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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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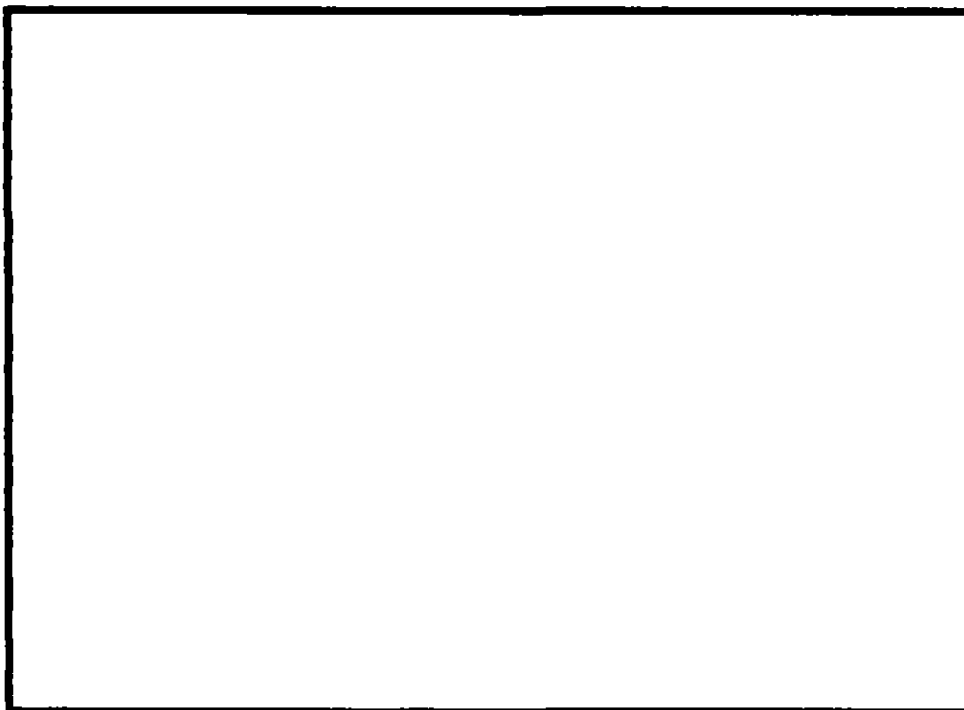
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ANEXOS

- ☒ Comprobante de pago de la tasa de presentación de la solicitud. \$463.000
- ☒ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Poderes, si fuere el caso. Fotocopia autenticada.
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(54) Title: CHEWABLE ANTIPLAQUE CONFECTIONERY DENTAL COMPOSITION

(57) Abstract: A chewable confectionery dental composition delivering to the mouth a unit dose of a plaque reducing enzyme
the composition comprising an enzyme and a non-cariogenic sweetener, the enzyme being incorporated in the composition at a
temperature less than about 80°C.

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CHEWABLE ANTIPLAQUE CONFECTIONERY DENTAL COMPOSITION**BACKGROUND OF THE INVENTION****1. Field of the Invention**

The present invention relates to a chewable confectionery composition which reduces the presence of dental plaque from the chewing surfaces of teeth and more particularly the invention relates to a chewable confectionery composition which contains a small but effective amount of an enzyme effective to disrupt or interfere with plaque formation and adhesion to tooth surfaces.

2. The Prior Art

Oral compositions such as toothpastes, gels and mouth washes are designed to loosen and remove plaque in conjunction with 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. 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 problem 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.

Plaque formation is an ongoing process. Although various oral care products are available to control plaque formation such as toothpastes and mouth rinse, the disadvantage of these products is that only a relatively short time during which the teeth are being brushed or the mouth is being rinsed is available for these preparations to take effect. A further disadvantage of these toothpaste and mouth rinse products is the general infrequency of use, that is, most dental hygiene products are used once or perhaps twice daily and seldom when they are most needed, e.g., after meals and snacks. Thus food deposits which build up as a result of eating throughout the day are left in the oral cavity for long periods of time thereby promoting microbial growth and formation of plaque on tooth surfaces.

It is known to the art to incorporate antimicrobial agents in oral compositions wherein these agents destroy or inhibit oral bacteria responsible for plaque formation. Other agents are also incorporated in the oral composition to reduce plaque formation on teeth. For example, it is known to incorporate enzymes such as proteases and carbohydrases in oral compositions, which enzymes disrupt or interfere with plaque formation and bacterial adhesion to tooth surfaces.

Chewable tablets and gums have been used as vehicles for introducing various chemical agents to tooth surfaces including enzymes such as amylase enzymes (US 4,740,368) oxidoreductases such as glucose oxidase and lactoperoxidase enzymes (US 4,564,519).

A critical requirement, however, for these compositions is that they are stable and have a long shelf-life, which requirement has limited the use of these compositions because normally, the active agents incorporated in these compositions that provide oral care benefits such as plaque reduction are not stable under ambient conditions of humidity and temperature and as a result the agents quickly become degraded to concentrations of limited efficacy and particularly, enzymes which denature during the manufacturing process.

In view of the inconvenience of using toothpaste and mouth rinse products when away from home, the art is seeking portable products in the form of chewable confections such as tablets and gums which can be used throughout the day, particularly after eating, and which provide antiplaque benefits comparable to those obtained by regular brushing with a toothpaste or use of a mouthrinse.

SUMMARY OF THE INVENTION

In accordance with the present invention, there is provided a chewable confectionery composition such as a chewable tablet or gum comprised of a small but effective amount of a plaque reducing enzyme, a non-cariogenic sweetener and optionally a plasticizing/softening agent.

Due to the inherent nature of the chewable tablet or gum product, prolonged contact with the tooth surfaces is achieved when the product is chewed, forming a paste with saliva containing the enzyme which coats the tooth surfaces. The delivery of the enzyme in a chewable tablet or gum form insures that an adequate dosage of the antiplaque enzyme is deliverable when the product is chewed by the user. The chewable confectionery composition of the present

invention is portable and can be packaged and stored in a consumers pocket or purse for consumption anytime and anywhere.

When the chewable confectionery composition of the present invention is placed within the mouth and chewed, an effective antiplaque amount of the enzyme is released from the composition into the saliva where it can reach the surface of the teeth to prevent further plaque accumulation. The tablet or gum of the present invention is formed so as to release the enzyme over a period of 0.5 to 2 minutes. Consistent daily use of the chewable tablets or gums of the present invention will then obtain maximum plaque reduction from the teeth of the consumer.

The term "chewable confectionery composition" as used herein includes within its meaning chewing gum, and chewable and orally soluble tablets, troches and lozenges.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The composition of the present invention as stated is a chewable product which reduces plaque and contains as the active ingredient, a protease enzyme. The product is preferably sugarless.

A representative chewable antiplaque tablet in accordance with the practice of this invention contains about 0.1 to 3% by weight of an enzyme, 0.5 to 5% by weight of a combination plasticizing/softening ingredient and about 50 to about 90% by weight of a non-cariogenic sweetener. In addition to the ingredients discussed above for tablets, chewable gum compositions will contain 10 to 40% by weight of a gum base.

As water promotes the denaturization of the papain enzyme, the presence of water in the chewable confectionery product of the present invention should be at relatively low concentrations in order to impart maximum stability and shelf life to the chewable. For this purpose, it has been found essential to limit the total amount of water present in the chewable product to no more than 5% by weight.

Enzymes

The enzymes useful in the practice of the present invention include carbohydrases such as glucoamylase and enzymes extracted from natural fruit products such as proteases which breakdown or hydrolyze proteins.

Protease enzymes useful in the practice of the present invention include those extracted from natural fruit products. The proteolytic enzymes are obtained from natural sources or by the action of microorganisms having a nitrogen source and a carbon source. Examples of proteolytic enzymes useful in the practice of the present invention include the naturally occurring enzymes papain (from papaya), bromelain (from pineapple), as well as serine proteases such as chymotrypsin. Additional enzymes include ficin and alcalase. Papain is a protease enzyme preferred for use in the practice of the present invention, the papain having an activity of 150 to 939 MCU per milligram as determined by the Milk Clot Assay Test of the Biddle Sawyer Group (see J. Biol. Chem., vol. 121, pages 737-745). The protease enzymes are included in the compositions of the present invention at a concentration of about 0.1 to about 3% by weight and preferably about 0.2 to about 2% by weight.

Enzymes which may beneficially be used in combination with the proteolytic enzymes and glucoamylase enzymes include carbohydrases such as glucoamylase, alpha-amylase, beta-amylase, , tannase and lipases such as plant lipase, gastric lipase and pancreatic lipase.

Glucoamylase is a saccharifying glucoamylase of *Aspergillus niger* origin cultivated by fermentation. This enzyme can hydrolyze both the alpha-D-1,6 glucosidic branch points and the alpha-1,4 glucosidic bonds of glucosyl oligosaccharides. Additional carbohydrases useful in accordance with this invention are alpha and beta-amylase, dextranase and mutanase. Glucoamylase is a preferred enzyme and is incorporated in the oral composition of the present invention at a concentration of about 0.001 to 2% by weight and preferably about 0.01 to 0.55% by weight.

The lipase enzyme is derived from a select strain of *Aspergillus niger*, exhibiting random cleaving of the 1,3 positions of fats and oils. The enzyme has maximum lipolytic activity at pH 5.0 to 7.0 when assayed with olive oil. The enzyme has a measured activity of 120,000 lipase units per gram. The lipase may be included in the dentifrice composition at a concentration of about 0.010 to about 5.0% by weight and preferably about 0.02 to about 0.10 % by weight.

The presence of tannase enzyme can be further beneficial in facilitating the breakdown of extrinsic stain. Tannase enzymes have been purified from *Aspergillus niger* and *Aspergillus alliaceus* and are useful in the hydrolysis of tannins, known to discolor the tooth surface.

Other suitable enzymes which can comprise the present invention include lysozyme, derived from egg white, which contains a single polypeptide chain crosslinked by four disulfide bonds having a molecular weight of 14,600 daltons. The enzyme can exhibit antibacterial properties

by facilitating the hydrolysis of bacterial cell walls cleaving the glycosidic bond between carbon number 1 of N-acetylmuramic acid and carbon number 4 of N-acetyl-D-glucosamine, which in vivo, these two carbohydrates are polymerized to form the cell wall polysaccharide. Additionally, pectinase, an enzyme that is present in most plants facilitates the hydrolysis of the polysaccharide pectin into sugars and galacturonic acid. Finally, glucanase, which may be utilized to catalyze the breakdown of complex carbohydrates to glucans and the hydrolysis of beta glucan to glucose.

Enzyme Stabilizing Agents

Enzyme stabilizing agents which protect the enzyme from inactivation by chelating metal impurities present in the chewable confectionery composition of the present invention may be incorporated in the composition include ethylene diamine tetraacetic acid (EDTA) and sodium gluconate at concentrations between 0.01 and 1% by weight, preferably between 0.1 and 0.5% by weight. Agents stabilizing the enzyme against oxidation include reducing agents such as sodium bisulfite, metal gallates, potassium stannate, sodium stannate, ammonium sulfate, 3,5,-di-tert-butyl-4-hydroxytoluene (BHT), Vitamin E (α , β , γ , forms) /Vitamin E acetate and ascorbic acid. Potassium stannate is an enzyme stabilizing agent preferred for use in the practice of the present invention. The reducing agent is present in the oral composition of the present invention at a concentration between about 0.05 to about 1.5% by weight, preferably between about 0.1 and about 0.75% by weight.

TABLETS

Plasticizing/Softening Agents

Plasticizing/softening agents suitable for use in the preparation of tablets in accordance with the practice of this invention, include propylene glycol, glycerol, acetylated monoglyceride, glyceryl triacetate, glyceryl diacetate, lecithin, glycerin, and mixtures thereof. In a preferred embodiment of this invention, a combination of lecithin and glycerin is used, generally in amounts of about 0.5% to about 3.0% by weight, 0.1% to about 1.0% lecithin and about 1.0% to about 1.0% by weight glycerin by weight, based on the weight of the total chewable tablet composition.

Sweeteners

The sweetening agent ingredient used in the practice of the present invention include bulk sweeteners such as the polyols of 5 to 12 carbon atoms substituted with 5 to 9 hydroxyl groups such as sugar alcohols including xylitol, sorbitol, mannitol. Sugar alcohols provide bulk or texture to the chewable compositions of the present invention and are utilized in amounts of about 25% to about 90% by weight preferably about 40% to about 85% by weight

Artificial sweeteners include as sodium or calcium saccharin salts, cyclamate salts, such as the sodium salt and the like, and the free acid form of saccharin; dipeptide based sweetening agents such as L-aspartyl-L-phenyl-alanine methyl ester, dihydrochalcone; glycyrrhizin; and the synthetic sweetener 3,6-dihydro-6-methyl-1, 1,2,3-oxathiazin-4-one-2,2-dioxide, particularly the potassium (Acesulfame-K), sodium and calcium salts. Artificial sweeteners are present in the chewable confectionery compositions of the present invention at a concentration of about 0.1 to about 1% by weight.

Preferred bulk sweeteners include Lycasin, a commercially available mixture of sorbitol, malitol and high molecular weight dextrans disclosed in Re 26,969 and Isomalt, a sugar alcohol of a disaccharide such as alpha-D-glucopyranosyl-1, 6-mannitol, its isomer, alpha, D-glucopyranosyl-1, 6-sorbitol or a mixture thereof which is obtained by the hydrogenation of palatinose which is converted from sucrose as a raw material with glycosyltransferase. A preferred artificial sweetener is aspartame.

In a preferred embodiment of this invention, the sweetening agent used is a combination of an artificial sweetener such as aspartame and acesulfame and the bulk sweeteners such as Lycasin and Isomalt, the artificial sweetener being present generally in amounts of about 0.05% to about 0.3% by weight and preferably about 0.18% to about 0.22% by weight and about 40% to about 60% by weight, preferably about 45% to about 55% by weight Lycasin and about 15% to about 35% by weight preferably about 20% to about 30% by weight Isomalt.

Flavoring Agents

One or more flavoring agents in liquid powder or encapsulated form are used in the chewable composition of this invention. A variety of flavors known in the art may be used, including essential oils, such as cinnamon, spearmint, peppermint, menthol, birch, anise wintergreen oil and eucalyptus oil. Natural fruit flavors derived from the essence of fruits, such as apple, pear, peach, strawberry, cherry, apricot, orange, watermelon, banana and the like; bean derived flavors such as coffee, cocoa and the like; wine derived curacao zin and the like, and pungent materials, such as affinin, pepper, mustard and the like. Flavoring agents are incorporated in the chewable confectionery compositions at a concentration of about 0.5 to about 5% by weight and preferably about 1.0 to about 3.0% by weight.

Other Ingredients

Calcium salts may be incorporated in the chewable compositions of the present invention as fillers and anticavity agents. Examples of the calcium salts to be used in the present invention as the anticaries agent are, for example, calcium chloride, calcium nitrate, calcium sulfate, dicalcium phosphate dihydrate, calcium carbonate, calcium citrate, calcium hydrogen pyrophosphate, calcium gluconate, calcium glycerophosphate, calcium hydroxide, calcium oxide, calcium silicate and the like, but not limited thereto. The calcium salt is present in the tablet or gum at a concentration of about 5 to about 20% by weight and preferably 7 to 10% by weight. Alkaline agents such as sodium bicarbonate may be incorporated in the chewable confectionery composition of the present invention to provide additional cleaning and breath freshening properties to the composition.

Chewing Gum

The chewing gum of the present invention is preferably a sugarless chewing gum containing the enzyme, as sugarless gums do not promote tooth decay. Chewing gum formulations in which the enzymes of the present invention may be incorporated are well known in the art and typically contain, in addition to, a chewing gum base, one or more plasticizing agents; at least one sweetening agent and at least one flavoring agent.

Gum base materials suitable for use in the practice of this invention are well known in the art and include natural or synthetic gum bases or mixtures thereof. Representative natural gums or elastomers include chicle, natural rubber, jehutong, balata, guttapercha, lechi caspi, sorva, guttakay, crown gum, perillo, or mixtures thereof. Representative synthetic gums or elastomers include butadiene-styrene copolymers, polyisobutylene and isobutylene-isoprene copolymers.

The gum base is incorporated in the chewing gum product at a concentration of about 10 to about 40% by weight and preferably about 20 to about 35% by weight.

Plasticizing/softening agents commonly used in chewing gum compositions are suitable for use in this invention, including gelatin, waxes and mixtures thereof in amounts of 0.1 to 5% by weight.

The sweetening agent ingredient used in the practice of this invention may be selected from a wide range of materials. Bulk sweeteners include the same sweeteners used for the preparation of chewable tablets as are artificial sweeteners. The bulk sweetener is present in the chewing gum composition of the present invention in amounts of about 40 to about 80 % by weight and preferably about 50 to about 75 % by weight. The artificial sweetener is present in the chewing

gum composition of the present invention in amounts of about 0.1 to about 2% by weight and preferably about 0.3 to 1% by weight.

In addition to the ingredients listed above, the gum compositions may also include conventional additives such as colorants, flavoring agents and the like. For example, titanium dioxide may be utilized as a colorant. A variety of flavors known in the art may be used, including essential oils, such as cinnamon, spearmint, peppermint, menthol, birch, anise and the like; natural fruit flavors derived from the essence of fruits, such as apple, pear, peach, strawberry, cherry, apricot, orange, watermelon, banana and the like; bean-derived flavors, such as coffee, cocoa and the like. Flavoring agents are incorporated in the chewing gum formulation at a concentration of about 0.5 to about 5 % by weight and preferably 1 to 3 % by weight.

Method of Manufacture

The challenge in incorporating enzymes into the confectionary composition is maintaining enzymatic stability and activity during storage. Enzymes are quaternary proteins whose structure, function, and stability are sensitive to chemical environment and processing parameters. Enzymes denature in harsh chemical environment and at high temperatures. Formulation and processing procedures are optimized at low moisture and low temperature for both the enzyme chewable tablet and the enzyme gum to preserve enzymatic activity and in vivo efficacy.

The chewable composition of the present invention is made by any suitable process where the protease enzyme is incorporated into the solid base material such that no water or a limited amount of ingredients that absorb water are used that would result in undesirable amounts of water being introduced into the composition during processing or storage. Further, at the time the enzyme is introduced into ingredients used to prepare the chewable composition that the temperature at the time of addition is less than about 80°C. Therefore, it is critical to the practice of the present invention that the composition contain less than 5% by weight water and preferably less than 3% by weight water and that the temperature at which processing of the enzyme occurs be less than about 80°C. The presence in the composition of water in amounts greater than 5% by weight or the use of temperatures in excess of 80°C will act to denature the protease enzyme thereby substantially reducing the efficacy of the enzyme in effecting plaque reduction on teeth.

One method for manufacturing the composition of the invention comprises first heating the base material to a temperature sufficient to drive off any water in the composition. The base

material is then cooled to a temperature at which the enzyme and other temperature sensitive ingredients such as plasticizers, other sweeteners are incorporated and mixed into the base material.

Formulations, equipment and processing techniques have been well developed in the art for preparing and packaging chewing gum and chewable tablets and lozenges. As the enzyme is subject to deterioration and inactivation under conditions such as high shear and elevated temperatures, processing conditions are controlled during the time period that the enzymes are admixed with the other ingredients of the formulation and converted into finished products so that the temperature at the time of admixture does not exceed about 80°C for any extended period of time.

The tablets of the confectionary composition of the present invention are conventionally made by grinding the ingredients once mixed and then compressing or molding the ingredients to form a suitable means for the delivery of the enzyme. In order to produce tablets it is necessary to have a free flowing material which has good self binding properties and which will not stick to the molding or compression equipment.

An illustrative procedure for formulating the chewing gum composition is as follows: the gum base is first melted in a heated kettle at 55°-65°C. One or more of the sweeteners are then added to the gum base followed by one or more flavors, plasticizer. All ingredients are then mixed for a sufficient period of time to ensure adequate dispersion. The mixture is then allowed to cool and the enzyme is added and is cut into suitable serving sizes.

In order to enhance shelf stability, in addition to the admixture used in the preparation of the chewable product being substantially free of water, the finished product should be packaged in a manner so as to minimize exposure to air and moisture.

The following Examples are illustrative of the present invention, but it is understood that the invention is not limited thereto.

Example I

Enzyme (papain) containing tablet and gum compositions were prepared using conventional base ingredients as set forth in Tables I and II below.

TABLE I	
CHEWABLE TABLET	
Ingredient	Wt. %
Papain	0.5
Lycasin 75%	48.9
Isomalt	23.1
Hydrogenated vegetable oil	8.7
Water	4.8
Gelatin (40% solution)	2.9
Starch coated dicalcium phosphate	8.7
Mono-diglyceride mixture	0.8
Lecithin	0.3
Aspartame	0.05
Aspartame K	0.05
Vanillin	0.05
Glycerin	0.1
Sodium bicarbonate	0.10
Mint flavor	0.19

The chewable tablet of Table I was prepared by boiling the Isomalt, Lycasin, water, fat, mono and diglyceride mixture, glycerin, and lecithin to 267-268°F (131°C) after which glycerin was added and the mixture cooled to 140°F (60°C). Thereafter sodium bicarbonate, papain, dicalcium phosphate and the remaining ingredients were added. Thereafter the mixture cooled to room temperature 72-77°F (23°C) was ground into powder and compressed into a tablet using a tablet press.

TABLE II		
CHEWING GUM		
Ingredient	Wt. %	
Gum base	31.20	
Sorbitol	28.08	
Mannitol	5.23	
Papain	1.00	
Acesulfame K	0.16	
Aspartame	0.16	
Menthol powder	1.00	
Liquid flavor	0.47	
Isonalt PF	11.70	
Isonalt DC	16.00	
Anticaking agents*	4.00	
Flavor	2.00	

* Magnesium stearate, talc, silica gel.

Papain Enzyme Activity

Papain activity was measured and monitored in the papain containing chewable tablets and chewing gums using the Protease Detection kit from Panvera Corp. The activity kit quantifies protease activity using a fluorescein thiocarbonyl (FTC)-casein substrate. FTC-casein is attacked by the protease, breaking down casein into TC-peptides. The amount of protease activity is determined by measuring the fluorescence expressed as relative fluorescence units (RFU). The fluorescence signal generated is proportioned to the level of activity of papain in the tablet or gum delivery system. For the purposes of comparison, chewable tablets designated "Tablet A" and chewing gum designated "Chewing Gum B" were prepared in which papain was not included in these compositions. The papain activities of the chewable tablet or Table I and the chewing gum of Table II are recorded in Tables III and IV below as are the papain activities of comparative tablet and gum compositions.

TABLE III		
Protease Activity		
Composition	Chewable Tablet Fluorescence	
	4 Weeks (RFU)	8 Weeks (RFU)
Table I	29,000	30,000
A	2,000	2,000

TABLE IV	
Chewing Gum Fluorescence	
Composition	4 Weeks (RFU)
Table II	38,000
B	1,500

The results recorded in Tables III and IV indicate that the enzyme activity in papain when incorporated in a chewable tablet or gum is retained over at least a 4 week period.

In Vivo Plaque Reduction Efficacy

The chewable tablet of Table I was tested for plaque reduction at 2- and 5- hours after chewing by human volunteers using plaque grown in vivo in an intra-oral retainer on hydroxyapatite disks. Confocal microscopy was used to visualize and quantify the changes in plaque coverage and plaque ultrastructure. Plaque removal was also measured by conventional light microscopy by staining the plaque before and after treatment with crystal violet indicator and measuring the changes in color intensity. Image Pro Analysis Software was used to perform the image analysis and the quantitative measurements. The color intensity was measured and used to determine stain removal. The greater the intensity, the greater the cleaning efficacy. These results are shown in Table V below.

TABLE V

Chewable Tablet Plaque Reduction Efficacy

	Total Area (Microns ²)	% Reduction from Baseline	Average Cluster Area (Microns ²)	% Reduction
Baseline	8681	—	54.45	—
2 hours	3537	59	20.10	63
5 hours	2959	66	26.18	52

Confocal images were made of the plaque before treatment (baseline) and 2 and 5 hours after treating with the tablet. Qualitatively, images showed that there is less bacterial coverage 2 and 5 hours after treatment in comparison to baseline. Image analysis was used to quantify these observations. The results recorded in Table V indicated that the total plaque area, measured by pixel counting, was significantly reduced in comparison to baseline and 2 and 5 hours after treatment. Table V also shows that the average cluster area of the plaque bacteria was significantly reduced after treatment demonstrating the significant efficacy in reducing plaque without the aid of mechanical assistance.

In a second study, the plaque before and after staining with crystal violet was viewed by conventional light microscopy. Image analysis was used to determine the white intensity measured in pixels, the higher the pixel number, the whiter the stain. The results from this study are shown in Table VI. The disks stained at baseline were more intensely colored (blue) than the disks stained 2 hours after treatment with the papain containing chewable tablet. The disks were 47.3% whiter than baseline, indicating less staining and therefore, less plaque. Similar results were observed with the papain chewing gum of Table II as shown in Table VII below.

✓

TABLE VI Chewable Tablet Staining Removal (White Intensity)					
	*	*	*	Average	Improvement from Baseline
Baseline	125	100	—	112.5	—
Treatment	240	200	200	213.3	47.3%

*Inventors: What are these units.

TABLE VII Chewing Gum Plaque Reduction Efficacy				
	Total Area (Microns ²)	% Reduction from Baseline	Average Cluster Area (Microns ²)	% Reduction
Baseline	47,832	—	2897	—
2 hours	38,137	16	2446	15
5 hours	27,267	52	1398	52

Claims

What is claimed is:

- 1. A chewable confectionery composition delivering to tooth surfaces a unit dose of a plaque reducing enzyme the composition comprising a small but effective amount of an enzyme which functions to disrupt or interfere with plaque formation and adhesion to tooth surfaces and a non-cariogenic sweetener, the enzyme being incorporated in the composition at a temperature less than about 80°C.**
- 2. The chewable confectionery composition of claim 1 wherein the enzyme is papain.**
- 3. The chewable confectionery composition of claim 1 wherein the composition is in the form of a tablet.**
- 4. The chewable confectionery composition of claim 1 wherein the composition is a chewing gum.**
- 5. The chewable confectionery composition of claim 1 wherein the composition has a moisture content of less than about 5% by weight.**
- 6. The chewable composition of claim 2 wherein the composition contains the enzyme papain at a concentration of about 0.1 to about 3.0% by weight.**
- 7. The chewable confectionery composition of claim 1 wherein the non-cariogenic sweetener is a sugar alcohol.**
- 8. The chewable confectionery composition of claim 1 wherein the non-cariogenic sweetener is an artificial sweetener.**
- 9. The chewable confectionery composition of claim 1 wherein the non-cariogenic sweetener is a sugar alcohol of a disaccharide.**
- 10. The chewable confectionery composition of claim 1 wherein the non-cariogenic sweetener is present in the composition at a concentration of about 25 to about 95% by weight.**

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US2004/021873

A. CLASSIFICATION OF SUBJECT MATTER

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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, FSTA, BIOSIS

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☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

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- "Z" document member of the same patent family

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21

C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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Corrected version
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Declaraciones bajo la Regla 4.17:

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— en cuanto al derecho del solicitante a reivindicar la prioridad de la solicitud más temprana (Regla 4.17(III)) para todas las designaciones

Publicado:

— con el informe de búsqueda internacional.

— antes del vencimiento del límite de tiempo para corregir las reivindicaciones y a ser republicada en el evento de recibir las correcciones.

Para códigos de dos letras y otras abreviaciones, referirse a las "Notas de guía sobre Códigos y Abreviaturas" que aparecen al comienzo de cada edición de la Gaceta del PCT

(54) Título: COMPOSICION DENTAL ANTIPLACA MASTICABLE DE CONFITERIA.

(57) Resumen: Una composición dental masticable de confitería que entrega a la boca una dosis unitaria de una enzima que reduce la placa, la composición comprende una enzima y un edulcorante no cariogénico, la enzima es incorporada en la composición a una temperatura menor a alrededor de 80 grados C.

15.10.2025
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**COMPOSICIÓN DENTAL ANTIPLACA MASTICABLE DE
CONFITERÍA**

ANTECEDENTES DE LA INVENCION

1. Campo de la Invención

La presente invención se refiere a una composición masticable de confitería que reduce la presencia de placa dental sobre las superficies de masticación de los dientes, y la invención se refiere más particularmente a una composición masticable de confitería que contiene una cantidad, pequeña pero efectiva, de una enzima que es efectiva para interrumpir y/o interferir en, la formación de la placa y la adherencia de la misma a las superficies dentales.

2. Arte Anterior

Las composiciones orales tales como las pastas dentales, geles y colutorios, tienen por objetivo aflojar y remover la placa en conjunción con un régimen regular de cepillado de los dientes. La placa dental se halla presente en algún grado, en forma de una película, sobre virtualmente la totalidad de las superficies dentales. Es un producto secundario del desarrollo microbiano, y comprende una densa capa microbiana consistente en una masa de microorganismos embebidos en una matriz de polisacáridos. La placa de por si se adhiere firmemente a las superficies dentales y es removida con dificultad, aún mediante un riguroso régimen de cepillado. Más aún, una vez removida, la placa vuelve a formarse rápidamente sobre la superficie dental. La placa puede formarse sobre

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cualquier parte de la superficie de los dientes, y se la encuentra particularmente en el margen gingival, en las fisuras en el esmalte, y sobre la superficie de los cálculos dentales. El problema asociado con la formación de la placa sobre los dientes, consiste en la tendencia de la placa a acumularse y a finalmente ocasionar una gingivitis, periodontitis y otros tipos de enfermedades periodontales, como también caries dental y cálculos dentales.

La formación de la placa es un proceso progresivo. Si bien se dispone de diversos productos de higiene oral para controlar la formulación de la placa, tales como pastas dentífricas y enjuagues bucales (colutorios), la desventaja de estos productos es que para que estas preparaciones surtan efecto se dispone de tan sólo un intervalo de tiempo muy breve durante el cual los dientes son sometidos a cepillado o la boca está siendo enjuagada. Otra de las desventajas de estas productos - pastas dentífricas y colutorios - es que por lo general su utilización es poco frecuente, es decir, la mayoría de los productos de higiene dental son utilizados una vez o tal vez dos veces, por día, y raramente cuando más se los necesita, por ejemplo después de las comidas y bocadillos. Por lo tanto los depósitos alimenticios que se acumulan como el resultado de las ingestas a lo largo del día quedan en la cavidad oral durante prolongados intervalos de tiempo, con lo cual promueven el desarrollo microbiano y la formación de la placa sobre la superficie de los dientes.

En el arte es conocida la inclusión de agentes antimicrobianos en las composiciones orales, mediante lo cual dichos agentes destruyen o inhiben las bacterias orales causantes de la formación de la placa. En la

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composición oral también se incluyen otros agentes para reducir la formación de la placa sobre los dientes. Por ejemplo, es conocida la inclusión de enzimas tales como proteasas y carbohidrasas en las composiciones orales, las cuales enzimas interrumpen, o interfieren con, la formación de la placa y la adherencia de las bacterias a las superficies de los dientes.

Se han utilizado tabletas y gomas masticables como vehículos para introducir diversos agentes químicos sobre la superficie de los dientes, y dichas tabletas y gomas masticables incluyen enzimas tales como las enzimas amilasas (US 4,740,368), oxidoreductasas tales como la glucosa oxidasa y las enzimas lactoperoxidasas (US 4,564,519).

Sin embargo, un requisito crítico para estas composiciones es que han de ser estables y tener una prolongada vida de espera en los estantes, el cual requisito ha limitado la utilización de estas composiciones ya que normalmente los agentes activos incorporados en dichas composiciones que proveen beneficios orales tales como la reducción de la placa, no son estables bajo condiciones ambientales de humedad y temperatura, por lo que dichos agentes se degradan rápidamente hasta quedar reducidos a concentraciones de limitada eficacia y en particular, las enzimas que se degradan durante el proceso de la manufactura.

Dada la incomodidad de utilizar productos -pasta dentífrica y colutorios- cuando uno está lejos de casa, en el arte se está tratando de obtener productos portátiles en forma de confites masticables tales como tabletas y gomas que puedan ser utilizados a lo largo del día, particularmente después de las comidas, y que provean beneficios antiplaca

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que sean comparables con los obtenidos mediante el cepillado regular con una pasta dentífrica o mediante el uso de un enjuague bucal.

SÍNTESIS DE LA INVENCION

De acuerdo con la presente invención se provee una composición masticable de confitería tal como una tableta o goma masticables, que comprende una cantidad, pequeña pero efectiva, de una enzima reductora de la placa, un endulzante no cariígeno y opcionalmente un agente plastificante/ablandador.

Debido a la naturaleza inherente del producto- tableta o goma masticables, se logra un prolongado contacto con las superficies dentales cuando el producto es mascado, formándose junto con la saliva una pasta que contiene la enzima y que recubre las superficies de los dientes. La administración de la enzima en forma de una tableta o goma masticables asegura que es posible administrar una dosis adecuada de la enzima antiplaca cuando el producto es mascado por el usuario. La composición masticable de confitería de la presente invención es portátil y puede ser envasada y guardada en el bolsillo o cartera del usuario/a para ser consumida en cualquier momento o lugar.

Cuando la composición masticable de confitería de la presente invención es colocada en la boca y mascada, es liberada una cantidad antiplaca efectiva de la enzima desde la composición hacia la saliva, mediante la cual puede llegar a ponerse en contacto con la superficie de los dientes de manera de impedir una mayor acumulación de la placa. La tableta o goma de la presente invención está formada de manera de liberar la enzima a lo largo de un periodo de 0,5 a 2 minutos. El uso diario

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constante de las tabletas o gomas, masticables, de la presente invención tendrá por lo tanto como resultado una máxima reducción de la placa de los dientes del consumidor.

Tal como se la utiliza en la presente, el significado de la expresión "composición masticable de confitería" incluye la goma de mascar; y las tabletas, comprimidos y pastillas masticables y solubles en la cavidad oral.

DESCRIPCIÓN DE LAS FORMAS DE REALIZACIÓN PREFERIDAS

Tal como se enuncia, la composición de la presente invención es un producto masticable que reduce la placa y que contiene a título de ingrediente activo una enzima proteasa. Es preferible que el producto no tenga azúcar.

De acuerdo con la práctica de la presente invención, una tableta antiplaca masticable representativa contiene aproximadamente 0,1 a 3% en peso de una enzima, 0,5 a 5% en peso de una combinación de ingredientes plastificantes/ablandadores y aproximadamente 50 a aproximadamente 90% en peso de un endulzante no cariígeno. Además de los ingredientes anteriormente mencionados para las tabletas, contendrán las composiciones de goma masticable de 10 a 40% en peso de una goma a título de base.

Dado que el agua promueve la desnaturalización de la enzima papaína, debería la presencia de agua en el producto de confitería masticable de la presente invención reducirse a concentraciones relativamente bajas a efectos de impartir al producto masticable una máxima estabilidad y vida de espera en los estantes. A tal efecto, se ha descubierto que es esencial limitar la máxima cantidad de agua presente en el producto masticable, a no más del 5% en peso.

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Las enzimas

Las enzimas útiles en la práctica de la presente invención incluyen las carbohidrasas tales como la glucoamilasa y las enzimas extraídas de los productos frutales naturales tales como las proteasas que descomponen o hidrolizan las proteínas.

Las enzimas proteasas útiles en la práctica de la presente invención incluyen aquellas extraídas de los productos frutales naturales. Las enzimas proteolíticas son obtenidas de fuentes naturales o mediante la acción de microorganismos que tienen una fuente de nitrógeno y una fuente de carbono. Los ejemplos de enzimas proteolíticas útiles en la práctica de la presente invención incluyen las siguientes enzimas que se presentan en la naturaleza: la papaína (de la papaya), la bromelaina (del ananá), como también las serina proteasas tales como la quimotripsina. Las enzimas adicionales incluyen la ficina y la alcalasa. La papaína es una enzima proteasa preferida para ser utilizada en la práctica de la presente invención, teniendo la papaína una actividad de 150 a 939 MCU por miligramo, medida mediante el Ensayo del Coágulo de Leche (Milk Clot Assay Test) del Biddle Sawyer Group (ver: J. Biol. Chem. Vol. 121, Págs. 737 - 745). Las enzimas proteasas son incluidas en las composiciones de la presente invención con una concentración de aproximadamente 0,1 a aproximadamente 3% en peso, y preferentemente de aproximadamente 0,2 a aproximadamente 2% en peso.

Las enzimas que pueden ser utilizadas beneficiosamente en combinación con las enzimas proteolíticas y con las enzimas glucoamilasa incluyen las carbohidrasas tales como la glucoamilasa, alfa-amilasa, beta-

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amilasa, tanasa y las lipasas tales como la lipasa de las plantas, lipasa gástrica y lipasa pancreática.

La glucoamilasa es una glucoamilasa sacarificante originada por el *Aspergillus niger* cultivado por fermentación. Esta enzima puede hidrolizar tanto los puntos de ramificación alfa-D-1,6-glucósidos como los enlaces alfa-1,4-glucósidos de los glucosil oligosacáridos. Entre las carbohidrasas adicionales útiles de acuerdo con la presente invención se encuentran la alfa y beta -amilasa, dextranasa y mutanasa. La glucoamilasa es una enzima preferida, y es incorporada en la composición oral de la presente invención con una concentración de aproximadamente 0,001 a 2% en peso, y preferentemente de aproximadamente 0,01 a 0,55% en peso.

La enzima lipasa es derivada de una cepa seleccionada de *Aspergillus Níger*, que presenta un desdoblamiento aleatorio de las 1,3 posiciones de grasas y aceites. La enzima tiene una actividad lipolítica bajo un pH de 5,0 a 7,0 al ser sometida a ensayo con aceite de oliva. La enzima tiene una actividad medida de 120.000 unidades de lipasa por gramo. La lipasa puede ser incluida en la composición dentífrica con una concentración de aproximadamente 0,010 a aproximadamente 5,0% en peso, y preferentemente de aproximadamente 0,02 a aproximadamente 0,10% en peso.

La presencia de la enzima tanasa puede ser también beneficiosa para facilitar la descomposición de una mancha extrínseca. Las enzimas tanasa han sido purificadas a partir del *Aspergillus Níger* y del *Aspergillus allianceus*, y son útiles en la hidrólisis de los taninos, de los cuales es sabido que descolorean la superficie de los dientes.

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Entre las otras enzimas adecuadas que pueden estar incluidas en la presente invención se incluyen la lisozima, derivada de la albúmina de huevo, que contiene una única cadena de polipéptidos reticulados por cuatro enlaces disulfuro que tienen un peso molecular de 14.600 dalton. La enzima puede presentar propiedades antibacterianas por el hecho de facilitar la hidrólisis de las paredes de las células bacterianas que desdobra el enlace glicósido entre el átomo de carbono número 1 del ácido .N-acetilmurámico y el átomo de carbono número 4 de la N-acetil-D-glucosamina, por lo cual, in vivo, estos dos carbohidratos son polimerizados de manera de formar el polisacárido de las paredes celulares. Adicionalmente, la pectinasa, que es una enzima que se halla presente en la mayoría de las plantas, facilita la hidrólisis del polisacárido pectina en forma de azúcares y ácido galactourónico. Finalmente, la glucanasa, que puede ser utilizada para catalizar la descomposición de los carbohidratos complejos en glucanos y la hidrólisis de beta-glucano de manera de obtener glucosa.

Agentes Estabilizadores de las Enzimas

Los agentes estabilizadores de enzimas que protegen la enzima contra su desactivación mediante la quelación de las impurezas metálicas presentes en la composición masticable de confitería de la presente invención, que pueden ser incluidos en la composición, abarcan el EDTA (ethylene diamine tetraacetic acid, ácido etilén diamina tetraacético) y el gluconato de sodio con concentraciones entre 0,01 y 1% en peso, preferentemente entre 0,1 y 0,5% en peso. Los agentes que estabilizan la enzima contra su oxidación incluyen agentes de reducción tales como el

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bisulfito de sodio, gallatos metálicos, estanato de potasio, estanato de sodio, sulfato de amonio, 3,5-di-ter-butil-4-hidroxitolueno (BHT), Vitamina E (las formas α , β , γ)/ acetato de Vitamina E y ácido ascórbico. El estanato de potasio es un agente estabilizante de las enzimas, preferido para ser utilizado en la práctica de la presente invención. El agente de reducción se halla presente en la composición oral de la presente invención con una concentración de aproximadamente 0,05 a aproximadamente 1,5% en peso, preferentemente entre aproximadamente 0,1 y aproximadamente 0,75% en peso.

TABLETAS

Agentes plastificantes/ablandadores

Los agentes plastificantes/ablandantes adecuados para ser utilizados en la preparación de las tabletas de acuerdo con la práctica de la presente invención incluyen el propilén glicol, glicerol, monoglicérido acetilad, triacetato de glicerilo, diacetato de glicerilo, lecitina, glicerina, y mezclas de los mismos. En una forma de realización preferida de la presente invención, se utiliza una combinación de lecitina y glicerina, generalmente en cantidades de aproximadamente 0,5% a aproximadamente 3,0% en peso, de 0,1% a aproximadamente 1,0% de lecitina y de aproximadamente 1,0% a aproximadamente 1,0% en peso de glicerina, referido al peso de la composición total de la tableta masticable.

Endulzantes

El agente endulzante utilizado en la práctica de la presente invención incluye los endulzantes masivos tales como los polioles de 5 a 12 átomos de carbono sustituidos con de 5 a 9 grupos hidroxilo tales como los

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alcoholes de azúcar que incluyen el xilitol, sorbitol, manitol. Los alcoholes de azúcar proveen masa o textura a las composiciones masticables de la presente invención, y son utilizados en cantidades de aproximadamente 25% a aproximadamente 90% en peso, preferentemente de aproximadamente 40% a aproximadamente 85% en peso.

Los endulzantes artificiales incluyen a título de sales sódicas o cálcicas de sacarina, sales de ciclamato tales como la sal sódica y similares, y la forma de ácido libre de sacarina; agentes endulzantes basados en dipéptidos tales como el metil éster de L-aspartil-L-fenil-alanina, dihidrocalcona; glicirizina; y el endulzante sintético 3,6-dihidro-6-metil-1,1,2,3-oxatiazín-4-ona-2,2-dióxido, particularmente las sales de potasio (Acesulfame-K), sódicas y cálcicas. Los endulzantes artificiales se hallan presentes en las composiciones masticables de confitería de la presente invención con una concentración de aproximadamente 0,1 a aproximadamente 1% en peso.

Los endulzantes masivos preferidos incluyen el Lycasin, que es una mezcla, disponible en el comercio de sorbitol, malitol y dextranos de elevado peso molecular, revelada en el documento Re 26.969, y el Isomalt, que es un alcohol de azúcar de un disacárido tal como el alfa-D-glucopiranosil-1,6-manitol, su isómero, el alfa-D-glucopiranosil-1,6-sorbitol, o una mezcla de los mismos que es obtenida mediante la hidrogenación de palatinosa que es convertida a partir de la sucrosa en forma de un material bruto con glicosiltransferasa. El aspartamo es un endulzante artificial preferido.

En una forma de realización preferida de la presente invención, el

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agente endulzante utilizado es una combinación de un endulzante artificial tal como aspartamo y acesulfamo y los endulzantes masivos tales como Lycasin e Isomalt, hallándose el endulzante artificial por lo general presentes en cantidades de aproximadamente 0,05% a aproximadamente 0,3% en peso y preferentemente entre aproximadamente 0,18% y aproximadamente 0,22% en peso y aproximadamente 40% a aproximadamente 60% en peso, preferentemente de aproximadamente 45% a aproximadamente 55% en peso de Lycasin, y aproximadamente 15% a aproximadamente 35% en peso, preferentemente de aproximadamente 20% a aproximadamente 30% en peso de Isomalt.

Agentes Saborizantes

En la composición masticable de la presente invención se utilizan uno o más agentes saborizantes en forma líquida, de polvo o encapsulada. Puede utilizarse una variedad de sabores conocidos en el arte, los cuales incluyen los aceites esenciales tales como la canela, menta verde, menta, mentol, abedul, anís, aceite de gualteria y aceite de eucalipto; sabores naturales de fruta derivados de la esencia de frutas tales como manzana, pera, durazno, frutilla, cereza, albaricoque, naranja, sandía, banana, y similares; los sabores derivados de porotos tales como café, cacao o similares; el curacao zin derivado del vino, y similares; y los materiales picantes tales como la afinina, pimienta, mostaza y similares. Los agentes saborizantes son incorporados en las composiciones masticables de confitería con una concentración de aproximadamente 0,5 a aproximadamente 5% en peso, y preferentemente de aproximadamente 1,0 a aproximadamente 3,0% en peso.

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Otros Ingredientes

En las composiciones masticables de la presente invención pueden incorporarse sales de calcio a título de rellenos y agentes anticavidad. Los ejemplos de sales de calcio a ser utilizadas en la presente invención a título de agentes anticaries incluyen a título no limitativo por ejemplo el cloruro de calcio, nitrato de calcio, sulfato de calcio, fosfato dicálcico dihidratado, carbonato de calcio, hidrógeno pirofosfato de calcio, gluconato de calcio, glicerofosfato de calcio, citrato de calcio, hidróxido de calcio, óxido de calcio, silicato de calcio y similares. La sal de calcio se halla presente en la tableta o goma con una concentración de aproximadamente 5 a aproximadamente 20% en peso, y preferentemente de 7 a 10% en peso. Los agentes alcalinos tales como el bicarbonato de sodio pueden ser incorporados en las composiciones masticables de confitería de la presente invención a efectos de proveer a la composición propiedades adicionales de limpieza y refrescadoras del aliento.

Goma de Mascar

La goma de mascar de la presente invención es preferentemente una goma de mascar sin azúcar que contiene la enzima, ya que las gomas sin azúcar ni promueven la caries dental. Las formulaciones de goma de mascar en las cuales pueden ser incorporadas las enzimas de la presente invención, son bien conocidas en el arte y típicamente contienen además de la base- goma de mascar, uno o más agentes plastificantes, por lo menos un agente endulzante y por lo menos un agente saborizante.

Los materiales base-goma adecuados para ser utilizados en la práctica de la presente invención son bien conocidos en el arte, e incluyen

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las bases de gomas naturales y sintéticas, o mezclas de las mismas. Las gomas o elastómeros naturales representativos incluyen el chicle, caucho natural, jelutong, balata, gutapercha, lechi caspi, sorva, guttacay, goma de corona, perillo, o mezclas de los mismos. Las gomas o elastómeros sintéticos representativos incluyen los copolímeros de butadieno-estireno, poliisobutileno y los copolímeros de isobutileno-isopreno.

La base de goma es incorporada en el producto-goma de mascar en una concentración de aproximadamente 10 a aproximadamente 40% en peso, y preferentemente de aproximadamente 20 a aproximadamente 35% en peso.

Los agentes plastificantes/ablandantes comúnmente utilizados en las composiciones de goma de mascar son adecuados para ser utilizados en la presente invención, e incluyen la gelatina, el agua y las mezclas de las mismas, en cantidades de 0,1 a 5% en peso.

El ingrediente agente endulzante utilizado en la práctica de la presente invención puede ser seleccionado en una amplia gama de materiales. Los endulzantes masivos incluyen los mismos endulzantes utilizados para la preparación de tabletas masticables que para los endulzantes artificiales. El endulzante masivo se halla presente en la composición de goma de mascar de la presente invención en cantidades de aproximadamente 40 a aproximadamente 80% en peso, y preferentemente de aproximadamente 50 a 75% en peso. El endulzante artificial se halla presente en la composiciones de goma de mascar de la presente invención en cantidades de aproximadamente 0,1 a aproximadamente 2% en peso, y preferentemente de aproximadamente 0,3 a 1% en peso.

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Además de los ingredientes anteriormente mencionados, las composiciones de goma también pueden incluir aditivos convencionales tales como colorantes, agentes saborizantes y similares. Por ejemplo, a título de colorante puede utilizarse el dióxido de titanio. Puede utilizarse una variedad de sabores conocidos en el arte, que incluyen los aceites esenciales tales como la canela, menta verde, menta, mentol, abedul, anís y similares; los sabores naturales de fruta derivados de la esencia de frutas tales como manzana, pera, durazno, frutilla, cereza, albaricoque, naranja, sandía, banana, y similares; los sabores derivados de porotos tales como el café, cacao y similares. Los agentes saborizantes son incorporados en la formulación de la goma de mascar con una concentración de aproximadamente 0,5 a aproximadamente 5% en peso, y preferentemente de aproximadamente 1,0 a aproximadamente 3,0% en peso.

Método de Manufactura

El desafío de la inclusión de las enzimas en la composición de confitería, consiste en mantener la estabilidad y actividad enzimáticas durante el almacenamiento. Las enzimas son proteínas cuaternarias cuya estructura, función, y estabilidad, son sensibles al entorno químico y a los parámetros de procesamiento. Las enzimas se desnaturalizan en los entornos químicos severos y a elevadas temperaturas. Los procedimientos de formulación y de procesamiento se optimizan a baja humedad y baja temperatura tanto para la tableta masticable de enzima como para la goma de enzima, de modo de preservar la actividad enzimática y la eficacia in vivo.

La composición masticable de la presente invención es hecha

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mediante cualquier proceso adecuado mediante el cual la enzima proteasa es incorporada en el material de base sólido de manera tal que no sean utilizados ninguna agua ni una cantidad limitada de ingredientes que absorban agua que tendrían como resultado la introducción de cantidades indeseables de agua en las composiciones durante su procesamiento o almacenamiento. Además, en el momento de la introducción de la enzima en los ingredientes utilizados para preparar la composición masticable, es conveniente que la temperatura en el momento de la adición sea inferior a aproximadamente 80°C. Por ello para la práctica de la presente invención es conveniente que la composición contenga agua en una concentración inferior al 5% en peso y preferentemente inferior a aproximadamente el 3% en peso, y que la temperatura a la cual tiene lugar el procesamiento de la enzima sea inferior a aproximadamente 80°C. La presencia en la composición de agua en cantidades superiores al 5% en peso, o la utilización de temperaturas superiores a 80°C, actuarán de manera de desnaturalizar la enzima proteasa, con lo cual se reduce de manera sustancial la eficacia de la enzima para reducir la placa sobre los dientes.

Uno de los métodos para manufacturar la composición de la invención es el que comprende empezar por calentar el material de base a una temperatura suficiente para expulsar cualquier agua presente en la composición. El material de base es seguidamente enfriado a una temperatura a la cual las enzimas y otros ingredientes sensibles a las temperaturas tales como los plastificantes, otros endulzantes, son incorporado y mezclados en el material de base.

En el arte se han desarrollado muy bien formulaciones, equipos y

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técnicas de procesamiento para preparar y envasar gomas de mascar y tabletas y pastillas masticables. Dado que la enzima está expuesta a deteriorarse y degradarse bajo condiciones tales como elevado corte y temperaturas elevadas, se controlan las condiciones de procesamiento durante el intervalo de tiempo en el cual las enzimas son incorporadas en la mezcla junto con los otros ingredientes de la formulación y convertidas en productos terminados, de manera tal que la temperatura en el momento del mezclado no supere aproximadamente 80°C durante cualquier periodo prolongado de tiempo.

Las tabletas de la composición de confitería de la presente invención son convencionalmente hechas mediante la molienda de los ingredientes una vez mezclados, después de lo cual se comprimen o moldean los ingredientes de manera de formar un medio adecuado para la inclusión de la enzima. A efectos de producir tabletas, es necesario disponer de un material de libre escurrimiento que tenga buenas propiedades autoligantes y que no se pegotee al equipo de moldeo o compresión.

Un procedimiento ilustrativo para formular la composición de gomas de mascar, es el siguiente: se empieza por derretir la base de goma en un caldero calentado a 55-65°C. Seguidamente a la base de goma son adicionados uno o más de los endulzantes, seguidos por uno o más saborizantes, y el plastificante. A continuación todos los ingredientes son mezclados durante un intervalo de tiempo suficiente para asegurar una dispersión adecuada. Seguidamente se deja que la mezcla se enfríe, se agrega la enzima y se corta en tamaños adecuados para servir.

A efectos de reforzar la estabilidad en los estantes, además de la

mezcla utilizada en la preparación del producto masticable que se halla esencialmente exento de agua, el producto terminado debería ser envasado de una manera tal de minimizar la exposición al aire y a la humedad.

Los siguientes ejemplos ilustran la presente invención, pero debe entenderse que la invención no se limita a los mismos.

Ejemplo I

Fueron preparadas unas tabletas y composiciones de goma que contenían enzima (papaina), mediante la utilización de ingredientes de base convencionales, tal como se indica en las siguientes Tablas I y II.

TABLA I TABLETA MASTICABLE	
Ingrediente	% en peso
Papaina	0,5
Lycasin al 75%	48,9
Isomalt	23,1
Aceite vegetal hidrogenado	8,7
Agua	4,8
Gelatina (solución al 40%)	2,9
Fosfato dicálcico recubierto con almidón	8,7
Mezcla de mono- y diglicéridos	0,8
Lecitina	0,3
Aspartamo	0,05
Aspartame K	0,05
Vanilina	0,05
Glicerina	0,1
Bicarbonato de sodio	0,10
Sabor a menta	0,19

Para preparar la tableta masticable de la Tabla I fue sometida a ebullición el Isomalt, Lycasin, agua, grasa, la mezcla de mono- y

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diglicéridos, glicerina y lecitina, a 131°C (256-268°C), después de lo cual se adicionó la glicerina, y la mezcla fue enfriada a 60°C (140°F). A continuación se adicionaron bicarbonato de sodio, papaína, fosfato dicálcico, y los ingredientes remanentes. Seguidamente se enfrió la mezcla a temperatura ambiente (23°C, 72-77°F), se la sometió a trituration hasta reducirla a polvo, y se comprimió en forma de una tableta mediante una prensa de tabletas.

TABLA II
GOMA DE MASCAR

Ingrediente	% en peso
Goma como base	31,20
Sorbitol	28,08
Manitol	5,23
Papaína	1,00
Acesulfame K	0,16
Aspartamo	0,16
Mentol en polvo	1,00
Sabor líquido	0,47
Isomalt PF	11,70
Isomalt DC	16,00
Agentes antitorta (*)	4,00
Sabor	2,00

(*) Estearato de magnesio, talco, gel de sílice

Actividad de la Enzima Papaína

La actividad de la papaína fue medida y sujeta a un seguimiento en las tabletas masticables y gomas de mascar que contenían papaína, para lo cual se utilizó el kit para la detección de proteasas (Protease Detection kit)

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de Panvera Corp. El kit de actividad cuantifica la actividad de las proteasas mediante un sustrato de FTC (fluoresceína tiocarbamoilo)-caseína. El FTC-caseína es atacado por la proteasa, con lo cual se descompone la caseína en TC-péptidos. El grado de la actividad de las proteasas es determinado mediante la medición de la fluorescencia expresada como unidades de fluorescencia relativas (UFR). La señal de fluorescencia generada es proporcional al nivel de la actividad de la actividad de la papaína en el sistema de entrega de la tableta o de la goma. A fines de comparación, fueron preparadas unas tabletas masticables, designadas "Tableta A" y goma de mascar designada "Goma de Mascar B", en cuyas preparaciones no se había incluido papaína. Las actividades de la papaína de la tableta masticable de la Tabla I y de la goma de mascar de la Tabla II, han sido consignadas en la siguientes Tablas III y IV, como también las actividades de la papaína de las composiciones comparativas de la tableta y de la goma.

TABLA III		
Actividad de la Proteasa		
Fluorescencia de las Tabletás Masticables		
Composición	4 semanas (UFR)	8 semanas (UFR)
Tabla I	29.000	30.000
A	2.000	2.000

TABLA IV	
Fluorescencia de la Goma de Mascar	
Composición	4 semanas (UFR)
Tabla II	38.000
B	1.500

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Los resultados consignados en las Tablas III y IV indican que la actividad de la enzima en la papaína, cuando es incorporada en una tableta o goma masticables, es retenida durante un periodo de por lo menos 4 semanas.

Eficacia de la Reducción de la Placa In Vivo

La tableta masticable de la Tabla I fue sometida a ensayo a efectos de determinar la reducción de la placa al cabo de 2 y 5 horas después del mascado por voluntarios humanos, para lo cual se utilizó la placa desarrollada in vivo en un retenedor intra-oral sobre discos de hidroxiapatita. Se utilizó la microscopía confocal para visualizar y cuantificar los cambios en la placa de recubrimiento y en la ultraestructura de la placa. También se midió la remoción de la placa mediante microscopía de luz convencional, para lo cual se tñó la placa, antes y después de su tratamiento, con un indicador violeta cristal, y se midieron los cambios en la intensidad de la luz. Se utilizó el Software Pro Analysis para llevar a cabo el análisis de la imagen y las mediciones cuantitativas. Se midió la intensidad del color, y se la utilizó para determinar la remoción de las manchas. Cuando mayor la intensidad, tanto mayor la eficacia de la limpieza. Estos resultados han sido consignados en la siguiente Tabla V.

TABLA V Eficacia de la Tableta Masticable para Reducir la Placa				
	Área Total (micrones ^2)	% de reducción con respecto a la línea de base	Área promedio del racimo ^2)	Reducción porcentual
Línea de base	8681	—	54,45	—
2 horas	3537	59	20,10	63
5 horas	2959	66	26,18	52

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Fueron hechas unas imágenes confocales de la placa antes del tratamiento (línea de base) y al cabo de 2 y 5 horas después del tratamiento con la tableta. Desde el punto de vista cualitativo, las imágenes mostraban que el recubrimiento bacteriano a las 2 y 5 horas después del tratamiento, es inferior al recubrimiento bacteriano en la línea de base. Se utilizó el análisis de imagen para cuantificar dichas observaciones. Los resultados consignados en la Tabla V indicaron que el área total de la placa, medida mediante el conteo de los pixels, era significativamente reducido en comparación con la línea de base y al cabo de 2 y 5 horas después del tratamiento. La Tabla V también muestra que el área promedio de racimo de las bacterias de la placa era significativamente reducido después del tratamiento, lo cual demuestra la eficacia significativa en la reducción de la placa sin la ayuda de una asistencia mecánica.

En un segundo estudio, la placa antes y después del tefido con violeta cristal fue observada mediante microscopía de luz convencional. Se utilizó el análisis de imagen para determinar la intensidad blanca medida en pixels; cuanto mayor el número de pixels, tanto más blanco el tefido. Los resultados de este estudio han sido mostrados en la Tabla VI. Los discos tefidos en la línea de base estaban coloreados (azul) con mayor intensidad que los discos tefidos dos horas después del tratamiento con la tableta masticable que contenía papafna. Los discos eran un 47,3% más blancos que la línea de base, lo cual indica un menor tefido y por lo tanto menos placa. Se observaron resultados similares con la goma de mascar con papafna, de la Tabla II, tal como se muestra en la siguiente Tabla VII.

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TABLA VI Remoción del Tefido Mediante Tableta Masticable (Intensidad Blanca)					
	*	*	*	Promedio	Mejora con respecto a la línea de base
Línea de base	125	100	—	112,5	—
Tratamiento	240	200	200	213,3	47,3 %

TABLA VII Eficacia en la reducción de la Placa Mediante Goma de Mascar				
	Área Total (micrones ^2)	% de reducción con respecto a la línea de base	Área promedio del racimo ^2)	Reducción porcentual
Línea de base	47.832	-	2897	—
2 horas	38.137	16	2646	15
5 horas	27.257	52	1398	52



REIVINDICACIONES

1. Una composición masticable de confitería que entrega a las superficies de los dientes una dosis unitaria de una enzima que reduce la placa, caracterizada porque comprende una cantidad pequeña pero efectiva, de una enzima que funciona de manera de interrumpir o de interferir con la formación de la placa y la adhesión de la misma a las superficies de los dientes, y un endulzante no cariígeno, habiendo sido la enzima incorporada en la composición a una temperatura inferior a aproximadamente 80°C.
2. La composición masticable de confitería de acuerdo con la reivindicación 1, caracterizada porque la enzima es papaína.
3. La composición masticable de confitería de acuerdo con la reivindicación 1, caracterizada porque la composición se encuentra en forma de una tableta.
4. La composición masticable de confitería de acuerdo con la reivindicación 1, caracterizada porque la composición es una goma de mascar.
5. La composición masticable de confitería de acuerdo con la reivindicación 1, caracterizada porque la composición tiene un contenido de humedad inferior a aproximadamente el 5% en peso.
6. La composición masticable de acuerdo con la reivindicación 2, caracterizada porque la composición contiene la enzima papaína con una concentración de aproximadamente 0,1 a aproximadamente 3,0% en peso.
7. La composición masticable de confitería de acuerdo con la reivindicación 1, caracterizada porque el endulzante no cariígeno es un

alcohol de azúcar.

8. La composición masticable de confitería de acuerdo con la reivindicación 1, caracterizada porque el endulzante no cariígeno es un endulzante artificial.

9. La composición masticable de confitería de acuerdo con la reivindicación 1, caracterizada porque el endulzante no cariígeno es un alcohol de azúcar de un disacárido.

10. La composición masticable de confitería de acuerdo con la reivindicación 1, caracterizada porque el endulzante no cariígeno se halla presente en la composición con una concentración de aproximadamente 25 a aproximadamente 95% en peso.

BUENOS AIRES, JULIO DE 2004.



RESUMEN

COMPOSICIÓN DENTAL ANTIPLACA MASTICABLE DE CONFITERÍA

Una composición masticable de confitería que entrega en la boca una dosis unitaria de una enzima reductora de la placa, comprendiendo la composición una enzima y un endulzante no cariígeno, habiendo sido la enzima incorporada en la composición a una temperatura inferior a aproximadamente 80°C.

TRANSMITTAL LETTER TO THE UNITED STATES RECEIVING OFFICE

Date	09 July 2004
International Application No.	
Attorney Docket No.	IR 7050-00

I. Certification under 37 CFR 1.10 (if applicable)

EV 380778421 US
Express Mail mailing number

09 July 2004
Date of Deposit

I hereby certify that the application/correspondence attached hereto is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to Assistant Commissioner for Patents, Washington, D.C. 20231.


Signature of person mailing correspondence

Carol Stanley
Typed or printed name of person mailing correspondence

II. ☒ New International Application

TITLE	CHEWABLE ANTIPLAQUE CONFECTIONERY DENTAL COMPOSITION
-------	--

Earliest priority date (Day/Month/Year)
11 July 2003

SCREENING DISCLOSURE INFORMATION: In order to assist in screening the accompanying international application for purposes of determining whether a license for foreign transmittal should and could be granted and for other purposes, the following information is supplied. (Note: check as many boxes as apply):

- A. ☐ The invention disclosed was not made in the United States.
- B. ☐ There is no prior U.S. application relating to this invention.
- C. ☒ The following prior U.S. application(s) contain subject matter which is related to the invention disclosed in the attached international application. (NOTE: priority to these applications may or may not be claimed on form PCT/RO/101 (Request) and this listing does not constitute a claim for priority).

application no.	USSN 10/618,331	filed on	11 July 2003
application no.		filed on	

- D. ☐ The present international application ☐ is identical ☐ contains less subject matter than that found in the prior U.S. application(s) identified in paragraph C.
- E. ☐ The present international application ☐ contains additional subject matter not found in the prior U.S. application(s) identified in paragraph C. above. The additional subject matter is found on pages and ☐ DOES NOT ALTER ☐ MIGHT BE CONSIDERED TO ALTER the general nature of the invention in a manner which would require the U.S. application to have been made available for inspection by the appropriate defense agencies under 35 U.S.C. 181 and 37 CFR 5.1. See 37 CFR 5.15

III. ☐ A Response to an Invitation from the RO/US. The following document(s) is (are) enclosed:

- A. ☐ A Request for An Extension of Time to File a Response
- B. ☐ A Power of Attorney (General or Regular)
- C. ☐ Replacement pages:

pages		of the request (PCT/RO/101)	pages		of the figures
pages		of the description	pages		of the abstract
pages		of the claims			

- D. ☐ Submission of Priority Documents

Priority document		Priority document	
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- E. ☐ Fees as specified on attached Fee Calculation sheet form PCT/RO/101 annex

IV. ☐ A Request for Rectification under PCT 91 ☐ A Petition ☐ A Sequence Listing Diskette

V. ☐ Other (please specify):

The person signing this form is that:	☐ Applicant	
	☒ Attorney/Agent (Reg. No.) 34,066	Ellen K. Park Typed name of signer
	☐ Common Representative	 Signature

EV3607421US

PCT REQUEST

Original (for SUBMISSION)

0	For receiving Office use only	
0-1	International Application No.	
0-2	International Filing Date	
0-3	Name of receiving Office and "PCT International Application"	
0-4	Form - PCT/RQ101 PCT Request	
0-4-1	Prepared Using	PCT-SAFE [EASY mode] Version 3.50 (Build 0002.158)
0-5	Petition The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	Receiving Office (specified by the applicant)	United States Patent and Trademark Office (USPTO) (RO/US)
0-7	Applicant's or agent's file reference	7050-00
I	Title of invention	CHEWABLE ANTIPLAQUE CONFECTIONERY DENTAL COMPOSITION
II	Applicant	
II-1	This person is:	applicant only
II-2	Applicant for	all designated States except US
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III-1-6	State of nationality	FR
III-1-7	State of residence	US

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II-2	Applicant and/or inventor	
III-2-1	This person is:	applicant and inventor
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III-2-7	State of residence	US
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III-3-2	Applicant for	US only
III-3-4	Name (LAST, First)	SULLIVAN, Richard, J.
III-3-5	Address:	35 Eton Way Somerset, New Jersey 08873 United States of America
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III-3-7	State of residence	US
III-4	Applicant and/or inventor	
III-4-1	This person is:	applicant and inventor
III-4-2	Applicant for	US only
III-4-4	Name (LAST, First)	MASTERS, James G.
III-4-5	Address:	1 Stephen Court Ringoos, New Jersey 08551 United States of America
III-4-6	State of nationality	US
III-4-7	State of residence	US
III-5	Applicant and/or inventor	
III-5-1	This person is:	applicant and inventor
III-5-2	Applicant for	US only
III-5-4	Name (LAST, First)	ROBINSON, Richard, S.
III-5-5	Address:	5 Riverview Terrace Hillsborough, New Jersey 08844 United States of America
III-5-6	State of nationality	US
III-5-7	State of residence	US

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IV-1	Agent or common representative; or address for correspondence The person identified below is hereby/ has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	agent
IV-1-1	Name (LAST, First)	PARK, Ellen, K.
IV-1-2	Address:	COLGATE-PALMOLIVE COMPANY 909 River Road Piscataway, New Jersey 08855 United States of America
IV-1-3	Telephone No.	732-878-7157
IV-1-4	Facsimile No.	732-878-7853
IV-1-5	e-mail	ellen_park@colpal.com
IV-1-6	Agent's registration No.	34055
V	DESIGNATIONS	
V-1	The filing of this request constitutes under Rule 4.9(a), the designation of all Contracting States bound by the PCT on the international filing date, for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents.	
VI-1	Priority claim of earlier national application	
VI-1-1	Filing date	11 July 2003 (11.07.2003)
VI-1-2	Number	10/618,331
VI-1-3	Country	US
VI-2	Priority document request The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s):	VI-1
VII-1	International Searching Authority Chosen	European Patent Office (EPO) (ISA/EP)

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VII	Declarations	Number of declarations	
VII-1	Declaration as to the identity of the inventor	-	
VII-2	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	1	
VII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	1	
VII-4	Declaration of inventorship (only for the purposes of the designation of the United States of America)	-	
VII-5	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	-	

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VIII-2-1	Declaration: Entitlement to apply for and be granted a patent Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent (Rules 4.17(I) and 51bis.1(a)(II)). In a case where the declaration under Rule 4.17(IV) is not appropriate: Name (LAST, First)	in relation to this international application COLGATE-PALMOLIVE COMPANY is entitled to apply for and be granted a patent by virtue of the following:
VIII-2-1(i) v)		an assignment from DU-THUMM, Laurence to COLGATE-PALMOLIVE COMPANY, dated 11 July 2003 (11.07.2003)
VIII-2-1(i) v)		an assignment from SEELES, Lori, H. to COLGATE-PALMOLIVE COMPANY, dated 11 July 2003 (11.07.2003)
VIII-2-1(i) v)		an assignment from SULLIVAN, Richard, J. to COLGATE-PALMOLIVE COMPANY, dated 10 July 2003 (10.07.2003)
VIII-2-1(i) v)		an assignment from MASTERS, James G. to COLGATE-PALMOLIVE COMPANY, dated 11 July 2003 (11.07.2003)
VIII-2-1(i) v)		an assignment from ROBINSON, Richard, S. to COLGATE-PALMOLIVE COMPANY, dated 10 July 2003 (10.07.2003)
VIII-2-1(i) x)	This declaration is made for the purposes of:	all designations

PCT REQUEST

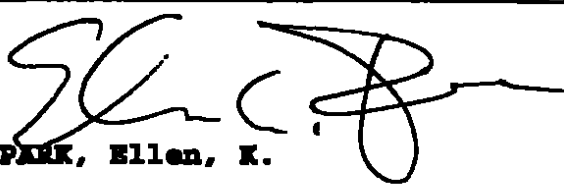
Original (for SUBMISSION)

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VII-3-1	Declaration: Entitlement to claim priority Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application specified below, where the applicant is not the applicant who filed the earlier application or where the applicant's name has changed since the filing of the earlier application (Rules 4.17(II) and 81bis.1(a)(II)) Name:	in relation to this international application COLGATE-PALMOLIVE COMPANY is entitled to claim priority of earlier application No. 10/618,331 by virtue of the following:
VIII-3-1(f) v)		an assignment from DU-THUMM, Laurence to COLGATE-PALMOLIVE COMPANY, dated 11 July 2003 (11.07.2003)
VIII-3-1(f) v)		an assignment from SEELES, Lori, H. to COLGATE-PALMOLIVE COMPANY, dated 11 July 2003 (11.07.2003)
VIII-3-1(f) v)		an assignment from SULLIVAN, Richard, J. to COLGATE-PALMOLIVE COMPANY, dated 10 July 2003 (10.07.2003)
VIII-3-1(f) v)		an assignment from MASTERS, James G. to COLGATE-PALMOLIVE COMPANY, dated 11 July 2003 (11.07.2003)
VIII-3-1(f) v)		an assignment from ROBINSON, Richard, S. to COLGATE-PALMOLIVE COMPANY, dated 10 July 2003 (10.07.2003)
VIII-3-1(f) x)	This declaration is made for the purposes of:	all designations

PCT REQUEST

Original (for SUBMISSION)

IX	Check list	number of sheets	electronic file(s) attached
IX-1	Request (including declaration sheets)	7	✓
IX-2	Description	14	-
IX-3	Claims	1	-
IX-4	Abstract	1	✓
IX-5	Drawings	0	-
IX-7	TOTAL	23	
	Accompanying items	paper document(s) attached	electronic file(s) attached
IX-8	Fee calculation sheet	✓	-
IX-17	PCT-SAFE physical media	-	✓
IX-19	Figure of the drawings which should accompany the abstract		
IX-20	Language of filing of the international application	English	
X-1	Signature of applicant, agent or common representative		
X-1-1	Name (LAST, First)	PARK, Ellen, K.	
X-1-2	Name of signatory		
X-1-3	Capacity		

FOR RECEIVING OFFICE USE ONLY

10-1	Date of actual receipt of the purported international application	
10-2	Drawings:	
10-2-1	Received	
10-2-2	Not received	
10-3	Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application	
10-4	Date of timely receipt of the required corrections under PCT Article 11(2)	
10-5	International Searching Authority	ISA/EP
10-6	Transmittal of search copy delayed until search fee is paid	

FOR INTERNATIONAL BUREAU USE ONLY

11-1	Date of receipt of the record copy by the International Bureau	
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CHEWABLE ANTIPLAQUE CONFECTIONERY DENTAL COMPOSITION**BACKGROUND OF THE INVENTION**

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1. Field of the Invention

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The present invention relates to a chewable confectionery composition which reduces the presence of dental plaque from the chewing surfaces of teeth and more particularly the invention relates to a chewable confectionery composition which contains a small but effective amount of an enzyme effective to disrupt or interfere with plaque formation and adhesion to tooth surfaces.

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2. The Prior Art

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Oral compositions such as toothpastes, gels and mouth washes are designed to loosen and remove plaque in conjunction with 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. 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 problem 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.

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Plaque formation is an ongoing process. Although various oral care products are available to control plaque formation such as toothpastes and mouth rinse, the disadvantage of these products is that only a relatively short time during which the teeth are being brushed or the mouth is being rinsed is available for these preparations to take effect. A further disadvantage of these toothpaste and mouth rinse products is the general infrequency of use, that is, most dental hygiene products are used once or perhaps twice daily and seldom when they are most needed, e.g., after meals and snacks. Thus food deposits which build up as a result of eating throughout the day are left in the oral cavity for long periods of time thereby promoting microbial growth and formation of plaque on tooth surfaces.

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It is known to the art to incorporate antimicrobial agents in oral compositions wherein these agents destroy or inhibit oral bacteria responsible for plaque formation. Other agents are also incorporated in the oral composition to reduce plaque formation on teeth. For example, it is known to incorporate enzymes such as proteases and carbohydrases in oral compositions, which enzymes disrupt or interfere with plaque formation and bacterial adhesion to tooth surfaces.

Chewable tablets and gums have been used as vehicles for introducing various chemical agents to tooth surfaces including enzymes such as amylase enzymes (US 4,740,368) oxidoreductases such as glucose oxidase and lactoperoxidase enzymes (US 4,564,519).

A critical requirement, however, for these compositions is that they are stable and have a long shelf-life, which requirement has limited the use of these compositions because normally, the active agents incorporated in these compositions that provide oral care benefits such as plaque reduction are not stable under ambient conditions of humidity and temperature and as a result the agents quickly become degraded to concentrations of limited efficacy and particularly, enzymes which denature during the manufacturing process.

In view of the inconvenience of using toothpaste and mouth rinse products when away from home, the art is seeking portable products in the form of chewable confections such as tablets and gums which can be used throughout the day, particularly after eating, and which provide antiplaque benefits comparable to those obtained by regular brushing with a toothpaste or use of a mouthrinse.

SUMMARY OF THE INVENTION

In accordance with the present invention, there is provided a chewable confectionery composition such as a chewable tablet or gum comprised of a small but effective amount of a plaque reducing enzyme, a non-cariogenic sweetener and optionally a plasticizing/softening agent.

Due to the inherent nature of the chewable tablet or gum product, prolonged contact with the tooth surfaces is achieved when the product is chewed, forming a paste with saliva containing the enzyme which coats the tooth surfaces. The delivery of the enzyme in a chewable tablet or gum form insures that an adequate dosage of the antiplaque enzyme is deliverable when the product is chewed by the user. The chewable confectionery composition of the present

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invention is portable and can be packaged and stored in a consumers pocket or purse for consumption anytime and anywhere.

5 When the chewable confectionery composition of the present invention is placed within the mouth and chewed, an effective antiplaque amount of the enzyme is released from the composition into the saliva where it can reach the surface of the teeth to prevent further plaque accumulation. The tablet or gum of the present invention is formed so as to release the enzyme over a period of 0.5 to 2 minutes. Consistent daily use of the chewable tablets or gums of the present invention will then obtain maximum plaque reduction from the teeth of the consumer.

10 The term "chewable confectionery composition" as used herein includes within its meaning chewing gum, and chewable and orally soluble tablets, troches and lozenges.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

15 The composition of the present invention as stated is a chewable product which reduces plaque and contains as the active ingredient, a protease enzyme. The product is preferably sugarless.

20 A representative chewable antiplaque tablet in accordance with the practice of this invention contains about 0.1 to 3% by weight of an enzyme, 0.5 to 5% by weight of a combination plasticizing/softening ingredient and about 50 to about 90% by weight of a non-cariogenic sweetener. In addition to the ingredients discussed above for tablets, chewable gum compositions will contain 10 to 40% by weight of a gum base.

25 As water promotes the denaturization of the papain enzyme, the presence of water in the chewable confectionery product of the present invention should be at relatively low concentrations in order to impart maximum stability and shelf life to the chewable. For this purpose, it has been found essential to limit the total amount of water present in the chewable product to no more than 5% by weight.

Enzymes

30 The enzymes useful in the practice of the present invention include carbohydrases such as glucoamylase and enzymes extracted from natural fruit products such as proteases which breakdown or hydrolyze proteins.

Protease enzymes useful in the practice of the present invention include those extracted from natural fruit products. The proteolytic enzymes are obtained from natural sources or by the action of microorganisms having a nitrogen source and a carbon source. Examples of proteolytic enzymes useful in the practice of the present invention include the naturally occurring enzymes papain (from papaya), bromelain (from pineapple), as well as serine proteases such as chymotrypsin. Additional enzymes include ficin and alcalase. Papain is a protease enzyme preferred for use in the practice of the present invention, the papain having an activity of 150 to 939 MCU per milligram as determined by the Milk Clot Assay Test of the Biddle Sawyer Group (see J. Biol. Chem., vol. 121, pages 737-745). The protease enzymes are included in the compositions of the present invention at a concentration of about 0.1 to about 3% by weight and preferably about 0.2 to about 2% by weight.

Enzymes which may beneficially be used in combination with the proteolytic enzymes and glucoamylase enzymes include carbohydrases such as glucoamylase, alpha-amylase, beta-amylase, , tannase and lipases such as plant lipase, gastric lipase and pancreatic lipase.

Glucoamylase is a saccharifying glucoamylase of *Aspergillus niger* origin cultivated by fermentation. This enzyme can hydrolyze both the alpha-D-1,6 glucosidic branch points and the alpha-1,4 glucosidic bonds of glucosyl oligosaccharides. Additional carbohydrases useful in accordance with this invention are alpha and beta-amylase, dextranase and mutanase. Glucoamylase is a preferred enzyme and is incorporated in the oral composition of the present invention at a concentration of about 0.001 to 2% by weight and preferably about 0.01 to 0.55% by weight.

The lipase enzyme is derived from a select strain of *Aspergillus niger*, exhibiting random cleaving of the 1,3 positions of fats and oils. The enzyme has maximum lipolytic activity at pH 5.0 to 7.0 when assayed with olive oil. The enzyme has a measured activity of 120,000 lipase units per gram. The lipase may be included in the dentifrice composition at a concentration of about 0.010 to about 5.0% by weight and preferably about 0.02 to about 0.10 % by weight.

The presence of tannase enzyme can be further beneficial in facilitating the breakdown of extrinsic stain. Tannase enzymes have been purified from *Aspergillus niger* and *Aspergillus allianceus* and are useful in the hydrolysis of tannins, known to discolor the tooth surface.

Other suitable enzymes which can comprise the present invention include lysozyme, derived from egg white, which contains a single polypeptide chain crosslinked by four disulfide bonds having a molecular weight of 14,600 daltons. The enzyme can exhibit antibacterial properties

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by facilitating the hydrolysis of bacterial cell walls cleaving the glycosidic bond between carbon number 1 of N-acetylmuramic acid and carbon number 4 of N-acetyl-D-glucosamine, which in vivo, these two carbohydrates are polymerized to form the cell wall polysaccharide. Additionally, pectinase, an enzyme that is present in most plants facilitates the hydrolysis of the polysaccharide pectin into sugars and galacturonic acid. Finally, glucanase, which may be utilized to catalyze the breakdown of complex carbohydrates to glucans and the hydrolysis of beta glucan to glucose.

Enzyme Stabilizing Agents

Enzyme stabilizing agents which protect the enzyme from inactivation by chelating metal impurities present in the chewable confectionery composition of the present invention may be incorporated in the composition include ethylene diamine tetraacetic acid (EDTA) and sodium gluconate at concentrations between 0.01 and 1% by weight, preferably between 0.1 and 0.5% by weight. Agents stabilizing the enzyme against oxidation include reducing agents such as sodium bisulfite, metal gallates, potassium stannate, sodium stannate, ammonium sulfate, 3,5-di-tert-butyl-4-hydroxytoluene (BHT), Vitamin E (α , β , γ , forms) /Vitamin E acetate and ascorbic acid. Potassium stannate is an enzyme stabilizing agent preferred for use in the practice of the present invention. The reducing agent is present in the oral composition of the present invention at a concentration between about 0.05 to about 1.5% by weight, preferably between about 0.1 and about 0.75% by weight.

TABLETS

Plasticizing/Softening Agents

Plasticizing/softening agents suitable for use in the preparation of tablets in accordance with the practice of this invention, include propylene glycol, glycerol, acetylated monoglyceride, glyceryl triacetate, glyceryl diacetate, lecithin, glycerin, and mixtures thereof. In a preferred embodiment of this invention, a combination of lecithin and glycerin is used, generally in amounts of about 0.5% to about 3.0% by weight, 0.1% to about 1.0% lecithin and about 1.0% to about 1.0% by weight glycerin by weight, based on the weight of the total chewable tablet composition.

Sweeteners

The sweetening agent ingredient used in the practice of the present invention include bulk sweeteners such as the polyols of 5 to 12 carbon atoms substituted with 5 to 9 hydroxyl groups such as sugar alcohols including xylitol, sorbitol, mannitol. Sugar alcohols provide bulk or texture to the chewable compositions of the present invention and are utilized in amounts of about 25% to about 90% by weight preferably about 40% to about 85% by weight

Artificial sweeteners include as sodium or calcium saccharin salts, cyclamate salts, such as the sodium salt and the like, and the free acid form of saccharin; dipeptide based sweetening agents such as L-aspartyl-L-phenyl-alanine methyl ester, dihydrochalcone; glycyrrhizin; and the synthetic sweetener 3,6-dihydro-6-methyl-1, 1,2,3-oxathiazin-4-one-2,2-dioxide, particularly the potassium (Acesulfame-K), sodium and calcium salts. Artificial sweeteners are present in the chewable confectionery compositions of the present invention at a concentration of about 0.1 to about 1% by weight.

Preferred bulk sweeteners include Lycasin, a commercially available mixture of sorbitol, malitol and high molecular weight dextrans disclosed in Re 26,969 and Isomalt, a sugar alcohol of a disaccharide such as alpha-D-glucopyranosyl-1, 6-mannitol, its isomer, alpha, D-glucopyranosyl-1, 6-sorbitol or a mixture thereof which is obtained by the hydrogenation of palatinose which is converted from sucrose as a raw material with glycosyltransferase. A preferred artificial sweetener is aspartame.

In a preferred embodiment of this invention, the sweetening agent used is a combination of an artificial sweetener such as aspartame and acesulfame and the bulk sweeteners such as Lycasin and Isomalt, the artificial sweetener being present generally in amounts of about 0.05% to about 0.3% by weight and preferably about 0.18% to about 0.22% by weight and about 40% to about 60% by weight, preferably about 45% to about 55% by weight Lycasin and about 15% to about 35% by weight preferably about 20% to about 30% by weight Isomalt.

Flavoring Agents

One or more flavoring agents in liquid powder or encapsulated form are used in the chewable composition of this invention. A variety of flavors known in the art may be used, including essential oils, such as cinnamon, spearmint, peppermint, menthol, birch, anise wintergreen oil and eucalyptus oil. Natural fruit flavors derived from the essence of fruits, such as apple, pear, peach, strawberry, cherry, apricot, orange, watermelon, banana and the like; bean derived flavors such as coffee, cocoa and the like; wine derived curacao zin and the like, and pungent materials, such as affinin, pepper, mustard and the like. Flavoring agents are incorporated in the chewable confectionery compositions at a concentration of about 0.5 to about 5% by weight and preferably about 1.0 to about 3.0% by weight.

Other Ingredients

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Calcium salts may be incorporated in the chewable compositions of the present invention as fillers and anticavity agents. Examples of the calcium salts to be used in the present invention as the anticaries agent are, for example, calcium chloride, calcium nitrate, calcium sulfate, dicalcium phosphate dihydrate, calcium carbonate, calcium citrate, calcium hydrogen pyrophosphate, calcium gluconate, calcium glycerophosphate, calcium hydroxide, calcium oxide, calcium silicate and the like, but not limited thereto. The calcium salt is present in the tablet or gum at a concentration of about 5 to about 20% by weight and preferably 7 to 10% by weight. Alkaline agents such as sodium bicarbonate may be incorporated in the chewable confectionery composition of the present invention to provide additional cleaning and breath freshening properties to the composition.

Chewing Gum

The chewing gum of the present invention is preferably a sugarless chewing gum containing the enzyme, as sugarless gums do not promote tooth decay. Chewing gum formulations in which the enzymes of the present invention may be incorporated are well known in the art and typically contain, in addition to, a chewing gum base, one or more plasticizing agents; at least one sweetening agent and at least one flavoring agent.

Gum base materials suitable for use in the practice of this invention are well known in the art and include natural or synthetic gum bases or mixtures thereof. Representative natural gums or elastomers include chicle, natural rubber, jelutong, balata, guttapercha, lechi caspi, sorva, guttakay, crown gum, perillo, or mixtures thereof. Representative synthetic gums or elastomers include butadiene-styrene copolymers, polyisobutylene and isobutylene-isoprene copolymers.

The gum base is incorporated in the chewing gum product at a concentration of about 10 to about 40% by weight and preferably about 20 to about 35% by weight.

Plasticizing/softening agents commonly used in chewing gum compositions are suitable for use in this invention, including gelatin, waxes and mixtures thereof in amounts of 0.1 to 5% by weight.

The sweetening agent ingredient used in the practice of this invention may be selected from a wide range of materials. Bulk sweeteners include the same sweeteners used for the preparation of chewable tablets as are artificial sweeteners. The bulk sweetener is present in the chewing gum composition of the present invention in amounts of about 40 to about 80 % by weight and preferably about 50 to about 75 % by weight. The artificial sweetener is present in the chewing

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gum composition of the present invention in amounts of about 0.1 to about 2% by weight and preferably about 0.3 to 1% by weight.

In addition to the ingredients listed above, the gum compositions may also include conventional additives such as colorants, flavoring agents and the like. For example, titanium dioxide may be utilized as a colorant. A variety of flavors known in the art may be used, including essential oils, such as cinnamon, spearmint, peppermint, menthol, birch, anise and the like; natural fruit flavors derived from the essence of fruits, such as apple, pear, peach, strawberry, cherry, apricot, orange, watermelon, banana and the like; bean-derived flavors, such as coffee, cocoa and the like. Flavoring agents are incorporated in the chewing gum formulation at a concentration of about 0.5 to about 5 % by weight and preferably 1 to 3 % by weight.

Method of Manufacture

The challenge in incorporating enzymes into the confectionary composition is maintaining enzymatic stability and activity during storage. Enzymes are quaternary proteins whose structure, function, and stability are sensitive to chemical environment and processing parameters. Enzymes denature in harsh chemical environment and at high temperatures. Formulation and processing procedures are optimized at low moisture and low temperature for both the enzyme chewable tablet and the enzyme gum to preserve enzymatic activity and in vivo efficacy.

The chewable composition of the present invention is made by any suitable process where the protease enzyme is incorporated into the solid base material such that no water or a limited amount of ingredients that absorb water are used that would result in undesirable amounts of water being introduced into the composition during processing or storage. Further, at the time the enzyme is introduced into ingredients used to prepare the chewable composition that the temperature at the time of addition is less than about 80°C. Therefore, it is critical to the practice of the present invention that the composition contain less than 5% by weight water and preferably less than 3% by weight water and that the temperature at which processing of the enzyme occurs be less than about 80°C. The presence in the composition of water in amounts greater than 5% by weight or the use of temperatures in excess of 80°C will act to denature the protease enzyme thereby substantially reducing the efficacy of the enzyme in effecting plaque reduction on teeth.

One method for manufacturing the composition of the invention comprises first heating the base material to a temperature sufficient to drive off any water in the composition. The base

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material is then cooled to a temperature at which the enzyme and other temperature sensitive ingredients such as plasticizers, other sweeteners are incorporated and mixed into the base material.

- 5 Formulations, equipment and processing techniques have been well developed in the art for preparing and packaging chewing gum and chewable tablets and lozenges. As the enzyme is subject to deterioration and inactivation under conditions such as high shear and elevated temperatures, processing conditions are controlled during the time period that the enzymes are admixed with the other ingredients of the formulation and converted into finished products so
10 that the temperature at the time of admixture does not exceed about 80°C for any extended period of time.

The tablets of the confectionary composition of the present invention are conventionally made by grinding the ingredients once mixed and then compressing or molding the ingredients to
15 form a suitable means for the delivery of the enzyme. In order to produce tablets it is necessary to have a free flowing material which has good self binding properties and which will not stick to the molding or compression equipment.

An illustrative procedure for formulating the chewing gum composition is as follows: the gum
20 base is first melted in a heated kettle at 55°-65°C. One or more of the sweeteners are then added to the gum base followed by one or more flavors, plasticizer. All ingredients are then mixed for a sufficient period of time to ensure adequate dispersion. The mixture is then allowed to cool and the enzyme is added and is cut into suitable serving sizes.

25 In order to enhance shelf stability, in addition to the admixture used in the preparation of the chewable product being substantially free of water, the finished product should be packaged in a manner so as to minimize exposure to air and moisture.

30 The following Examples are illustrative of the present invention, but it is understood that the invention is not limited thereto.

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Example I

Enzyme (papain) containing tablet and gum compositions were prepared using conventional base ingredients as set forth in Tables I and II below.

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TABLE I		
CHEWABLE TABLET		
Ingredient		Wt. %
Papain		0.5
Lycasin 75%		48.9
Isomalt		23.1
Hydrogenated vegetable oil		8.7
Water		4.8
Gelatin (40% solution)		2.9
Starch coated dicalcium phosphate		8.7
Mono-diglyceride mixture		0.8
Lecithin		0.3
Aspartame		0.05
Aspartame K		0.05
Vanillin		0.05
Glycerin		0.1
Sodium bicarbonate		0.10
Mint flavor		0.19

The chewable tablet of Table I was prepared by boiling the Isomalt, Lycasin, water, fat, mono and diglyceride mixture, glycerin, and lecithin to 267-268°F (131°C) after which glycerin was added and the mixture cooled to 140°F (60°C). Thereafter sodium bicarbonate, papain, dicalcium phosphate and the remaining ingredients were added. Thereafter the mixture cooled to room temperature 72-77°F (23°C) was ground into powder and compressed into a tablet using a tablet press.

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TABLE II		
CHEWING GUM		
Ingredient	Wt. %	
Gum base	31.20	
Sorbitol	28.08	
Mannitol	5.23	
Papain	1.00	
Accesulfame K	0.16	
Aspartame	0.16	
Menthol powder	1.00	
Liquid flavor	0.47	
Isomalt PF	11.70	
Isomalt DC	16.00	
Anticaking agents*	4.00	
Flavor	2.00	

* Magnesium stearate, talc, silica gel.

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Papain Enzyme Activity

Papain activity was measured and monitored in the papain containing chewable tablets and chewing gums using the Protease Detection kit from Panvera Corp. The activity kit quantifies protease activity using a fluorescein thiocarbamoyl (FTC)-casein substrate. FTC-casein is attacked by the protease, breaking down casein into TC-peptides. The amount of protease activity is determined by measuring the fluorescence expressed as relative fluorescence units (RFU). The fluorescence signal generated is proportioned to the level of activity of papain in the tablet or gum delivery system. For the purposes of comparison, chewable tablets designated "Tablet A" and chewing gum designated "Chewing Gum B" were prepared in which papain was not included in these compositions. The papain activities of the chewable tablet or Table I and the chewing gum of Table II are recorded in Tables III and IV below as are the papain activities of comparative tablet and gum compositions.

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TABLE III		
Protease Activity		
Composition	Chewable Tablet Fluorescence	
	4 Weeks (RFU)	8 Weeks (RFU)
Table I	29,000	30,000
A	2,000	2,000

✓ 69

TABLE IV	
Chewing Gum Fluorescence	
Composition	4 Weeks (RFU)
Table II	38,000
B	1,500

5 The results recorded in Tables III and IV indicate that the enzyme activity in papain when incorporated in a chewable tablet or gum is retained over at least a 4 week period.

In Vivo Plaque Reduction Efficacy

10 The chewable tablet of Table I was tested for plaque reduction at 2-and 5- hours after chewing by human volunteers using plaque grown in vivo in an intra-oral retainer on hydroxyapatite disks. Confocal microscopy was used to visualize and quantify the changes in plaque coverage and plaque ultrastructure. Plaque removal was also measured by conventional light microscopy by staining the plaque before and after treatment with crystal violet indicator and measuring the changes in color intensity. Image Pro Analysis Software was used to perform the image analysis and the quantitative measurements. The color intensity was measured and used to
15 determine stain removal. The greater the intensity, the greater the cleaning efficacy. These results are shown in Table V below.

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TABLE V

Chewable Tablet Plaque Reduction Efficacy

	Total Area (Microns²)	% Reduction from Baseline	Average Cluster Area (Microns²)	% Reduction
Baseline	8681	—	54.45	—
2 hours	3537	59	20.10	63
5 hours	2959	66	26.18	52

5 Confocal images were made of the plaque before treatment (baseline) and 2 and 5 hours after treating with the tablet. Qualitatively, images showed that there is less bacterial coverage 2 and 5 hours after treatment in comparison to baseline. Image analysis was used to quantify these observations. The results recorded in Table V indicated that the total plaque area, measured by pixel counting, was significantly reduced in comparison to baseline and 2 and 5 hours after treatment. Table V also shows that the average cluster area of the plaque bacteria was significantly reduced after treatment demonstrating the significant efficacy in reducing plaque without the aid of mechanical assistance.

15 In a second study, the plaque before and after staining with crystal violet was viewed by conventional light microscopy. Image analysis was used to determine the white intensity measured in pixels, the higher the pixel number, the whiter the stain. The results from this study are shown in Table VI. The disks stained at baseline were more intensely colored (blue) than the disks stained 2 hours after treatment with the papain containing chewable tablet. The disks were 47.3% whiter than baseline, indicating less staining and therefore, less plaque. Similar results were observed with the papain chewing gum of Table II as shown in Table VII below.

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TABLE VI Chewable Tablet Staining Removal (White Intensity)					
	*	*	*	Average	Improvement from Baseline
Baseline	125	100	—	112.5	—
Treatment	240	200	200	213.3	47.3%

*Inventors: What are these units.

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TABLE VII Chewing Gum Plaque Reduction Efficacy				
	Total Area (Microns^2)	% Reduction from Baseline	Average Cluster Area (Microns^2)	% Reduction
Baseline	47,832	—	2897	—
2 hours	38,137	16	2446	15
5 hours	27,267	52	1398	52

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Claims

What is claimed is:

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1. A chewable confectionery composition delivering to tooth surfaces a unit dose of a plaque reducing enzyme the composition comprising a small but effective amount of an enzyme which functions to disrupt or interfere with plaque formation and adhesion to tooth surfaces and a non-cariogenic sweetener, the enzyme being incorporated in the composition at a temperature less than about 80°C.

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2. The chewable confectionery composition of claim 1 wherein the enzyme is papain.

3. The chewable confectionery composition of claim 1 wherein the composition is in the form of a tablet.

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4. The chewable confectionery composition of claim 1 wherein the composition is a chewing gum.

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5. The chewable confectionery composition of claim 1 wherein the composition has a moisture content of less than about 5% by weight.

6. The chewable composition of claim 2 wherein the composition contains the enzyme papain at a concentration of about 0.1 to about 3.0% by weight.

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7. The chewable confectionery composition of claim 1 wherein the non-cariogenic sweetener is a sugar alcohol.

8. The chewable confectionery composition of claim 1 wherein the non-cariogenic sweetener is an artificial sweetener.

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9. The chewable confectionery composition of claim 1 wherein the non-cariogenic sweetener is a sugar alcohol of a disaccharide.

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10. The chewable confectionery composition of claim 1 wherein the non-cariogenic sweetener is present in the composition at a concentration of about 25 to about 95% by weight.

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ABSTRACT

- 5 **A chewable confectionery dental composition delivering to the mouth a unit dose of a plaque reducing enzyme the composition comprising an enzyme and a non-cariogenic sweetener, the enzyme being incorporated in the composition at a temperature less than about 80°C.**

PCT

GENERAL POWER OF ATTORNEY

(for several international applications filed under the Patent Cooperation Treaty)

(PCT Rule 90.5)

The undersigned person(s):

(Family name followed by given name; for a full legal entity, full official designation. The address must include postal code and name of country.)

COLGATE-PALMOLIVE COMPANY
300 Park Avenue
New York, New York 10022
United States of America

hereby appoint(s) the following person as:

☒ agent

☐ common representative

Name and address

(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

Bernard Lieberman, Rosemary M. Milano, Ellen K. Park and Clifford E. Wilkins, Jr. of

COLGATE-PALMOLIVE COMPANY
909 River Road.
P.O. Box 1343
Placataway, New Jersey 08855-1343
United States of America

to represent the undersigned before

☒ all the competent International Authorities

☐ the International Searching Authority only

☐ the International Preliminary Examining Authority only

in connection with any and all international applications filed by the undersigned with the following Office

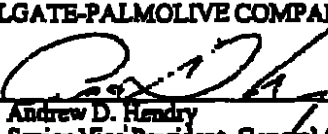
RO/US

as receiving Office

and to make or receive payments on behalf of the undersigned.

Signature(s) (where there are several persons, each of them must sign; next to each signature, indicate the name of the person signing and the capacity in which the person signs, if such capacity is not obvious from reading this power):

COLGATE-PALMOLIVE COMPANY

By 
Andrew D. Hendry
Senior Vice President, General Counsel and Secretary

Date: April 8, 2004

PCT (ANNEX - FEE CALCULATION SHEET)

Original (for SUBMISSION)

(This sheet is not part of and does not count as a sheet of the international application)

0	For receiving Office use only	
0-1	International Application No.	
0-2	Date stamp of the receiving Office	
0-4	Form PCT/RO/101 (Annex) PCT Fee Calculation Sheet Prepared Using	PCT-SAFE [EASY mode] Version 3.50 (Build 0002.158)
0-8	Applicant's or agent's file reference	7050-00
2	Applicant	COLGATE-PALMOLIVE COMPANY
12	Calculation of prescribed fees	fee amount/multiplier Total amounts (USD)
12-1	Transmittal fee T	⇒ 300
12-2-1	Search fee S	⇒ 1818
12-2-2	International search to be carried out by	EP
12-3	International filing fee (first 30 sheets) H	1035
12-4	Remaining sheets	0
12-5	Additional amount (A)	0
12-6	Total additional amount I2	0
12-7	H + I2 = I	1035
12-12	EASY Filing reduction R	-74
12-13	Total international filing fee (I-R) I	⇒ 961
12-14	Fee for priority document Number of priority documents requested	1
12-15	Fee per document (P)	20
12-16	Total priority document fee: P	⇒ 20
12-17	TOTAL FEES PAYABLE (T+S+H+P)	⇒ 3099
12-19	Mode of payment	authorization to charge deposit account
12-20	Deposit account instructions The receiving Office	United States Patent and Trademark Office (USPTO) (RO/US)
12-20-1	Authorization to charge the total fees indicated above.	✓
12-20-2	Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.	✓
12-20-3	Authorization to charge the fee for priority document.	✓
12-21	Deposit account No.	03-2457
12-22	Date	09 July 2004 (09.07.2004)
12-23	Name and signature	DUNNE, Elizabeth, M. <i>Elizabeth M. Dunne</i>

PATENT COOPERATION TREATY

Corrected version

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From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT AND
THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY, OR THE DECLARATION

To:

COLGATE PALMOLIVE COMPANY
Attn. Park, Ellen K.
909 River Road
Piscataway, NJ 08855
UNITED STATES OF AMERICA

(PCT Rule 44.1)

Date of mailing
(day/month/year)

07/12/2004

Applicant's or agent's file reference

7050-00

FOR FURTHER ACTION

See paragraphs 1 and 4 below

International application No.

PCT/US2004/021873

International filing date
(day/month/year)

09/07/2004

Applicant

COLGATE - PALMOLIVE COMPANY

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes
1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.
3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

- ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.
- ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Reminders

Shortly after the expiration of 18 months from the priority date, the International application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

Within 18 months from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later); otherwise, the applicant must, within 20 months from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of 30 months (or later) will apply even if no demand is filed within 18 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the International Searching Authority



European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 851 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Maria Cajide

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report and the written opinion of the International Searching Authority, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the letter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only (see *PCT Applicant's Guide*, Annexes B1 and B2).

The attention of the applicant is drawn to the fact that amendments to the claims under Article 19 are not allowed where the International Searching Authority has declared, under Article 17(2), that no international search report would be established (see *PCT Applicant's Guide*, Volume I/A, paragraph 286).

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 18 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 7050-00	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/US2004/021873	International filing date (day/month/year) 09/07/2004	(Earliest) Priority Date (day/month/year) 11/07/2003
Applicant COLGATE - PALMOLIVE COMPANY		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.

2. ☐ Certain claims were found unsearchable (See Box II).3. ☐ Unity of invention is lacking (see Box III).

4. With regard to the title,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regards to the drawings,

- a. the figure of the drawings to be published with the abstract is Figure No. _____

☐ as suggested by the applicant.

☐ as selected by this Authority, because the applicant failed to suggest a figure.

☐ as selected by this Authority, because this figure better characterizes the invention.

- b. ☐ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/US2004/021873

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A23G3/00 A23G3/30 A61K7/16 A61K7/28

corrected version

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A23G A61Q A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, FSTA, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ES 2 131 006 A (BIOCOSMETICS S L) 1 July 1999 (1999-07-01) the whole document	1-10
X	GB 1 294 767 A (DAINIPPON PHARMACEUTICAL) 1 November 1972 (1972-11-01)	1,3-5, 7-10
Y	page 4, lines 17-25 - lines 71-85 page 5, line 1 - line 16; claims; example 9	2,6
X	US 4 178 362 A (HOOGENDOORN HENDRIK ET AL) 11 December 1979 (1979-12-11)	1,3-5,7, 9,10
Y		2,6
	-/--	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"S" document member of the same patent family

Date of the actual completion of the international search

3 December 2004

Date of mailing of the international search report

- 7 DEC 2004

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Boddaert, P

INTERNATIONAL SEARCH REPORT

corrected version

International Application No.

PCT/US2004/021873

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PATENT ABSTRACTS OF JAPAN vol. 0164, no. 73 (C-0991), 2 October 1992 (1992-10-02) - & JP 4 173056 A (AJINOMOTO CO INC), 19 June 1992 (1992-06-19)	1,4,7-10
Y	abstract	2,6
X	----- US 2002/006385 A1 (TSUCHIYA RIE) 17 January 2002 (2002-01-17) paragraphs [0015], [0037], [0040]; claims	1-4,8
X	----- US 3 235 460 A (ENNEVER JOHN J) 15 February 1966 (1966-02-15)	1,4,8
Y	column 1 - column 3; claims; examples	2,6
X	----- PATENT ABSTRACTS OF JAPAN vol. 0123, no. 49 (C-529), 20 September 1988 (1988-09-20) & JP 63 104908 A (SHISEIDO CO LTD), 10 May 1988 (1988-05-10)	1,4,8
	abstract	
X	----- US 4 353 891 A (GUGGENHEIM BERNHARD ET AL) 12 October 1982 (1982-10-12)	1
	claims; example 4	
X	----- PATENT ABSTRACTS OF JAPAN vol. 0145, no. 71 (C-0790), 19 December 1990 (1990-12-19) - & JP 2 258816 A (KAO CORP), 8 October 1990 (1990-10-08)	1
	abstract	
Y	----- US 5 747 005 A (BARELS RONALD R ET AL) 5 May 1998 (1998-05-05)	2,6
	column 5, line 26 - line 34; claims	
Y	----- GB 824 680 A (MERCK & CO INC) 2 December 1959 (1959-12-02)	2,6
	page 3, line 90 - line 93; example 7	
Y	----- US 4 992 420 A (NEESER JEAN-RICHARD) 12 February 1991 (1991-02-12)	2,6
	column 3, line 1 - line 37	
Y	----- US 5 320 830 A (LUKACOVIC MICHAEL F ET AL) 14 June 1994 (1994-06-14)	2,6
	the whole document	

INTERNATIONAL SEARCH REPORT

Information on patent family members

Corrected version
International Application No.
PCT/US2004/021973

51

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
ES 2131006	A	01-07-1999	ES 2131006 A1 01-07-1999
GB 1294767	A	01-11-1972	JP 49016956 B 25-04-1974
			CA 983869 A1 17-02-1976
			DE 2040440 A1 09-12-1971
			FR 2090333 A6 14-01-1972
			US 3929579 A 30-12-1975
			US 3985869 A 12-10-1976
US 4178362	A	11-12-1979	NL 6908379 A 07-12-1970
			US 4150113 A 17-04-1979
			AT 306243 B 26-03-1973
			BE 751390 A2 03-12-1970
			CA 926777 A1 22-05-1973
			CH 531885 A 31-12-1972
			DE 2027019 A1 17-12-1970
			DK 127839 B 21-01-1974
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			FR 2045815 A1 05-03-1971
			GB 1309282 A 07-03-1973
			IE 34220 B1 05-03-1975
			IL 34588 A 30-06-1974
			IT 1050166 B 10-03-1981
			JP 48038863 B 20-11-1973
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			ZA 7003487 A 27-01-1971
JP 4173056	A	19-06-1992	NONE
US 2002006385	A1	17-01-2002	AU 734737 B2 21-06-2001
			AU 9621398 A 10-05-1999
			CA 2305804 A1 29-04-1999
			CN 1275906 T 06-12-2000
			WO 9920239 A1 29-04-1999
			EP 1023037 A1 02-08-2000
			JP 2001520179 T 30-10-2001
US 3235460	A	15-02-1966	BE 642516 A
JP 63104908	A	10-05-1988	NONE
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			AT 309364 B 10-08-1973
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			AU 468059 B2 18-12-1975
			AU 3474371 A 03-05-1973
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			ES 396270 A1 01-01-1975
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			IE 35734 B1 12-05-1976
			IT 1043849 B 29-02-1980

INTERNATIONAL SEARCH REPORT

Information on patent family members

corrected version

International Application No

PCT/US2004/021873

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4353891	A	JP 56045587 B	27-10-1981
		NL 7114567 A ,B,	28-04-1972
		NO 135147 B	08-11-1976
		NO 762862 A ,B,	27-04-1972
		SE 400091 B	13-03-1978
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JP 2250816	A	08-10-1990	NONE
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		AT 86475 T	13-10-1989
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		JP 8505390 T	29-04-1996
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		WO 9415579 A1	16-12-1996
		US 5437856 A	21-07-1994
			01-08-1995

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43bis.1)**

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/US2004/021873

International filing date (day/month/year)
09.07.2004

Priority date (day/month/year)
11.07.2003

International Patent Classification (IPC) or both national classification and IPC
A23G3/00, A23G3/30, A61K7/16, A61K7/28

Applicant
COLGATE-PALMOLIVE COMPANY

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 68.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:  European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Boddaert, P Telephone No. +31 70 340-3471 
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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

~~Submitted version~~ 25

International application No.
PCT/US2004/021873

Box No. II Priority

1. ☒ The following document has not been furnished:

- ☒ copy of the earlier application whose priority has been claimed (Rule 43bis.1 and 66.7(a)).
- ☐ translation of the earlier application whose priority has been claimed (Rule 43bis.1 and 66.7(b)).

Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43bis.1 and 84.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	
	No: Claims	1-10
Inventive step (IS)	Yes: Claims	
	No: Claims	1-10
Industrial applicability (IA)	Yes: Claims	1-10
	No: Claims	

2. Citations and explanations

see separate sheet

**WRITTEN PINION F THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/US2004/021873

Re Item V

Reference is made to the following documents :

- D1 : ES 2 131 006 A (BIOCOSMETICS S L) 1 July 1999 (1999-07-01)
D2 : GB 1 294 767 A (DAINIPPON PHARMACEUTICAL) (1972-11-01)
D3 : US 4 178 362 A (HOOGENDOORN HENDRIK ET AL) (1979-12-11)
D4 : PATENT ABSTRACTS OF JAPAN vol. 0164, no. 73 (C-0991), 2 October 1992
(1992-10-02) -& JP 4 173056 A (AJINOMOTO CO INC), 19 June 1992 (1992-06-19)
D5 : US 2002/006385 A1 (TSUCHIYA RIE) 17 January 2002 (2002-01-17)
D6 : US 3 235 460 A (ENNEVER JOHN J) 15 February 1966 (1966-02-15)

Remark :

a. The terms 'about', 'a small but effective amount', 'an enzyme which functions to disrupt or interfere with plaque formation' used in claims 1,5,6,10 are either relative terms or define the subject-matter in terms of the result to be achieved or do not appear to have a precise meaning, contrary to Article 6 PCT. These unclear features have not been taken into account for assessing novelty.

b. Claim 1 refers to a product produced by a specific process ("the enzyme being incorporated in the composition at a temperature less than about 80°C"). Such type of claims are admissible only if the products as such fulfill the requirements for patentability. A product is not rendered novel merely by the fact that it is produced by means of a new process. Claims defining a product in terms of a process are to be construed as claims to the product as such.

1. The present application does not meet the requirements of Article 33(2) PCT because the subject-matter of claims 1-10 is not new.

a. Document D1 discloses (abstract,claims,examples) a chewing gum or a tablet comprising 0.2-5% papain and a non-cariogenic sweetener, the papain enzyme functioning to disrupt or interfere with dental plaque and tartar formation.

The subject-matter of claims 1-10 is therefore not new.

b. Document D2 discloses (p4-p5l.16,ex.9,claims) a chewing gum or a chewable tablet comprising an enzyme for the prevention and treatment of dental plaque and a non-

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/US2004/021873

cariogenic sweetener (artificial sweetener , sugar alcohol).

The subject-matter of claims 1,3-5,7-10 is therefore not new.

c. It appears documents D3 (ex.7-9) , D4 (abstract, examples) , D5 (par. 15, 37,40,claims) and D6 (col.1-3,examples,claims) also deprive claims 1,3-5,7,9,10 ; 1,4,7-10 ; 1-4,8 and 1,4,8 respectively , of novelty.

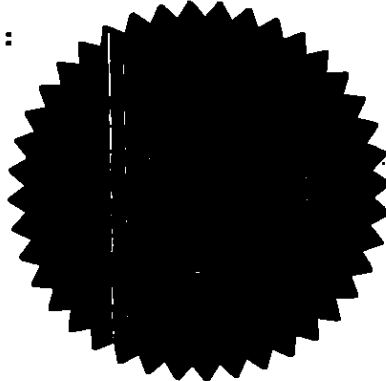
APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. COUNTRY: UNITED STATES OF AMERICA
2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:
ELAINE M FLYNN
3. ACTING IN THE CAPACITY OF:
COUNTY CLERK
4. BEARS THE SEAL/STAMP OF:
COUNTY OF MIDDLESEX

CERTIFIED

5. AT TRENTON, NEW JERSEY
6. THE 28TH DAY OF DECEMBER 2005
7. BY: John E McCormac, CPA, NEW JERSEY TREASURER
8. NO. A247520
9. SEAL/STAMP:
10. SIGNATURE



John E McCormac

92 89

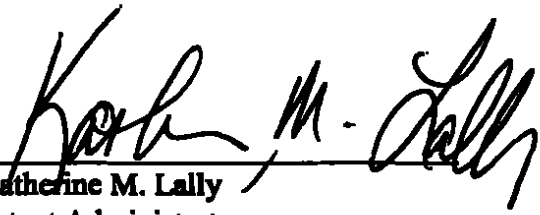
7050-00

COUNTY OF MIDDLESEX

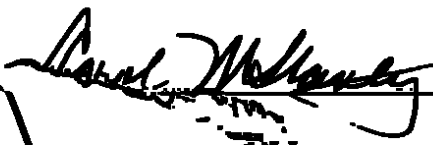
STATE OF NEW JERSEY

UNITED STATES OF AMERICA

I, Katherine M. Lally, of COLGATE-PALMOLIVE COMPANY, do hereby declare that the copy attached hereto is a true photocopy of the assignment in support of U.S. Serial No. 10/618,331 filed July 11, 2003.


Katherine M. Lally
Patent Administrator
Colgate-Palmolive Company

Subscribed and sworn to
before me this 17 day
of November, 2005.


David M. Lally
Notary Public
New Jersey
Notary November 18, 2005

Columbus

92 89

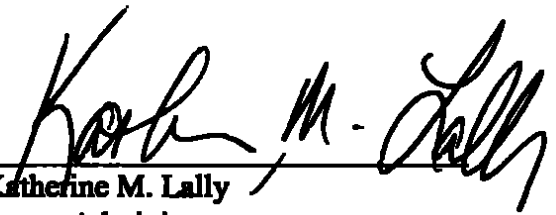
7050-00

COUNTY OF MIDDLESEX

STATE OF NEW JERSEY

UNITED STATES OF AMERICA

I, Katherine M. Lally, of COLGATE-PALMOLIVE COMPANY, do hereby declare that the copy attached hereto is a true photocopy of the assignment in support of U.S. Serial No. 10/618,331 filed July 11, 2003.

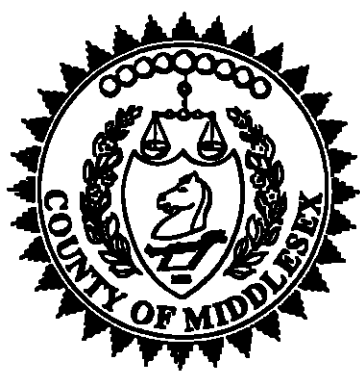

Katherine M. Lally
Patent Administrator
Colgate-Palmolive Company

Subscribed and sworn to
before me this 17 day
of November, 2005.


Carol M. Stauley
Notary Public of New Jersey
My Commission Expires November 18, 2005

Colma Inc

STATE OF NEW JERSEY } ss.
County of Middlesex



I, ELAINE M. FLYNN, Clerk of the County of Middlesex, do hereby certify that

CAROL M STANLEY

whose name is subscribed to the annexed certificate or proof of acknowledgment of the annexed instrument was at the time of taking the same a

NOTARY PUBLIC OF NEW JERSEY

acting in and for said county, duly commissioned and sworn, and qualified to act as such; that as such

NOTARY PUBLIC OF NEW JERSEY

he was duly authorized by the laws of the State of New Jersey to take and certify depositions; to administer oaths and affirmations; to take affidavits and certify the acknowledgment and proof of deeds and other written instruments for lands, tenements and hereditaments to be read in evidence or recorded in this state; and further, that I am well acquainted with the handwriting of such

NOTARY PUBLIC OF NEW JERSEY

and verify that the signature to such proof or acknowledgment is genuine.

IN TESTIMONY WHEREOF, I have hereunto set my hand and affixed the seal of the County of Middlesex, this 18 day of November 20 25

Elaine M. Flynn CLERK

97

ASSIGNMENT

WHEREAS, we, Laurence Du-Thumm, Lori H. Szeles, Richard J. Sullivan, James G. Masters and Richard S. Robinson (below referred to as ASSIGNORS, residing, respectively, as set forth hereinafter, have made an invention for which application for Letters Patent of the United States was filed in the United States Patent and Trademark Office as Application Serial No. USSN 10/618,331 filed July 11, 2003 naming the ASSIGNORS as an inventor, and entitled Chewable Antiplaque Confectionery Dental Composition; and

WHEREAS, Colgate-Palmolive Company, a corporation duly organized and existing under the laws of the State of Delaware, United States of America and having its principal office and place of business at 300 Park Avenue, New York, New York 10022, and offices and place of business at 909 River Road, Piscataway, New Jersey 08855 (below referred to as "ASSIGNEE"), is desirous of obtaining the entire right, title and interest in and to the aforesaid invention and patent application and corresponding patent rights worldwide;

NOW, THEREFORE, in consideration of good and valuable consideration, the receipt and sufficiency of which is hereby acknowledged, ASSIGNORS, by these presents do sell, assign and transfer to ASSIGNEE, the full and exclusive right, title and interest in and to the aforesaid invention, the aforesaid U.S. and all corresponding foreign patent applications, all divisional, continuation, continuation-in-part, reissue and reexamination applications of the aforesaid U.S. application, and all Letters Patent or comparable rights issuing thereon in the United States and in all foreign countries, together with the right of priority under the International Convention for the Protection of Industrial Property, Inter-American Convention Relating to Patents, Designs and Industrial Models, and any other international agreements to which the United States of America adheres, and the ASSIGNORS hereby authorize and request the U.S. Commissioner of Patents and Trademarks and all foreign Patent Offices to issue all Letters Patent or comparable rights issuing on any application as aforesaid to ASSIGNEE, or to its successors, assigns or legal representatives;

ASSIGNORS hereby covenant that ASSIGNORS have full right to convey the entire interest herein assigned, and that ASSIGNORS have not executed, and will not execute, any agreement in conflict herewith;

ASSIGNORS agree to communicate to ASSIGNEE or to its successors, assigns or legal representatives any and all facts known to them or any of them respecting said invention, and without further remuneration to testify in any legal proceeding, sign all lawful papers, execute all divisional, continuation, continuation-in-part, reissue and reexamination applications, make all rightful oaths and generally do all lawful acts to aid ASSIGNEE or its successors, assigns or legal representatives to obtain and enforce proper patent protection for said invention in all countries and to enhance or perfect ASSIGNEE's title in and to the invention and patent rights therein.

ASSIGNORS hereby authorize attorneys for ASSIGNEE to enter on this document any applicable serial numbers and filing dates after ASSIGNORS' execution of this document.

This Assignment is effective as of July 11, 2003.

92

IN TESTIMONY WHEREOF, I hereunto set my hand and seal this 11 day of July 2003.

Address:

Laurence Du-Thum
1311 Pheasant Hollow Drive
Plainsboro, New Jersey 08536, USA

State of New Jersey
County of Middlesex

On this 11th day of July 2003, before me, a Notary Public in and for the State and County aforesaid, personally appeared the above signatory, known to me to be the person of that name, who executed the foregoing instrument in my presence.

MARIA V. LOGATTO
Notary Public of New Jersey
My Commission Expires 8/8/2005

Maria V. Logatto
NOTARY PUBLIC

IN TESTIMONY WHEREOF, I hereunto set my hand and seal this 11 day of July 2003.

Address:

Lori H. Szeles
44 Watson Court
Howell, New Jersey 07731, USA

State of New Jersey
County of Middlesex

On this 11th day of July 2003, before me, a Notary Public in and for the State and County aforesaid, personally appeared the above signatory, known to me to be the person of that name, who executed the foregoing instrument in my presence.

MARIA V. LOGATTO
Notary Public of New Jersey
My Commission Expires 8/8/2005

Maria V. Logatto
NOTARY PUBLIC

IN TESTIMONY WHEREOF, I hereunto set my hand and seal this 10 day of July 2003.

Address:

Richard J. Sullivan
35 Eton Way
Somerset, New Jersey 08873, USA

State of New Jersey
County of Middlesex

On this 10th day of July 2003, before me, a Notary Public in and for the State and County aforesaid, personally appeared the above signatory, known to me to be the person of that name, who executed the foregoing instrument in my presence.

MARIA V. LOGATTO
Notary Public of New Jersey
My Commission Expires 8/8/2005

Maria V. Logatto
NOTARY PUBLIC

IN TESTIMONY WHEREOF, I hereunto set my hand and seal this 11 day of July 2003.

Address:

James G. Masters
1 Stephen Court
Ringoes, New Jersey 08551, USA

State of New Jersey
County of Middlesex

On this 11th day of July 2003, before me, a Notary Public in and for the State and County aforesaid, personally appeared the above signatory, known to me to be the person of that name, who executed the foregoing instrument in my presence.

MARIA V. LOGATTO
Notary Public of New Jersey
My Commission Expires 8/8/2005

Maria V. Logatto
NOTARY PUBLIC

IN TESTIMONY WHEREOF, I hereunto set my hand and seal this 10 day of July 2003.

Address:

Richard S. Robinson
5 Riverview Terrace
Hillsborough, New Jersey 08844, USA

State of New Jersey
County of Middlesex

On this 10th day of July 2003, before me, a Notary Public in and for the State and County aforesaid, personally appeared the above signatory, known to me to be the person of that name, who executed the foregoing instrument in my presence.

MARIA V. LOGATTO
Notary Public of New Jersey
My Commission Expires 8/8/2005

Maria V. Logatto
NOTARY PUBLIC

96

94

TRADUCCIÓN AL ESPAÑOL del documento de cesión de solicitud de patente a Colgate-Palmolive Company, firmado por los cedentes y el cesionario.

APOSTILLA

(Convención de La Haya del 5 de Julio de 1961)

- 1. PAÍS: ESTADOS UNIDOS DE AMERICA**
- 2. ESTE DOCUMENTO PÚBLICO HA SIDO FIRMADO POR:**
ELAINE M. FLYNN
- 3. ACTUANDO EN CAPACIDAD DE:**
FUNCIONARIO DEL CONDADO
- 4. LLEVA EL SELLO/TIMBRE DE:**
CONDADO DE MIDDLESEX

CERTIFICADO

- 5. EN TRENTON, NEW JERSEY**
- 6. EL 28 DE DICIEMBRE DE 2005**
- 7. POR John E. McCormac, CPA, TESORERO DE NEW JERSEY**
- 8. NO. A247520**
- 9. SELLO/TIMBRE**
- 10. FIRMA**

John E. McCormac (Firma)

95

CONDADO DE MIDDLESEX

ESTADO DE NEW JERSEY

ESTADOS UNIDOS DE AMERICA

Yo Katherine M. Lally, de COLGATE-PALMOLIVE COMPANY, declaro que la copia anexa al presente es una fotocopia verdadera de la cesión como base de U.S. número de serie 10/618,331 presentada el 11 de julio de 2003.

(Firma)

Katherine M. Lally
Administrador de Patentes
Colgate Palmolive Company

Suscrito y jurado
Ante mi este 17
de noviembre de 2005.

Carol M. Stanley (Firma)
Carol M. Stanley
Notario Público de New Jersey
Mi comisión expira el 18 de Noviembre de 2005.

ESTADO DE NEW JERSEY
Condado de Middlesex

Yo, Elaine M. Flinn, Funcionario del Condado de Middlesex, certifico que
Carol M. Stanley

Cuyo nombre aparece suscrito al certificado de prueba de reconocimiento del instrumento adjunto era al momento de tomar el mismo un

NOTARIO PUBLICO DE NEW JERSEY

Actuando en y para dicho condado, debidamente comisionada y juramentada, y calificada para actuar como tal; que como tal

NOTARIO PUBLICO DE NEW JERSEY

Estaba debidamente autorizada por las leyes del Estado de New Jersey para tomar y certificar declaraciones; para administrar juramentos y promesa solemnes; para tomar declaraciones juradas por escrito y certificar el reconocimiento y la prueba de instrumentos jurídicos y otros instrumentos escritos para tierras, arrendamientos y herencias ser leídos como evidencia o registrados en este estado; y además, que estoy familiarizada con la firma de tal

NOTARIO PUBLICO DE NEW JERSEY

Y verifico que la firma de tal prueba o reconocimiento es genuina.

EN TESTIMONIO DE LO CUAL, e firmado el presente y fijado el sello del Condado de Middlesex este 18 de noviembre de 2005.

Elaine M. Flinn (Firma)

96

CESIÓN

CONSIDERANDO QUE, nosotros, Laurence Du-Thumm, Lori H. Szeles, Richard J. Sullivan, James G. Masters y Richard S. Robinson (referidos debajo como CEDENTES), reediendo, respectivamente, como se establece adelante, hemos hecho una invención para la cual se presentó solicitud de patente de Estados Unidos en la Oficina de Marcas y Patentes de Estados Unidos como solicitud con número de serie USSN 10/681,331 presentada el 11 de julio de 2003, nombrando a los CEDENTES como inventores y titulada Composición dental antiplaca masticable de confitería; y

CONSIDERANDO QUE, Colgate-Palmolive Company, una corporación debidamente organizada y existente bajo las leyes del Estado de Delaware, Estados Unidos de América y que tiene sus oficinas principales y lugar de operación en 300 Park Avenue, New York, New York 10022, y oficinas y lugar de operación en 909 River Road, Piscataway, New Jersey 08855 (referido debajo como CESIONARIO), tiene deseos de obtener la totalidad del derecho, título e intereses en y para la invención y solicitud de patente mencionadas arriba y los correspondientes derechos de patente alrededor del mundo.

AHORA, POR LO TANTO, en consideración de la consideración buena y valiosa, el recibo y la suficiencia de la cual se reconocen, los CEDENTES, por la presente venden, ceden y transfieren al CESIONARIO el derecho, título e interés completo y exclusivo en y para la invención arriba mencionada, la solicitud de patente de los Estados Unidos arriba mencionada y todas las solicitudes de patente extranjeras correspondientes, todas las solicitudes de división, continuación, continuación parcial, reemisión y reexaminación de la solicitud de patente de los Estados Unidos arriba mencionada, y todas las Patentes o derechos comparables emitidos sobre la misma en los Estados Unidos y en todos los países extranjeros, junto con el derecho de prioridad bajo la Convención Internacional para la Protección de la Propiedad Industrial, la Convención Interamericana Relacionada con Patentes, Diseños y Modelos Industriales, u cualquier otro acuerdo internacional al cual se adhieran los Estados Unidos, y los CEDENTES por la presente autorizan y solicitan al Comisionado de Marcas y Patentes de los Estados Unidos y a todas las Oficinas de Patentes extranjeras a emitir todas las patentes o derechos comparables que puedan surgir de cualquier solicitud al CESIONARIO, o sus sucesores, cesionarios o representantes legales;

Los CEDENTES garantizan que los CEDENTES tienen pleno derecho para comunicar la totalidad del interés aquí cedido, y que los CEDENTES no han ejecutado, y no ejecutarán, ningún acuerdo en conflicto con el presente;

Los CEDENTES acuerdan comunicar al CESIONARIO o a sus sucesores, cesionarios o representantes legales cualquiera y todos los hechos conocidos por ellos o por cualquiera de ellos respecto a dicha invención, y sin remuneración adicional testificar en cualquier proceso legal, firmar todos los papeles legales, ejecutar todas las solicitudes de división, continuación, continuación parcial, reemisión y reexaminación, hacer todos los juramentos correctos y en general hacer todos los actos legales para ayudar al CESIONARIO o sus sucesores, cesionarios o representantes legales a obtener y hacer valer la protección de patente para dicha invención en todos los países y a mejorar o perfeccionar el derecho del CESIONARIO en y para la invención y los derechos de patente de la misma.

Los CEDENTES por la presente autorizan a los abogados del CESIONARIO a ingresar en este documento cualquier número de serie y fecha de presentación aplicable después que el CEDENTE ha ejecutado este documento.

Esta cesión es efectiva desde: Julio 11 de 2003

29 97

EN TESTIMONIO DE LO CUAL he puesto mi firma y fijado mi sello este 11 de julio de 2003

(Firma)

Laurence Du-Thumm
Dirección: 1311 Pheasant Hollow Drive
Plainsboro, New Jersey 08536, E.U.A.

Estado de New Jersey
Condado de Middlesex

Este 11 de julio de 2003, ante mí, un notario público en y para el Estado y Condado arriba mencionados, apareció personalmente el arriba firmante, a quien conozco como la persona de ese nombre quien ejecutó el instrumento anterior en mi presencia.

MARIA V. LOGATTO
Notario Público de New Jersey
Mi comisión expira 8/8/2005

(Firma)

NOTARIO PUBLICO

EN TESTIMONIO DE LO CUAL he puesto mi firma y fijado mi sello este 11 de julio de 2003:

(Firma)

Lori H. Szeles
Dirección: 44 Watson Court
Howell, New Jersey 07731, E.U.A

Estado de New Jersey
Condado de Middlesex

Este 11 de julio de 2003, ante mí, un notario público en y para el Estado y Condado arriba mencionados, apareció personalmente el arriba firmante, a quien conozco como la persona de ese nombre quien ejecutó el instrumento anterior en mi presencia.

MARIA V. LOGATTO
Notario Público de New Jersey
Mi comisión expira 8/8/2005

(Firma)

NOTARIO PUBLICO

EN TESTIMONIO DE LO CUAL he puesto mi firma y fijado mi sello este 10 de julio de 2005:

(Firma)

Richard J. Sullivan
Dirección: 35 Eton Way
Somerset, New Jersey 08873, E.U.A

Estado de New Jersey
Condado de Middlesex

Este 10 de julio de 2003, ante mí, un notario público en y para el Estado y Condado arriba mencionados, apareció personalmente el arriba firmante, a quien conozco como la persona de ese nombre quien ejecutó el instrumento anterior en mi

VSD 98

EN TESTIMONIO DE LO CUAL he puesto mi firma y fijado mi sello este 11 de julio de 2003

Dirección: (Firma)
James G. Masters ¹,
1 Stephen Court
Ringoes, New Jersey 08551, E.U.A

Estado de New Jersey
Condado de Middlesex

Este 11 de julio de 2003, ante mi, un notario público en y para el Estado y Condado arriba mencionados, apareció personalmente el arriba firmante, a quien conozco como la persona de ese nombre quien ejecutó el instrumento anterior en mi presencia.

MARIA V. LOGATTO
Notario Público de New Jersey
Mi comisión expira 8/8/2005

(Firma)
NOTARIO PUBLICO

EN TESTIMONIO DE LO CUAL he puesto mi firma y fijado mi sello este 10 de julio de 2003

Dirección: (Firma)
Richard S. Robinson
5 Riverview Terrace
Hollsborough, New Jersey, E.U.A.

Estado de New Jersey
Condado de Middlesex

Este 10 de julio de 2003, ante mi, un notario público en y para el Estado y Condado arriba mencionados, apareció personalmente el arriba firmante, a quien conozco como la persona de ese nombre quien ejecutó el instrumento anterior en mi presencia.

MARIA V. LOGATTO
Notario Público de New Jersey
Mi comisión expira 8/8/2005

(Firma)
NOTARIO PUBLICO

201 : 99



252373 Form 1-

I, NORMAN GOODMAN, County Clerk and Clerk of the Supreme Court of the State of New York, in and for the County of New York, a Court of Record, having by law a seal, DO HEREBY CERTIFY pursuant to the Executive Law of the State of New York, that

Rosie S. Dizon

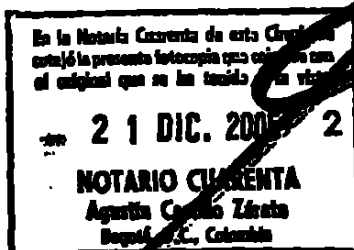
whose name is subscribed to the annexed affidavit, deposition, certificate of acknowledgment or proof, was at the time of taking the same a NOTARY PUBLIC in and for the State of New York duly commissioned, sworn and qualified to act as such; that pursuant to law, a commission or a certificate of his official character, with his autograph signature has been filed in my office; that at the time of taking such proof, acknowledgment or oath, he was duly authorized to take the same; that I am well acquainted with the handwriting of such NOTARY PUBLIC or have compared the signature on the annexed instrument with his autograph signature deposited in my office, and I believe that such signature is genuine.

IN WITNESS WHEREOF, I have hereunto set my hand affixed my official seal this

OCT 30 2001

FEE PAID \$3.00


County Clerk and Clerk of the Supreme Court, New York County



Apostille

102 100

(Convention de La Haye du 5 Octobre 1961)

1. Country: **United States of America**
This public document
2. has been signed by **Norman Goodman**
3. acting in the capacity of **County Clerk**
4. bears the seal/stamp of the county of **New York**

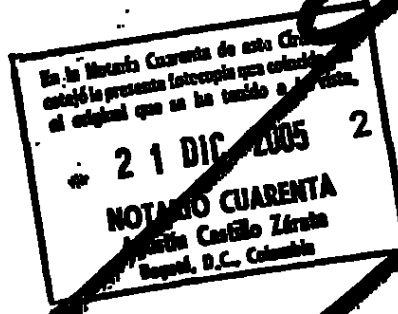
Certified

5. At New York, New York
6. the 30th day of October 2001
7. by Special Deputy Secretary of State, State of New York
8. No. NYC-9786540B
9. Seal/Stamp
10. Signature

Aqil M. Qureshi

Aqil M. Qureshi
Special Deputy Secretary of State

04136606.POL (REV 2/8/99)



Brigard & Castro

SANTA FE DE BOGOTÁ - COLOMBIA

PODER

POWER OF ATTORNEY

Yo (nosotros)

domicillado(s) en

Nombros(amos) a: RAMIRO CASTRO DUQUE y/o JUAN PABLO CADENA SARMIENTO y/o BEATRIZ JARAMILLO S.

de Santafé de Bogotá, Colombia, apoderados verdaderos y legales con poder especial, amplio y suficiente, para recabar de las oficinas y autoridades colombianas administrativas, judiciales y de policía, en cualquier instancia o recurso, la obtención de patentes de invención, registros de marcas, diseños industriales, modelos de utilidad, depósitos de nombres comerciales y emblemas, registros de derechos de autor y contratos sobre los mismos, obtención de certificados de obtentor de variedades vegetales, así como sus prórrogas, renovaciones, anotaciones de traspaso, cambios de nombre y/o domicilio; elaborar, tramitar y registrar contratos de licencia y licencias de cualesquiera clases; intervenir como demandante o como demandado en cualquier instancia y recurso ante cualquier juez, corporación, funcionario público o autoridad en acciones judiciales, administrativas y de policía tales como: oposiciones al registro de marcas; acciones de caducidad, cancelación y nulidad; acciones reivindicatorias, acciones derivadas de la obtención o explotación de licencias; acciones de competencia desleal; demandas penales; acciones de indemnización de perjuicios, reclamos y observaciones a solicitudes de patentes, diseños industriales, modelos de utilidad, en el ejercicio de medidas cautelares y en otras acciones o medidas similares.

A este efecto, lo(s) facuto(amos) para elevar solicitudes, formular descripciones, enmiendas, protestas, declaraciones, oposiciones, cancelaciones, nulidades, apelaciones y reclamos; pagar impuestos, cuotas y gravámenes prescritos por la ley; renunciar o desistir a derechos concedidos o en curso de concesión; recibir toda clase de documentos y valores, dando el descargo respectivo, y, en general, para dar ante dichas autoridades todos los pasos necesarios al efecto indolado y tomar todas las medidas que creyeran conducentes al resguardo de mis (nuestros intereses), con todas las demás facultades legales necesarias.

Este poder comprende la facultad de ratificar o confirmar en mi (nuestro) nombre lo actuado así como la facultad de desistir, transigir, comprometer, y la de sustituirlo en todo o en parte y revocar sustituciones. Asimismo nombros(amos) a: RAMIRO CASTRO DUQUE y/o JUAN PABLO CADENA SARMIENTO y/o BEATRIZ JARAMILLO S. domiciliado(s) en la Carrera 7 No. 18-56 Piso 9, mi (nuestros) apoderados en Colombia, con facultades para recibir notificaciones y designar apoderados judiciales o extrajudiciales.

Otorgado y firmado en

hoy de

Firma

Nombre

I (We)

COLGATE-PALMOLIVE COMPANY, a Delaware corporation, of 300 Park Avenue, New York, New York 10022, U. S. A.

Herby appoint RAMIRO CASTRO DUQUE and/or JUAN PABLO CADENA SARMIENTO and/or BEATRIZ JARAMILLO S.

of Santafé de Bogotá, Colombia, my (our) true and lawful attorneys with special, ample and sufficient power to obtain from the Colombian administrative, judicial and police offices and authorities, in any instance, privileges of patents of invention, registration of trademarks, industrial designs and utility models; registration of commercial names and emblems, registration of copyright and contracts related thereto, certificates of obtainers of vegetable varieties, as well as extensions, renewals and record of assignments and changes of name and domicile related to the above; to prepare, prosecute and register licenses of any kind; to act as plaintiff or defendant in any instance or recourse, and before any judge, corporation, public official or authority in judicial, administrative and police actions, such as: oppositions to the registration of trademarks; caducity, cancellation and nullity actions; claim actions derived from the obtaining or exploitation of licenses, action of unfair competition; penal demands, actions of indemnities for damages; claims or observations on patent applications, models, industrial designs and utility models; in the exercise of preventive measures; and in other actions or similar proceedings.

To that effect they are hereby empowered to file applications, formulate descriptions, amendments, protests, declarations, oppositions, cancellations, nullities, appeals and claims; to pay taxes, quotas and assessments prescribed by law, renounce or waive the rights granted or in the process of granting; to receive all kind of documents and valuables, giving the respective release of receipt, and, in general, to take before said authorities the necessary steps to such effect, and any measures that they may deem pertinent to the safeguard of my (our) interest(s) with all the other necessary legal powers.

This power includes the faculty to ratify or confirm desist, settle and compromise on my (our) behalf, and to substitute this power in whole or in part and to revoke substitutions. At the same time I (We) hereby appoint RAMIRO CASTRO DUQUE and/or JUAN PABLO CADENA SARMIENTO and/or BEATRIZ JARAMILLO S.

domiciled in Carrera 7 No. 18-56, Piso 9, my (our) attorney(s) in fact, with powers to receive notifications and to designate judicial and extrajudicial attorneys.

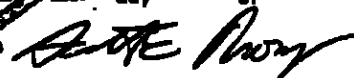
Granted and signed in New York, N.Y.

This OCT 29 2001 day

of

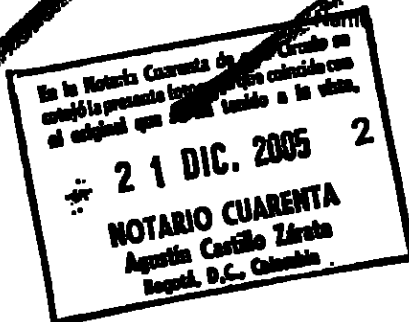
2001

Signature



SCOTT E THOMPSON

VICE PRESIDENT &
ASSOCIATE GENERAL COUNSEL
TRADEMARK



CERTIFICADO NOTARIAL (SOCIEDAD)

NOTARIAL CERTIFICATE (CORPORATION)

Hoy de de
personalmente compareció ante mí

a quien conozco, y de quien me consta que firmó el
anterior documento, debidamente juramentado declaró
y dijo que él es

de

Sociedad legalmente constituida para un periodo de
duración que aún no ha terminado; que el declarante
está autorizado por dicha compañía para conferir este
poder; que el sello estampado por él al pie de tal poder,
en nombre y representación de la expresada compañía,
es el sello oficial de ella; y que el objeto para el cual se
confiere este instrumento está comprendido dentro del
de la sociedad.

El suscrito Notario hace constar que tuvo a la vista las
pruebas de la existencia de la sociedad.

Estado de
con fecha

y que quien confiere el presente poder es su
representante.

On this OCT 29 2001 day of of
personally appeared before me

to me known, and known to me to be the person who
signed the foregoing instrument who being by me duly
sworn did depose and say that he (she) is the

SCOTT E THOMPSON
VICE PRESIDENT &
ASSOCIATE GENERAL COUNSEL
TRADEMARK
COLGATE-PALMOLIVE COMPANY

Which is legally constituted for a term not yet expired,
that deponent is authorized by said Company to confer
this Power of Attorney: that the seal affixed hereunto
by the deponent in the name and on behalf of said
Corporation is the corporate seal thereof; and that the
purpose for which this instrument is granted is
included within the corporate purpose of company.

The undersigned Notary Public attests that he has seen
the documents that prove the existence of the
company.

State of Delaware
under date of May 13, 1997

and that he (she) who grants the present power of
attorney is its Representative.

Notario Público (sello)

Rosie S. Dizon
Notary Public (sello)

CERTIFICADO NOTARIAL
PERSONA NATURAL

ROSIE S. DIZON
Notary Public, State of New York
No. 31-4941117
Qualified in New York County
Commission Expires Aug. 15, 2002

COUNTY

Hoy de de , compareció(eron)
ante mí

a quien (es) conozco y me consta que es(son) la(s)
persona(s) firmante(s) del documento que precede y
quien(es) declara(n) que otorgan el mismo para los
fines y propósitos que en él se expresan.

On this OCT 29 2001 day of of
personally appeared before me

SCOTT E THOMPSON
who is(are) known to me and who I attest executed
the foregoing document and he (they) declared he
(they) granted the document for the purposes and
that are expressed.

Notario Público (sello)

Rosie S. Dizon
Notary Public (sello)

LEGALIZACION POR APOSTILLA ES REQUERIDA

Es la Notaría Cuarenta de este Estado en
cuyo territorio se encuentra el lugar donde se
otorgó la presente escritura que se ha tenido a la vista.
21 DIC. 2005
NOTARIO CUARENTA
Agustín Cuarenta
Bogotá, D.C. Colombia

ROSIE S. DIZON
Notary Public, State of New York
No. 31-4941117
Qualified in New York County
Commission Expires Aug. 15, 2002

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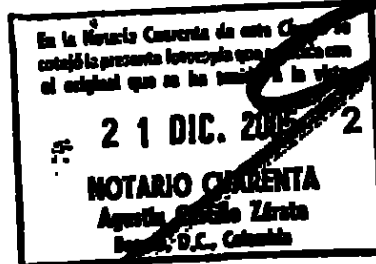
APOSTILLE

(Convención de La Haya del 5 de Octubre de 1961)

- 1. País: ESTADOS UNIDOS DE AMERICA**
Este documento público
- 2. ha sido firmado por Norman Goodman**
- 3. actuando en capacidad de Oficial del Condado**
- 4. lleva el sello/timbre del condado de New York**

CERTIFICADO

- 5. en New York, New York**
- 6. el 30 de Octubre de 2001**
- 7. por Secretario de Estado Encargado Especial, Estado de New York**
- 8. No. NYC-9786540B**
- 9. Sello/Timbre**
- 10. Firma**
(Firma)
Aquil M. Qureshi
Secretario de Estado Encargado Especial



106 104

Estado de New York)
) ss.
Condado de New York)

252373

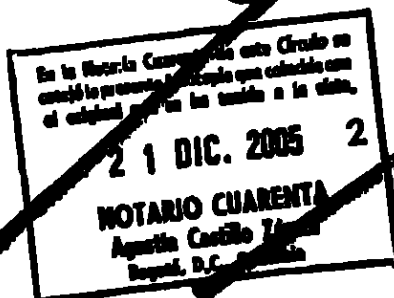
CERTIFICO POR MEDIO DE LA PRESENTE de acuerdo con la Ley Ejecutiva del Estado de New York, que

cuyo nombre está suscrito al acta notarial, deposición, certificado de reconocimiento o prueba, era al momento de tomar el mismo NOTARIO PÚBLICO en y para el Estado de New York debidamente comisionado, juramentado y calificado para actuar como tal; que de acuerdo con la ley, una comisión o un certificado de este carácter oficial, con su firma autógrafa ha sido presentada en mi oficina; que al momento de tomar tal prueba, reconocimiento o juramento, estaba debidamente autorizado para tomar el mismo; que estoy bien familiarizado con la escritura de tal NOTARIO PÚBLICO o he comparado la firma en el instrumento anexo con la firma autógrafa depositada en mi oficina, y creo que tal firma es genuina.

30 de Outubro de 2001

TARIFA PAGADA \$3.00

Oficial del Condado y Oficial de la Corte Suprema, Condado de New York





GAVIRI A'

ORGANIZACIÓN ELECTORAL
REGISTRADURÍA NACIONAL DEL ESTADO CIVIL

REGISTRO CIVIL DE DEFUNCIÓN

Indicativo
Serial

5562241

Datos de la oficina de registro														
Clase de oficina: Registraduría		Notaría ☒		Consulado		Corregimiento		Inspección de Policía						
Código 9795														
País - Departamento - Municipio - Corregimiento o Inspección de Policía														
COLOMBIA CUNDINAMARCA BOGOTÁ D.C. NOTARIA 32.														
Datos del Inscrito														
Apellidos y nombres completos														
CASTRO DUQUE RAMIRO														
Documento de identificación (Clase y número)								Sexo (en Letras)						
C.C. No. 170322 DE BOGOTÁ								MASCULINO						
Datos de la defunción														
Lugar de la Defunción: País - Departamento - Municipio - Corregimiento o Inspección de Policía														
COLOMBIA CUNDINAMARCA BOGOTÁ D.C.														
Fecha de la defunción				Hora		Número de certificado de defunción								
Año	2	0	0	4	Mes	1	0	Día	3	0	04:10 PM	A-	2094375.	
Pronunciación de muerte										Fecha de la sentencia				
Lugar que profiere la sentencia										Año				
Documento presentado										Nombre y cargo del funcionario				
Autorización Judicial ☐										Certificado Médico ☒				
ANDRÉS DÍAZ CAMPOS.-										R.M. No. 79982662				
Datos del denunciante										Apellidos y nombres completos				
EDGAR DAVID REGINO II.										Firma				
Documento de identificación (Clase y número)								Firma						
C.C. No. 15.030.154 DE LORICA/ CORDOBA								Firma						
Primer testigo										Apellidos y nombres completos				
Documento de identificación (Clase y número)										Firma				
Segundo testigo										Apellidos y nombres completos				
Documento de identificación (Clase y número)										Firma				
Fecha de inscripción										Notario y firma del Registrador que autoriza				
Año	2	0	0	4	Mes	1	0	Día	0	2	BLANCA RIVERA RESTREPO			
PADRES: ALFONSO CASTRO										ESPACIO PARA NOTAS				
MERCEDES DUQUE.														

ORIGINAL PARA LA OFICINA DE REGISTRO

NOTARIA 32

DEL CIRCULO DE SANTA FE DE BOGOTA, D.C.

Germán Eleázar Moreno L.
Notario

COMO SECRETARIO DELEGADO EN LA NOTARIA TREINTA Y DOS (32) DEL
CIRCULO DE BOGOTA

CERTIFICO, QUE:

La presente acta es fiel copia del original tomada del registro
civil de defunciones serial indicativo número: 56224
que expido en la ciudad de Bogotá D.C. hoy: 05 NOV 2004

SECRETARIO DELEGADO

NELSON FLORES C.
SECRETARIO DELEGADO PARA COPIAS
DECRETO 1334 DE 1989

108
106

SUPERINTENDENCIA Y COMERCIO
Radicación : 06002293 03200600 Folios: 107
Fecha (AND): 2006-01-12 16:00:21
Trámite : 011 PCT-PATENT 378 FASE INCI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCION	()	()
- Indicación de que se solicita la concesión de una patente. - Datos de identificación del solicitante o de la persona que se presenta la solicitud. - Descripción de la invención. - Dibujos de ser estos pertinentes. - Comprobante de Pago de las tasas establecidas.	() () () () ()	() () () () ()
COMPLETA ()		INCOMPLETA () ()

DISEÑO INDUSTRIAL ()		
- Indicación de que se solicita el registro de Diseño Industrial - Datos de identificación del solicitante o de la persona que presenta la solicitud. - Representación gráfica o fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño. - Comprobante de pago de las tasas establecidas	() () () ()	() () () ()
COMPLETA ()		INCOMPLETA () ()

ESQUEMA DE TRAZADO ()		
- Indicación de que solicita el registro de un Esquema de trazado. - Datos de identificación del solicitante o de la persona que presenta La solicitud. - Representación gráfica del esquema de trazado - Comprobante de pago de las tasas establecidas.	() () () ()	() () () ()
COMPLETA ()		INCOMPLETA () ()

Firma Responsable:

Fecha:

12 Jun 10

109 107

 Industria y Comercio SUPERINTENDENCIA		SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO DIVISION DE NUEVAS CREACIONES EXTRACTO PARA PUBLICACIÓN SOLICITUD DE PATENTE DE INVENCION PCT	
(21) N° de solicitud		(51) Int Ct	
22) Fecha de solicitud		(71) Solicitante(s) COLGATE – PALMOLIVE COMPANY	
(30) Prioridad	(31) No. Prioridad	32) Fecha	(33) Pais
	10/518,331	11-07-2003	US
		(72) Inventor(es) Lawrence Du-Thumm, Lori H. Szeles, Richard J. Sullivan, James G. Matara, Richard S. Robinson	
		(74) Agente: JUAN PABLO CADENA SARMIENTO	
(85) Fecha inicio fase nacional: 11-02-2006		(87) Publicación internacional	
(86) Datos relativos a la presentación de la solicitud PCT		Fecha: 27-01-2005	
Fecha de presentación de la solicitud: 09-07-2004		N° publicación: WO 2005/006872 A1	
No. De solicitud PCT/U82004/021873			
(54) Título: COMPOSICIÓN DENTAL ANTIPLACA MASTICABLE DE CONFITERÍA			

Resumen:

Una composición dental masticable de confitería que entrega a la boca una dosis unitaria de una enzima que reduce la placa, la composición comprende una enzima, un edulcorante no cariogénico, la enzima se incorpora a la composición a una temperatura menor de alrededor de 80°C.

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10.8

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor (a)
CADENA SARMIENTO JUAN PABLO
Apoderado(a) y/o Representante de
COLGATE PALMOLIVE COMPANY

REFERENCIA	Radicación No.	6 2293
	Solicitud internacional	US2004/021873
	Fecha inicio fase nacional	11/02/2006
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	2897

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. Debe aclarar el nombre del inventor James G. Masters por cuanto difiere de la publicación internacional y del documento de cesión aportado con la solicitud.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

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 No.10 de 2001.

ALIX CARMENZA GONZALEZ DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de
fecha 10 MAR. 2006
jramos