is about 1,000:1 to 10:1 by weight. Other variants of ionone such as gamma-ionone, dihydroionone and alaphamethyl ionone may also be employed. Furthermore, as used herein, the term "an ionone ketone derivative" includes isomeric forms of ionones, e.g. irone. It is convenient to employ it in oral compositions in amounts of about 0.0005-1% by weight, preferably about 0.001-1%. Alpha-ionone is preferred.

In British Pat. No. 1,311,060, it was theorized that amelioration of oral malodors by ionone may have occurred due either to an ability to block odor receptor sites in the olfactory epithelium or to low olfactory thresholds for the compound and possibly a combination of both. Regardless of the reason for the effect, however, it is not long-lasting. When reduction in breath odor is evaluated after an overnight sleep period, little, if any, reduction is found. On the other hand, when an ionone is in combination with a salt which provides zinc ions, there are synergistic effects in countering breath odor for a prolonged period.

Aqueous solutions and dispersions of control, placebo and various zinc ion-ionone materials can be tested in an in vitro system and in vivo. In the in vitro test, whole human saliva with L-cysteine as substrate is incubated for 3 hours or overnight at 37° C. in an airtight container. After incubation, the headspace volatile sulfur compound ("VSC", the main cause of offensive breath odor) formation is measured by an instrumental GC-flame photometric technique. Since breath odor has been attributed to the presence of VSC's such as hydrogen sulfide, methyl mercaptan and to a lesser extent, dimethyl sulfide, resulting from putrefactive processes occurring in the oral cavity, the in vitro test provides results comparable to in vivo sensory evaluations.

In vivo tests are done on a panel of randomly equally divided people into two groups, one of which uses a control mouthrinse against the other which uses a test mouthrinse. Initially for one week, each group rinses

with its respective mouthrinse for one minute each night before sleep. During the following week, each group rinses with the opposite product.

Baseline breath samples are obtained from each subject in order to evaluate breath during the morning after awakening but without prior brushing, rinsing, eating and drinking. Two breath samples are taken from each subject ten minutes apart during which time the subjects keep their mouths closed.

Aqueous dispersion or solutions of zinc salt-ionone material may be produced by separately adding the zinc salt in a dilute solution, a paste or in the dry state, and the ionone to water. The ionone may be conveniently and preferably included as a component added to a flavoring oil, such as oil of peppermint.

While particularly good results in terms of countering breath odor inhibition are obtained by simply applying the aqueous solutions or dispersions of the zinc salt-ionone material, it is understood that it is within the broader aspect of the invention to incorporate zinc salt and ionone material into oral compositions generally, such as clear or cloudy mouth rinses, mouth sprays and toothpastes, which contain an aqueous oral or dental vehicle, or powders which can be readily dispersed or dissolved in an aqueous vehicle. When the oral composition is a simple solution or a mouth rinse or mouth spray the zinc salt and ionone material is typically dissolved in water and a non-toxic alcohol.

The vehicle in a toothpaste, often referred to as a dental vehicle contains liquids and solids. In general, the liquid comprises water and often a humectant such as glycerine, sorbitol, propylene glycol or polyethylene glycol 400 including suitable mixtures thereof. It is usually advantageous to use a mixture of both water and one or two humectants. The total liquid content is generally about 20-90% by weight of the vehicle. The liquid content of the toothpaste generally includes about 5-40% of water. The preferred humectants are glycerine and sorbitol, for instance in amount of about 10-50% by weight.

When the oral composition is a toothpaste, the dental vehicle contains as a solid portion, a gelling agent. The gelling agent includes alkali metal carboxymethyl cellulose, carrageenans such as viscarin and i-carrageenan, gelatin, starch, glucose, sucrose, polyvinyl pyrrolidone, polyvinyl alcohol, gums such as gum tragacanth and gum karaya, hydroxypropyl cellulose, methyl cellulose, carboxyethyl cellulose, sodium alginate, Laponite CP or SP, which are each synthetic inorganic complex silicate clays sold under trademark by Laporte Industries, Ltd., and magnesium aluminum silicate gel as well as mixtures thereof. The solid portion or gelling agent of the vehicle is typically present in amount of about 0.25-10% by weight of the toothpaste and preferably about 0.5-5% by weight. Alkali metal carboxymethyl cellulose includes the lithium, sodium and potassium salts. Sodium carboxymethyl cellulose is preferred.

Any suitable substantially water-insoluble polishing agent may be added to the dental vehicle of a toothpaste. There is a relatively large number of such materials known in the art. Representative materials include, for example, dicalcium phosphate, tricalcium phosphate, insoluble sodium metaphosphate, silica, sodium aluminosilicate (silica containing combined alumina), aluminum hydroxide, magnesium carbonate, calcium carbonate, calcium pyrophosphate, calcium sulfate, bentonite, etc., including suitable mixtures thereof. It is preferred to use the water-insoluble phosphate, sodium

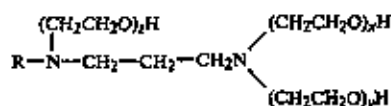
metaphosphate and/or a calcium phosphate, such as dicalcium phosphate dihydrate. In general, these polishing agents will comprise a major proportion by weight of the solid ingredients. The polishing agent content is variable, but will generally be up to about 75% by weight of the total composition, generally about 20-75%; although, even lower amounts of polishing agent can be employed.

Any suitable or compatible surface-active or detergent material may be incorporated in the dental vehicle. Such compatible materials are desirable to provide additional detergent, foaming and antibacterial properties depending upon the specific type of surface-active material and are selected similarly. These detergents are water-soluble organic compounds usually, and may be anionic, nonionic, or cationic in structure. It is preferred to use the water-soluble non-soap or synthetic organic detergents usually. Suitable detergent materials are known and include, for example, the water-soluble salts of higher fatty acid monoglyceride monosulfate detergent (e.g., sodium coconut fatty acid monoglyceride monosulfate), higher alkyl sulfates (e.g., sodium lauryl sulfate), alkyl aryl sulfonate (e.g., sodium dodecyl benzene sulfonate), methylcocoyl taurate, higher fatty acid esters of 1,2-dihydroxypropanesulfonate and the like.

Further detergent materials include the substantially saturated higher aliphatic acyl amides of lower aliphatic amino carboxylic acid compounds, such as those having 12 to 16 carbons in the acyl radical. The amino acid portion is derived generally from the lower aliphatic saturated monoamino carboxylic acids having about 2 to 6 carbons, usually the monocarboxylic acid compounds. Suitable compounds are the fatty acid amides of glycine, sarcosine, alanine, 3-aminopropanoic acid and valine having about 12 to 16 carbons in the acyl group. It is preferred to use the N-lauroyl myristoyl and palmitoyl sarcoside compounds, however, for optimum effects.

The amide compounds may be employed in the form of the free acid or preferably as the water-soluble salts thereof, such as the alkali metal, ammonium, amine and alkylamine salts. Specific examples thereof are sodium and potassium N-lauroyl, myristoyl and palmitoyl sarcosides, ammonium and ethanolamine, N-lauroyl sarcoside, N-lauroyl sarcosine, and sodium N-lauroyl glycine and alanine. For convenience herein, reference to "amino carboxylic acid compound", "sarcoside", and the like refers to such compounds having a free carboxylic group or the water-soluble carboxylate salts.

Other particularly suitable surface-active materials include nonionic agents such as condensates of sorbitan monostearate with approximately 20 moles of ethylene oxide, condensates of ethylene oxide with propylene glycol ("Pluronic"—Pluronic is a Trade Mark) and castor oil ester (e.g. C remopher EL) and amphoteric agents such as quaternized imidazole derivatives, which are available under the trade mark MIRANOL such as MIRANOL C2M. Cationic surface-active germicides and anti-bacterial compounds such as diisobutyl phenoxethoxyethyl dimethyl benzyl ammonium chloride, tertiary amines having one fatty alkyl group (of from 12-18 carbon atoms) and two (polyoxyethylene groups attached to the nitrogen (typically containing a total of from 20 to 50 ethoxy groups per molecule) and salts thereof with acids, and compounds of the structure:



wherein

R is a fatty alkyl group typically containing from 12 to 18 carbon atoms, and x, y and z total 3 or higher, as well as salts thereof with mineral or organic acids, may also be used.

The various surface-active materials may be used in any suitable amount, generally from about 0.05 to about 10% by weight, and preferably from about 0.5 to 5% by weight of the dentifrice composition.

Various other materials may be incorporated in the vehicles of this invention. Examples thereof are preservatives, silicones, chlorophyll compounds, ammoniated materials such as urea, diammonium phosphate and mixtures thereof, materials which can increase contrast with the particles, such as zinc oxide or titanium dioxide and other constituents. These adjuvants are incorporated in the instant compositions in amounts which do not substantially adversely affect the properties and characteristics suitably selected and used in proper amount depending upon the particular type of preparation involved.

Antibacterial agents may also be employed in the vehicles of the instant invention. Typical antibacterial agents include:

N¹-(4-chlorobenzyl)-N³-(2,4-dichlorobenzyl)biguanide;
p-chlorophenyl biguanide;
4-chlorobenzhydryl biguanide;
4-chlorobenzhydrylguanidylurea;
N-3-lauroxypropyl-N-p-chlorobenzylbiguanide;
1,6-di-p-chlorophenylbiguanide hexane;
1-(lauryldimethylammonium)-8-(p-chlorobenzyl-dimethyl ammonium)octane dichloride;
5,6-dichloro-2-guanidinobenzimidazole;
N¹-p-chlorophenyl-N³-laurylbiguanide;
5-amino-1,3-bis(2-ethylhexyl)-3-methylhexahydro pyrimidine;
and their non-toxic acid addition salts.

The antibacterial agent, when present, is employed in amounts of about 0.1-5% by weight, preferably about 0.05-5%.

Any suitable flavoring or sweetening materials may be employed in supplementing the ionone component of the present invention. It is preferable to include the ionone ketone terpene as an additive to flavoring oil; the presence of flavoring oil improves the taste of the zinc-containing product. Examples of suitable supplemental flavoring oils include oils of spearmint, peppermint, wintergreen, sassafras, clove, sage, eucalyptus, marjoram, cinnamon, lemon and orange, as well as methylsalicylate. Mint oils such as oil of peppermint is most preferred. Suitable sweetening agents include sucrose, lactose, maltose, sorbitol, sodium cyclamate, saccharine, acetosulfam, N-1- α -aspartyl-L-phenylalanine-methyl ester ("aspartame"), xylitol, chalcone materials. Suitably, flavor and sweetening agent may together comprise from about 0.01 to 5% by weight or more of the compositions of the instant invention, each typically being about 0.005-2.5%. In a typical modification of a flavoring oil such as oil of peppermint which contains about 75% peppermint and the remainder anethole, menthol and/or carvone, about 0.5-1.5% ionone is

added thereto. Similar modifications may be made to other flavoring oils.

A fluorine-containing compound having a beneficial effect on the care and hygiene of the oral cavity, e.g., diminution of enamel solubility in acid and protection of the teeth against decay may also be incorporated in the vehicle. Examples thereof include sodium fluoride, stannous fluoride, potassium fluoride, potassium stannous fluoride (SnF₂-KF), sodium hexafluorostannate, stannous chlorofluoride, sodium fluorozirconate, and sodium monofluorophosphate. These materials, which disassociate or release fluorine-containing ions in water, suitably may be present in an effective but non-toxic amount, usually within the range of about 0.01 to 1% by weight of the water-soluble fluorine content thereof.

When the oral preparation is a liquid such as mouth rinse or mouth spray which typically contains 20-99% by weight of an aqueous vehicle comprising non-toxic lower aliphatic alcohol, preferably having about 1-30% by weight alcohol such as ethanol, n-propyl, or isopropyl alcohol with the remainder water. Flavor and/or sweetener and surface active agent are also generally present. Mouth sprays also contain a suitable amount of an orally acceptable propellant material such as a fluorocarbon, e.g. Freon on isobutane to propel the spray from a pressurized container.

The oral preparations are typically applied by brushing the teeth with dispersion assisted by saliva in the oral cavity or by rinsing to disperse in the oral cavity for 30-90 seconds at least once daily.

The oral preparations should have a pH practicable for use. The pH range of about 4-9, preferably about 5-7.5, is considered the most practicable for use.

The invention may be practiced and illustrated in accordance with specific embodiments thereof which are described in the following examples. All amounts and proportions set forth in the specification are by weight, unless otherwise indicated.

EXAMPLE 1

Groups of panelists are formed for comparative VSC breath analysis by gas chromatography in combination with a flame photometric detection system according to the procedure described by Solis-Gaffar, Journal of Dental Research, Vol. 54, No. 2, pages 351-357, 1975.

The rinses have formulations A, B, C, and D below.

PRODUCT FORMULATIONS			
Ingredients	A		C
	Zinc Chloride Mouth Rinse	Percent	High mint α -ionone with zinc
Ethanol	10.000		10.000
Fluoronic 108	1.000		1.000
Sodium saccharin	0.045		0.045
Glycerin	8.000		8.000
Zinc chloride	0.250		0.250
Flavor (Peppermint oil)	0.218		0.218 (inclu- ding 1% α -ionone)
Water (deionized/distilled)	80.487		
	100.000		
	D		B
	Placebo Mouth Rinse		High mint α -ionone without zinc

-continued

PRODUCT FORMULATIONS		
Ethanol	10.000	10.000
Puronic 108	1.000	1.000
Sodium saccharin	0.045	0.045
Glycerin	8.000	8.000
Flavor (Peppermint Oil)	0.218	0.218 (including 1% α -ionone)
Water (deionized/distilled)	80.737	
	100.000	

These studies are designed as two compartment, single blind and randomized with a cross-over phase. The subjects in each study are randomly assigned to use either the test or placebo rinse. During the cross-over phase each subject switches to the opposite rinse. Each phase consists of two treatments with either the test or placebo rinse. Breath samples are taken the following morning prior to brushing, rinsing, eating and drinking, two samples being taken ten minutes apart. During the period the subjects keep their mouths closed.

The results are summarized in the following table. (Beta-ionone gives similar results to alpha-ionone with and without the presence of zinc): VSC levels are the headspace amounts of the volatile sulfur compounds hydrogen sulfide (H_2S), methyl mercaptan (CH_3SH) and dimethyl sulfide ($(CH_3)_2S$) in incubated putrescent saliva systems measured after overnight incubation in an airtight container by an instrumental GC-flame photometric technique.

The VSC from the mouth air samples have been identified as H_2S , CH_3SH , and $(CH_3)_2S$. H_2S and CH_3SH account for 90% of the total sulfur volatiles detected instrumentally. Both these compounds have an objectionable putrid odor and the efficacy of the experimental rinse can be measured by its influence on the reduction of these volatiles in the oral cavity. The $(CH_3)_2S$ appeared in small amounts and was not included in the calculations.

TABLE

Study	Treatment	No. of Subjects	Duration of Effects	VSC			Significance
				Initial	Final	% Reduction	
1. A.	Zn/ Cl_2	12	3 hours	13.60	10.30	-24	0.05
D.	Placebo	12	3 hours	13.30	11.70	-13	N.S. (Not Significant)
2. B.	High Mint/ α -ionone (without zinc)	15	overnight	14.58	15.12	—	N.S.
C.	High Mint/ α -ionone w/Zinc	15	overnight	15.69	7.34	-53	0.001
3. C.	High Mint/Zn/ α -ionone	19	overnight	16.98	9.03	-46	0.001
D.	Placebo	19	overnight	16.45	15.95	2.57	N.S.

The clinical studies that (1) Zinc is effective up to 3 hours (1A); (2) Zinc/high peppermint/ α -ionone flavor is effective overnight; high peppermint/ α -ionone without zinc is not effective overnight (2C and 3C); and (3) Zinc/high peppermint/ α -ionone is significantly more effective than placebo (3). The combination of (Zn/high mint is significantly and synergistically more effective than either one by itself.

EXAMPLE 2

The following mouthrinse is prepared for countering breath odors for overnight periods when used immediately before sleep without additional rinsing:

PARTS	
Ethyl alcohol (95%)	15
*Flavor (high peppermint)	0.22
Zinc Acetate, dihydrate	0.40
Sodium saccharin	0.03
Polyoxyethylene (20)	2.00
sorbitan	
Monoisotonic	
Glycerine	8.00
Water	Q.S. to 100

(Sodium cyclamate may replace sodium saccharin.)

*Flavor Composition

PARTS	
Peppermint	74.75
Anethole	9.75
Menthol	9.75
Carvone	4.75
α -ionone	1.00

(Each of beta-ionone, dihydroionone and alpha-methyl ionone may replace alpha-ionone.)

EXAMPLE 3

The following toothpaste is prepared for countering breath odors for overnight periods when brushed on teeth and dispersed in the oral cavity immediately before sleep:

	A	B
	PARTS	PARTS
Glycerine	25	25
Sodium Carboxymethyl Cellulose	1.3	—
Hydroxyethyl cellulose	—	1.0
Sodium Benzoate	0.50	0.50
Sodium Saccharin	0.20	0.20
Titanium Dioxide	0.40	0.40
Zinc chloride	—	1.00
Zinc Acetate	1.00	—
Sodium fluoride	—	0.22
Zeo 49** (Davison)	29.00	29.00
Sodium Lauryl-sulfate	1.50	—

Sodium methyl cocoyl taurate	—	1.50
Flavor*	1.00	1.00
Water	Q.S. to 100	Q.S. to 100

*High peppermint plus α -ionone as in Example 1.

**Zeo 49 is a sodium aluminosilicate composed of silica containing about 1% of combined alumina.

EXAMPLE 4

The following mouth spray dispenser is from propellant is prepared countering breath odors for overnight periods when sprayed into the oral cavity immediately before sleep from a isobutane pressurized container:

	Parts
Sodium Saccharin	0.20
Caster Oil Ester (Cremophor EL)	0.50
Zinc Chloride	1.00
Alpha-ionone	0.01
Ethanol	15.00
Water	Q.S. to 100

Although this invention has been described with reference to specific examples, it will be apparent to one skilled in the art that various modifications may be made thereto which fall within its scope.

We claim:

1. An oral synergistic volatile sulfur compound breath-odor controlling aqueous composition consisting essentially of a non-toxic zinc salt and an ionone terpene ketone, the ratio of zinc ions to ionone being about 1000:1 to 5:1 by weight in an aqueous vehicle, said zinc salt being present in amount of about 0.1-5% by weight of zinc ion and said ionone being present in amount of about 0.0005-1% by weight.

2. The oral composition claimed in claim 1 wherein said zinc salt is present in amount which provides about 0.02-1% by weight of zinc ion and said ionone ketone terpene derivative is present in amounts of about 0.001-1% by weight.

3. The oral composition claimed in claim 1 wherein said ionone terpene ketone is selected from the group consisting of alpha-ionone, beta-ionone, gamma-ionone, dihydroionone, alpha-methylionone and irone.

4. The oral composition claimed in claim 3 wherein said ionone ketone terpene is alpha-ionone.

5. The oral composition claimed in claim 1 wherein said zinc salt is selected from the group consisting of zinc chloride and zinc acetate.

6. The oral composition and claimed in claim 5 wherein said zinc salt is zinc chloride.

7. The oral composition claimed in claim 1 wherein said vehicle is a dental vehicle containing liquid portion comprising water and a humectant and a solid portion comprising a gelling agent and said oral composition is a toothpaste.

8. The oral composition claimed in claim 1 wherein said ionone ketone terpene derivatives is present in a component of a flavoring oil in amounts of about 0.5-1% by weight of said flavoring oil.

9. The oral composition claimed in claim 8 wherein said flavoring oil is oil of peppermint which oil of peppermint is present in said oral composition in amounts of about 0.005-2% by weight.

10. The oral composition claimed in claim 1 wherein said vehicle is an aqueous alcohol vehicle wherein said alcohol is a non-toxic lower aliphatic alcohol and said oral preparation is a mouthrinse or mouthspray.

11. A method of synergistically countering volatile sulfur compound breath odor which consists essentially of dispersing in the oral cavity an oral preparation comprising an aqueous vehicle and a zinc salt which provides about 0.01-5% by weight of zinc ions and about 0.0005-1% by weight of ionone ketone terpene derivative the ratio of zinc ions to ionone ketone terpene being about 1000:1 to 5:1 by weight.

12. The method of countering breath odor claims in claim 11 wherein said ionone ketone derivative alpha-ionone and said zinc salt is zinc chloride.

* * * * *

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172

132
137

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

2020
Bogotá, D.C.,

Abogado
112 JUAN PABLO CADENA SARMIENTO
Apoderado

ASUNTO Radicación 04-098267
 Trámite 002
 Evento 001
 Actuación 430
 Oficio 7087
 Folios 23

Patente de Invención ☒ Patente de Modelo de Utilidad ☐

Vía Nacional ☐

Vía PCT (fase nacional) ☒ Cap. I ☐ Cap. II ☒

No. Sol. Internacional PCT/US03/06204
Fecha de Presentación Interna. 27 de Febrero de 2003

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:

1. Documentos estudiados

- 1.1. Descripción: Folios: 22 a 33 como se radicó inicialmente
- 1.2. Reivindicaciones: Folios 34 a 36 como se radicó inicialmente
 Folios 113 a 114 modificadas
- 1.3. Prioridad: Folios: 01
 US, 04 de Marzo de 2002, 60/361,511
 US, 05 de Febrero de 2003, 10/358,710
- 1.4. Respuesta del solicitante Folios: 109 a 112

2. Análisis de la Prioridad

La fecha de prioridad del 4 de Marzo de 2002 y su correspondiente documento, son aceptados para el estudio de patentabilidad.

3. Objeto de la invención

- Título de la solicitud: "ENJUAGUE BUCAL REFRESCANTE DEL ALIENTO, ANTIMICROBIANO" Folio 1

El objeto de la presente solicitud de patente de invención consiste en un enjuague bucal refrescante del aliento con efecto antimicrobiano.

Reivindicación 1-13: Una composición

El problema planteado en esta solicitud es la necesidad de composiciones de enjuagues bucales con efecto antimicrobiano y mejoramiento del aliento.

Para solucionar este problema técnico la solicitud en estudio proporciona una composición oral sinérgica que comprende un compuesto de zinc atóxico y cloruro de cetilpiridinio.

- **Clasificación Internacional de Patentes (IPC):** A61K8/27; A61K8/35; A61K8/49; A61Q11/00; A61K8/19; A61K8/30; A61Q11/00

4. De la solicitud de Patente (según el caso)

4.1. Descripción (artículo 28 D. 486)

- No se encontraron datos comparativos con las composiciones previamente divulgadas en el estado de la técnica que demuestren su efecto inesperado y superior al adicionar cloruro de cetilpiridinio y una cetona de terpeno ionona

4.2. Reivindicaciones (artículo 30 D 486)

- La reivindicación 1 en su preámbulo sólo se refiere a la composición oral sinérgica que comprende un compuesto de zinc atóxico y cloruro de cetilpiridinio, el solicitante debe especificar claramente la formulación que pretende proteger.
- La reivindicación 4 referenciada a la 2 y la reivindicación 7 referida a la 1, se encuentran equivalentes en su contenido, siendo posible organizarlas dentro del capítulo reivindicatorio bajo sólo una.

5. Determinación del Estado de la Técnica

La fecha que se ha tenido en cuenta para determinar el Estado de la Técnica es:

Fecha de presentación de la solicitud prioritaria: 4 de Marzo de 2002

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es: 04/03/02 se encontraron los siguientes documentos del estado de la técnica relacionados, que pueden afectar la patentabilidad del objeto de la presente solicitud:

Nº	Documento	Título	Fecha de publicación
D1	WO 90/15592	"Anti-plaque dentifrice"	27/12/1990
D2	WO 00/51559	"Oral composition for inhibiting oral malodor"	08/09/2000
D3	US 4,689,214	"Composition to counter breath odor"	25/08/1987

7. Análisis de patentabilidad (artículo 14 D486)

7.1. Nivel inventivo (artículo 18 D486)

Los elementos característicos esenciales de la composición oral sinérgica que controla el olor del aliento de compuestos volátiles de azufre presentada en la reivindicación 1 son:

- **Un compuesto de zinc atóxico** en una proporción de 0.01-5% en peso (0.02 a 2% en peso-reivindicación 2)
- **Cloruro de cetilpiridinio** en una proporción de 0.0005-3% en peso (0.01-1% en peso-reivindicación 2)
- **Cetona de terpeno de ionona** (0.0005%-2% en peso)

La proporción de iones de zinc a cloruro de cetilpiridinio 1000:1 a 2:1 por peso.

La composición según las reivindicaciones 9 y 13 referidas a la 1 es un dentífrico y un enjuague bucal o aerosol bucal respectivamente.

Anterioridades

D1 enseña previamente se refiere a composiciones de un gel dentífrico que comprende una cantidad de una **sal de zinc** tal como **cloruro de zinc** y un compuesto de amonio cuaternario tal como **cloruro de cetilpiridinio** y un agente gelificante.

Las sales de zinc usadas en la composición pueden ser **cloruro de zinc**, **acetato de zinc**, sulfato de zinc entre otros, en las proporciones **0.1-5% por peso** (Sal de zinc) y **0.01-0.5% por peso** (Cloruro de cetilpiridinio). (Ver página 5, líneas 1-11, 14-21, reivindicación 2)

D2 enseña previamente composiciones orales en enjuague bucal para inhibir el mal aliento, conteniendo un **agente antibacteriano** en una proporción de **0.005-0.05% W/V** y un **compuesto de zinc** tal como **acetato de zinc** en una proporción de **0.05-0.5%**. El agente antibacteriano es seleccionado de bis-guanidinas y compuestos de amonio cuaternario. Dicha composición es útil para eliminar y reducir los compuestos de sulfuro volátil en la cavidad oral (Ver resumen, página 1, líneas 1-7)

El documento D2 se refiere además al uso de las **sales de zinc** en la actividad antibacteriana, reducción de la placa y formación de ácido, entre las cuales se encuentran **cloruro**, sulfato y citrato. (Ver página 1, líneas 25-31)

D2 describe lo divulgado previamente en las patentes US 4.289.753 y UK 2.052.978, refiriéndose al uso de los **compuestos de zinc en asociación con un agente antibacteriano tal como cloruro de cetilpiridinio** (Ver página 2, líneas 1-5) y cuya sal es **cloruro de zinc** (Ver página 2, línea 8)

D2 menciona que los agentes catiónicos bacterianos pueden ser **cloruro de cetilpiridinio** o cloruro de benzalconio, los cuales inhiben la formación de sulfuro volátil en la cavidad oral, relativamente con altas concentraciones (Ver página 2, líneas 18-22), sin embargo la combinación de una **sal de zinc** con un agente catiónico antibacteriano a **bajas concentraciones produce un efecto sinérgico en la inhibición de sulfuro volátil** (Ver ejemplo 1, tabla 1). Las combinaciones de zinc y bajas concentraciones del agente antibacteriano causan una mayor inhibición de VSCs (compuestos de azufre volátiles) que los agentes individualmente. La importancia de la invención reside en el hecho que el uso de bajas concentraciones de agentes antibacterianos los efectos indeseados se pueden evitar (Ver página 3-líneas 1-12). Adicionalmente se refiere al uso del **acetato de zinc** para el mal olor (Ver página 4, líneas 27-31)

135
136

D2 en la tabla 1, ejemplo 1 se refiere al índice de FIC el cual si es menor de 1 el efecto sinérgico se puede demostrar (Ver página 6) (Ver resultados No 8)

El ejemplo 2 de D2 describe el experimento con la combinación de 0.3% de acetato de zinc y 0.025% de cloruro de cetilpiridinio, concluyéndose que las combinaciones de este tipo pueden inhibir el mal olor oral **por ocho horas o más**, bajo condiciones normales. (Ver página 8, líneas 23-27)

Las composiciones cuyos elementos característicos son un compuesto de zinc atóxico tales como cloruro de zinc o acetato de zinc y cloruro de cetilpiridinio según las reivindicaciones 1-3, en las proporciones 0.1-5% y 0.1-0.5% en peso (D1) y 0.05-0.5% y 0.005-0.05% w/v (D2), respectivamente en enjuague bucal o dentífrico, ya se encontraban previamente descritas en el estado de la técnica, demostrándose su efecto sinérgico en concentraciones bajas del agente antibacteriano tal como **cloruro de cetilpiridinio y una sal de zinc** (Tabla 1, ejemplo 1, D2)

D3 enseña una composición para prevenir y controlar el olor del mal aliento proveyendo iones de zinc y un derivado de cetona terpénica ionona (Ver resumen, columna 1, líneas 6-8, 44-47, 52-58, 64-68)

La sal de zinc se encuentra presente en cantidades que proveen entre 0.01-5% por peso de iones de zinc y preferiblemente entre 0.02%-1% de iones de zinc en la composición oral (Columna 2, líneas 15-18-D3)

La solubilidad de la **sal de zinc** para proveer iones de zinc parece ser un factor en la actividad contra la formación del olor. Sin embargo, el efecto es **sinérgicamente** mejorado cuando la **cetona de ionona** terpeno se encuentra presente y además por un periodo de tiempo prolongado (Columna 2, líneas 19-23, líneas 47-50-D3)

En cuanto a las formulaciones D3 divulga la incorporación de la sal de zinc y el material de ionona en composiciones orales tal como **rinses, sprays** y dentífricos, los cuales contienen un vehículo acuoso oral o dental o polvos los cuales pueden ser rápidamente dispersos o disueltos en un vehículo acuoso. Cuando la composición oral es una **solución simple** o un **rinse** o un **spray**, la sal de zinc y la ionona se disuelven en agua o en un **alcohol no tóxico**. (Ver columna 3, líneas 21-27)

En el caso de los dentífricos, D3 utiliza una **porción líquida** constituida por un **humectante y agua** y una **porción sólida de agente gelificante**. (Ver columna 3, líneas 29-57)

Adicionalmente las composiciones pueden contener un **germicida activo catiónico** y **compuestos antibacterianos** como cloruro de diisobutilfenoxietoxietil dimetil bencil amonio y aminas terciarias entre otras, en una cantidad de **0.1-5% en peso** (Columna 4, líneas 60-68)

Cualquier agente saborizante o endulzante puede ser empleado para suplementar el componente de ionona en D3, los cuales incluyen aceite como hierbabuena (Ver columna 5, líneas 48-68)

El documento D3 por lo tanto ya sugiere las **composiciones orales de una sal de zinc atóxica, un compuesto antibacteriano y un terpeno cetónico de ionona**. El solicitante a diferencia utiliza específicamente el cloruro de cetilpiridinio, como antibacteriano.

Tabla 1 "Nivel Inventivo"

Solicitud presentada	D1	D2	D3
Sal de zinc (Reivindicación 1): 0.01-5% en peso Cloruro de zinc y Acetato de zinc (Reivindicación 3)	Sal de zinc 0.1-5% por peso Cloruro de zinc y Acetato de zinc (Ver reivindicación 1-4)	Acetato de zinc 0.05-0.5% (Ver resumen, página 1, líneas 1-7, reivindicación 1) 0.3% (Ver Tabla 1-página 6 y 7)	SI Sal de zinc 0.1-5% por peso del ión (Reivindicación 1)
Cloruro de Cetilpiridinio (Reivindicación 1)	SI 0.1-0.5% por peso (Ver reivindicación 8-9)	SI 0.005-0.05% w/v (Ver resumen, página 1, líneas 1-7, reivindicación 1) 0.025% (Ver Tabla 1-página 6 y 7)	SI Antibacteriano 0.1-5% en peso NO Cloruro de cetilpiridinio
Cetona de terpeno ionona (0.0005-2% en peso) (Reivindicación 1) Alfa-ionona Beta-ionona Gama-ionona Dihidro-ionona Alfa-metilionona Una ionona (Reivindicación 5)	NO	NO	SI La proporción de iones de zinc a ionona es 1000:1 y 5:1 0.0005-2% en peso (Reivindicación 1) Alfa-ionona Beta-ionona
Aceite saborizante 0.5-1% por peso de ionona terpeno (Reivindicación 10) Aceite de Hierbabuena 0.005-2% en peso (Reivindicación 11)	SI 8.3 % v/w (en la formulación) Diferencia: no presenta ionona (Ver ejemplo, página 7)	NO	SI Aceite saborizante 0.5-1% por peso de ionona terpeno (Reivindicación 8) Aceite de Hierbabuena 0.005-2% en peso (Reivindicación 12)
Alcohol alifático inferior (Reivindicación 12)	NO	NO	SI (Ver reivindicación 10)

La solicitud no presenta el efecto superior e inesperado y su aporte al estado de la técnica de las composiciones que pretende reivindicar de enjuague o aerosol bucal, mediante la adición de una sal de zinc atóxica, cloruro de cetilpiridinio y una ionona de terpeno cetónica a las composiciones previamente divulgadas en el estado de la técnica, demostrando su capacidad sinérgica frente a las composiciones ya divulgadas.

El problema técnico objetivo a resolver como es "obtener composiciones de enjuagues bucales con efecto antimicrobiano y mejoramiento del aliento" no queda resuelto con la solicitud presentada pues es claro que los enjuagues o aerosoles bucales con cloruro de cetilpiridinio, sales de zinc, una terpeno de ionona cetona y un aceite saborizante, serían logrados por el experto en la materia fácilmente con ayuda de los documentos D1 y D3 o D2 y D3, careciendo por lo tanto de habilidad inventiva.

137
178

Es evidente para el experto en la materia que con el uso de los documentos D1 y D3 o D2 y D3 se obtienen las composiciones de la solicitud presentada, careciendo por lo tanto de nivel inventivo.

8. **Conclusión:**

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

N°	Documento N°	Reivindicaciones afectadas	Requisito que afecta
D1	WO 90/15592	1-13	Nivel Inventivo
D2	WO 00/51559	1-13	Nivel Inventivo
D3	US 4,689,214	1-13	Nivel Inventivo

8. **Respuesta a los argumentos del solicitante:**

- El solicitante debe comparar con las composiciones previamente divulgadas en el estado de la técnica, el efecto superior sobre los compuestos volátiles de azufre (VSCs) que demuestren su efecto superior, pues el documento D2 ya divulgaba el efecto sinérgico en concentraciones bajas del agente antibacteriano tal como **cloruro de cetilpiridinio y una sal de zinc** (Tabla 1, ejemplo 1) y el ejemplo 2 describe el experimento con la combinación de 0.3% de acetato de zinc y 0.025% de cloruro de cetilpiridinio, donde pueden inhibir el mal olor oral **por ocho horas o más**, bajo condiciones normales. (Ver página 8, líneas 23-27). El solicitante sólo reporta el enjuague bucal A con **CPC/acetato de zinc/alfaionona** y el enjuague bucal B con **acetato de zinc/alfaionona** sin su comparación con **acetato de zinc/CPC (D2)**.
- Los datos del solicitante para disminución de compuestos volátiles de azufre (VSCs) se registran para tres horas y la noche, sin presentar datos comparativos con las composiciones previamente divulgadas en el estado de la técnica.
- El solicitante no presenta datos comparativos de la tabla 5 de la descripción con lo previamente divulgado en el estado del arte, tal como las composiciones de **D3** con otro tipo de antibacterianos.

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 60 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

30 mayo 2007

CONCEPTO TÉCNICO No.01285

EXAMINADOR TÉCNICO
Código No. 202070