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Tooth Remineralization Patents

A. Key Ingredients in Patents

B. List of Patents / Abstracts

C. Excerpts of Select Patents

SUMMARY OF KEY INGREDIENTS --

Dentifrice for dental remineralization
US4177258
An **antinucleating agent such as ethylenediamine tetramethylenephosphonic acid** or water soluble salt thereof, the pH about **6.8-7.5.**

TOOTHPASTE COMPOSITION
KR840001942
5-35% synthetic hydroxyapatite powder, **30-35% abrasive material that contains calcium phosphate or calcium pyrophosphate**, **0.1-20% NaCl, 0.003-3% MgCl2, and 30-35% water by weight.**

Prophylactic dental paste comprising dicalcium phosphate and method of using it for cleaning, polishing and remineralizing teeth.
EP0040938
60 percent by weight of dicalcium phosphate, (which may be anhydrous dicalcium phosphate, dicalcium phosphate dihydrate or a mixture of the two)

MEANS & METHOD FOR THE REMINERALIZATION & PROPHYLAXY OF DENTAL ENAMEL DEMINERALIZATION
BG92020
0.4 to 10 collagen

DENTIFRICE COMPOSITION
JP7223930
Tricalcium phosphate, a mixture (molar ratio of Ca/P: 1.30-1.67 of tetracalcium phosphate with calcium primary phosphate (anhydride or monohydrate), a mixture (molar ratio of Ca/P: 1.30-1.67) of tetracalcium phosphate with secondary calcium phosphate (anhydride or monohydrate), a mixture (molar ratio of Ca/P: 1.30-1.50) of tricalcium phosphate with calcium primary phosphate, etc.,

Artificial saliva and its preparing method
CN1130066
Sodium chloride, potassium chloride, calcium chloride, magnesium chloride, acidic and alkaline sodium phosphate

DENTIFRICE COMPOSITION
JP9040539

Hydroxyapatite) and 0.05-10wt.% carbamide peroxide -- a **synergistic effect is exhibited by mixing both**, A mixture of more than two species **of tricalcium phosphate, calcium hydrogen phosphate, calcium dihydrogen phosphate, octacalcium phosphate and calcium pyrophosphate can be used instead of hydroxyapatite as the calcium compound.**

Dentifrice for the mineralization and remineralization of teeth
US6372198
Coenzyme Q10, selenium, and bromine

COMPOSITION FOR CARIES PREVENTION
CA2485836
0.01 to 10% by weight of sodium carboxymethylcellulose having the etherification degree of 0.7 to 1.0 is used in a composition blended with a casein phosphopeptide - amorphous calcium phosphate complex (CPP - ACP)

Methods for treating dental conditions using tissue scaffolds
US2007248933
TGF-beta supergene family, that promotes regeneration and differentiation of healthy dental tissue in vivo

Calcium phosphate complex and salts in oral delivery systems
CN101415398
Phosphopeptide o r phosphoprotein stabilized calcium phosphate

ORAL COMPOSITION FOR STABILIZATION, (RE)CALCIFICATION AND (RE)MINERALIZATION OF TOOTH ENAMEL AND DENTINE
US2008152598
Calcium form of zeolite

ORAL CARE PRODUCTS COMPRISING BUFFER SYSTEMS FOR IMPROVED MINERALIZATION/REMINERALIZATION BENEFITS.
MX2009008303
Calcium salt, a phosphate salt, a sodium salt and a potassium salt. For example, the molar ratio of the sodium salt to the potassium salt ranges from about 3 to about 4.

DENTAL PROPHYLACTIC PASTE
WO2011031606
Water soluble silicate

COMPOSITIONS AND METHODS FOR IMPROVING OVERALL TOOTH HEALTH AND APPEARANCE.
MX2010014220
Surface-active **organophosphate** compounds, an antimicrobial agent preferably selected from quaternary ammonium compounds and polyvalent metal salts, an anticalculus agent.

CALCIUM PEROXYPHOSPHATES AND USE THEREOF IN DENTAL COMPOSITIONS
US2011142768
Calcium peroxymonophosphate or calcium diperoxymonophosphate

NOVEL TYPE OF ANION-CONTAINING CALCIUM PHOSPHATE COMPOUND FOR DENTAL REMINERALIZATION
US2012129135
The anion-containing calcium phosphate compound has the following formula: **(Ca+2)x(anion-**

a)y(PO4-3)z wherein 2x=(a*y+3z); a is an integer of 1 to 3; and each of x, y and z is not 0.

Dentifrice compositions
US4327079
0.1 to 20% by weight of NaCl and/or KCl and 0.003 to 3% by weight of MgCl2

DENTAL FORMULATION
WO9319728
Water soluble phosphate, particularly a pyrophosphate or tripolyphosphate, to inhibit demineralization

TOOTH-PASTE
SK280006
Combination of silicilic acids and dicalcium phosphate dihydrate (brushite)

TOOTH PASTE COMPOSITION
JP9124451
A natural **zeolite such as gismondine, garronite, analcime or wirakite or a synthetic zeolite such as stilbite or Ca-mordenite) and (B) hydroxyapatite**. , **preferably 5-30%,** based on the whole amount of the composition.

REMINERALIZATION MATERIAL FOR ORGANOMINERAL TISSUES
BG103544
Zn2+ ions is preferred in presence of quantities less than 1%, better closer to 0.2%

CHEWING GUM WITH DENTAL HEALTH BENEFITS EMPLOYING CALCIUM LACTATE

WO0042861
Calcium lactate.

REMINERALIZATION PROMOTERS
WO2005003753
Starch phosphate, maltodextrin phosphate, reducing maltodextrin phosphate, oligosaccharide phosphate,

Oral and dental care product
US2007154411
Proteins, protein hydrolysates and protein hydrolysate derivatives

Formulation of dual eicosanoid system and cytokine system inhibitors for use in the prevention and treatment of oral diseases and conditions
US2006079467
Free-B-Ring flavonoids and flavans isolated from a single plant or multiple plants, preferably in the **Scutellaria, Oroxylum, Acacia or Uncaria genus** of plants

CALCIUM BINDING PEPTIDES
WO2007038683
Aspartic acid, glutamic acid, asparagine, alanine and glutamine, and Y and Z are amino acids selected from **alanine, serine, threonine, phosphoserine, phosphothreonine**, and their derivatives. These compounds **have the property of binding tightly and specifically to calcified surface.**

MATERIAL FOR FILLING ROOT CANALS OF TEETH
RU2197939
Zeolite at the quantity of 10-70% and **contains calcium being 1.5-45 mg** higher/g enriched zeolite

Dental cleaning formulation and manufacturing process
US6602490
Potassium Citrate and Disodium Edetate.

METHOD FOR MINERALIZATION OF ROOT TOOTH TISSUE
EA200801499
Sodium hydrogen carbonate; 0.01% Myramistin solution for suppressing the activity of pathogenic microflora and for enhancing focal defense reactions; calcium glycerophosphate and nanocrystalline calcium hydroxyappatite as remineralizing components

BIOACTIVE GLASS COMPOSITION
JP2008120681
Silica-based bioactive glass

GEL FOR REMINERALIZATION OF TOOTH TISSUES
EA200800988
Calcium glycerophosphate 0.1-3.0, a source of **magnesium ions 0.01-0.50, guar gum 0.03-0.30** as active components, **Magnesium chloride, magnesium sulfate or magnesium nitrate** is used as a source of magnesium ions.

Method for in-vitro induction of remineralization of dentin
CN102172334
Agar gel CaCl2 solution mineralization system containing phosphate can induce the deposition and growth of strip nano crystals

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PATENTS ABSTRACTS

PROCESSES AND COMPOSITIONS FOR REMINERALIZATION OF DENTAL ENAMEL
GB1452125

Remineralizing teeth PROCTER & GAMBLE CO 12 Oot 1973 [13 Oct 1972] 47800/73 Heading A5B A pack for remineralizing teeth comprises (A) a cation in water-soluble form which cation is capable of forming an insoluble preciptate and (B) an anion in water-soluble form which is capable of forming with the cation an insoluble precipitate adapted to remineralize subsurface dental enamel, one of both of components (A) and (B) containing a flavouring agent, the components being compatible with the oral environment and being such as to have a pH from 3 to 10 in solution. In use, the two components are applied sequentially to the tooth, the remineralizing precipitate being thereby formed in situ. Cations specified are calcium, indium, barium, lanthanium, manganese, lead, tin, zinc, zirconium, iron, titanium, vanadium, cadmium, magnesium, aluminium, strontium, cesium, samarium, praseodymium, neodymium, nickel, lithium (with phosphate), molybdenum, vanadium, tungsten. Anions specified are fluoride, phosphate, fluorophosphate, silicofluoride, molybdate, sulphate, tungstate, 8-hydroxyquinolate, tartrate, sorbate, carbonate, iodate, stearate, hydroxide, palmitate, myristate, laurate, oxalate, decyl sulphonate, lauryl sulphonate, myristyl sulphonate, cetyl sulphonate, octadecyl sulphonate, silicate, hexadecyl sulphonate, aluminate. Physical forms of the two components specified are: mouthwashes, toothpastes, beverages, candy drops, foods, toothpowders, chewing gum, toothpaste in which one component is encapsulated and a multilayer lozenge.

Process and composition for the remineralization and prevention of demineralization of animal teeth including humans
US4397837

Compositions for the remineralization and prevention of demineralization of the teeth of animals including humans in the form of two phases, one phase containing a water-soluble calcium compound and the other phase containing a water-soluble phosphate and optionally a water-soluble fluorine compound. The concentration of calcium and phosphate (PO4) ions is about 50 to 35,000 ppm and 50 to 40,000 ppm respectively, and the amount of fluorine compound is about 0.01 to 5.0%, all by weight of the total composition. The compositions may also contain at least one of a conventional flavoring substance, aroma substance, surfactant, astringent, polishing agent, thickener and preservative.

Processes and compositions for remineralization of dental enamel
US4083955

Two compositions containing respectively a cation and an anion, such as calcium ion and phosphate ion, are sequentially applied to dental enamel resulting in remineralization of subsurface dental enamel.

Stable solution for dental remineralization
US4183915

An aqueous solution useful for remineralizing subsurface carious lesions of dental enamel which solution contains sources of calcium ions and phosphate ions as well as fluoride ions and further includes as an agent to stabilize the solution against precipitation, an antinucleating agent such as ethylenediamine tetramethylenephosphonic acid or water soluble salt thereof, the pH of the solution being about 5-9, preferably close to physiological conditions, such as about 6.8-7.5.

Dentifrice for dental remineralization
US4177258

A dentifrice useful for remineralizing subsurface carious lesions of dental enamel which contains sources of calcium ions and phosphate ions as well as fluoride ions and further includes as agent to stabilize against precipitation of the calcium and phosphate ions, an **antinucleating agent such as ethylenediamine tetramethylenephosphonic acid** or water soluble salt thereof, the pH of the dentifrice being about 5-9, preferably close to physiological conditions, such as about **6.8-7.5.**

TOOTHPASTE COMPOSITION
KR840001942

A dentifrice includes synthetic hydroxyapatite powder. This compsn. was found effective in removing plaque from teeth surfaces and in the remineralization of the enamel. The toothpaste consists of **5-35% synthetic hydroxyapatite** powder, **30-35% abrasive material that contains calcium phosphate or calcium pyrophosphate**, 20-35% filler that contains a glycerine or sorbitol group, **0.1-20% NaCl, 0.003-3% MgCl2, and 30-35% water by weight.** The compositon should be either neutral or alkali.

Prophylactic dental paste comprising dicalcium phosphate and method of using it for

cleaning, polishing and remineralizing teeth.
EP0040938

A prophylactic dental paste for professional use containing at least **60 percent by weight of dicalcium phosphate**, (which may be anhydrous dicalcium phosphate, dicalcium phosphate dihydrate or a mixture of the two) not only satisfactorily cleans the tooth surface but provides a tooth with higher luster or polish. The use of the prophylatic dental paste of the invention, in which the dicalcium phosphate has the same calcium to phosphorus atom ratio found in the tooth, aids in remineralization of the cleaned tooth surface.

DENTAL REMINERALIZATION COMPOSITION
CA1165953

An aqueous composition useful for remineralizing subsurface carious lesion, of dental enamel which comprises an aqueous solution which contains sources of calcium ions and phosphate ions as well as fluoride ions and further includes as an antinucleating agent, to stabilize the solution against precipitation, 2-phosphono-butane-tricarboxylic acid 1,2,4 or water soluble salt thereof, the pH of the solution being about 5-9, preferably close to physiological conditions, such as about 6.8-7.5.

Anticariogenic remineralizing dentifrice
US4460565

A dentifrice containing two or more fluorine compounds, at least one soluble salt producing phosphate ions, and at least one substance providing calcium ions, and as a result thereof having good remineralization properties. Preferred compositions contain as the fluorine compounds a fluoride and a monofluorophosphate, as phosphate compounds a cyclic metaphosphate and a linear phosphate, and as calcium compound a calcium salt of an organic acid.

Method of making a clear, stable aqueous mouthwash solution and the solution made by that method for the enhancement of cells of the oral cavity and the remineralization of teeth
US4606912

A solutions for optimizing the environmental conditions within the human oral cavity is disclosed which enhances the functioning of cells of the oral cavity and promotes remineralization of teeth. These solutions are effective in treating and preventing caries and periodontal disease and reducing mouth odor and are easily and safely used by the lay population. A method of making the solutions which totally prevents the formation of calcium phosphate crystals, for example hydroxyapatite, is disclosed.

MEANS & METHOD FOR THE REMINERALIZATION & PROPHYLAXY OF DENTAL ENAMEL DEMINERALIZATION
BG92020

The means and the method are used in dentistry for the prophylaxy and treatment of initial forms of dental caries. The means contains water soluble calcium and phosphate salts having constant ion activity in suitable gel form which is indifferent and does not affect the oral cavity mucous membrane and teeth and does not stimulate the development of dental scale. By the method, lasting and more stable penetration of the phosphate-calcium ions and filling of the enamel cracks is

achieved. By it, a two-stage gel system is used consisting of phosphate anionic gel and calcium cationic gel which are applied successively in such a manner that calcium phosphates participating in the remineralization of the enamel precipitate on the dental surface. The gels contain from 5 to 15% methylcellulose. Water soluble phosphate salts are contained in the phosphate anionic gel in concentrations, in %: from **0.4 to 10 collagen**; 0.2-1 biologically active substance; 0.01 to 1 fluoride additives, and other microelements up to 0.2. The cationic gel contains in %: from 0.5 to 12 calcium soluble salts, 0.1-1 collagen, 0.01-1 biologically active substances and 0.01-2 microelements.

DENTIFRICE COMPOSITION
JP7223930

PURPOSE:To obtain a dentifrice composition having pH of nearly neutrality and capable of efficiently removing dental plaque an promoting remineralization of the tooth surface and making the tooth surface glossy by blending calcium salt powder having ability capable of converting to hydroxyapatite in the presence of saliva in oral cavity. CONSTITUTION:This dentifrice composition contains calcium salt powder (especially **octacalcium phosphate**) capable of converting to hydroxyapatite by contacting with water (especially saliva in oral cavity) and it has **pH 5-8**. As the calcium salt powder, **tricalcium phosphate, a mixture (molar ratio of Ca/P: 1.30-1.67 of tetracalcium phosphate with calcium primary phosphate (anhydride or monohydrate), a mixture (molar ratio of Ca/P: 1.30-1.67) of tetracalcium phosphate with secondary calcium phosphate (anhydride or monohydrate), a mixture (molar ratio of Ca/P: 1.30-1.50) of tricalcium phosphate with calcium primary phosphate, etc**., is preferably used. This composition can not only remove a contaminant such as dental plaque, but repair also damage by promotion of remineralization of the toot surface.

Artificial saliva and its preparing method
CN1130066

An artificial saliva is prepared by mixing and compounding of sodium fluoride, **sodium chloride, potassium chloride, calcium chloride, magnesium chloride, acidic and alkaline sodium phosphate**, antiseptic and sterilized distilled water, its pH value being 0.4-6.0. This invention features that it changes symptoms of xerostomia patient, and promotes remission of oral mucosa hyperemia and heals erosive surface, while it prevents dental caries, promotes remineralization of decalcified teeth during radiactive therapy and stops the occurrence of intensified dental caries after radiactive therapy.

DENTIFRICE COMPOSITION
JP9040539

PROBLEM TO BE SOLVED: To obtain a dentifrice composition having an action removing pigmentation of teeth and also promoting remineralization of the surface of the teeth. SOLUTION: This composition contains 0.1-90wt.% a calcium compound (e.g.; **hydroxyapatite) and 0.05-10wt.% carbamide peroxide**. Hydroxyapatite has an action performing remineralization of the surface enamel of teeth, carbamide peroxide has an action removing pigmentation of teeth and a **synergistic effect is exhibited by mixing both**, then a whitening and a removing action of pigmentation of the teeth are exceedingly increased and simultaneously a mineralization effect of the surface of the teeth is reserved. A mixture of more than two species **of tricalcium phosphate, calcium hydrogen phosphate, calcium dihydrogen phosphate, octacalcium phosphate and calcium pyrophosphate can be used instead of hydroxyapatite as the calcium compound.**

Chewing gum compositions and the use thereof for remineralization of lesions in teeth
US5645853

This invention relates to chewing gum compositions and methods utilizing same which are useful to remineralize subsurface dental enamel. More specifically, this invention relates to stable, single-part chewing gum compositions containing calcium and phosphate salts which when applied to lesions in dental enamel result in remineralization of subsurface dental enamel and/or mineralization of tubules in dentin thereby counteracting caries and/or hypersensitivity.

Processes and compositions for the remineralization of teeth
US5817296

The present invention relates to remineralization, without demineralization, by applying to the teeth a composition which is present in either one or in two phases and which does not react to any large extent until introduced into the oral cavity and upon such introduction does not rapidly precipitate. One phase systems contain at least one water-soluble calcium compound, at least one other water-soluble, non-toxic compound containing a divalent metal different from calcium, and at least one water-soluble inorganic phosphate compound. If desired at least one water-soluble fluorine compound may be added to the system. In two phase systems one phase contains the calcium and the divalent metal compounds and the other the phosphate and optionally, the fluoride compound. In this way the ions which effect remineralization can be absorbed by the dental enamel and their subsequent, but controlled, reaction causes rehardening of demineralized areas in the dental enamel.

Chewing gum products and the use thereof for remineralizing subsurface dental lesions
US5958380

This invention relates to a stable, single-part chewing gum product and methods of using same to effect remineralization of subsurface lesions in teeth and/or mineralization of exposed dentinal tubules. The chewing gum product contains a water-soluble cationic portion, a water-soluble anionic portion and a stabilizing component which substantially inhibits reaction between the cationic and anionic portions during storage of the chewing gum product but which allows the cationic and anionic portions to be simultaneously released at a substantially equal rate from the product when the product is chewed in the presence of saliva and/or water. The cationic portion is composed of at least one water-soluble calcium salt, and the anionic portion contains at least one water-soluble phosphate and, optionally, at least one water-soluble fluoride salt. The stabilizing component may be at least one water-soluble divalent metal salt other than calcium salt, the divalent metal salt being disposed in the cationic portion of the product. Alternatively, the stabilizing component may be a desiccating agent or an encapsulating coating, wherein the encapsulating coating is disposed on particles of one or both of the cationic and anionic portions.

Processes and compositions for the remineralization of teeth
US5833957

The present invention relates to remineralization, without demineralization, by applying to the teeth a composition which is present in either one or in two phases and which does not react to any large extent until introduced into the oral cavity and upon such introduction does not rapidly precipitate. One phase systems contain at least one water-soluble calcium compound, at least one other water-

soluble, non-toxic compound containing a divalent metal different from calcium, and at least one water-soluble inorganic phosphate compound. If desired at least one water-soluble fluorine compound may be added to the system. In two phase systems one phase contains the calcium and the divalent metal compounds and the other the phosphate and optionally, the fluoride compound. In this way the ions which effect remineralization can be absorbed by the dental enamel and their subsequent, but controlled, reaction causes rehardening of demineralized areas in the dental enamel.

PROCESSES AND COMPOSITIONS FOR REMINERALIZATION AND PREVENTION OF DEMINERALIZATION OF DENTAL ENAMEL.
MX9709490

The present invention relates to the problems of remineralization, without demineralization of dental enamel by applying to the teeth a composition which is present in two phases which do not react with one another until introduced into the oral cavity. One phase contains at least one water-soluble calcium compound and the other contains at least one water-soluble inorganic phosphate and at least one water-soluble fluorine compound. In this way the ions which effect remineralization can be absorbed by the dental enamel and their subsequent reaction causes rehardening of demineralized areas in the dental enamel.

COMPOSITION AND METHOD FOR REMINERALIZATION OF TEETH.
MX9801062

This invention relates to non-aqeuous compositions and method utilizing same which are useful to remineralize subsurface dental enamel. More specifically, this invention relates to stable, single-part compositions containing calcium and phosphate salts which may be in a hydrophilic, non-aqueous vehicle and which when applied to lesions in dental enamel result in remineralization of subsurface dental enamel and/or mineralization of tubules in dentin thereby counteracting caries and/or hypersensitivity.

REMINERALIZING PRODUCTS AND METHODS FOR TEETH.
MX9801063

Products and methods are provided for the remineralization of lesions formed in the subsurfaces of teeth and/or mineralization of tubules in exposed dentin of teeth, wherein the products generally contain at least one water-soluble calcium salt, at least one divalent metal salt other than calcium salt, at least one water-soluble phosphate salt, and, optionally, at least one water-soluble fluoride salt. The water-soluble salts are then mixed to form an aqueous mixed solution having a pH of from about 4.5 to about 7.0. Cations released by the divalent metal salt stabilize the aqueous solution such that phosphate and calcium ions released by the salts do not react to any large extent until the product is introduced into the oral cavity and, upon introduction into the oral cavity, the ions do not rapidly precipitate. This gives the cations and anions sufficient time to diffuse through the tooth surface to the lesion(s) and/or tubules where the ions form a precipitate, thereby remineralizing the lesion(s) and/or mineralizing the tubule(s).

Two-part oral products and methods of using same to remineralize teeth
US5858333

A two-part oral product capable of remineralizing subsurface lesions and/or mineralizing exposed dentinal tubules in teeth is composed of cationic and anionic discrete parts. The cationic discrete part contains at least one water-soluble calcium salt and, preferably, at least one non-toxic, water-soluble salt of a divalent metal other than calcium, and a first pharmaceutically acceptable carrier. The anionic discrete part contains at least one water-soluble phosphate salt and, preferably, at least one water-soluble fluoride salt, and a second pharmaceutically carrier. Preferably, one of the carriers is an aqueous carrier and the other of the carriers is a non-aqueous carrier. The cationic and anionic parts are simultaneously released from the product upon mixing of the product with water and/or saliva to form the mixed aqueous solution. In this way, calcium ions released by the calcium salt and phosphate ions released by the phosphate salt are simultaneously delivered to the tooth surfaces by the solution. To effect subsurface remineralization and/or mineralization, the parts are mixed together to form the mixed aqueous solution, and the solution is then promptly applied to the teeth for a period of time sufficient to allow calcium ions and phosphate ions to diffuse through the tooth surface to the subsurface, where the ions react to form an insoluble precipitate onto the lesion and/or tubule, thereby remineralizing such lesion and/or mineralizing such tubule.

SOLID PRODUCTS AND METHODS FOR THE REMINERALIZATION OF TEETH
WO9934772

Solid products for remineralizing subsurface lesions and/or mineralizing exposed tubules in dentin containing an anionic component composed of at least one phosphate salt and a cationic component composed of at least one calcium salt. The cationic components and the anionic components are mixed in a carrier component and then coated on an insoluble, solid substrate. Subsurface lesions and/or exposed dentin tubules in a tooth are remineralized by the rapid and simultaneous release of the calcium and phosphate salts into water and/or saliva such that the subsurface lesions and dentin tubules are permeated by the calcium and phosphate ions. The calcium and phosphate ions precipitate as water-insoluble calcium phosphate in the subsurface lesions or dentin tubules. The products may be in the form of dental floss, tooth picks, dental adhesives, and implants.

IMPROVED PRODUCTS AND METHODS FOR THE REMINERALIZATION OF TEETH
KR20000036009

PURPOSE: Improved products and methods for remineralizing subsurface lesions in teeth and for mineralizing exposed tubules in dentin are provided to prevent demineralization thereof. CONSTITUTION: A liquid product for remineralizing subsurface lesions and/or for mineralizing exposed dentin tubules in teeth, comprises: (a) a cationic component comprising at least one partially water-soluble calcium salt; (b) an anionic component comprising at least one water-soluble phosphate salt and at least one water-soluble fluoride salt; and (c) a separating means disposed to separate the components (a) and (b), wherein the components (a) and (b) have a pH in water such that a mixed aqueous composition formed by mixing the components (a) and (b) with water and/or saliva has a pH of from about 4.0 to about 10.0; further wherein the product contains an amount of the calcium salt such that in the mixed aqueous composition a first portion of the calcium salt exists as dissolved calcium cations and a second portion of the calcium salt exists as undissolved calcium salt, the aqueous composition further comprising dissolved phosphate anions released by the phosphate salt and dissolved fluoride anions released by the fluoride salt.

Processes for the remineralization and mineralization of teeth
US6036944

A method for remineralizing one or more subsurface lesions in a tooth and/or mineralizing one or

more exposed dentinal tubules in the tooth involves dispensing effective amounts of at least one water-soluble calcium salt, at least one water-soluble non-toxic divalent metal compound wherein the divalent metal is other than calcium, at least one water-soluble phosphate salt and, optionally, a water-soluble fluoride salt; mixing the salts and compound to form a non-carbonated mixture having a pH in water such that a non-carbonated aqueous solution containing the mixture has a pH of from 4.5 to about 7.0; and then applying the non-carbonated mixture as the non-carbonated aqueous solution to a surface of the tooth for a sufficient period of time to allow sufficient amounts of calcium, phosphate and, if present, fluoride, ions in the solution to diffuse into the subsurface of the tooth where the diffused ions then react to form an insoluble precipitate onto the lesions and/or exposed tubules, thereby remineralizing the lesions and/or mineralizing the tubules.

Products and methods for the remineralization and prevention of demineralization of teeth
US6485708

Improved one-part and two-part liquid products such as, e.g., mouthwashes, mouthrinses, toothpastes, gels and the like, for remineralizing subsurface lesions and/or mineralizing exposed dentin tubules in teeth contain a cationic component, an anionic component and a separating means for separating the cationic and anionic components. The anionic component contains water-soluble phosphate and fluoride salts, while the cationic component contains at least one partially water-soluble calcium salt and preferably at least one water-soluble salt of a divalent metal other than calcium. The tooth is treated with a mixed aqueous composition formed by mixing the cationic and anionic components with water and/or saliva. The mixed aqueous composition has a pH of from about 4.0 to about 10.0 and, in addition to dissolved calcium cations and dissolved phosphate and fluoride anions, contains a quantity of undissolved calcium salt. The use of the partially water-soluble calcium salt delays precipitation of the cations and anions in the aqueous composition until after the ions have diffused through the tooth surface to the subsurface and/or dentin so as to effect remineralization and/or mineralization, respectively.

Remineralization of teeth
US6214321

An oral product and method is provided for remineralizing teeth. The product includes a first composition containing a water soluble calcium phosphate salt or monolithic combination of calcium and phosphate salts in a carrier with the first composition having a pH less than 7, and a second composition containing an alkaline material and a fluoride ion source in a carrier to achieve a pH greater than 7.5. The first and second compositions are separated from one another prior to use. When combined upon application to teeth, the first and second compositions generate hydroxyapatite depositing same on dental enamel.

Dentifrice for the mineralization and remineralization of teeth
US6372198

Dentifrice compositions for mineralizing and remineralizing a surface or subsurface of at least one tooth, are described. The compositions primarily include at least one water soluble calcium salt, at least one water soluble phosphate salt, and at least one antioxidant, such as **coenzyme Q10**. Additionally, at least one water soluble non-toxic divalent metal compound, wherein the metal is other than calcium, such as magnesium, may also be added. Furthermore, at least one selenium-containing material, as well as at least one bromine-containing material, may also be added to the composition. The respective materials are then mixed and formed into a paste and applied to the tooth surface for a sufficient period of time to allow sufficient amounts of calcium and phosphate

ions in the mixture to diffuse through the tooth surface, where the diffused ions react together to form an insoluble precipitate on the surface or subsurface of the tooth. The **co-enzyme Q10, selenium, and bromine** are believed to contribute to the overall health of the oval cavity, especially gum tissues.

Products and methods for the remineralization and prevention of demineralization of teeth
US2001051136

Improved solid products for remineralizing subsurface lesions and/or mineralizing exposed tubules in dentin contain an anionic component, a cationic component and a separating component for separating the anionic and cationic components in the product. The anionic component contains at least one water-soluble phosphate salt and the cationic component contains at least one partially water-soluble calcium salt. To remineralize subsurface lesions and/or mineralize exposed dentin tubules in a tooth, the anionic and cationic components are mixed with water and/or saliva to form a mixed aqueous composition having a pH of from greater than about 4.0 to about 10.0, which is then applied to the tooth.; Because of the partial water-solubility of the calcium salt, the calcium cations and the phosphate anions in the mixed aqueous composition remain soluble for a period of time sufficient to allow the cations and anions to diffuse through the surface of the tooth to the subsurface and/or dentin, where the diffused cations and anions react to form an insoluble precipitate on the lesion for remineralization thereof and/or on the exposed tubule for mineralization thereof. The products may be in the form of chewing gums, lozenges, candies, edible food products, and the like.

Composition for remineralization of a tooth
US2002044912

A composition for remineralization of a tooth, adapting to a tooth surface demineralized due to dental caries and forming a compound within the tooth to gradually release a phosphate ion and a calcium ion therein, is comprised of a solution A to be first applied to a tooth surface, containing 1 to 30% by weight of a calcium salt, with the remainder being a volatile solvent; and a solution B that is an aqueous solution containing 1 to 30% by weight of a phosphate and preferably a fluoride in an amount of 0.0001 to 5% by weight, where at least one of the solution A and the solution B preferably further contains a surfactant in an amount of 0.0005 to 1 % by weight.

ANTI-CARIOUS CANDIES AND CONFECTIONS
WO02058582

Composition and kit used for growing apatite on dental material, e.g. remineralization of carious defects, uses gelatin gel containing phosphate ions, gel free from phosphate ions and medium containing calcium ions

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Dental Composition
DE10223157

comprising (a) a first gel comprising gelatin and phosphate ions, (b) a second gel free from phosphate ions and (c) a medium containing calcium ions is claimed. Independent claims are also included for the following: (1) Kit comprising components (a), (b) and (c); (2) Use of (i) gel (a), (ii) gel (b) as coating on (a) and (iii) medium (c) for growing apatite on dental material.

THERAPEUTIC AND PROPHYLACTIC TOPICAL-DESTINATION FACILITY IN THE FORM OF SELF-STICKING FILM FOR REMINERALIZATION OF SOLID DENTAL TISSUES
RU2238078

FIELD: stomatology. ^ SUBSTANCE: invention relates to facility appropriate to prevent and to treat caries and hyperesthesia as well as remineralization of solid dental tissues. Facility is made in the form of biocompatible polymer film composed of hydrophilic and hydrophobic layers, the former including fluoride ions, calcium compounds, and phosphorus-containing compounds as well as antimicrobial and auxiliary substances. ^ EFFECT: achieved strictly controlled and simultaneous supply of calcium, phosphate, and fluoride ions. ^ 14 cl,

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COMPOSITION FOR CARIES PREVENTION
CA2485836

To obtain a composition for caries prevention, which has effects for efficiently suppressing demineralization and promoting remineralization and stability in keeping for a long time, **0.01 to 10% by weight of sodium carboxymethylcellulose having the etherification degree of 0.7 to 1.0 is used in a composition blended with a casein phosphopeptide - amorphous calcium phosphate complex (CPP - ACP**) and / or a casein phosphopeptide - amorphous calcium fluoride phosphate complex (CPP - ACFP), a sodium carboxymethylcellulose, a viscosity regulator and water.

Dental releasing materials
US2007123604

The present invention relates to methods and compositions of dental materials containing nano-sized calcium phosphate and other fillers that release calcium, phosphate and fluoride. This invention further relates to dental compositions for restorations, stress-bearing applications, artificial crowns, anterior and posterior tooth fillings, adhesives, cavity liners, cements, bases, orthodontic devices, prostheses, and sealants utilizing high stress-bearing materials that release materials for the remineralization of decayed tooth structures.

Composite material, useful e.g. as neo- and /or remineralization component in the production of cleaning composition and care of the teeth, comprises highly water-soluble calcium salts and ampholytic polymer component
DE102005052370

Composite material comprises high water-soluble calcium salts, where the calcium salts in the form of single crystallite or particle and majority of the calcium salts are crystallite form with an average particle diameter of less than 1000 nm, preferably 300 nm; and ampholytic polymer component, which exhibits an isoelectric point of 5-7.4. Independent claims are included for: (1) a procedure for the preparation of the composite material comprising precipitating aqueous solution of water-soluble calcium salt and aqueous solution of water-soluble phosphate- and/or fluoride salt in the presence of polymer component; (2) a mouth-, dental care and -cleaning agent with a content of composite material; (3) a sweet comprising a content of composite material; and (4) a composite for the induction or promotion of new formation of bone fabric with the composite material. - ACTIVITY : Osteopathic.

Dental whitening compositions
US2006115437

A whitening system has a de-sensitizing effect as well as re-mineralizing capability. The system may be a one-component or a two-component composition. The system may also be an unfoamed, a foamed or a foamable composition. For a one-component system, a sparingly soluble calcium phosphate salt may be in dry particle form with at least one gelling agent, wherein the salt is capable of sustained release of both calcium and phosphate ions into saliva upon exposure of the particle thereto and providing a hydroxyapatite remineralization. In a two component system, a first component has at least one peroxide compound, at least one source of phosphate and at least one gelling agent; and a second component has at least one source of calcium, strontium and/or mixtures thereof. The second component may also contain at least one gelling agent, and the composition maybe present as a foam or is foamable. The composition may be packed in a two-compartment syringe, or be present in a carrier or coated onto a substrate.

Process for treating teeth
US2006216247

An acidic solution is applied to the tooth surface in the oral cavity and has the ingredients thymol, eucalyptol and menthol. It kills bacteria in the mouth and makes the environment acidic. The acidity in the oral cavity causes demineralization to occur, releasing calcium and phosphate through open pores in the tooth surface. The acidic solution is removed from the oral cavity after a predetermined amount of time. The non-acidic mouthwash is applied to the tooth surface subsequent to the removal of the acidic solution. It has sodium fluoride and works to neutralize acidic conditions in the oral cavity allowing remineralization to occur. Calcium and phosphate ions fill the open pores in the tooth surface, hardening the enamel. After a predetermined amount of time the user removes the non-acidic solution

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CALCIUM PHOSPHATE SALTS IN ORAL COMPOSITIONS SUITABLE AS A TOOTH REMINERALIZING AGENT
WO2007092763

The present invention is generally directed to an oral composition comprising a calcium phosphate salt and a combination of acids having differing solubilities in the oral cavity, for tooth mineralization or remineralization. The presence of a combination of acids in the oral composition acts to maximize the release of calcium and phosphate ions from the oral composition over an extended period of time, in order to promote the precipitation of enamel-like crystals on the surfaces of the teeth, or in subsurface regions therein

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Methods for treating dental conditions using tissue scaffolds
US2007248933

The invention provides methods, apparatus and kits for regenerating dental tissue in vivo that are useful for treating a variety of dental conditions, exemplified by treatment of caries. The invention uses tissue scaffold wafers, preferably made of PGA, PLLA, PDLLA or PLGA dimensioned to fit into a hole of corresponding sized drilled into the tooth of subject to expose dental pulp in vivo. In certain embodiments the tissue scaffold wafer further comprises calcium phosphate and fluoride.

The tissue scaffold wafer may be secured into the hole with a hydrogel, a cement or other suitable material. Either the wafer or the hydrogel or both contain a morphogenic agent, such as a member encoded by the **TGF-beta supergene family**, that promotes regeneration and differentiation of healthy dental tissue in vivo, which in turn leads to remineralization of dentin and enamel. The tissue scaffold may further include an antibiotic or anti-inflammatory agent.

Calcium phosphate complex and salts in oral delivery systems
CN101415398

The present invention relates to oral delivery systems, such as confectioner y and chewing gum compositions, and methods for remineralizing tooth enamel in mammals. In particular, the oral delivery systems include a **phosphopeptide o r phosphoprotein stabilized calcium phosphate** or calcium fluoride phosphate complex and a salt selected from calcium salts, phosphate salts and combinations thereof. The delivery systems promote remineralization of tooth enamel of consumers.

Dental Whitening Compositions
US2008050408

Dental whitening system has a de-sensitizing effect as well as re-mineralizing capability. The system may be a one-component or a two-component composition. The system may also be an unfoamed, a foamed or a foamable composition. For a one-component system, a sparingly soluble calcium phosphate salt may be in dry particle form with at least one gelling agent, wherein the salt is capable of sustained release of both calcium and phosphate ions into saliva upon exposure of the particle thereto and providing a hydroxyapatite remineralization. In a two component system, a first component has at least one peroxide compound, at least one source of phosphate and at least one gelling agent; and a second component has at least one source of calcium, **strontium** and/or mixtures thereof. The second component may also contain at least one gelling agent, and the composition maybe present as a foam or is foamable. The composition may be packed in a two-compartment syringe, or be present in a carrier or coated onto a substrate.

ORAL COMPOSITION FOR STABILIZATION, (RE)CALCIFICATION AND (RE)MINERALIZATION OF TOOTH ENAMEL AND DENTINE
US2008152598

An oral composition for the stabilization, recalcification and remineralization of dental enamel, providing efficient protection from tooth decay. The oral composition uses the calcium form of zeolite, phosphate salts soluble in water, and matrix proteins of teeth. The efficiency of this solution is based on the adjustment of pH in the mouth cavity to the required value while at the same time incorporating the calcium ions from the **calcium form of zeolite** into the dental enamel and dentin in the presence of matrix proteins of the teeth. Calcium and phosphate ions stabilizes the crystal structure of calcium hydroxyapatite in tooth enamel and dentin.

Recalcification Promoter And Composition For Oral Cavity
US2010129298

It is intended to provide a remineralization promoter for tooth enamel and a composition for an oral cavity, which can highly effectively promote the remineralization of tooth enamel and strongly

inhibit dental caries. The remineralization promoter for tooth enamel and the composition for an oral cavity are characterized by containing amorphous hydroxyapatite and/or amorphized hydroxyapatite showing two peaks at 2[theta]=31 to 35 DEG in X-ray diffraction. The amorphized hydroxyapatite is obtained by reacting calcium salt with phosphate in an aqueous solution and drying the reaction solution at a temperature of 10 to 70 DEG C.

TOOTH FLUORIDATING AND REMINERALIZING COMPOSITIONS AND METHODS, BASED ON NANOAGGREGATE FORMATION
WO2008147997

CALCIUM PHOSPHATE COMPLEX AND SALTS IN ORAL DELIVERY SYSTEMS.
MX2008012524

The present invention relates to oral delivery systems, such as confectionery and chewing gum compositions, and methods for remineralizing tooth enamel in mammals. In particular, the oral delivery systems include a phosphopeptide or phosphoprotein stabilized calcium phosphate or calcium fluoride phosphate complex and a salt selected from calcium salts, phosphate salts and combinations thereof. The delivery systems promote remineralization of tooth enamel of consumers.

Preparation method of inorganic calcium phosphate salt/biodegradable polymer fiber film composite material
CN101507841

The invention discloses a method for preparing composite material from inorganic calcium phosphate salt/biodegradable polymer fiber membrane. The method comprises the steps of superposing more than two inorganic calcium phosphate salt/biodegradable polymer fiber membranes to form a multilayer composite fiber membrane and hot press molding on the multilayer composite fiber membrane, wherein the orientation degree of fibers in the inorganic calcium phosphate salt/biodegradable polymer fiber membranes is more than 80 percent, and the included angle of the fiber orientation of adjacent layers of the multilayer composite fiber membrane is between 0 and 90 degrees. The method has the advantages of high adaptability, simple process, low cost and good repeatability.; The prepared composite material has biological activity and remineralization performance, high mechanical properties and direction controlability.

FUNCTIONALIZED CALCIUM PHOSPHATE HYBRID SYSTEMS FOR THE REMINERALIZATION OF TEETH AND A METHOD FOR PRODUCING THE SAME
US2010291164

A dental remineralizing system, including a functionalized calcium-containing complex having an organic surfactant component mechanochemically attached to a distressed calcium phosphate component and blended with the comestible material.

ORAL CARE PRODUCTS COMPRISING BUFFER SYSTEMS FOR IMPROVED MINERALIZATION/REMINERALIZATION BENEFITS.
MX2009008303

Oral products for the improved mineralization/remineralization of teeth are provided. In an embodiment, the present disclosure provides an oral product comprising a **calcium salt, a phosphate salt, a sodium salt and a potassium salt. For example, the molar ratio of the sodium salt to the potassium salt ranges from about 3 to about 4**.

ANTICARIOUS CHEWING GUM, CANDY, GEL, TOOTHPASTE, AND DENTIFRICE
JP2010047575

PROBLEM TO BE SOLVED: To provide an anticarious delivery vehicle releasing calcium phosphate ions which diffuse into partially demineralized tooth enamel or dentin, leading to remineralization and repair of caries lesions, dental plaque, open dentinal tubules and exposed dentin without the use of fluoride. ; SOLUTION: The chewing gums, candies, confectioneries, toothpastes, dentifrices and gel include non-toxic sparingly soluble calcium compounds and phosphate compounds as additives and release calcium ions and phosphate ions into the oral cavity gradually and persistently for a period not less than 5 minutes. ; C

DENTAL PROPHYLACTIC PASTE
WO2011031606

A dental prophylactic paste having excellent flowability during the manufacturing process, minimal to no splattering during use, and remineralization characteristics is provided. The prophylactic paste includes at least one water soluble calcium salt; a water soluble phosphate salt, a **water soluble silicate**; and a moisture retention agent. The paste has a splatter rating of less than 3. The splatter rating of the paste refers to the tendency of the paste to splatter during a dental cleaning procedure. The lower the splatter rating, the less the paste has a tendency to splatter. A paste having a splatter rating of less than 3 is considered to have good handability.

COMPOSITIONS AND METHODS FOR IMPROVING OVERALL TOOTH HEALTH AND APPEARANCE.
MX2010014220

Disclosed are oral care compositions comprising selected surface-active **organophosphate** compounds and methods of use to provide protection of teeth from erosion caused by the action of chemicals, such as harsh abrasives and acids. The surface-active organophosphate compounds are substantive to teeth, the phosphate groups binding the calcium in teeth and thus preventing loss of calcium from dissolution when contacted with acids. The organophosphate compound may also deposit a protective surface coating that prevents contact of teeth with erosive challenges. Selected organophosphate compounds contain one or more phosphate groups and are combined in the oral care composition with one or more of a fluoride ion agent, an antimicrobial agent preferably selected from quaternary ammonium compounds and polyvalent metal salts, an anticalculus agent and additional surfactant, to provide benefits including superior anti-erosion, anticaries, antiplaque and anti-staining as demonstrated by enhanced fluoride uptake, remineralization, resistance to acid demineralization and antimicrobial activities, resulting in improved overall tooth health, structural integrity and appearance.

CALCIUM PEROXYPHOSPHATES AND USE THEREOF IN DENTAL COMPOSITIONS
US2011142768

Calcium peroxyphosphate compounds and dental compositions comprising these compounds that combine both whitening/stain removal of teeth with remineralization are disclosed. The calcium peroxyphosphate compounds are capable of releasing, in an aqueous environment, whitening and remineralization effective amounts of calcium ion, phosphate ion, and active oxygen. Preferred compounds are **calcium peroxymonophosphate or calcium diperoxymonophosphate** compounds. These compounds may be used in humans and other animals, including other mammals.

Method for in-vitro induction of remineralization of dentin
CN102172334

The invention discloses a method for induction of remineralization of tissue of tooth, which comprises the following steps: preparing a dental film; preparing a dentin remineralization inducing mineralization system solution; and remineralizing the dentin. In the invention, the micro environment of the calcification of the tissue of the tooth in a gel matrix is stimulated, a calcium phosphate ion dispersing hydrogel system is constructed, and the biomimetic mineralization of the dentin is induced in vitro. The surface deposits are qualitatively characterized by constructing an agar gel mineralization system on the surface of the acid-corroded dentin in vitro and by suing a scanning electron microscope (SEM) and a micro-Fourier transform infrared spectrometer (FTIR). Results show an agar gel CaCl2 solution mineralization system containing phosphate can induce the deposition and growth of strip nano crystals on the surface of acid-corroded dentin surface, and that the deposited apatite crystals are densely arranged in an interlaced shape. The method is simple, convenient, quick and low in cost, and is an effective technical method for the biomimetic mineralization of the dentin.

Calcium phosphate complex and salts in oral delivery systems
AU2011202746

The present invention relates to oral delivery systems, such as confectionery and chewing gum compositions, and methods for remineralizing tooth enamel in mammals. In particular, the oral 5 delivery systems include a phosphopeptide or phosphoprotein stabilized calcium phosphate or calcium fluoride phosphate complex and a salt selected from calcium salts, phosphate salts and combinations thereof. The delivery systems promote remineralization of tooth enamel of consumers.

SOLID-STATE METHOD FOR PRODUCING FUNCTIONALIZED CALCIUM PHOSPHATE HYBRID ORGANIC/INORGANIC CHEMICAL SYSTEMS FOR DENTAL REMINERALIZATION APPLICATIONS
US2012114718

A method of repairing weakened teeth, including combining a first predetermined amount of an inorganic calcium source with a second predetermined amount of an organic material to define a mixture, placing the mixture in a milling vessel operationally connected to a planetary mill, introducing milling media into the milling vessel, milling the mixture to impart sufficient kinetic energy to break down the organic and inorganic materials into substantially smaller intermediate particles and fuse the intermediate particles together to yield functionalized molecules having both organic and inorganic chemical characteristics, combining a functionalized calcium phosphate/organic compound with a fluoridated formulation to define a hybrid system, and applying the hybrid system to the weakened teeth.

NOVEL TYPE OF ANION-CONTAINING CALCIUM PHOSPHATE COMPOUND FOR DENTAL REMINERALIZATION
US2012129135

The invention provides an anion-containing calcium phosphate compound, composition and dental patch comprising the same and their use in remineralizing teeth. The anion-containing calcium phosphate compound has the following formula: **(Ca+2)x(anion-a)y(PO4-3)z wherein 2x= (a*y+3z); a is an integer of 1 to 3; and each of x, y and z is not 0.**

MINERAL TRIOXIDE AGGREGATE (MTA) COMPOSITION AND USE
US2012156308

The present application discloses a fast-setting mineral trioxide aggregate (MTA) with fluoride release for practical treatment of diseases in teeth and bone, e.g. for caries treatment and/or prevention. The cariostatic MTA contain calcia-silica-alumina cement with moderately increased tricalcium aluminate content allowing high calcium hydroxide release. The MTA composition support remineralization and biomineralization, and it is suitable for stimulation of hard tissue regeneration. MTA embodiments contain superplasticizerand nanosilicate for improved mechanical properties. The MTA compositions include optional radiocontrast and nano-enriched leachable fluorine, nitrate, strontium, and phosphate. The fast-setting MTA paste exhibits flow-to-clay-like consistency, which allows new practical applications including cavity lining, temporary restoration, bonding, and cementations in one MTA embodiment. The high calcium hydroxide and high fluoride release are suitable for caries prevention and treatment, and per se inhibition of dental symptoms.

A novel type of dual anion-containing calcium phosphate compound for dental remineralization
TW201221145

The invention provides an anion-containing calcium phosphate compound, composition and dental patch comprising the same and their use in remineralizing teeth. The anion-containing calcium phosphate compound has the following formula: (Ca<SP>+2</SP>)x (anion<SP>-a</SP>)y (PO4<SP>-3</SP>)z wherein 2x = (a*y + 3z); a is an integer of 1 to 3; and each of x, y and z is not 0.

ANTIMICROBIAL COMPOSITIONS FOR TOOTH FLUORIDATION AND REMINERALIZATION
WO2012119155

Compositions and methods for delivering, in an oral environment, **chlorhexidine** in combination with beneficial ions selected from calcium, phosphate, fluoride, **silver**, and carbonate ions are described. These compositions and methods may involve the formation of chlorhexidine compounds either prior to use or in situ. Representative compounds include chlorhexidine fluoride (ChxF), chlorhexidine phosphate (ChxP), chlorhexidine calcium fluoride (ChxCF), chlorhexidine phosphate fluoride (ChxPF), chlorhexidine calcium phosphate (ChxCP), chlorhexidine calcium phosphate fluoride (ChxCPF), chlorhexidine silver calcium phosphate fluoride (ChxACPF) or the compositions or methods which will form these noble chlorhexidine compounds when applied to the tooth. Two or more of these chlorhexidine compounds may be formed as an aggregate, or one or more of these chlorhexidine compounds may be formed as an aggregate with calcium fluoride

(CaF2).

Mouth-and dental-care prepns - contg hydroxyl-apatite and/or disinfectants
DE2134862

Mouth- and tooth-care preparations (e.g. toothpastes, tooth powders, chewing tablets, pastilles, chewing gums, gum ointments, mouthwashes, gargles) contg. finely divided hydroxylapatite and/or an orally tolerable mucous membrane promoting disinfectant, and pref. also contg. an osmotically acting inorganic salt combination and a local anaesthetic. - The hydroxylapatite has a favourable and lasting effect on dental hypersensitivity and hyperaesthesia, due to remineralization of the dentine with effective blocking of dentine capillaries, inhibiting transmission of the pain reflex to the pulpa. The disinfectant-contg. compositions have a favourable effect on mouth odour due to elimination of putrefactive bacteria from the mucosa.

STABLE COMPOSITION FOR TOOTH REMINERALIZATION
JP55053212

An aqueous solution useful for remineralizing subsurface carious lesions of dental enamel which solution contains sources of calcium ions and phosphate ions as well as fluoride ions and further includes as an agent to stabilize the solution against precipitation, an antinucleating agent such as ethylenediamine tetramethylenephosphonic acid or water soluble salt thereof, the pH of the solution being about 5-9, preferably close to physiological conditions, such as about 6.8-7.5.

Dentifrice compositions
US4327079

A dentifrice composition containing synthetic hydroxyapatite powder which is neutral or weakly alkaline or contains **0.1 to 20% by weight of NaCl and/or KCl and 0.003 to 3% by weight of MgCl2**. The dentifrice composition is very effective in fortifying a surface of a tooth, promoting remineralization of the surface of the tooth and eliminating plaque from the tooth.

REMINERALIZATION OF TOOTH
JP3048613

PURPOSE: To enable the teeth to be remineralized by applying a nonastringent composition for oral cavity in the form of dentifrice or mouthwash containing each specified amount of xylitol and fluoride ion feed compound(s) to a demineralized portion of tooth structure. CONSTITUTION: Remineralization of a demineralized portion of tooth structure is accomplished by applying, to the above portion, a nonastringent composition for oral cavity in the form of dentifrice or mouthwash containing 10-20wt.% of xylitol and such an amount of at least one fluoride ion feed compound as to be enough to feed a total of 150-1,800ppm of fluoride ion so that sodium fluoride feeds a majority of such fluoride ion.

COMPOSITION FOR REMINERALIZATION OF DEMINERALIZED TOOTH PART
RU2092153

DENTAL FORMULATION
WO9319728

This invention concerns inhibiting tooth enamel demineralization by using a **water soluble phosphate, particularly a pyrophosphate or tripolyphosphate**, to inhibit demineralization while not negatively impacting remineralization.

TOOTH-PASTE
SK280006

Proposed is a toothpaste with the usual components and containing as the polishing agent a combination of silicilic acids and dicalcium phosphate dihydrate (brushite), this toothpaste having a particularly effective restoring action on the tooth surface. This action is due to controlled remineralization in, in particular, enamel scratches and Tomes' pits. This action can be reinforced by the addition of magnesium ions and/or fluorophosphate ions.

TOOTH PASTE COMPOSITION
JP9124451

PROBLEM TO BE SOLVED: To obtain the subject composition capable of adsorbing off halitosis-causing substances to prevent the halitosis, and excellent in the dental caries- preventing effect due to the remineralization of tooth surfaces by simultaneously using a zeolite and synthetic hydroxyapatite. SOLUTION: This tooth paste composition contains (A) a zeolite (e.g. a natural **zeolite such as gismondine, garronite, analcime or wirakite or a synthetic zeolite such as stilbite or Ca-mordenite) and (B) hydroxyapatite**. The component A is preferably a zeolite of the formula: (MI,MII1/2)m (Alm Sin O2(m+n)).-xH2 O, (n>=m) (MI, MII are those each subjected to an ion exchange treatment using a monovalent and/or divalent cation excluding Li<+> and K<+> , especially preferably Ca<2+>). The component A is preferably compounded in an amount of 1.0-50.0%, **preferably 5-30%,** based on the whole amount of the composition.

IMPROVED PRODUCTS AND METHODS FOR THE REMINERALIZATION AND PREVENTION OF DEMINERALIZATION OF TEETH
WO9813012

Improved one-part and two-part liquid products such as, e.g., mouthwashes, mouthrinses, toothpastes, gels and the like, for remineralizing subsurface lesions and/or mineralizing exposed dentin tubules in teeth contain a cationic component, an anionic component and a separating means for separating the cationic and anionic components. The anionic component contains water-soluble phosphate and fluoride salts, while the cationic component contains at least one partially water-soluble calcium salt and preferably at least one water-soluble salt of a divalent metal other than calcium. The tooth is treated with a mixed aqueous composition formed by mixing the cationic and anionic components with water and/or saliva. The mixed aqueous composition has a pH of from about 4.0 to about 10.0 and, in addition to dissolved calcium cations and dissolved phosphate and fluoride anions, contains a quantity of undissolved calcium salt. The use of the partially water-soluble calcium salt delays precipitation of the cations and anions in the aqueous composition until after the ions have diffused through the tooth surface to the subsurface and/or dentin so as to effect

remineralization and/or mineralization, respectively.

REMINERALIZATION MATERIAL FOR ORGANOMINERAL TISSUES
BG103544

The material can be appled for primary filling in the treatment of caries in particular deep ones. It remineralizes the dentine with a composition very close to the original one having high microhardness. It can also be applied as an ingredient of a promedicament for teeth such as tooth pastes, elixirs, cotton threads and powders. The material includes a mixture of cation and anion exchange resins, charged with Ca2+, F- and PO43- ions, in appr. mole ratio of 2:1:1. Material where the resins also have a charge of **Zn2+ ions** is preferred in presence of quantities less than 1%, better closer to 0.2%, of the dry weight of the resin. Resins are suitable the base of which is of laterally cross linked polystyrene with 2 to 14% divinylbenzene.

Bioactive glass compositions and methods of treatment using bioactive glass
US6244871

A novel silica based bioactive glass composition that can be used in conjunction with a delivery agent such as a toothpaste, gel, etc. having a particle size range <90 mum which will form a rapid and continuous reaction with body fluids due to the immediate and long term ionic release of Ca and P from the core silica particles, to produce a stable crystalline hydroxy carbonate apatite layer deposited onto and into the dentin tubules for the immediate and long term reduction of dentin hypersensitivity and tooth surface remineralization.

CHEWING GUM WITH DENTAL HEALTH BENEFITS EMPLOYING CALCIUM LACTATE
WO0042861

A chewing gum and method for the remineralization of tooth enamel is provided. The chewing gum comprises an insoluble base portion, a water soluble portion, a flavor, and a therapeutically effective amount of **calcium lactate.**

CHEWING GUM WITH DENTAL BENEFITS INCLUDING CALCIUM IN A FOOD GRADE ACID
WO0062762

Methods and chewing gums for the remineralization of tooth enamel are provided. To this end a sugar free chewing gum comprising an insoluble portion, a water soluble portion, a flavor, calcium carbonate, and a food grade acid is provided as well as methods of using same.

Prophylactic mouthwash solution, especially for use together with an abrasive powder, comprises an antimicrobial or bacteriostatic and tooth-remineralizing agent
DE10026716

Prophylactic mouthwash solution comprises an agent (I) that has antimicrobial or bacteriostatic

activity and contributes to the remineralization of teeth.

DENTIN DESENSITIZING TOOTH CARE AGENT PROVIDING INTENSIVE REMINERALIZATION AND ANTI-CARIES ACTION
RU2005106291

FIELD: stomatology. ^ SUBSTANCE: claimed composition contains salts releasing fluoride ions and potassium ions and pH 8-9.9, wherein pH level is buffered with phosphate salt. ^ EFFECT: tooth care agent of improved effect.

REMINERALIZATION PROMOTERS
WO2005003753

Substances or compositions having a function of keeping metal ions such as Ca ion in a soluble state and a function of promoting remineralization and repairing tooth decay at the early stage are utilized in foods, drinks, seasonings, taste improving agents, oral hygiene products, detergents, metal suppliers, metal absorption promoters, cosmetics, feeds and fertilizers. A remineralization promoter that is a composition containing at least one member selected from the group consisting of **starch phosphate, maltodextrin phosphate, reducing maltodextrin phosphate, oligosaccharide phosphate**, reducing oligosaccharide phosphate, organic acids and saccharides and having a function of exerting a calcipexis ratio of 5% or higher, preferably 10% or higher, in a specific remineralization test reaction; and foods, drinks, seasonings, taste improving agents, oral hygiene products, detergents, metal suppliers, metal absorption promoters, cosmetics, feeds or fertilizers characterized by containing the above-described remineralization promoter.

Oral and dental care product
US2007154411

The invention relates to oral and dental hygiene products comprising a) a composite material consisting of calcium salts which are slightly soluble in water, in the form of nanoparticulate primary particles having a length of from 5 to 150 nm and a cross section of from 2 to 50 nm and protein components selected from **proteins, protein hydrolysates and protein hydrolysate derivatives**, and b) 10 to 35% by weight of a cleaning agent mixture, the cleaning agent mixture comprising from 0.01 to 5% by weight of aluminum oxide polishing agent. The oral and dental hygiene products ensure a thorough cleaning of the teeth with simultaneous and long-lasting remineralization of the tooth surface.

Chewable mass for the remineralization of tooth enamel
US2007116799

A method of producing chewable mass for remineralization of tooth enamel, including the steps of preparing an aqueous solution of at least one acidifying agent suitable as a foodstuff, adding a reactive calcium source to the aqueous solution, adding the solution to a thickener, wherein phosphoric acid is added during at least one of the preceding steps, thoroughly mixing all of the components to form a mass, and forming and drying the mass. The chewable mass has a calcium content of between 30 and 190 mMol/kg of finished product.

Induced remineralisation of human tooth enamel
US2005220724

The present application relates to the induced remineralization of human tooth enamel and in particular to the building up of apatite on tooth material.

Formulation of dual eicosanoid system and cytokine system inhibitors for use in the prevention and treatment of oral diseases and conditions
US2006079467

The present invention provides a novel composition of matter comprised of a mixture of two specific classes of compounds-**Free-B-Ring flavonoids and flavans**-for use in the prevention and treatment of diseases and conditions associated with mouth, gums and teeth. This composition of matter simultaneously inhibits cyclooxygenase (COX) and lipoxygenase (LOX) enzymatic activity and reduces cytokine production at the mRNA level in normal, aged and damaged periodontal cells and tissues. This invention further provides a method for the prevention and treatment of diseases and conditions of the mouth, gums and teeth. The method for preventing and treating diseases and conditions of the mouth, teeth and gums is comprised of administering to a host in need thereof a therapeutically effective amount of a composition comprising a mixture of Free-B-Ring flavonoids and flavans synthesized and/or isolated from a single plant or multiple plants, preferably in the **Scutellaria, Oroxylum, Acacia or Uncaria genus** of plants and pharmaceutically and/or cosmetically acceptable carriers. Finally the present invention provides a method for the prevention and treatment of diseases and conditions of the mouth, teeth or gums, including but not limited to periodontal diseases, such as gingivitis, periodontitis, pulpitis, periodontal conditions caused by the physical implantation of oral dentures, trauma, injuries, bruxism, neoplastic and other degenerative processes; material alba, pellicles, dental plagues, calculus, and stains. Use of the composition described herein also affords the benefit of maintaining optimum saliva production and pH, minimizing bacterial growth, reducing the formation of pellicles and plague, inhibiting tooth decalcification and tooth caries (decay), promoting remineralization, which yields healthy gums, whitening teeth, maintaining healthy oral hygiene and reducing oral malodour (halitosis).

Induced Remineralisation of Human Dental Enamel
US2007218017

The present application relates to the induced remineralization of human tooth enamel and in particular to the building up of apatite on tooth material.

Oral and dental hygiene product
US2006222602

An oral and dental hygiene product comprising a) a composite material containing poorly water-soluble calcium salts in the form of nanoparticulate primary particles which are between 5 and 150 nm long and have a cross-section of between 2 and 50 nm, and protein constituents selected from proteins, protein hydrolysates and protein hydrolysate derivatives, and b) between 0.1 and 9 wt. % of a cleaning agent, in relation to the total weight of the product. The inventive oral and dental hygiene product ensures an effective and long-lasting remineralization of the surface of the tooth, and a protective cleaning action of the cleaning or polishing agent.

CALCIUM BINDING PEPTIDES
WO2007038683

Disclosed herein are a class of compounds comprising peptides of the sequence (X-Y-Z)n, wherein X is an amino acid selected from **aspartic acid, glutamic acid, asparagine, alanine and glutamine**, and Y and Z are amino acids selected from **alanine, serine, threonine, phosphoserine, phosphothreonine**, and their derivatives. These compounds **have the property of binding tightly and specifically to calcified surfaces**, making them useful for a variety of applications including remineralization of tooth and bone surfaces, diagnosis of bone and tooth defects, treatment of bone and tooth defects, and analysis of the presence and location of calcified deposits both in vitro and in vivo and in industrial, synthetic, medical, dental, and research applications where identification, localization, or manipulation of calcification is desirable.

MOUTH AND TEETH CLEANING AND/OR REMINERALIZATION METHOD
WO2007101511

The invention relates to a method for cleaning the mouth and teeth, remineralizing or neomineralizing the dental material, and/or reducing the sensitivity of teeth to pain. Said method is characterized in that the teeth are treated with an electric tooth brushing apparatus, preferably an untrasonic toothbrush, and an oral care product and/or a dentifrice comprising calcium salts that are difficult to dissolve in water and/or the composite materials thereof. Also disclosed is a kit that is used in the inventive method.

Products and methods for the remineralization and prevention of demineralization of teeth
US6451290

Improved solid products for remineralizing subsurface lesions and/or mineralizing exposed tubules in dentin contain an anionic component, a cationic component and a separating component for separating the anionic and cationic components in the product. The anionic component contains at least one water-soluble phosphate salt and the cationic component contains at least one partially water-soluble calcium salt. To remineralize subsurface lesions and/or mineralize exposed dentin tubules in a tooth, the anionic and cationic components are mixed with water and/or saliva to form a mixed aqueous composition having a pH of from greater than about 4.0 to about 10.0, which is then applied to the tooth.; Because of the partial water-solubility of the calcium salt, the calcium cations and the phosphate anions in the mixed aqueous composition remain soluble for a period of time sufficient to allow the cations and anions to diffuse through the surface of the tooth to the subsurface and/or dentin, where the diffused cations and anions react to form an insoluble precipitate on the lesion for remineralization thereof and/or on the exposed tubule for mineralization thereof. The products may be in the form of chewing gums, lozenges, candies, edible food products, and the like.

Composition for remineralization of a tooth
AU5435001

A composition for remineralization of a tooth, adapting to a tooth surface demineralized due to dental caries and forming a compound within the tooth to gradually release a phosphate ion and a calcium ion therein, is comprised of a solution A to be first applied to a tooth surface, containing 1 to 30% by weight of a calcium salt, with the remainder being a volatile solvent; and a solution B that is an aqueous solution containing 1 to 30% by weight of a phosphate and preferably a fluoride in an amount of 0.0001 to 5% by weight, where at least one of the solution A and the solution B

preferably further contains a surfactant in an amount of 0.0005 to 1 % by weight.

MATERIAL FOR FILLING ROOT CANALS OF TEETH
RU2197939

FIELD: medicine, therapeutic stomatology. SUBSTANCE: method deals with treating teeth in case of chronic granulating and granulomatous periodontitis. Material for filling root canals of teeth consists of powder mixed upon liquid and contains inorganic components in its powder part - mineralizers of dental tissue, roentgenocontrast filler. It contains enriched ion-exchange natural mineral named **zeolite** at the quantity of 10-70% against powder weight, zeolite is enriched with calcium ions and **contains calcium being 1.5-45 mg** higher/g enriched zeolite against in zeolite before enrichment. Filling material causes no inflammations, allergic reactions and has no destructive impact upon periodontium tissues. It provides, also, optimization of reparative osteogenesis, remineralization of dental tissues and prolongs duration of filling and tooth functionality. EFFECT: higher efficiency of filling process

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Dental cleaning formulation and manufacturing process
US6602490

A dental hygiene preparation of very low toxicity, but with good remineralization properties and effectiveness in removing food particles and plaques from the tooth surfaces is particularly indicated for use by elderly patients and those with compromised immune systems. The preparation uses a nonfermentable sweetener in lieu of Sodium Fluoride, Sodium Monofluorophasphate or Stannous Fluoride as a caries-preventive agent in combination with **Potassium Citrate and Disodium Edetate.**

Oral compositions for treating tooth hypersensitivity
US2007258916

Oral Compositions for Treating Tooth Hypersensitivity Disclosed herein are oral compositions for decreasing tooth hypersensitivity. In one aspect, the compositions induce remineralization of dentine using bioactive glass, thereby reducing tooth sensitivity.

METHOD FOR MINERALIZATION OF ROOT TOOTH TISSUE
EA200801499

The present invention relates to medicine, namely, dentistry, and may be used in the treatment of caries of a tooth root. The object of the invention is to improve the efficiency of remineralization of hard tooth tissues for the purpose of reducing treatment periods of progressive and/or rapidly progressive supragingival carious stains without dentine defects on the vestibular and/or oral surface of a tooth root. The method consists in the subsequent use, in the course of the medical treatment of demineralization of tissues of a tooth root for the purpose of cleaning a tooth root and for Ph normalization, of the following substances: **sodium hydrogen carbonate; 0.01% Myramistin solution for suppressing the activity of pathogenic microflora and for enhancing focal defense reactions; calcium glycerophosphate and nanocrystalline calcium hydroxyappatite as remineralizing components**, and finally a fluorinated photocurable dentine cylant (desensitizer) is applied for providing a long-term contact of the above medicaments with complex cavity of a tooth root and for reducing dentine sensitivity of exposed tooth roots. The

affected surface of a tooth root is exposed to medicaments during 3 procedures for 2.5 minutes at one day interval.

BIOACTIVE GLASS COMPOSITION
JP2008120681

PROBLEM TO BE SOLVED: To provide a composition which is easily applicable and immediately adheres to a tooth structure, and chemically and physically interacting with the tooth structure. ; SOLUTION: A novel **silica-based bioactive glass** composition that can be used in conjunction with a delivery agent such as a toothpaste and gel has a particle size range of smaller than 90 [mu]m, and forms a rapid and continuous reaction with body fluids by virtue of the immediate and long-term ionic release of Ca and P from the core silica particles, to produce a stable crystalline hydroxy carbonate apatite layer deposited onto and into the dentin tubules for the immediate and long-term recovery-from dentin hypersensitivity and tooth surface remineralization.

GEL FOR REMINERALIZATION OF TOOTH TISSUES
EA200800988

The inventive technical result is aimed at practical realization of an effective remineralization composition using available components. A patient can use the composition without any assistance for prophylaxis of caries, for treating non-carious lesions, including dental hyperesthesia and improving tooth appearance (color and brightness). The inventive result is achieved by using a gel which comprises in wt.%: xylitol 2-25, **calcium glycerophosphate 0.1-3.0,** a source of **magnesium ions 0.01-0.50, guar gum 0.03-0.30** as active components as also inert components used for preparing tooth gels. **Magnesium chloride, magnesium sulfate or magnesium nitrate** is used as a source of magnesium ions.

STOMATOLOGICAL LACQUER
WO2010134833

A stomatological lacquer can be used for the prophylaxis and treatment of caries, hyperaesthesia, and accelerated remineralization of tooth dentine and enamel. Said lacquer comprises copal dissolved in a mixture of organic solvents, specifically - in one part of isopropyl alcohol and two parts of ethyl acetate and chlorobutanol, and also fluorinating, remineralizing and antiseptic components in the following ratios (% by mass): copal - 9.0 - 15.0; aminofluoride - 0.5 - 6.0; sodium fluoride - 0.1 - 1.0; alcoholic colloid (gel) of nano-sized hydroxyapatite - 0.2 - 5.0; chlorobutanol - 0.2 - 6.0; isoamyl acetate - 3.0 - 15.0; solvents - up to 100. Furthermore, the alcoholic colloid comprises not less than 0.2 and not more than 20% of nano-sized hydroxyapatite.

ORAL COMPOSITION FOR IMPROVING REMINERALIZATION
KR20110090216

PURPOSE: An oral composition for promoting remineralization is provided to enhance tooth strength without irritation to human oral cavity mucous. CONSTITUTION: An oral composition for promoting remineralization contains 0.005-1.0 weight parts of pearl powder. The diameter of the pearl powder particle is 0.05-0.30 mm. The composition is manufactured in the form of toothbrush, oral cleaning agent, mouth rinse, or chewing gum. The oral composition enhances the

strength of teeth.

TOOTHBRUSH WITH REACTIVE COMPOSITION FOR REMINERALIZATION OF TEETH
WO2012015422

A toothbrush having brush means and a means to support the brush means; and a one or two part therapeutic tooth treatment composition which becomes activated when wet incorporated on the brush means or within the toothbrush means to support the brush means in a manner such that the composition remains inactive during storage and is only activated when contacted with water or saliva; and a method comprising brushing a tooth with the toothbrush so that the brush means become wet with saliva, optionally wetting the brush means with water immediately prior to brushing a tooth, and the composition becomes activated to form a therapeutic composition to provide remineralization, whitening, and/or fluoridation.

Method for in-vitro induction of remineralization of dentin
CN102172334

The invention discloses a method for induction of remineralization of tissue of tooth, which comprises the following steps: preparing a dental film; preparing a dentin remineralization inducing mineralization system solution; and remineralizing the dentin. In the invention, the micro environment of the calcification of the tissue of the tooth in a gel matrix is stimulated, a calcium phosphate ion dispersing hydrogel system is constructed, and the biomimetic mineralization of the dentin is induced in vitro. The surface deposits are qualitatively characterized by constructing an agar gel mineralization system on the surface of the acid-corroded dentin in vitro and by suing a scanning electron microscope (SEM) and a micro-Fourier transform infrared spectrometer (FTIR). Results show an **agar gel CaCl2 solution mineralization system containing phosphate** can induce the deposition and growth of strip nano crystals on the surface of acid-corroded dentin surface, and that the deposited apatite crystals are densely arranged in an interlaced shape. The method is simple, convenient, quick and low in cost, and is an effective technical method for the biomimetic mineralization of the dentin.

DUAL ACTION DENTIFRICE COMPOSITIONS TO PREVENT HYPERSENSITIVITY AND PROMOTE REMINERALIZATION.
MX2011009421

The invention encompasses combinations of bioactive glass composition and potassium salts that are useful in conjunction with delivery agent such as, for example, toothpastes, mouthwashes, and oral gels. In certain embodiments, the compositions of the invention form a rapid and continuous reaction with body fluids (e.g., saliva) to promote the immediate and long- term release of Ca and P ions to produce a stable crystalline layer deposited onto and into the dentin tubules for the immediate and long term reduction of dentin hypersensitivity and tooth surface remineralization.

COMPOSITIONS, METHODS AND KITS FOR REMINERALIZATION AND INHIBITION OF DENTAL CARIES IN TEETH
WO2012078980

Methods, compositions and kits are provided for enhancing remineralization of a tooth or bone

containing hydroxyapatite and inhibiting caries progression or loss of hydroxyapatite using a bisphosphonate or pyrophosphonate. The tooth or tooth surface contains a trauma or defect, for example the tooth contains a caries that is identified using a detectable probe. The bisphosphonate or pyrophosphonate is contacted to the tooth and/or oral cavity and binds to the hydroxyapatite material in the tooth or bone and prevents loss of hydroxyapatite material or strengthens the hydroxyapatite. The amount and extent of enhanced remineralization or of inhibition of caries progression and loss of hydroxyapatite are determined by techniques including photography, light microscopy and fluorescence microscopy.

Dental care chewing gum
CN102524504

The invention relates to a chewing gum, in particular to a chewing gum capable of whitening, protecting and repairing teeth. The chewing gum comprises a dental care element, and is characterized in that: the dental care element consists of peroxide carrying oxygen-containing free radicals, fluoride containing soluble fluorine, and a gel containing remineralizing components. The chewing gum can clean an oral cavity, effectively removes dental plaque, promotes remineralization of enamel, prevents tooth decay, has a repairing effect on fine decayed tooth gaps and holes which have been present, and removes various color spots formed to whiten teeth, so that the teeth are repaired and cared gradually in the process of chewing the chewing gum.

Remineralising dental care agent
EP2286786

Tooth care agent (I) comprises an active agent complex of hydroxyapatite, fluoride and xylitol to increase remineralization activity of hydroxyapatite and fluoride.

PATENT EXCERPTS

US4177258

This invention relates to a dentifrice which is effective to remineralize various lesions in dental enamel.

It is known that dental caries begin with lesions of so-called "white spots," which are demineralized areas below the surface of intact dental enamel. If unchecked, surface enamel above a sub-surface lesion eventually collapses, leading to cavitation and subsequent loss of tooth structure.

In accordance with certain of its aspects, this invention relates to a remineralizing dentifrice comprising an aqueous humectant vehicle having dissolved therein at least 50 ppm of calcium ions and at least 50 ppm of phosphate ions, the ratio of calcium to phosphate ions being from about 0.01 to about 100:1, the amount of calcium ions and phosphate ions being insufficient to precipitate and sufficient to effect remineralization of dental enamel; said dentifrice further comprising a gelling agent, a compound which provides fluoride anticaries agent and an antinucleating agent selected from the group of acids and orally acceptable water-soluble salts thereof consisting of:

diamine tetramethylenephosphonic acids of the formula (M2 O3 PH2 C)2 N(CH2 PO3 M2)2 wherein n is an integer from 1 to 10; phosphonoacetic acid or salt thereof of the formula M2 O3 PCH2 COOM;

peroxydiphosphate of the formula M4 P2 O8 ;
an oligomer ##STR1## in which M is hydrogen or an orally acceptable cation; R1, R2, R3, and R4 are independently hydrogen, methyl or ethyl; Y is at least one hydrophilic member of the group consisting of COOM, --CONH2 and CH2 OH; X is at least one hydrophobic member of the group consisting of --CN, --COOR, --COOR5 OR, --CONHR and COONHR5 COR; R is C1-8 alkyl; R5 is C1-4 alkylene a is 0-7 and a+b is about 4-15;

said dentifrice having a pH of about 5 to about 9.

The antinucleating properties of the agents employed in the present invention appear to be effective to prevent precipitate formation from the calcium and phosphate ions in the dentifrice particularly with the fluoride ions also present... an antinucleating agent (e.g., a diphosphonate) can in sufficient quantity at a physiological pH completely absorb onto a spherical nucleated particle of hydroxyapatite as it forms and entirely block crystal growth. In this way, the formation of large insoluble crystals of apatite is prevented and coated small hydroxyapatite crystals of higher water solubility are attained.

It has been found that not all antinucleating agents can successfully stabilize calcium ions and phosphate ions against precipitating to form large insoluble apatite crystals. For instance, such insoluble crystals from which it is sought to use antinucleating agents such as sodium hexametaphosphate, sodium pyrophosphate, sodium phytate and mellitic acid as well as disodium phosphonoethane-1,2-dicarboxylate, 1,1-diphosphonopropane-2,3-dicarboxylic acid monohydrate, 3-amino-1-hydroxypropane-1,1-diphosphonic acid and imino-diacetic-N-methylene phosphonic acid. On the other hand, the antinucleating agents of the present invention successfully stabilize the calcium ions and phosphate ions against precipitation as large insoluble apatite crystals at a pH between about 5 and about 9. Preferably, the pH is about 6.8 to about 7.5, which approximates usual human physiological conditions and is optimum for effecting remineralization. Desirably, the antinucleating agent of the invention is present in amount of about 10 to 5000 ppm (1.times.10@-5 M to 1.times.10@-2 M) of the dentifrice, preferably about 250 to 2500 ppm (5.times.10@-5 M to 5.times. 10@-2 M), such as about 2250 ppm (5.times.10@-3 M).

The antinucleating agent of the invention is desirably a diamine tetramethylenephosphonic acid of the formula (M2 O3 PH2 C)2 --N(CH2)n --(CH2 PO3 M2)2...

The polyamine polyphosphonic compounds which are most preferred are ethylenediamine tetra (methylenephosphonic acid), (hereinafter EDITEMPA) and its water-soluble orally acceptable salts, (e.g., sodium, potassium, and ammonium and other pharmaceutically acceptable salts; most preferably the tri-, tetra- or penta-sodium salts)

The desirable oligomer antinucleating agents and methods for their preparation are described in U.S. Pat. Nos. 3,646,099 and 3,859,260 ....

These oligomers are anionic and of relatively low and accurately regulated degree of polymerization, (in contrast to the conventional free radical redox polymerization conducted with an oxidative initiator such as hydrogen, alkyl, or acyl peroxides, persulfates or hydroperoxides in relatively large amounts and a reductive activator such as NaHSO3, Na2 S2 O4 or sodium formaldehyde sulfoxylate in relatively low amounts generally added subsequently to the polymerization medium) are prepared by a reductive polymerization in which a much larger amount of a bisulfite salt, e.g. NaHSO3 (sodium bisulfite, sodium acid sulfite), a reducing agent, is the initiator charged initially with the monomer, and an oxidizing agent is added in smaller amounts as the activator during the polymerizing or oligomerizing process...

The oligomerization is carried out in water in the presence of a relatively large amount of the bisulfite reducing initiator, expressed in mols of monomer/gram formula weight (gFW) of reducing initiator is about 4 to 15, this ratio determining the degree of oligomerization.

The reductive initiator is preferably a water soluble bisulfite salt (M in the formula), especially alkali metal, such as sodium or potassium, but bisulfite salts containing other orally acceptable cations of the type referred to above may be employed.

In practice, enough oxidative activator is used to effect 100% conversion of the monomers to oligomers. The amount of such activator, expressed as gFW activator/gFw initiator may range from 0.0001 to 0.1 but usually is from about 0.0001 to 0.1. Examples of these oxidative activators are ammonium, sodium potassium persulfate, hydrogen peroxide and other water soluble oxidants commonly employed in the polymerization art.

Following completion of the oligomerization reaction, any free carboxylic acids groups in the oligomer molecules may, if desired be partially or completely neutralized, preferably at least 60%, by treating the aqueous oligomer solution with a suitable base to convert such groups to their salts with orally acceptable cations as referred to above. These aqueous oligomer solutions have a highly desirable low viscosity, and low molecular weight range depending on the monomer units in the oligomer.

It will be understood that the oligomer formula above is not intended to depict the actual structure of the oligomer molecule, the bracketed units of which formula are randomly distributed in the molecule with the --SO3 M group being normally bonded to a terminal carbon atom in the oligomer chain devoid of X and or Y substituents. In the oligomers preferred for use herein, a is zero, Y is --COOM, R1 -R4 are H, and M is alkali metal, e.g. sodium, b being about 10, as derived from acrylic acid. An oligomer of the formula above in the form of its sodium salt, with a molecular weight of about 1,000, containing about 10 acrylic acid monomeric units, is commercially available under the trade name ND-2 (a product of UniRoyal).

The effective antinucleating agents render the remineralizing dentifrice stable at normally occurring temperatures, e.g., about 15 DEG C.-40 DEG C. The remineralizing agents can diffuse effectively through an intact enamel surface in order to act on subsurface lesions.

The stability provided by the effective antinucleating agents prevents spontaneous precipitation on enamel surfaces and thereby permits diffusion of the remineralizing components to subsurface lesions.

One or more sources of each calcium ions and phosphate ions may be employed. When the source is normally insoluble such as a calcium phosphate, it is solubilized during preparation of the solution, by maintaining an acid pH of about 6 or less (e.g., about 2.5 to 6) during preparation of the remineralizing solution, particularly before the effective antinucleating agent is added.

The normally insoluble sources of calcium and phosphate ions may be a single compound such as tricalcium phosphate (which substantially corresponds to hydroxyapatite, Ca5 (PO4)3 OH or 3Ca3 (PO4)2 .multidot.Ca(OH)2, bone meal or dicalcium phosphate (dihydrate or anhydrous). When dissolved, particularly in the presence of fluoride ions, formation of hydroxyapatite, fluorohydroxyapatite and fluorapatite occurs.

Examples of other normally water-soluble or normally water-insoluble (but soluble at pH of about 6 or less) sources of calcium ion, but not phosphate ion, which can be used in the remineralizing dentifrice of the invention include calcium salts with acetate, gluconate, nitrate, stearate, lactate, formate, molybdate, tungstate, sulfate, alkyl sulfonate (e.g. lauryl sulfonate), oleate, tartrate, sorbate, iodate, silicate, aluminate, benzoate, citrate, fumarate, butyrate, isobutyrate, malate, maleate, propionate, valerate and the like. Mixtures of such calcium sources with each other or with calcium phosphate may be employed.

Examples of sources of phosphate ions, but not calcium ion, which can be used in the remineralizing dentifrice of the invention include the normally water-soluble or normally water-insoluble (but soluble at pH of about 6 or less) salts including alkali metal (e.g. sodium and

potassium), ammonium, magnesium, barium and strontium orthophosphates and acid orthophosphates, metaphosphates, pyrophosphates, as well as glycerophosphates, fructose-6-phosphate, sorbitol-6-phosphate, glucose-1-phosphate, glucose-6-phosphate and the like. Mixtures of such phosphate sources with each other or with calcium phosphate may be employed.

Tricalcium phosphate or the other sources of calcium and phosphate which together form hydroxyapatite when dissolved are employed with the mole ratio of calcium ion to phosphate ion being preferably about 1.2 to about 2:1, e.g., about 1.4 to about 1.7:1. A ratio of calcium to phosphate of 1.67:1 corresponds to the ratio of calcium to phosphate in dental enamel. The amount of calcium ion and phosphate ion in the dentifrice is sufficient to effect remineralization, there being typically at least about 500 ppm of each of calcium ion and phosphate ion. The maximum amount of calcium ion and phosphate ion desirable is that which would not result in precipitate formation. This could vary depending on the ion sources and the pH conditions. Typically, about 35,000 ppm of calcium ion and about 40,000 ppm of phosphate can be employed and precipitation still avoided.

In the prior art it has been difficult to maintain the solubility of calcium phosphate, particularly in the presence of a fluoride source. As previously indicated, this is overcome in the present invention when the effective antinucleating agents are employed. Examples of fluoride ion sources (including complex fluoride ions) include alkali metal (e.g., sodium potassium and lithium) ammonium, alkaline earth metal (e.g., calcium, barium, strontium, magnesium), aluminum, zinc, stannous, indium, zirconium, copper, nickel, palladium and organonitrogen such as alkylamine (e.g., hexylamine) compounds with fluoride ion sources. Sources of fluoride ions include fluoride, fluorophosphate (including monofluorophosphate, difluorophosphate and polyfluorophosphate), silicofluoride, fluorozirconate, fluoroborate and fluorostannite. Typical compounds are sodium fluoride, zinc fluoride, stannous fluoride and sodium monofluorophosphate. Sodium fluoride and sodium monofluorophosphate are preferred. The fluoride source compound is desirably present in amount to provide about 1 ppm to 10,000 ppm(0.0001%- 1%)fluoride to the remineralizing dentifrice e.g., about 1 ppm to 1000 ppm (0.0001-0.76%)sodium monofluorophosphate, preferably about 5 ppm fluoride. The amount of the compound employed should not be sufficient to result in precipitate formation. For instance, in the case of a fluoride source of low solubility, such as calcium fluoride, the amount of the compound employed should not exceed 1500 ppm.

The stable remineralizing dentifrice may be made by first preparing a stock solution of soluble calcium ions from a solution of a water-soluble salt such as calcium chloride and phosphate ions from a solution of a water salt such as sodium dihydrogen phosphate; one or both of the calcium or phosphate solutions preferably containing antinucleating agent such as EDITEMPA, prior to forming the stock solution in order to prevent spontaneous precipitation. A preferred final concentration of calcium ions and phosphate ions in the stock solution is about 1.5 mM and 0.9 mM respectively. A water-soluble salt such as sodium fluoride, stannous fluoride or sodium monofluorophosphate is then added to the stock solution and the pH adjusted, typically to about 5 to 9, typically about 6 to 7, for instance with sodium hydroxide.

The stock solution is then mixed into a dentifrice containing an aqueous humectant vehicle and a gelling agent typically in about equal amounts in order to dissolve the calcium and phosphate ions in the dentifrice.

Alternatively, an insoluble calcium phosphate source such as hydroxyapatite or dicalcium phosphate can be solubilized in clear solution by reducing the pH to about 2-4, typically about 2.8-3.8 with acids such as phosphoric acid, hydrochloric acid and the like. After the antinucleating agent and fluoride are added and the pH raised typically to about 6 to 7, the thus formed solution is mixed into a dentifrice containing an aqueous humectant vehicle in typically about equal amounts, thereby dissolving calcium and phosphate ions therein.

The dentifrice can be maintained for a long period of time, remaining effective when brought into contact with dental material to remineralize sub-surface lesions.

The dentifrice typically contains about 10-50% of a dentally acceptable water-insoluble polishing material. Preferably the polishing material does not include calcium and phosphate moieties. Insoluble polishing materials containing calcium and phosphate moieties, such as dicalcium phosphate, would not provide calcium ions and phosphate ions in the amounts provided by the solubilized material in the dentifrice of the invention. Desirable polishing agents include hydrated alumina, silica (colloidal, precipitated or crystalline), dolomite, bentonite, melamineformaldehyde resin, urea formaldehyde resin and the like. Hydrated alumina and silica are preferred. The dental cream also generally contains humectant such as glycerine, sorbitol, propylene glycol or polyethylene glycol 400 and gelling agent such as sodium carboxymethyl cellulose or Irish Moss. Also, surface active agent flavoring and/or sweetening material, antibacterial agent, antibacterial preservative, (e.g. sodium benzoate or methyl-4-hydroxy benzote), silicone material, chlorophyll compound or ammoniated material may be present.

The following examples illustrate the invention but do not limit it. All parts, amounts and proportions are by weight unless otherwise noted.

EXAMPLE 1

A stock solution of hydroxyapatite (tricalcium phosphate) is prepared by adding a solution containing calcium chloride to a solution of sodium dihydrogen phosphate to a final concentration of 1.5 mM calcium ions and 0.9 mM phosphate ions; the sodium dihydrogen phosphate solution containing EDITEMPA to provide the stock solution with 1.times.10@-5 M thereof and phosphoric acid to provide the stock solution with a pH of about 3.

The pH is raised to 7 with 1 N potassium hydroxide. Sodium monofluorophosphate is then added to a concentration of 5 ppm fluoride in the stock solution following which sodium chloride is added to give an electrolyte concentration of 50 mM and additional water is added to 1 liter.

The solution thus formed is added in 1:1 ratio to the following dental cream formulation:

PARTS

Glycerine 10.00
Sorbitol (70%) 17.00
Water 23.70
Sodium Benzoate 0.50
Sodium Saccharin 0.20
Sodium Carboxymethyl
Cellulose 1.10
Precipitated Silica 45.00
Sodium Lauryl Sulfate 1.50
Flavor 1.00

The dental cream remains stable upon storage and the calcium ions and phosphate ions remain dissolved therein.

EXAMPLE 2

Similar dental creams to that of Example 1 are prepared in which the solution containing calcium ions and phosphate ions contains each of PAA (concentration 5.times.10@-3 M); PODP (concentration 5.times.10@-4); and UniRoyal Oligomer ND-2 (concentration 5.times.10@-4 M). The dental creams are stable upon storage and the calcium ions and phosphate ions remain dissolved therein.

EXAMPLE 3

A stock solution of hydroxyapatite (tricalcium phosphate) is prepared by adding hydroxyapatite to water to a final concentration of 1.5 mM calcium ions and 0.9 mM phosphate ions. 0.25 grams of sodium benzoate (from 0.05% solution thereof) are then added to the solution to minimize bacterial growth.

Phosphoric acid is then added to 500 ml of the stock solution to produce a clear solution at pH 3, after which the pH is raised to 6 with 1 N potassium hydroxide. Next EDITEMPA is added and mixed into the solution to a concentration of 1.times.10@-5 M thereof, following which additional potassium hydroxide is added to produce a pH of 7. Sodium monofluorophosphate is then added to a concentration of 5 ppm fluoride in the stock solution following which sodium chloride is added to give an electrolyte concentration of 50 mM and additional water is added to 1 liter.

The solution thus formed is added in 1:1 ratio to the dental cream formulation set forth in Example 1. The dental cream remains stable upon storage and the calcium ions and phosphate ions remain dissolved therein.

EXAMPLE 4

A similar dental cream to that of Example 3 is prepared in which dicalcium phosphate dihydrate is solubilized in the stock solution in place of hydroxyapatite to give a concentration of 60 ppm of calcium ions and 400 ppm of phosphate ions in the stock solution. The dental cream remains stable upon storage and the calcium ions and phosphate ions remain dissolved therein.

EP0040938

[0001] This invention relates to a new composition for cleaning and polishing teeth by dental prophylaxis and more specifically to a dental prophylactic paste comprising dicalcium phosphate dihydrate...

SUMMARY OF THE INVENTION

[0007] These and other advantages are achieved by a prophylactic dental paste comprising greater than about 70 percent by weight of dicalcium phosphate, based on the total weight of the paste. There is also provided a prophylaxis method comprising applying to a tooth surface a dental prophylactic paste containing at least about 60 percent by weight dicalcium phosphate, based on the total weight of the paste.

[0008] The term "dicalcium phosphate" as it is used in the specification and claims shall mean dicalcium phosphate dihydrate, anhydrous dicalcium phosphate and mixtures thereof.

[0009] Dicalcium phosphate, and particularly dicalcium phosphate dihydrate, is commonly used as a polishing agent in dentifrices to clean teeth with a toothbrush. Broadly described, dicalcium phosphate dihydrate is prepared by the addition of a lime slurry to phosphoric acid under conditions such that dicalcium phosphate dihydrate is precipitated. In many cases, the dicalcium phosphate also contains other ingredients to inhibit spontaneous hydrolysis and/or dehydration. Stabilizing agents such as alkali metal pyrophosphate and trimagnesium phosphate are added to the dicalcium phosphate dihydrate during its preparation to stabilize the dicalcium phosphate dihydrate. Processes for preparing dicalcium phosphate stabilized against spontaneous hydrolysis and/or dehydration have been disclosed in U.S. 2,287,699, U.S. 3,012,852 and U.S. 4,193,973.

[0010] As is known to those skilled in the art, anhydrous dicalcium phosphate can be prepared in accordance with the teachings in U.S. 3,647,371 by adding lime to aqueous phosphoric acid while the reaction temperature is maintained sufficiently high to insure production of dicalcium phosphate substantially free from its water of crystallization.

[0011] The dicalcium phosphate useful in the prophylactic dental paste of the present invention can be dicalcium phosphate dihydrate or anhydrous dicalcium phosphate or mixtures of the two. However, as is known to those skilled in the art, anhydrous dicalcium phosphate frequently has a radioactive dentine abrasivity (RDA), as determined according to the method of Grabenstetter et al, JOURNAL OF DENTAL RESEARCH, Vol. 37, page 1060 (1958) of from about 1,000 to 1,400. Hence, the use of anhydrous dicalcium phosphate with such high abrasivi- ties should be avoided in the prophylactic dental paste of the present invention to avoid loss of hard tooth structure due-to abrasion. The dicalcium phosphate in the prophylactic dental paste should have an RDA of less than 1,000. and it is preferred that the paste have an RDA of less than about 750. As is known to those skilled in the art, anhydrous dicalcium phosphate having an RDA value of about 50 to about 150 has been prepared according to the teachings of U.S. 3,647,371 and such anhydrous dicalcium phosphate is suitable for use in the paste of the present invention. On the other hand, dicalcium phosphate dihydrate has an RDA value of less than 500 and its use is preferred in the paste of the present invention. However, as will occur to those skilled in the art in view of the present disclosure, a mixture of dicalcium phosphate dihydrate and anhydrous dicalcium phosphate can be used, particularly if the anhydrous dicalcium phosphate has an RDA value of less than 750, as the dicalcium phosphate for the paste of the present invention, and a mixture of dicalcium phosphate dihydrate and anhydrous dicalcium phosphate can be used if higher abrasivity is required provided that the RDA value of the prophylactic dental paste is less than 1,000 and preferably less than 750.

[0012] The prophylactic dental paste of the present invention should contain at least about 60 percent by weight of dicalcium phosphate, preferably greater than 70 percent by weight dicalcium phosphate, to insure that there is adequate polishing agent for the dental prophylaxis to remove stains and other dental debris. On the other hand, a paste containing more than about 90 percent by weight dicalcium phosphate, based on the total weight of the paste, can become so viscous that it is difficult to apply to the teeth using conventional cleaning techniques. Thus, it is preferred that the paste contain between about 75 weight percent and 85 weight percent, based on the total weight of the paste, to provide a paste having sufficient polishing agent to effectively clean the teeth while maintaining a sufficiently low viscosity to permit ease of use.

[0013] The balance of the formulation is water and optionally other ingredients that are typically used in a prophylactic dental paste, such as flavoring agents like oil of wintergreen, oil of peppermint, oil of spearmint, oil of sassafras, oil of anise and the like; sweetening agents such as saccharin, dextrose, levulose, sodium cyclamate and the like; binders such as water soluble salts of cellulose ethers such as sodium carboxymethyl cellulose and sodium carboxymethyl hydroxyethyl cellulose; natural gums such as gum arabic and the like; humectants such as glycols, glycerin, sorbitol and other polyhydric alcohols; and coloring agents. The prophylactic dental paste of the present invention can be used in a conventional manner to clean teeth professionally using conventional equipment and techniques. The optimum amount of paste, the degree of cleaning and polishing desired, the RDA of the paste and the like can be determined in accordance with conventional techniques.

[0014] When teeth are cleaned professionally to remove plaque, tartar, pellicle and other dental debris and the enamel of the teeth is exposed, it is frequently desirable to treat the teeth with fluoride to inhibit caries formation. Accordingly, the paste can optionally contain a source of fluoride ion, such as monofluorophosphate and the like, to aid in this treatment. In addition, although Applicants do not wish to be bound by any particular theory, it is believed that the dicalcium phosphate used in the prophylactic dental paste of the present invention in contact with the teeth free of tartar, plaque and pellicle, aids in the remineralization of the tooth surface, an advantage not found with the prophylactic dental paste compositions of the prior art.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0015] This invention is illustrated by but not limited to the following Examples wherein all percentages are by weight unless otherwise noted.

EXAMPLE I

[0016] A carrier gel is prepared by mixing the following ingredients in the indicated amounts:

[0017] A series of prophylactic dental pastes are each prepared by combining 75 grams of the above carrier gel with 175 grams of the following polishing agents: (1) chalk; (2) flour of pumice; (3) zirconium silicate; and (4) dicalcium phosphate dihydrate containing 0.6 percent tetrapotassium pyrophosphate and 2 percent trimagnesium phosphate stabilizers, and having an RDA of about 250.

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[0003] The present invention relates generally to dentifrices, and more particularly to dentifrice compositions containing enhanced levels of minerals for mineralizing and remineralizing teeth, as well as various chemical compounds for promoting beneficial oral cavity health...

DETAILED DESCRIPTION OF THE INVENTION

[0078] The present invention is primarily directed to dentifrice compositions, and particularly those dentifrice compositions containing enhanced levels of minerals for mineralizing and remineralizing teeth, as well as various chemical compounds for promoting beneficial oral cavity health.

[0079] In accordance with one aspect of the present invention, not only are enhanced levels of water soluble calcium salts and phosphate salts employed, but divalent metals, such as magnesium, strontium, tin, and zinc, are optionally employed as well. These divalent metals aid in the aforementioned mineralization and remineralization processes.

[0080] Water-soluble calcium salts and compounds suitable for practicing the present invention are, by way of a non-limiting example, calcium chloride, calcium bromide, calcium nitrate, calcium acetate, calcium gluconate, calcium benzoate, calcium glycerophosphate, calcium formate, calcium fumarate, calcium lactate, calcium butyrate and calcium isobutyrate, calcium malate, calcium maleate, calcium propionate, or mixtures of water-soluble calcium compounds. In the compositions of the invention for the mineralization/remineralization of human dental enamel, the calicum ions are preferably present in a range from about at least 18 mmol/L to about 1.5 mol/L.

[0081] Water-soluble inorganic phosphate salts and compounds suitable for practicing to the present invention are, by way of a non-limiting example, alkali salts and ammonium salts of orthophosphoric acid, such as potassium, sodium or ammonium orthophosphate, monopotassium phosphate, dipotassium phosphate, tripotassium phosphate, monosodium phosphate, disodium phosphate and trisodium phosphate. The concentration of the phosphate ions is preferably about at least 18 mmol/L to about 1.5 mol/L.

[0082] If desired, water-soluble salts yielding both calcium and phosphate ions, such as monobasic-calcium orthophosphate, may be employed.

[0083] With respect to the stabilizing divalent metal compound, it is also possible to employ any water-soluble, non-toxic divalent metal compound which will stabilize the calcium and phosphate ions so that they do not rapidly or prematurely precipitate before diffusing into the teeth. In practice, however, it has been found that at least one member selected from the group consisting of magnesium, strontium, tin, and zinc, with magnesium being preferred, are the most effective in stabilizing the system.

[0084] Suitable magnesium compounds are, by way of a non-limiting example, magnesium acetate, magnesium ammonium sulfate, magnesium benzoate, magnesium bromide, magnesium borate, magnesium citrate, magnesium chloride, magnesium gluconate, magnesium glycerophosphate, magnesium hydroxide, magnesium iodide, magnesium oxide, magnesium propionate, magnesium

D-lactate, magnesium DL-lactate, magnesium orthophosphate, magnesium phenolsulfonate, magnesium pyrophosphate, magnesium sulfate, magnesium nitrate, and magnesium tartrate.
[0085] Suitable strontium compounds are, by way of a non-limiting example, strontium acetate, strontium ammonium sulfate, strontium benzoate, strontium bromide, strontium borate, strontium caprylate, strontium carbonate, strontium citrate, strontium chloride, strontium gluconate, strontium glycerophosphate, strontium hydroxide, strontium iodide, strontium oxide, strontium propionate, strontium D-lactate, strontium DL-lactate, strontium pyrophosphate, strontium sulfate, strontium nitrate, and strontium tartrate.

[0086] Suitable tin compounds are, by way of a non-limiting example, stannous acetate, stannous ammonium sulfate, stannous benzoate, stannous bromide, stannous borate, stannous carbonate, stannous citrate, stannous chloride, stannous gluconate, stannous glycerophosphate, stannous hydroxide, stannous iodide, stannous oxide, stannous propionate, stannous D-lactate, stannous DL-lactate, stannous orthophosphate, stannous
pyrophosphate, stannous sulfate, stannous nitrate, and stannous tartrate.

[0087] Suitable zinc compounds are, by way of a non-limiting example, zinc acetate, zinc ammonium sulfate, zinc benzoate, zinc bromide, zinc borate, zinc citrate, zinc chloride, zinc gluconate, zinc glycerophosphate, zinc hydroxide, zinc iodide, zinc oxide, zinc propionate, zinc D-lactate, zinc DL-lactate, zinc pyrophosphate, zinc sulfate, zinc nitrate, and zinc tartrate. Preferred zinc compounds are zinc acetate, zinc chloride, zinc sulfate, and zinc nitrate...

[0093] In the case of two separate components, the pH of a component of such toothpaste or gel comprised of the active cationic or anionic ingredients each has a pH of more than about 3. The mixture of the two portions which is placed in the mouth, however, must have a pH of from 4.5 to about 7.0, preferably from about 5.0 to about 7.0, more preferably from about 5.0 to about 5.75. The pHs of the cationic portion and the anionic portion can be adjusted so long as the above pH parameters are not exceeded...

[0100] In accordance with another aspect of the present invention, trace minerals, such as selenium and bromine, that are believed to have beneficial effects on the overall health of the oral cavity are also preferably employed in the dentifrice composition of the present invention. Although these trace minerals may be added to the dentifrice composition of the present invention from various chemical suppliers, it is preferred to use mineral water from a natural source, such as a spring. Examples of such naturally-occurring springs are located in the southeastern portion of Michigan, for example in the Mount Clemens area, and have been identified as having some of the highest, if not the highest, levels of naturally-occurring minerals, as well as trace minerals, of any springs in the world. Although the exact mechanisms of the health benefits have not been thoroughly explained, it is generally recognized that several different types of trace minerals, such as selenium and bromine, have been identified as having potentially beneficial effects on overall health, and specifically on the health of the oral cavity, either acting alone or in concert with other minerals, vitamins, and/or enzymes.

EXAMPLE I
INGREDIENT AMOUNT (grains/gallon)

Ferrous carbonate <0.13
Ferrous sulfide <0.16
Lithium chloride 9.3
Magnesium carbonate <0.085
Magnesium bromide 1600
Magnesium chloride 850
Magnesium iodide 0.77
Magnesium sulfate 70
Potassium chloride 160
Potassium sulfate 102

Rubidium 0.26
Sodium carbonate <0.11
Sodium diborate 12.5
Sodium chloride 4500
Sodium selenite <0.013
Sodium silicate 0.28
Sodium sulfite 0.37
Sodium sulfate 83
Sodium tellurite <0.11
Strontium sulfate 28
Sulfur 80

[0106] Coenzyme Q10 (also known as Co Q10, Q10, vitamin Q10, ubiquinone, or ubidecarenone) is a benzoquinone compound synthesized naturally in the human body. The "Q" and the "10" in the name refer to the quinone chemical group and the 10 isoprenyl chemical subunits, respectively, that are part of this compound's structure. The term "coenzyme" denotes it as an organic (contains carbon atoms), nonprotein molecule necessary for the proper functioning of its protein partner (an enzyme or enzyme complex). Coenzyme Q10 is used by the cells of the body in a process known variously as aerobic respiration, aerobic metabolism, oxidative metabolism, or cell respiration. Through this process, energy for cell growth and maintenance is created inside cells in compartments called mitochondria. Coenzyme Q10 is also used by the body as an endogenous antioxidant. An antioxidant is a substance that protects cells from free radicals, which are highly reactive chemicals, often containing oxygen atoms, capable of damaging important cellular molecules such as DNA and lipids.

[0107] It has recently been suggested that oral and/or intravenous administration of coenzyme Q10 may be beneficial in the treatment of various diseases, including periodontal disease. In certain clinical studies, it has been observed that the oral administration, for example, in the form of pills, capsules, and powders, of coenzyme Q10 has alleviated the symptoms of periodontal disease, including inflammation, swelling, and bleeding of the gum tissues.

[0108] Accordingly, in accordance with a preferred embodiment of the present invention, the dentifrice composition of the present invention preferably contains an amount of coenzyme Q10. It is believed that the coenzyme Q10, when present in sufficient amounts, will have a therapeutic effect on the soft tissues surrounding, adjacent to, or in proximity to, the tooth structure (e.g., gum tissues) and thus aid in the prevention and treatment of various periodontal diseases. The form of the coenzyme Q10, for example, powder or liquid, is not thought to be critical.

[0109] By way of a non-limiting example, a dentifrice composition, in accordance with one aspect of the present invention, is presented below

EXAMPLE II

AMOUNT INGREDIENT (WEIGHT PERCENTAGE)

Deionized water 130 ml (16.26)
Mineral water 40 ml (5.0)
Sodium saccharin 0.7 g (0.086)
Methylparaben 1.3 g (0.16)
Sodium carboxymethylcellulose (CMC) 2.2 g (0.28)
Sorbitol (70 vol. %) 200 ml (25.0)
Glycerine (97 vol. %) 45 ml (5.625)
Dicalcium phosphate dihydrate 330 g (41.25)
Dicalcium phosphate anhydrous 25 g (3.125)
Carageenan (marine colloids) 10 g (1.25)
Sodium monofluorophosphate (optional) 0.79 g (0.1)

Coenzyme Q10 (optional) 2.4 g (0.31)
Sodium lauryl sulfate 13 g (1.625)
Sodium sulfoacetate (optional) 23 g (2.87)
Wintergreen flavoring 0.6 ml (0.075)
Cinnamon flavoring 4 ml (0.5)

[0110] As previously noted, the dentifrice composition of the present invention is then formed into a suitable paste, gel, powder, or liquid, for use by a consumer. The consumer then places an appropriate amount (e.g., 2.0-2.5 g of the dentifrice per application, preferably three applications per day) of the dentifrice composition of the present invention on a toothbrush and proceeds to brush in a normal manner, whereupon the key ingredients of the dentifrice composition of the present invention, i.e., the calcium ions and phosphate ions, aided by the optional magnesium, contact the teeth and act in manner to cause the mineralization and remineralization of various surfaces and subsurfaces of the teeth, as previously described. The other optional ingredients of the dentifrice composition of the present invention, i.e., the various trace minerals such as selenium and bromine, as well as the coenzyme Q10, act to aid in the overall health of the oral cavity, especially the gum tissues. If the level of the coenzyme Q10 needs to be raised in order to have a therapeutic effect, additional amounts of coenzyme Q10 may be added to the dentifrice composition of the present invention. Additionally, because coenzyme Q10 may have a tendency to cause the dentifrice composition to take on a slightly orange color, whitening agents, such as titanium dioxide, may be employed to restore a whiter appearance to the dentifrice composition.

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SUMMARY OF THE INVENTION

[0012] The present inventors made wholeheartedly investigations in order to solve the above problems, and as the result, they found out the method to obtain the excellent composition for the caries prevention. That is, in the composition comprising (a) the casein phosphopeptide-amorphous calcium phosphate complex (CPP-ACP) and/or the casein phosphopeptide-amorphous calcium fluoride phosphate complex (CPP-ACFP), (b) a sodium carboxymethylcellulose, (c) a viscosity regulator, and (d) water, when the sodium carboxymethylcellulose having a specific etherification degree was used, the composition for the caries prevention, which has the effects for efficiently suppressing the demineralization and promoting the remineralization, and the excellent stability in keeping for a long time, was obtained. Then, the present invention was completed.

[0013] In a first aspect of the present invention, composition for the oral cavity to prevent the caries comprises (a) 1 to 30% by weight of the casein phosphopeptide-amorphous calcium phosphate complex (CPP-ACP) and/or the casein phosphopeptide-amorphous calcium fluoride phosphate complex (CPP-ACFP), (b) 0.01 to 10% by weight of the sodium carboxymethylcellulose, having the etherification degree of 0.7 to 1.0, (c) 0.5 to 40% by weight of the viscosity regulator, and (d) a residual amount of water. This composition is used by coating on the tooth. In a second aspect of the present invention, a composition for oral cavity to prevent a caries comprises (a) 1 to 30% by weight of the casein phosphopeptide-amorphous calcium phosphate comply (CCP-ACP) and/or the casein phosphopeptide-amorphous calcium fluoride phosphate complex (CCP-ACFP), (b) 0.01 to 10% by weight of the sodium carboxymethylcellulose having the etherification degree of 0.7 to 1.0, (c) 0.5 to 40% by weight of the viscosity regulator, (e) 0.01 to 5.0% by weight of the fluoride compound, and (d) a residual amount of water, and being used by applying on a tooth. In a third aspect of the present invention, the fluoride compound is at least one selected from the group consisting of sodium fluoride, stannous fluoride, sodium monofluoro phosphate in the composition for oral cavity to prevent a caries according to the second aspect of the present invention.

[0014] Hereinafter, the composition for the caries prevention of the present invention will be explained. (a) The casein phosphopeptide-amorphous calcium phosphate complex (CPP-ACP) and/or the casein phosphopeptide-amorphous calcium fluoride phosphate complex (CPP-ACFP) are

not especially limited, if it is approved as foods or in dentistry. For example, the material prepared by the method of mixing calcium, an inorganic phosphoric acid, and fluoride if necessary with phosphopeptide, filtrating the mixed material, and drying, is preferably used in respect of the composition and crystallinity (refer to published Japanese translation of PTC international publication for patent application 2002-500626).

[0015] At this time, the blending amount of the casein phosphopeptide-amorphous calcium phosphate complex (CPP-ACP) and/or the casein phosphopeptide-amorphous calcium fluoride phosphate complex (CPP-ACFP) (a) is 1 to 30% by weight of the whole composition, preferably 1 to 10% by weight especially. If said amount is less than 1% by weight, the supplying of calcium and phosphorus is not sufficient, so that the prevention effect of the caries can not be obtained. If said amount exceeds 30% by weight, the viscosity of the composition becomes too high.

[0016] The etherification degree of the sodium carboxymethylcellulose (b), which is blended to obtain stability in keeping for a long time, is 0.7 to 1.0, preferably 0.85 to 0.95 especially. Because, if the etherification degree is less than 0.7, the blending effect can not be obtained, and if said amount exceeds 1.0, the sodium carboxymethylcellulose is easily influenced by calcium existing in the CPP-ACP and/or the CPP-ACFP, so that the preservation property becomes to be insufficient, since an insoluble precipitate is generated or said sodium carboxymethylcellulose is gelled.

[0017] The blending amount of the sodium carboxymethylcellulose having the etherification degree of 0.7 to 1.0 is 0.01 to 10% by weight of the whole composition, preferably 1 to 5% by weight especially. If said amount is less than 0.01% by weight, the viscosity of the composition is low and it easily flows with saliva at the time of the applying on the tooth. Therefore, the prevention effect of the caries can not be obtained. If said amount exceeds 10% by weight, the viscosity of the composition is high and it can not easily spread at the time of the applying on the tooth, and the sense of use is also bad.

[0018] In the composition for the caries prevention of the present invention, it is necessary to use (c) the viscosity regulator, in order to use the composition by applying on the tooth and to obtain the prevention effect of the caries by (a) the casein phosphopeptide-amorphous calcium phosphate complex (CPP-ACP) and/or the casein phosphopeptide-amorphous calcium fluoride phosphate complex (CPP-ACFP) being stayed in the oral cavity. As for (c) the viscosity regulator, for example, a natural material, such as gum guaiac, carob bean gum, Tara gum, tamarind seed gum, gum arabic, tragacanth gum, karaya gum, carrageenan, xanthan gum, gellan gum, curdlan, chitin, chitosan or chitosamine, an organic synthetic material, such as glycerin, propylene glycol, sodium alginate, propylene glycol ester alginate, sodium starch glycolate, sodium starch phosphate ester, sodium polyacrylate or polyvinyl pyrrolidone, or an inorganic synthetic material, such as calcium carbonate, calcium silicate, a silica fine powder, amorphous hydrous silica or hydrophobic silica, can be used...

[0021] Since the composition for the caries prevention of the present invention is directly coated on the tooth, pH is adjusted in the range of 5.5 to 9.5 preferably. Although the method for keeping said range is not limited especially, for example, an aqueous solution of phosphate, which is one of the constitution components of the CPP-ACP and the CPP-ACFP, or phosphate salt is added to adjust the pH preferably...

DETAILED DESCRIPTION OF PREFERRED EMBODIMENT

Blending of the demineralization liquid (pH 4.8)
lactic acid: 0.1 mol/L
calcium chloride: 1.5 m.mol/L
potassium dihydrogen phosphate: 0.9 m.mol/L
sodium carboxymethylcellulose (cellogen HE-1500F, made by Daiichi Kogyo Seiyaku Co., Ltd.) 1% by weight

[0043] Clearly from Table 3, it was identified that the composition for the caries prevention being excellent in the caries prevention and the stability in keeping for a long time, could be obtained, by selecting the specific sodium carboxymethylcellulose having the specific etherification degree and blending said sodium carboxymethylcellulose with the composition for the caries prevention containing the CPP-ACP and/or CPP-ACFP.

[0044] The composition for the caries prevention of the present invention contains the CPP-ACP and/or CPP-ACFP and is blended with sodium carboxymethylcellulose having the etherification degree of 0.7 to 1.0, so that it has promoting effect of the remineralization and excellent stability in keeping for a long time. Therefore, said composition has the great value for contributing to dental medicine.

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DETAILED DESCRIPTION OF THE INVENTION

[0066] In various embodiments, the present invention involves employing oral compositions for the stabilization, recalcification and remineralization of dental enamel and dentin and protection of teeth against tooth caries. The invention relates to the use of the calcium form of zeolite, water-soluble phosphate salts and matrix proteins of teeth for pH adjustment in the mouth and simultaneous building of calcium and phosphate ions from the oral solution into tooth enamel and dentin in the presence of tooth matrix proteins to stabilize the crystal structure of calcium hydroxyapatite in tooth enamel and dentin.

[0067] As used herein, the term "dental matrix protein" is defined as structural and/or adhesive and include those of enamel. Examples of the matrix proteins of the invention are collagen, elastin, ameloblastin, sheathlin, However, the term may also include amelogenins, praline-rich non-amelogenins, tuftelin, tuft proteins, serum proteins and other proteins. The terms "matrix proteins", "dental matrix proteins", "enamel matrix proteins" and "matrix proteins of the teeth" are used interchangeably throughout the specification.

[0068] Dentin is defined herein as the substance between the enamel or cementum and the pulp chamber. It is secreted by the odontoblasts of the dental pulp. An odontoblast is a cell involved in dentinogenesis, which is the creation of dentin, the substance under tooth enamel. The odontoblasts secrete dentin throughout life, which may be an attempt to compensate for natural wearing down of the enamel. These cells are responsible for producing the calcified dental matrix. The dental matrix protein is one of the dental noncollagenous matrix proteins that has been implicated in regulation of mineralization.

[0069] Since the calcium ions are bound in the microcrystalline particles of inorganic carriers (zeolite), they are not active until "free" from the zeolite crystal framework. Hence it follows, that although the concentrations of calcium and phosphate ions in the oral composition are favorable (or more than favorable) for total remineralization, the speed of remineralization is controlled by the rates of release of calcium ions from the zeolite microcrystals during the exchange of calcium ions from the zeolite with other ions from the solution. The calcium ions released from zeolite microcrystals are incorporated, together with equivalent quantity of phosphate ions into the dental enamel and dentin, and remineralize them. If the composition contains dental matrix proteins, the same improves the above mentioned processes by its action as the precursor for the transformation of the "unripe" calcium hydroxyapatite into the "ripe" calcium hydroxyapatite. "Ripe" calcium hydroxyapatite is more stable than "unripe" calcium hydroxyapatite. The components of calcium hydroxyapatite; calcium ions, phosphate ions and dental matrix protein integrally construct the dental enamel and/or dentin by a self-organized process (restitutio ad integrum).

[0070] In one aspect, the invention can be in the form of a toothpaste. In other aspects the oral composition may be in the form of chewing gum, gel, mouth rinse, candy, lozenge, film,

transbuccal patch and other preparations which can be kept in the mouth cavity.

[0071] In various embodiments of the oral composition, the extract and/or the oil of the medicinal herb milfoil may be present in the amounts from about 0.01 to about 0.025 wt %, as a mild anti-inflammatory agent.

[0072] Although the essential role of the calcium form of zeolite in the oral composition for the stabilization, recalcification and remineralization of dental enamel (OKSRCD) based on this invention is supplying active calcium ions, the calcium form of zeolite has also another crucial role in the control and maintenance of optimal pH for the stabilization and remineralization of dental enamel and dentin. Table 1 shows the pH values of the liquid phases of the suspensions containing 1 g of the calcium form of zeolite (types I, II and III) in 10, 100 and 1000 ml of demineralized water.
[0000]

The data in Table 1 shows that in all cases the starting pH of the demineralized water, i.e., 4.8 increased after addition of the calcium form of zeolite.
For a constant concentration of suspension, expressed as the volume of water in which 1 g of zeolite is suspended, pH decreases in the sequence: pH(type I)=7-9.2>pH(type II)=6-8.2>pH(type III)=4.92-7.6. Hence, with the increase of the molar ratio Si/Al in the framework structure of zeolite, i.e., Si/Al(type D<Si/Al(type II)<Si/Al(type III). As shown in table 1, for a given type of zeolite, pH depends on the concentration of suspension, so that using calcium form of different types of zeolites (having Si/Al in the range from 1 to 10) in the suspensions containing 1 g of zeolite in 10, 100 and 1000 ml of water, the suspensions having pH in the range from about 5 to 9 can be obtained...

1. Mixing together water suspensions of a calcium form of zeolite and water solution of phosphate ions [e.g., addition of (Na,H)-phosphate salts into a water suspension of zeolite and/or addition of calcium form of zeolite into water solution of phosphate] considerably changes the pH of the mixture (see Table 3) relative to the water suspension of a calcium form of zeolite (see Table 1) and water solution of (Na,H)-phosphate (see Table 2) alone.

2. Although the presence of a calcium form of zeolite considerably influences the pH value of mixtures (calcium form of zeolite suspended in phosphate solution; see Tables 1-3), equilibrium pH value is determined by the type and concentration of the dissolved phosphate ions, but is not influenced by the type of zeolite and its content in the investigated range (0.1-10 wt. %; see Table 3 and FIG. 1)

3. pH of the suspension of the calcium form of zeolite(s) in the water solution(s) of Na3PO4 does not change significantly with the increase of concentrations of PO4<3-> ions in the concentration range from about 0.0001.5 mol dm<-3 > to about mol 0.0008 mol dm<-3 > (equilibrium pH is from about 8.12 to about 8.5 in the concentration range of PO4<3-> ions; see FIG. 1). At concentrations of PO4<3-> ions higher than 0.0008 mol dm<-3> , pH increases with their increasing concentration and reaches the maximum pH value of about 11.7 for concentrations of PO4<-> ions higher than 0.0167 mol dm<-3> .

4. pH of the suspension of the calcium form of zeolite(s) in the water solution(s) of Na2HPO4 changes little with the change of concentration of HPO4<-> ions; pH does change from about 7.80 to 8.11 when the concentration of HPO4<-> ions increased 0.00014 mol dm<-3 > to 0.167 mol dm<-3 > (see FIG. 1).

5. pH of the suspension of the calcium form of zeolite(s) in the water solution(s) of NaH2PO4 is approximately constant (about 7.7) for low concentrations of H2PO4<-> ions (from about 0.00017 mol dm<-3 > to about 0.0008 mol dm<-3>), and progressively decreases with the increased concentration of H2PO4<-> for the concentration of H2PO4<-> higher than 0.0008 mol dm<-3 > and reaches the pH value of about 6.4 at concentrations of H2PO4<-> ions of about 0.17 mol

dm<-3 > (see Table 3 and FIG. 1).

[0080] The optimal pH (7.5-8) can be achieved by mixing a calcium form of zeolite (0.1-10 wt. %, regardless of the type) with 0.00015 mol dm<-3 > to about 0.0008 mol dm<-3 > solution of Na3PO4, or with 0.00014 mol dm<-3 > to 0.167 mol dm<-3 > solution of Na2HPO4, or with 0.00017 mol dm<-3 > to about 0.0008 mol dm<-3 > solution of NaH2PO4. As shown in FIG. 1, pH values higher than 8 can be obtained only with Na3PO4 for the concentrations of PO4<3-> ions higher than 0.0008 mol dm<-3> . At the same time, these results show that pH remains approximately constant when the systems containing PO4<3-> and H2PO4<-> are diluted by a factor of 5, and when the system containing HPO4<2-> ions is diluted by a factor of 1200.

[0083] In order to prove the conclusion resulted from the investigation of the influence of pH on the stability of teeth, samples of teeth were treated with solutions prepared in the following way: (i) solution (L-Ca)o was prepared by a centrifugal separation of the solid phase (calcium form of zeolite of type I) from the suspension (1 g of the calcium form of zeolite in the 100 ml demineralized water; pH 8.01), stirred for 24 hours at room temperature and; (ii) solution (L-Na)o was prepared by a centrifugal separation of the solid phase (sodium form of zeolite of type I) from the suspension (1 g of the sodium form of zeolite in the 100 ml demineralized water; pH=10.5), stirred for 24 hours at room temperature. The solution (L-Ca)0 contained 0.01 mg Ca<2+> ions/cm<3 > (see Table 4) as a consequence of equilibrium of the process of substitution of H<+> ions from the water according to the equation:
[0000]
CaZ+2H2O<=>H2Z+Ca<2+> +2OH<-> (1)

The results presented in Table 4 show the concentrations of calcium in alkaline solutions (L-Ca)1-(L-Ca)4 are approximately 1440 times lower than in the acidic solutions K1-K4, and that the concentrations of calcium in the alkaline solutions (L-Na)5-(L-Na)7 are approximately 5600 times lower than in the acidic solutions K5-K7, after contact with the samples of teeth. This means that the decalcification in the alkaline solutions L-Ca and L-Na has been reduced more than 3 three orders of magnitude (at pH=8.01) or more (at pH=10.5) relative to decalcification in the acidic solutions K (pH=3.5). Although the greater effect of stabilization at a higher pH value (solution (L-Na)0; pH=10.5) was expected, the reduction of the concentration of calcium in the solution (L-Ca)0 from the starting value of 0.01 mg/cm<3 > to approximately 0.0026 mg/dm<3 > clearly indicates that about 75% of calcium ions from the solution (L-Ca)0 was incorporated in the dental enamel during treatment. The alkaline environment established by the presence of the calcium form of zeolite not only significantly lowers the process of decalcification, but also stimulates the process of calcification.

[0085] In order to prove the process of (re)calcification during treatment and to separate the influence of stabilization of dental enamel in the alkali environment from the influence of (re)calcification on the lowering of demineralization in the acidic medium, samples of teeth were been divided into two approximately equal parts, and thereafter the samples were treated as follows:

The concentrations of calcium ions in the solutions after decalcification in the acidic medium are shown in Table 5. The designations A1-A3 correspond to the solutions obtained after decalcification of the teeth from the series A. The designations B1-B3 correspond to the solutions obtained after decalcification of the teeth from the series B. The designations A1-(Ca)-A3-(Ca) correspond to the solutions obtained after decalcification of the teeth from the series A, which were previously treated with the suspension containing 1 g of the calcium form of zeolite of type I in 100 ml of demineralized water. The designations B1-(Na)-B3-(Na) correspond to the solutions obtained after decalcification of the teeth from the series B, which were previously treated with the suspension contained 1 g of the sodium form of zeolite of type I in 100 ml of demineralized water. The meaning of X+ is the percentage of the concentration of calcium ions in alkaline solution relative to the concentration of calcium ions in the corresponding acidic solution, e.g., X+=75% means that the concentration of calcium ions in alkaline solution is 75 of the concentration of

calcium ions in the acidic solution, or in the other words, that the concentration of calcium ions in the alkaline solution is 25% (=100-X+) lower than in the corresponding acidic solution.

[0086] The concentrations of calcium in the solutions A-(Ca)n and B-(Na)n are 9-25 lower than in the solutions An and Bn. However, the average lowering in the concentration of calcium ions in the solutions A-(Ca)n is about 19.5%, relative to the concentrations of calcium ions in the solutions An, while the average lowering in the concentration of calcium ions in the solutions B-(Na)n is about 6.4% relative to the concentrations of calcium ions in the solutions Bn. Hence one can conclude that the increased level of stabilization of teeth in the suspension of calcium forms of zeolite in comparison with the suspension of sodium form of zeolite is caused by the incorporation of calcium from the calcium form of zeolite into the dental enamel (calcification) during the treatment...

[0088] It is important to emphasize that the rate of remineralization and the amount of deposited hydroxyapatite can be adjusted with the concentrations of phosphate and calcium form of zeolite in the suspension. It is especially important that the excess of one of the components (calcium or phosphate ions) does not change the chemical composition of deposited hydroxyapatite, i.e., that the amount of deposited hydroxyapatite is determined by the concentration of component that is in deficit (i.e., by the concentration of calcium ions in the mentioned case).
[0089] Based on the presented results, we conclude that the decreased dissolution of tooth enamel and dentin (demineralization, expressed as the concentration of calcium and/or phosphate ions), of teeth treated with the oral composition, relative to the untreated teeth, can be ascribed to the stabilization of mineral portion of tooth (enamel and dentin) by the activity of an excess of OH<-> ions in the mildly alkaline environment and by simultaneous incorporation of calcium and phosphorus from the oral composition into the enamel and dentin (remineralization). Since demineralization is a time dependent process and demineralization and (re)remineralization are parallel processes, it can be assumed that the time of treatment of teeth with the oral composition significantly influences effects of stabilization, (re)calcification and (re)mineralization of teeth.

[0090] The results of testing of an influence of the time of treatment of teeth with the oral composition according to the invention are shown on FIG. 4. Depending on the cumulative time of treatment (10-300 minutes), the stability of dental enamel and dentin increases from 7 to 29% with respect to the untreated teeth (see FIG. 4). The results in FIG. 4 show that the value S % increases with treatment time; S % reached the maximum value (>23%) in approximately 60 minutes, and further treatment does not have a significant effect. Therefore, one can conclude that the reduction of demineralization after treatment with oral composition is caused by deposition of hydroxyapatite on the surface of tooth enamel (remineralization), and by stabilization of the newly formed enamel under optimal pH conditions. It was also shown that an addition of enamel matrix protein in the oral composition increases the rate of remineralization, and at the same time increases the tooth stability 30-50% relative to the oral composition without enamel matrix protein.

EXAMPLE 1

[0091] Enamel matrix protein (EMP) is a component of mineralized tissues such as bone, dentin, cementum and calcified gristly. Enamel matrix protein is a significant component of the extracellular bone matrix and has been suggested to constitute approximately 8% of all non-collagenous proteins found in bone and cementum. Enamel matrix protein was originally isolated from the bovine cortical bone (powder) as a 23-kDa glycopeptide with high sialic acid content, as described in separate reports in Biochim. Biophys. Acta. 1965 101:327-35. Shortly modified protocol: Purification of enamel matrix protein isolated from bone powder was achieved by ion exchange chromatography on a DEAE-cellulose column. The eluting buffer for isolation of enamel matrix protein was 50 mM of sodium acetate containing 7 M urea and 0.5% (wt/vol) Triton X-100 at pH 6.0. After digestion of bone powder with 7 M urea overnight (o/n) aliquots of 10 ml was dialysis against PBS o/n and lyophilized. Powder was resuspended in 0.05 M potassium acetate buffer pH 5.0. After equilibration of the DEAE columns by washing with a buffer, samples of the fractions were applied in a 0.05 M-acetate buffer, pH 5-0. Elution with a flow rate of about 10

ml/hr was carried out either with a linear gradient of 0.0-1.0 M NaCl in 0.05 M-acetate buffer, pH 5.0. One-minute fractions were collected during a total run time of 60 min, respectively. Fractions were collected between 0.6 to 0.9 M of NaCl of linear gradient and then dialysis against PBS o/n at +40C and lyophilized. The final product contains 1.32*10<-4> -0.1 wt. % of enamel matrix proteins. Enamel matrix protein in these examples was upregulated process of dentin mineralization after 7 days of therapy by our composition.
The term "upregulated" as used herein refers to the process by which the number of components increases in response to external variables...

When the invention is used in the form of toothpaste, in accordance with the invention, the components are present in the following amounts:
[0000]

1. Calcium form of zeolite: 0.1-10 wt. %
2. Phosphate ions: 0.00132-2 wt. %
3. Matrix proteins: 1.32 * 10<-4> -0.1 wt. %

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SUMMARY

[0004] The present disclosure relates to oral care products for the improved mineralization/remineralization of teeth of a consumer. In an embodiment, the present disclosure provides an oral product comprising a calcium salt, a phosphate salt, a sodium salt and a potassium salt. For example, the molar ratio of the sodium salt to the potassium salt can, in an embodiment, range from about 3 to about 4.

DETAILED DESCRIPTION

[0052] The present disclosure relates to oral care products for the improved mineralization/remineralization of teeth of consumer. In a general embodiment, the present disclosure provides an oral product comprising a calcium salt, a phosphate salt, a sodium salt and a potassium salt. The molar ratio of the sodium salt to the potassium salt can range be any suitable range such as, for example, from about 3 to about 4. The phosphate salt and the sodium/potassium salt can originate from the same or different compounds.

[0053] Stimulated saliva can promote mineralization through the addition of calcium, phosphate and buffer ions. Oral products such as confections and chewing gum can be designed with technologies that offer an effective portable and great tasting means to significantly enhance this baseline salivary mineralization rate. In embodiments, the present disclosures provides oral care products that promote a sustained high level release of ions like calcium, phosphate, sodium and potassium salts for an extended period time in the oral cavity. These ions in turn interact to precipitate amorphous "apatitic-like" calcium-phosphate (CaP) crystals which are sufficient in size to diffuse through a pellicle or plaque layer and lesion surface zone of teeth. Over time, and repeated use, these CaP crystals accumulate and transform to enamel-like structures that reconstitute the subsurface mineral matrix.

[0054] It has been surprisingly discovered that the use of a combination sodium and potassium salts in an oral product containing a calcium salt, acts to promote upon placement of this composition in an oral cavity for mastication or consumption, for release and precipitation of the calcium, potassium, and phosphate ions present therein the oral cavity, and thus also acts to promote the subsequent remineralization of the teeth exposed thereto. In particular, this disclosure relates to the use of a sodium salt to potassium salt molar ratio (Na/K) of about 3.0 to about 4.0 in oral products. For example, this ratio is designed to act as a phosphate buffer system to maintain a physiological pH=7.4@37[deg.] C., a favorable remineralization environment.

[0055] In an embodiment, the total amount of the sodium salt and the potassium salt comprises from about 0.01% to about 10% by weight of the oral product. In another embodiment, the total amount of the sodium salt and the potassium salt comprises from about 6.0% to about 8.0% by weight of the oral product.

[0056] Without being held to any particular theory, it is generally believed that, upon initial placement of the product in the oral cavity, calcium, phosphate, sodium and potassium ions are released yielding a Ca/P molar ratio of about 1.50 to about 2.0, preferably from about 1.50 to 1.70. Thus, a precipitate of potassium-substituted amorphous apatite can form, adhere to oral surfaces, and rapidly transform to enamel-like crystal layer. During acid challenge caused by lactic acid from oral plaque bacteria, dissolution of the precipitated potassium-substituted amorphous apatite layer re-establishes favorable remineralization conditions by releasing calcium and phosphate ions near the enamel surface of teeth. Surprisingly, the disclosure offers an opportunity for remineralization without the employment of acids to oral products through its unique buffer system by employing a molar ratio of sodium to potassium of about 3.0 to about 4.0.

[0057] In an embodiment, a suitable calcium salt such as, for example, a partially soluble calcium salt such as calcium citrate, is able to deliver a sustained high level of calcium ions from an oral product to the saliva. In another embodiment, a blend of soluble sodium phosphate dibasic and potassium-phosphate monobasic is encapsulated in polyvinylacetate (PVAc) (e.g. high molecular weight) to provide a sustained, high level delivery of phosphate ions (PO4) from gum to the saliva.

[0058] The oral products of the present disclosure includes, but are not limited to, chewing gums, candies/confections, gels, toothpastes, foams, oral rinses and/or dentifrices. Compounds that release calcium, phosphate, potassium or sodium ions may be selected from a number of commercially available compounds, and other compounds that are recognized as food additives in other contexts. All such additives encompassed herein are intended to be non-toxic. For the purpose of this disclosure, the term "non-toxic" is intended to conform with accepted and established definitions of safety, such as described by the designation "generally accepted as safe" by the Food and Drug Administration. Also, encompassed in this definition are those compounds that have been added to food for some time and which are recognized as safe under conditions of their intended use. The additives of the disclosure, including calcium salts, are sufficiently non-toxic for oral use at the intended levels on a regular basis, and are preferably stable for a desired shelf life

[0059] Calcium Salts

[0060] Although different calcium salts may be employed for mineralization/remineralization of teeth, typical calcium salts include, but are not limited to, the calcium salts of sulfates (e.g., calcium sulfate, anhydrous calcium sulfate, calcium sulfate hemihydrate, calcium sulfate dihydrate), gluconates, (borogluconate), glycerophosphates, polyphosphates, lactates (lactate-gluconate, lactobionate), malates, citrates, tartrates, fumarates, malonates, nitrates, acetates, ascorbates, benzoates, bisulfites, carbonates, chlorides, diglutamates, disodiums, ferrocyanides, formates, fumarates, guanylates, sulfites, hydroxides, inosinates, propionates, peroxides, silicates, sorbates, sulfites, and succinates, as well as calcium oxide, calcium panthothenate, calcium 5'-ribonucleotides and the like, alone or in any combination. The calcium salts employed may be monoprotic, diprotic or triprotic.

[0061] Potassium Salts

[0062] Although different potassium salts may be employed for mineralization/remineralization of teeth, typical potassium salts include, but are not limited to potassium acetates, potassium adipates, potassium aluminium silicates, potassium ascorbates, potassium benzoates, potassium bicarbonates, potassium bisulfites, potassium bromates, potassium carbonates, potassium chlorides, potassium citrates, potassium ferrocyanides, potassium fumarates, potassium gluconatse potassium hydrogen sulfites, potassium hydroxide, potassium lactates, potassium malates, potassium metabisulfites, potassium nitrates, potassium nitrites, potassium phosphates, potassium propionates, potassium

sodium tartrates, potassium sorbates, potassium sulfates, potassium sulfites, potassium tartrates and the like, alone or in combination. The potassium salts employed may be monoprotic, diprotic or triprotic.

[0063] Sodium Salts

[0064] A variety of sodium salts may be employed for mineralization/remineralization of teeth, typical sodium salts include, but are not limited to sodium acetates, sodium adipates, sodium aluminum phosphates, sodium ascorbates, sodium benzoates, sodium bicarbonates, sodium bisulfites, sodium carbonates, sodium citrates, sodium dehydroacetates, sodium erythorbates, sodium erythorbins, sodium ethyl para-hydroxybenzoates, sodium formates, sodium fumarates, sodium gluconates, sodium hydrogen acetates, sodium chlorides, sodium hydroxides, sodium lactates, sodium malates, sodium metabisulfites, sodium methyl para-hydroxybenzoates, sodium nitrates, sodium nitrites, sodium orthophenyl phenols, sodium propionates, sodium propyl para-hydroxybenzoates, sodium sorbates, sodium stearoyl lactylates, sodium succinates, sodium sulfites, sodium tartrates, sodium tetraborates, soda ash (Na2CO3), chile saltpeter (NaNO3), monosodium glutamate (MSG), di-, tri-, and tetra-sodium phosphates, and the like, alone or in any combination. The most common source of sodium is sodium chloride, but it occurs in and may be derived from many other minerals such as soda niter, cryolite, amphibole, zeolite, etc. The sodium salts employed may be monoprotic, diprotic or triprotic.

[0065] Salt Separation: Encapsulation, Agglomeration Physical & Coatings

[0066] In an embodiment, the potassium and sodium salts employed are encapsulated or coated with a barrier layer, in order for example to limit, or substantially prevent the salts from interacting with one or more of the ingredients employed in an oral product. Physical modifications of the potassium and sodium salts by encapsulation with another substrate may increase or delay their release by modifying the solubility or dissolution rates of the salts. For example, the potassium and sodium salts may be coated with silicon dioxide. Still further, the potassium and sodium salts may be encapsulated (e.g. co-encapsulated) together with polyvinylacetate (PVAc). Typically, the amount of PVAc present in the encapsulation matrix is at least about 10% by weight, about 30% by weight, or about 60% by weight or more, the concentration potassium and sodium salts falling within a range of about 0.01% to about 80%, or about 20% to about 70%, or about 30% to about 60% based on the total weight of the encapsulation matrix.

[0067] Any standard technique which gives full or partial encapsulation of the salts can be used. These techniques include, but are not limited to, spray drying, spray chilling, fluid-bed coating, extrusion, coextrusion, inclusion, granulation, roll compaction and coacervation. These encapsulation techniques, which give full or partial encapsulation of the salts can be used individually or in combination in a single step process or multiple step process. For example, the salts may be spray-dried, followed by fluid-bed coating of the resultant powder.

[0068] The encapsulation techniques of the potassium and sodium salts here described are standard coating techniques and generally give varying degrees of coating, from partial to full coating, depending on the coating composition used in the process. Also, the coating compositions may be susceptible to water permeation of varying degrees. Generally, coating compositions having high organic solubility, good film forming properties and low water solubility give better delayed release of the salts. Such compositions include, but are not limited to, acrylic polymers and copolymers, carboxyvinyl polymer, polyamides, polysterene, polyvinyl acetate, polyvinyl acetate phthalate, polyvinylpyrrolidone and waxes. Although all of these materials may be used for encapsulation of the salts, typically only food-grade materials should be considered.

[0069] The polymers used for encapsulation of the sodium phosphate and potassium phosphate salts can have any suitable molecular weight. In an embodiment, the polymer(s) used for encapsulation of the sodium phosphate and potassium phosphate salts have a molecular weight of about 1.5*10<3 > g/mol. The polymer(s) used for encapsulation of the sodium phosphate and

potassium phosphate salts can have a molecular weight of about 80*10<3 > g/mol. The polymer(s) used for encapsulation of the sodium phosphate and potassium phosphate salts can also have a molecular weight of about 80 to about 100*10<3 > g/mol. Alternatively, the polymer(s) used for encapsulation of the sodium phosphate and potassium phosphate salts can have a molecular weight of about 150*10<3 > g/mol.

[0070] Two standard food-grade coating materials that are good film formers but are not water soluble are shellac and zein. Others which are more water soluble, but are good film formers are materials like agar, alginates, a wide variety of derivatives like ethyl cellulose, methyl cellulose, sodium hydroxymethyl cellulose, and hydroxypropylcellulose, dextrin, gelatin, starches, and modified starches. These ingredients which are generally approved for food use give a fast release when used as an encapsulant for the salts. In an embodiment, acacia or maltodextrin is used to encapsulate the salts. In still another embodiment, PVAc is used to encapsulate the salts.

[0071] The amount of coating or encapsulating material on the salts may also control the length of time of release from oral products. Generally, the higher the level of water-insoluble coating and the lower amount of salts, the slower the release of the salt during mastication. Also, the higher the usage level of a water-soluble coating, the slower the release rate. In an embodiment, to obtain the desired salt release to blend with a oral product's flavor release, the encapsulant is typically a minimum of about 1.0% by weight of the coated salts. For example, the encapsulant is a minimum 1.0% by weight of the encapsulation matrix.

[0072] Another method of giving a modified release of the salts is through the process of agglomeration of the salts with an agglomerating agent which partially coats the potassium and sodium salts. This method includes the step of mixing the salt and an agglomerating agent with a small amount of water or solvent. The mixture is prepared in such a way as to have individual wet particles in contact with each other so that a partial coating can be applied. After the water or solvent is removed, the mixture is ground and used as a powdered, coated product.

[0073] Materials that can be used as agglomerating agents are the same as those used in encapsulation procedures mentioned previously. However, since the coating is only a partial encapsulation, and the potassium and sodium salts can be slightly water soluble, some agglomerating agents are more effective in modifying the release of the salts than others. Suitable agglomerating agents include, but are not limited to, organic polymers like acrylic polymers and copolymers, polyvinyl acetate (PVAc), polyvinylpyrolidone, waxes, shellac, and zein. Other agglomerating agents include, but are not limited to, agar, alginates, a wide range of cellulose derivatives like ethyl cellulose, methyl cellulose, sodium hydroxymethylcellulose, hydroxypropylmethyl cellulose, dextrin, gelatin, modified and unmodified starches, and vegetable gums like guar gum, locust bean gum, and carrageenan. Even though the agglomerated salts may be only partially coated, when the quantity of the coating is increased compared to the quantity of the salt, the release of the salt can be delayed longer during mastication. In an embodiment, the level of the agglomerating agent is at least 5% by weight of agglomeration matrix.

[0074] The potassium salt and sodium salts may be coated together or separately. The salts may be coated in a two-step or multiple step process, either alone or in combination. The salts may be encapsulated with any of the materials described previously and then the encapsulated salts can be agglomerated as described previously to obtain an encapsulated/agglomerated molar ratio of sodium salt to potassium salt, for example, of about 3.5.

[0075] In another embodiment, the sodium salt and/or potassium salt may be absorbed onto another component which is porous and becomes entrapped in the matrix of the porous component. Common materials used for absorbing the salts include, but are not limited to, silicas, silicates, pharmasorb clay, spongelike beads or microbeads, amorphous sugars like spray-dried dextrose, sucrose, alditols, amorphous carbonates and hydroxides including aluminum and calcium lakes, vegetable gums and other spray dried materials. Insoluble materials will give the salts a delayed release while water soluble materials will give the salts a fast release from an oral product.

[0076] Depending on the type of the absorbent material and how it is prepared, the amount of salts that can be loaded onto the absorbent will vary. Generally, materials like polymers or spongelike beads or microbeads, amorphous sugars and alditols and amorphous carbonates and hydroxides absorb an amount equal to about 10% to about 40% of the weight of the absorbent. Other materials like silicas and pharmasorb clays may be able to absorb about 20% to about 80% of the weight of the absorbent.

[0077] The general procedure for absorbing the potassium and/or sodium salt onto an absorbent may be characterized as follows: an absorbent, like fumed silica powder, can be mixed in a powder blender and an aqueous solution of the slightly water soluble salts can be sprayed onto the powder as mixing continues. The aqueous solution can be about 1.0% by weight of the salts and higher solid levels may be used if temperatures of up to 90[deg.] C. are used. Generally, water is the solvent, but other solvents like alcohol can also be used if approved for food use. As the powder mixes, the liquid is sprayed onto the powder. Spraying is stopped before the mix becomes damp. The still free flowing powder is removed from the mixer and dried to remove the water or other solvent, then ground to a specific particle size.

[0078] After the salt(s) is absorbed onto an absorbent or fixed onto an absorbent, the potassium salt and/or sodium salt can be coated by encapsulation, either or fully or partially, as described elsewhere herein. Alternatively, another form of encapsulation may be used, which is by entrapment of an ingredient by fiber extrusion or fiber spinning into a polymer.

[0079] In view of the foregoing, it is to be noted that the four primary methods to obtain a controlled release of the remineralizing/mineralizing agents (e.g. salts) of the present disclosure are (1) encapsulation (either fully or partially), (2) agglomeration, (3) fixation or absorption, and (4) entrapment into a extruded compound. These four methods may be combined in any usable manner which physically modifies the release or dissolvability of the sodium and potassium salts included in this disclosure.

[0080] Other methods of treating the sodium salt and/or potassium salt to modify or physically isolate the salts from other ingredients may also have some effect on their release rate, dissolvability or stability. In an embodiment, the potassium salt may be added to one layer of a multi-layered chewing gum composition, and the sodium salt may be added to a different layer of the multi-layered chewing gum composition, and the calcium salt may be added to another different layer of the chewing gum composition.

[0081] In yet another embodiment, the potassium and sodium salts may be encapsulated and added to the liquid inside a liquid center oral product. The calcium salt may be added to the material surrounding the liquid center. The center fill of an oral product may comprise one or more carbohydrate syrups, glycerin, thickeners, flavors, acidulants, colors, sweeteners in conventional amounts. The ingredients are combined in a conventional manner. This method of delivery of the sodium, potassium, and calcium salts can allow for a smooth release rate, and can reduce or eliminate possible reactions of the salts prior to consumption thereby enhancing release, improving remineralization/mineralization and yield improved shelf stability.

[0082] Another embodiment of isolating the potassium salt and/or sodium salt is to use them in a coating/panning of an oral product. For example, pellet or ball gum is prepared as conventional chewing gum, but formed into pellets that are pillow shaped, or formed into balls. The pellets/balls can then be sugar or polyol coated or panned by conventional techniques to make a unique coated chewing gum. Depending on the salts employed, they can be quite stable and slightly water soluble, making them easy additions to a hot sugar solution for sugar panning. The salts can also be added as a powder blended with other powders often used in some types of panning procedures.

[0083] Conventional panning procedures generally coat with sucrose, but recent advances in panning have allowed the use of other carbohydrate materials to be used in the place of sucrose. Some of these components include, but are not limited to, dextrose, maltose, palatinose, xylitol,

lactitol, hydrogenated isomaltulose and other alditols, or a combination thereof. These materials may be blended with panning modifiers including, but not limiting to, gum Arabic, maltodextrins, corn syrups, gelatin, cellulose type materials like carboxymethylcellulose (CMC), or hydroxymethylcellulose (HMC), starch and modified starches, vegetable gums like alginates, locust bean gum, gum Arabic, guar gum, and gum tragacanth, insoluble carbonates like calcium carbonate or magnesium carbonate or talc.

[0084] Antitack agents may be added as panning modifiers which allow the use of a variety of carbohydrates and sugar alcohols to be used in the development of new panned or coated oral products. For example, the oral products can include, but are not limited to, chewing gums, candies, pressed tablets, mints, chewy candies, hard boiled candies, chocolates, nougats, gels, confectionery pastes, liquids and the like, alone or in any combination. Flavors may also be added with the coating and with the salts of the disclosure to yield unique product characteristics.

[0085] In yet another embodiment, another type of coating may be employed to isolate the potassium salt and/or sodium salt from each other and other oral product ingredients. This technique is referred to as a film coating. For example, a film like shellac, Zein, or cellulose-type material is applied onto a product, including but not limiting to chewing gums, candies, pressed tablets, mints, chewy candies, hard boiled candies, chocolates, nougats, gels, confectionery pastes, liquids and the like, alone or in any combination, forming a thin film on the surface of the product. The film may be applied by mixing a polymer, a plasticizer and a solvent (pigments are optional) and spraying the mixture onto surface of another product, coating, or material. This may be accomplished in conventional type panning equipment, or in more advanced side-vented coating pans. When a solvent like alcohol is used, extra precautions are needed to prevent fires and explosions, and specialized equipment is used.

[0086] Some film polymers can use water as the solvent in film coating. Recent advances in polymer research and in film coating technology eliminates the problems associated with applying solvents to a coating. These advances make it possible to apply aqueous films to a variety of finished products, including chewing gums, candies, and the like. As the potassium salt and/or sodium salt employed may be slightly water soluble, they can be added to this aqueous film solution and applied with the film to another product surface, coating, or material. The aqueous film, or even the alcohol solvent film, in which the salt or salts may be dispersed may also contain a flavor along with the polymer and plasticizer. By adding the salt or salts to the polymer/plasticizer/solvent system, either as an emulsion or solution, the salt or salts can be added with sweeteners or flavors to balance taste. The potassium salt and/or sodium salt can also be dissolved in the aqueous solvent and coated on the surface with the aqueous film.

[0087] Oral Products

[0088] The present disclosure is directed to various oral products, including for example chewing gums (e.g., tablet gums, pellet or dragee gums, stick gums, compressed gums, co-extruded layered gums, bubble gums, etc.), candies, confectioneries, chocolates, gels, confectionery pastes, toothpastes, mouth rinses and dentifrices.

[0089] In one embodiment, the oral product of the present disclosure is a chewing gum. In another embodiment, the oral product is a co-extruded layered gum, wherein for example the gum comprises one layer which comprises the calcium salt and either: (i) one layer which comprises the co-encapsulated sodium salt and potassium salt having a molar ratio of approximately 3:5 respectively; or, (ii) two layers which comprise the sodium salt in one layer and the potassium salt in another layer having a molar ratio of approximately 3:5. For example, the layer comprising the calcium salt can be present (i.e. sandwiched) therebetween. In this way, the calcium, sodium and potassium salts are essentially encapsulated in the gum base, and thus premature contact of these salts are limited, and likely, substantially prevented...

[0116] Chewing gum generally conveys oral care benefits. In addition to mechanical cleaning of

the teeth provided by the chewing action, saliva stimulated by chewing, flavor and taste from the product conveys beneficial properties in reducing bad breath, neutralizing acid, and the like. Saliva also contains beneficial polypeptides and other components which may improve the oral environment. These include: antimicrobial proteins, such as lysozyme, lactoferrin, peroxidases, and histatins; inhibitors of spontaneous crystallization, such as statherin.

[0128] Methods of Mineralization or Remineralization

[0129] In general, mineralization or remineralization of a tooth surface may be accomplished by administering an oral product of the disclosure using conditions and techniques known in the art. Regardless of the form of the oral products, it is desirable for its duration in the oral cavity, as well as the rate at which the calcium, potassium, and sodium salts are released from the oral product to be controlled so as to optimize the effectiveness of the product in mineralizing or remineralizing the tooth surface.

[0130] For example, in the case of chewing gum, administration typically comprises chewing the gum for at least mi 5 to about 60 minutes, or 10 to about 30 minutes. Generally, a subject is encouraged to chew the gum for a certain period of time for a minimum of about 5 minutes, about 10 minutes, about 15 minutes, about 20 minutes or more.

[0131] Without being bound to any particular theory, the inventor of the present disclosure believes that by employing a calcium salt with a molar blend of about 3.0 to about 4.0 of sodium salt and potassium salt offers optimum salt solubility and mineralization/remineralization effects. Further, in oral products that remain in the oral cavity for extended periods of time, this disclosure provides a stability and sustained release of high levels of calcium and phosphate ions over long periods of time. Still further, this disclosure offers mineralization/remineralization effects without the need of incorporating a food acid to stimulate release of the salts from an oral product and into the oral cavity of a consumer for mineralization/remineralization effects.

EXAMPLES

[0132] By way of example and not limitation, the following examples are illustrative of various embodiments of the present disclosure and further illustrate experimental testing conducted with the oral care products in accordance with embodiments of the present disclosure,

[0131] Without being bound to any particular theory, the inventor of the present disclosure believes that by employing a calcium salt with a molar blend of about 3.0 to about 4.0 of sodium salt and potassium salt offers optimum salt solubility and mineralization/remineralization effects. Further, in oral products that remain in the oral cavity for extended periods of time, this disclosure provides a stability and sustained release of high levels of calcium and phosphate ions over long periods of time. Still further, this disclosure offers mineralization/remineralization effects without the need of incorporating a food acid to stimulate release of the salts from an oral product and into the oral cavity of a consumer for mineralization/remineralization effects.

[0135] Treatment Cycle:

[0136] Artificial saliva with active treatments (1 hr, 4* daily)

TABLE 1

Quantity Dissolved

Reagents	in 1 L	Molarity
KCl	1.114 g	K, Cl: 14.9 mM
CaCl2-2H2O	0.213 g	Ca: 1.45 mM

KH2PO4 0.738 g PO4: 5.4 mM
NaCl 1.658 g Na, Cl: 6.5 mM
Porcine Muscin 2.200 g Ca: P = 0.27[3] and (viscosity) I.S. = 0.058

[0142] Based on the data provided, one can make the following observations:

No significant dose response was observed with Ca-lactate at 500 and 1500 ppm respectively.

The addition of phosphate salts (709 ppm) to a Ca-lactate (500 ppm) solutions provided significantly higher enamel rehardening over Ca-lactate alone (500 and 1500 ppm respectively). This indicated that phosphate addition was a key driver for remineralization.

A molar blend of Na/K phosphate salts provided higher enamel rehardening over diammonium phosphate salts at equal phosphate ion concentration. This indicated that Na/K phosphate molar blend may be a better pH buffer over the ammonium ion.

At equivalent calcium and phosphate ion concentrations, solutions with the citrate anion provided higher enamel rehardening over the lactate anion. It is hypothesized the triprotic citrate anion could potentially provide a mineralization/remineralization template through simultaneous adsorption to the tooth surface and sequestering of Ca ions. The lactate anion though is monoprotic and may not provide this templating effect.

At equivalent mass percent (0.38%) in solution, Ca-citrate (21% Ca) provided higher enamel rehardening over Ca-lactate (13% Ca) through the addition of higher concentrations of Ca ions. This indicated that greater calcium addition was a key driver for mineralization/remineralization.

EXAMPLE

Oral Care Product Formulations
[0148]

Chewing Gum Compositions:

Ingredients (Weight %)	Ex. 1	Ex. 2	Ex. 3	Ex. 4	Ex. 5	Ex. 6	Ex. 7
Gum Base	33.23	30.60	31.10	35.60	35.1	34.23	31.87
Sorbitol	41.12	39.00	35.00	35.50	35.1	42.72	41.00
Calcium citrate	6.75	7.50	10.00	8.50	4.50	*	3.34
Calcium glycerophosphate	*	*	*	*	*	7.75	3.34
Encapsulated sodium phosphate (47%) and potassium phosphate (13%)	5.00	7.50	10.00	*	*	6.00	7.00
Encapsulated sodium phosphate (35%) and potassium phosphate (15%)	*	*	*	6.00	12.00	*	*
Calcium carbonate	7.00	7.00	7.00	7.00	5.00	4.00	8.50
Glycerin	4.00	5.50	4.00	4.50	5.00	3.00	2.50
Encapsulated sweetener	0.75	0.75	0.75	0.75	0.25	1.00	1.25
Flavor	1.30	1.30	1.30	1.30	1.50	1.00	1.00
Menthol	0.45	0.45	0.45	0.45	0.75	*	*
Color	0.15	0.15	0.15	0.15	0.05	0.15	0.15
WS-23	0.15	0.15	0.15	0.15	0.50	*	*
High intensity sweetener	0.10	0.10	0.10	0.10	0.25	0.15	0.05
Total Weight %	100%	100%	100%	100%	100%	100%	100%

[0149]

TABLE 5

Chewing Gum Compositions:

Ingredients (Weight %)	Ex. 8	Ex. 9	Ex. 10	Ex. 11	Ex. 12	Ex. 13
Sugar	50.50	32.30	*	*	*	*
Xylitol	*	32.30	63.60	*	*	*
Sorbitol	*	*	*	63.60	40.90	20.00
Mannitol	*	*	*	*	12.00	25.00
Gum Base	19.20	19.20	19.60	19.60	25.50	30.00
Corn syrup	15.90	1.40	*	*	*	*
Glycerin	1.40	12.90	12.90	12.90	5.60	8.00
Cooling Agent	0.20	*	*	*	*	0.50
Flavor	0.80	0.90	0.90	0.90	1.00	1.50
Encapsulated sodium phosphate (47%) and potassium phosphate (13%)	*	*	*	*	*	7.50
Encapsulated Sodium Phosphate	3.00	*	3.00	*	4.00	*
Encapsulated Potassium Phosphate	3.00	*	*	3.00	4.00	*
Encapsulated Calcium citrate	*	*	*	*	7.00	*
Calcium Citrate	6.00	6.00	*	*	*	7.50
Total Weight %	100%	100%	100%	100%	100%	100%

[0150]

TABLE 6

Coating Compositions

Ingredients (Weight %)	Ex. 14	Ex. 15	Ex. 16	Ex. 17	Ex. 18	Ex. 19
Xylitol	90.00	90.00	87.74	*	*	*
Maltitol	*	*	*	80.10	74.70	67.2
Maltitol Powder	*	*	*	10.00	15.00	20.00
Gum Arabic	4.00	5.00	7.00	8.50	7.50	9.00
Flavor	0.50	0.50	0.66	0.70	0.90	0.5
Titanium Dioxide	0.50	0.84	-	0.50	0.50	0.5
Talc	0.10	0.10	0.10	0.10	0.10	0.2
Wax	0.10	0.10	0.10	0.10	0.10	0.2
Color	*	*	1.40	*	0.20	0.40
Encapsulated sodium phosphate (47%) and potassium phosphate (13%)	4.80	*	*	*	*	*
Encapsulated Sodium Phosphate	*	*	3.00	*	*	*
Encapsulated Potassium Phosphate	*	*	*	3.00	*	*
Encapsulated Calcium citrate	*	*	*	*	1.00	*
Sodium Phosphate	*	*	*	*	*	2.00
Calcium Citrate	*	4.00	*	*	*	*
Total Dry Weight %	100%	100%	100%	100%	100%	100%

[0151]

TABLE 7

Hard Candy Compositions

Ingredients (Weight %)	Ex. 20	Ex. 21	Ex. 22	Ex. 23	Ex. 24
Corn Syrup	37.00	*	*	45.3	*
Sugar	46.50	*	*	45.0	*
Polyalcohol	*	86.30	80.00	*	92.8
Flavor	1.00	3.00	2.00	5.0	3.5
Color	0.50	0.50	1.00	0.5	0.4
Encapsulated sodium and potassium phosphate (50% sodium phosphate	7.50	5.00	8.50	*	3.00

and 10% potassium phosphate)
Calcium Citrate 7.50 5.00 8.50 4.00 *
High Intensity Sweetener * 0.20 * 0.20 0.3
Total Dry Weight % 100% 100% 100% 100% 100%
[0152]

TABLE 8

Pressed Mint Compositions

Ingredients (Weight %) EX. 25 EX. 26 EX. 27 EX. 28 EX. 29
Sorbitol 82.85 93.85 87.85 96.85 94.85
Flavor 1.00 1.00 1.00 1.00 1.00
Mg Stearate 0.95 0.95 0.95 0.95 0.95
High Intensity Sweetener 0.20 0.20 0.20 0.20 0.20
Encapsulated sodium and potassium 7.50 2.00 5.00 * 1.00
phosphate (50% sodium phosphate
and 10% potassium phosphate)
Calcium Citrate 7.50 2.00 5.00 1.00 2.00
Total Dry Weight % 100% 100% 100% 100% 100%
[0153]

TABLE 9

Oral Rinse Composition

Ingredients (Weight %) Ex. 30 Ex. 31 Ex. 32

Calcium citrate 10.00 * *
Sodium phosphate and * 8.00 *
potassium phosphate in a molar ratio of 3:4
Chlorhexidene gluconate * * 0.12%
Ethanol 11.60 11.60 11.60
Sodium saccharin 0.15 0.15 0.15
FD&C Blue No. 1 0.001 0.001 0.001
Peppermint oil 0.50 0.50 0.50
Glycerin 10.00 10.00 10.00
Tween 50.00 50.00 50.00
Water 17.74 19.74 27.63
Total Weight % 100% < > 100% < > 100% < >

[0154] Example 33: Examples 30 and 31 are kept in separate chambers of an oral mouthrinse composition and upon dispensing the mouthrinse they are released into the oral cavity of a consumer simultaneously.

[0155] Example 34: Examples 30, 31 and 32 are kept in separate chambers of an oral mouthrinse composition and upon dispensing the mouthrinse they are released into the oral cavity of a consumer simultaneously.

[0156] Example 35: Example 30 is used a liquid center in a multilayered chewing gum composition with the chewing gum of Example 4 and the coating composition of Example 15.

WO2011031606 (A2)
DENTAL PROPHYLACTIC PASTE

The inventors of the present invention have discovered that remineralization properties can be achieved while providing improved handability by controlling the ratio of the moisture retention agent, water, and silicate matrix to the total amount of calcium and phosphate salts and when present, fluoride containing compounds. In particular, it is desirable that the silicate matrix and a total amount of the calcium and phosphate in the paste be present in a ratio that ranges from about 0.25:1 to 0.75:1. In a preferred embodiment, the amount of sodium silicate and methyl salicylate and a total amount of the calcium and phosphate salts and fluoride containing compounds in the prophy paste are present in a ratio ranging from about 0.15 to 0.3:1.

Further, it is also desirable for the moisture retention agent and a total amount of the calcium and phosphate salts in the paste be present in a ratio ranging from about 1.5:1 to 5.5:1. In a preferred embodiment, the ratio of the silicate matrix to the total amount of the calcium and phosphate in the paste is about 0.3:1. In one embodiment, the water and a total amount of the calcium and phosphate salts in the paste are present in a ratio from about 0.4:1. In further embodiments, the amount water and a total amount of the calcium and phosphate salts and fluoride containing compound in the prophy paste are present in a ratio ranging from about 0.1 :1 to 0.3:1 , with a ratio of about 0.2:1 being somewhat more preferred. The prophy may also include abrasive agents. Suitable abrasive agents include amorphous aluminum silicate, also commonly known as pumice, fused sodium potassium aluminum silicate, also commonly know as perilite, diatomaceous earth, and combinations thereof. When present, the amount of abrasive agent generally ranges from about 24 to 48 weight percent, based on the total weight of the prophy paste, and in particular from about 26 to 44 weight percent, and more particularly from about 28 to 42 weight percent. Preferably, the ratio of abrasive agent to the total amount of calcium and phosphate salts and fluoride in the paste ranges from about 1.5:1 to 3.5:1 , with a ratio ranging from about 1.5:1 to 3:1 being somewhat more preferred, and a ratio of 2:1 to 3:1 , being even more preferred.

In one embodiment, the present invention provides a dental prophylactic paste having low splattering and remineralization properties comprising from about 3 to 6 weight percent of a phosphate salt, from about 2 to 12 weight percent of a calcium salt; from about 0.02 to 12 weight percent of a fluoride containing compound, from about 1 to 8 weight percent of a combination of an alkali silicate and a salicylate, from about 0.02 to 2 weight percent of sodium carboxymethyl cellulose, from about 36 to 42 weight percent glycerin, from about 2 to 6 percent water, and from about 24 to 48 weight percent of an abrasive agent.

While not wishing to be bound by theory, it believed that the calcium, phosphate, and fluoride ions diffuse through the tooth surface to remineralize the demineralized tooth enamel. In one embodiment, the prophy paste is applied to a patient's tooth enamel using a rapidly rotating rubber cup or cup brush during a routine dental professional cleaning. While the length of contact time between the paste and tooth surface is not critical, it is desirable for the time to be great enough to allow the calcium, phosphate, and when present, fluoride ions, to remineralize the demineralized portions of the tooth. Generally, it is desirable for the prophy paste to remain in contact with the tooth surface for at least 10 seconds prior rinsing.

Suitable water-soluble calcium compounds include calcium chloride, calcium bromide, calcium nitrate, calcium acetate, calcium gluconate, calcium benzoate, calcium glycerophosphate, calcium formate, calcium fumarate, calcium lactate, calcium butyrate and calcium isobutyrate, calcium malate, calcium maleate, calcium propionate, calcium valerate or mixtures of water-soluble calcium compounds. In a preferred embodiment, the water-soluble calcium compound comprises calcium malate. Typically, the concentration of the water-soluble calcium compound in the prophy paste is from about 1 to 15 weight percent, based on the total weight of the composition, and in particular, from about 2 to 12 weight percent. In a preferred embodiment, the amount of the water- soluble calcium compound is from about 6 to 10 weight percent.

Suitable water-soluble inorganic phosphates within the scope of the present invention are, for example, alkali salts and ammonium salts of orthophosphoric acid, such as potassium, sodium or

ammonium orthophosphate, monopotassium phosphate, dipotassium phosphate, tripotassium phosphate, monosodium phosphate, disodium phosphate and trisodium phosphate and tricalcium phosphate. In a preferred
embodiment, the water-soluble phosphate compound comprises disodium hydrogen phosphate or tricalcium phosphate. Typically, the concentration of the water-soluble phosphate compound in the prophy paste is from about 1 to 15 weight percent, based on the total weight of the composition, and in particular, from about 2 to 12 weight percent. In a preferred embodiment, the amount of the water-soluble phosphate compound is from about 3 to 8 weight percent.

In order to effect remineralization of the dental enamel, an effective amount of the desired cations and anions must be employed in the oral cavity. Preferably, the concentration of the calcium ions in the mouth during application of the prophy paste is at least about 2 milligram/gram, and more preferably more than about 15 milligrams/grams. Preferably, the concentration of the phosphate ions in the mouth during application of the prophy paste is at least about 2 milligram/gram, and more preferably more than about 5 milligrams/grams. Preferably, the concentration of the fluoride ions in the mouth during application of the prophy paste is at least about 2 milligram/gram, and more preferably more than about 10 milligrams/grams.
In addition to the remineralization properties discussed above, prophy pastes in accordance with the present invention also exhibits excellent handability in relation to the manufacturing process as well as use by the end user. In particular, the prophy paste demonstrates little to no splattering during the step of loading the paste into the cup of the applicator tip as well as when the paste is applied to the teeth of the dental patient.

The desirable handability properties of the inventive prophy pastes are due in part to the combination of the silicate matrix, water, and moisture retention agent.

Further, it has been discovered that by selecting the appropriate ratio of the remineralization components (e.g., calcium, phosphate, fluoride) to the silicate matrix components, moisture retention agent, and water, prophy pastes having remineralization properties as well as improved handability can be achieved. Further the desirable handability / splatter control properties are achieved within the scope of the inventive prophy paste when the combination ratios of remineralization components to silicate matrix is about 3 to about 5.5 to 1 , remineralization components to moisture retention agents is about 0.4 to about 0.6 to 1 and remineralization components to water is about 3 to about 13 to 1 with the ratio of 6 to about 10 to 1 being preferred.

Alkali metal silicates that can be used in the present invention includes sodium silicate and potassium silicate, and combinations thereof. The alkali metal silicate is typically present in an amount ranging from about 2 to 10 weight percent, based on the total weight of the composition, and in particular, from about 3 to 6 weight percent. Salicylates that can be used in accordance with the present invention include methyl salicylate, also commonly known as sweet birch oil or oil of wintergreen.

In a preferred embodiment, the silicate matrix comprises a combination of sodium silicate, methyl salicylate and sodium carboxymethycellulose. In this
embodiment, the sodium silicate and methyl salicylate together form the silicate matrix of the composition in the ratios of sodium silicate 2.0 to 6.0 to methyl salicylate 0.1 to 1.2 parts.

Glycerin is a preferred moisture retention agent.

TABLE 1
Sample 1 : Course Grit
Ingredient Name (% w/w)
Purified Water 1.40
Glycerin 37.00
Calcium Malate 8.00

Sodium MFP 9.40
Sodium Phosphate Dibasic 5.00
Sodium Silicate 5.00
Methyl Salicylate 0.80
Pumice 0 6.25
Pumice FF 25.0
Flavorant 0.90
Sodium Carboxymethyl Cellulose 0.05
Sodium Saccharin 0.04
Monosodium Phosphate 0.16
Red 40 1 %/Glycerin 1.00
Total 100 TABLE 2
Sample 2: Medium Grit
Ingredient Name I (% w/w)
Purified Water 1.65
Glycerin 37.00
Calcium Malate 8.00
Sodium MFP 9.40
Sodium Phosphate Dibasic 5.00
Sodium Silicate 5.00
Methyl Salicylate 0.80
Pumice FF 31.00
Flavorant 0.90
Socium Carboxymethyl Cellulose 0.05
Sodium Saccharin 0.04
Monosodium Phosphate 0.16
Blue #1/Blue #2/Glycerin 1.00
Total i 100

US2008247973

[0010] The present invention relates to oral care compositions comprising selected surface-active organophosphate compounds to provide protection of teeth from erosion caused by the action of chemicals, such as harsh abrasives and acids. The surface-active organophosphate compounds are substantive to teeth, the phosphate groups binding the calcium in teeth and thus preventing loss of calcium from dissolution when contacted with acids.

...Examples of suitable agents include alkyl and alkyl (poly)alkoxy phosphates such as lauryl phosphate (tradenames MAP 230K and MAP 230T from Croda); PPG5 ceteareth-10 phosphate (available from Croda under the tradename Crodaphos SG); Laureth-1phosphate (tradenames MAP L210 from Rhodia, Phosten HLP-1 from Nikkol Chemical or Sunmaep L from Sunjin); Laureth-3 phosphate (tradenames MAP L130 from Rhodia or Foamphos L-3 from Alzo or Emphiphos DF 1326 from Huntsman Chemical); Laureth-9 phosphate (tradename Foamphos L-9 from Alzo); Trilaureth-4 phosphate (tradenames Hostaphat KL 340D from Clariant or TLP-4 from Nikkol Chemical); C12-18 PEG 9 phosphate (tradename Crafol AP261 from Cognis); Sodium dilaureth-10 phosphate (tradename DLP-10 from Nikkol Chemical). Particularly preferred agents are polymeric, for example those containing repeating alkoxy groups as the polymeric portion, in particular 3 or more ethoxy, propoxy isopropoxy or butoxy groups.
[0027] Additional suitable polymeric organophosphate agents include dextran phosphate, polyglucoside phosphate, alkyl polyglucoside phosphate, polyglyceryl phosphate, alkyl polyglyceryl phosphate, polyether phosphates and alkoxylated polyol phosphates. Some specific examples are PEG phosphate, PPG phosphate, alkyl PPG phosphate, PEG/PPG phosphate, alkyl PEG/PPG phosphate, PEG/PPG/PEG phosphate, dipropylene glycol phosphate, PEG glyceryl phosphate, PBG (polybutylene glycol) phosphate, PEG cyclodextrin phosphate, PEG sorbitan phosphate, PEG alkyl sorbitan phosphate, and PEG methyl glucoside phosphate.

[0028] Suitable non-polymeric phosphates include alkyl mono glyceride phosphate, alkyl sorbitan phosphate, alkyl methyl glucoside phosphate, alkyl sucrose phosphates.

[0030] The amount of organophosphate agent required is an effective amount to provide the protection from erosion due to acid or abrasive challenges. Preferably, the protection will last for at least about an hour after use of the composition. An effective amount of organophosphate agent will typically be from about 0.01% to about 35%, preferably from about 0.035% to about 20%, more preferably from about 0.035% to about 10%, and most preferably from about 0.035% to about 5%, by weight of the total oral composition.

[0036] The present compositions may comprise a metal ion source that provides stannous ions, zinc ions, copper ions, or mixtures thereof as antimicrobial agent. The metal ion source can be a soluble or a sparingly soluble compound of stannous, zinc, or copper with inorganic or organic counter ions. Examples include the fluoride, chloride, chlorofluoride, acetate, hexafluorozirconate, sulfate, tartrate, gluconate, citrate, malate, glycinate, pyrophosphate, metaphosphate, oxalate, phosphate, carbonate salts and oxides of stannous, zinc, and copper.

[0037] Stannous, zinc and copper ions have been found to help in the reduction of gingivitis, plaque, sensitivity, and improved breath benefits. An effective amount is defined as from at least about 50 ppm to about 20,000 ppm metal ion of the total composition, preferably from about 500 ppm to about 15,000 ppm. More preferably, metal ions are present in an amount from about 3,000 ppm to about 13,000 ppm and even more preferably from about 5,000 ppm to about 10,000 ppm. This is the total amount of metal ions (stannous, zinc, copper and mixtures thereof) for delivery to the tooth surface.

[0038] Dentifrices containing stannous salts, particularly stannous fluoride and stannous chloride, are described in U.S. Pat. No. 5,004,597 to Majeti et al. Other descriptions of stannous salts are found in U.S. Pat. No. 5,578,293 issued to Prencipe et al. and in U.S. Pat. No. 5,281,410 issued to Lukacovic et al. In addition to the stannous ion source, other ingredients needed to stabilize the stannous may also be included, such as the ingredients described in Majeti et al. and Prencipe et al.

[0039] The preferred stannous salts are stannous fluoride and stannous chloride dihydrate. Other suitable stannous salts include stannous acetate, stannous tartrate and sodium stannous citrate. Examples of suitable zinc ion sources are zinc oxide, zinc sulfate, zinc chloride, zinc citrate, zinc lactate, zinc gluconate, zinc malate, zinc tartrate, zinc carbonate, zinc phosphate, and other salts listed in U.S. Pat. No. 4,022,880. Zinc citrate and zinc lactate are particularly preferred. Examples of suitable copper ion sources are listed in U.S. Pat. No. 5,534,243. The combined metal ion source(s) will be present in an amount of from about 0.05% to about 11%, by weight of the final composition. Preferably, the metal ion sources are present in an amount of from about 0.5 to about 7%, more preferably from about 1% to about 5%. Preferably, the stannous salts may be present in an amount of from about 0.1 to about 7%, more preferably from about 1% to about 5%, and most preferably from about 1.5% to about 3% by weight of the total composition. The amount of zinc or copper salts used in the present invention ranges from about 0.01 to about 5%, preferably from about 0.05 to about 4%, more preferably from about 0.1 to about 3.0%....

Anticalculus Agent

[0041] The present compositions may optionally include an anticalculus agent, such as a pyrophosphate salt as a source of pyrophosphate ion. The pyrophosphate salts useful in the present compositions include the mono-, di- and tetraalkali metal pyrophosphate salts and mixtures thereof. Disodium dihydrogen pyrophosphate ($Na_2H_2P_2O_7$), sodium acid pyrophosphate, tetrasodium pyrophosphate ($Na_4P_2O_7$), and tetrapotassium pyrophosphate ($K_4P_2O_7$) in their unhydrated as well as hydrated forms are the preferred species. In compositions of the present invention, the pyrophosphate salt may be present in one of three ways: predominately dissolved, predominately undissolved, or a mixture of dissolved and undissolved pyrophosphate.
[0042] Compositions comprising predominately dissolved pyrophosphate refer to compositions

where at least one pyrophosphate ion source is in an amount sufficient to provide at least about 0.025% free pyrophosphate ions. The amount of free pyrophosphate ions may be from about 1% to about 15%, from about 1.5% to about 10% in one embodiment, and from about 2% to about 6% in another embodiment. Free pyrophosphate ions may be present in a variety of protonated states depending on the pH of the composition.

[0043] Compositions comprising predominately undissolved pyrophosphate refer to compositions containing no more than about 20% of the total pyrophosphate salt dissolved in the composition, preferably less than about 10% of the total pyrophosphate dissolved in the composition. Tetrasodium pyrophosphate salt is a preferred pyrophosphate salt in these compositions. Tetrasodium pyrophosphate may be the anhydrous salt form or the decahydrate form, or any other species stable in solid form in the dentifrice compositions. The salt is in its solid particle form, which may be its crystalline and/or amorphous state, with the particle size of the salt preferably being small enough to be aesthetically acceptable and readily soluble during use. The amount of pyrophosphate salt useful in making these compositions is any tartar control effective amount, generally from about 1.5% to about 15%, preferably from about 2% to about 10%, and most preferably from about 3% to about 8%, by weight of the dentifrice composition.

[0045] The pyrophosphate salts are described in more detail in Kirk-Othmer Encyclopedia of Chemical Technology, Third Edition, Volume 17, Wiley-Interscience Publishers (1982).

[0046] Optional agents to be used in place of or in combination with the pyrophosphate salt include such known materials as longer chain (3 or more) polyphosphates including tripolyphosphate, tetrapolyphosphate and hexametaphosphate; synthetic anionic polymers, including polyacrylates and copolymers of maleic anhydride or acid and methyl vinyl ether (e.g., Gantrez), as described, for example, in U.S. Pat. No. 4,627,977, to Gaffar et al. as well as, e.g., polyamino propane sulfonic acid (AMPS), diphosphonates (e.g., EHDP; AHP), polypeptides (such as polyaspartic and polyglutamic acids), and mixtures thereof.

Other Active Agents

[0047] Still another active agent that may be included in the present compositions is a tooth bleaching active selected from the group consisting of peroxides, perborates, percarbonates, peroxyacids, persulfates, and combinations thereof. Suitable peroxide compounds include hydrogen peroxide, urea peroxide, calcium peroxide, sodium peroxide, zinc peroxide and mixtures thereof. A preferred percarbonate is sodium percarbonate. Preferred persulfates are **oxones**.

[0048] Preferred peroxide sources for use in dentifrice formulations are calcium peroxide and urea peroxide. Hydrogen peroxide and urea peroxide are preferred for use in mouthrinse formulations. The following amounts represent the amount of peroxide raw material, although the peroxide source may contain ingredients other than the peroxide raw material. The present composition may contain from about 0.01% to about 30%, preferably from about 0.1% to about 10%, and more preferably from about 0.5% to about 5% of a peroxide source, by weight of the composition.

[0049] In addition to whitening, the peroxide also provides other benefits to the oral cavity. It has long been recognized that hydrogen peroxide and other peroxygen-compounds are effective in curative and/or prophylactic treatments with respect to caries, dental plaque, gingivitis, periodontitis, mouth odor, recurrent aphthous ulcers, denture irritations, orthodontic appliance lesions, postextraction and postperiodontal surgery, traumatic oral lesions and mucosal infections, herpetic stomatitis and the like. Peroxide-containing agents in the oral cavity exert a chemomechanical action generating thousands of tiny oxygen bubbles produced by interaction with tissue and salivary enzymes. The swishing action of a mouthrinse enhances this inherent chemomechanical action. Such action has been recommended for delivery of other agents into infected gingival crevices. Peroxide mouthrinses thus prevent colonization and multiplication of anaerobic bacteria known to be associated with periodontal disease.

[0050] Another optional active agent that may be added to the present compositions is a dentinal desensitizing agent to control hypersensitivity, such as salts of potassium, calcium, strontium and tin including nitrate, chloride, fluoride, phosphates, pyrophosphate, polyphosphate, citrate, oxalate and sulfate.

Tooth Substantive Agent

[0051] The present invention may include a tooth substantive agent such as polymeric surface active agents (PMSA's), which are polyelectrolytes, more specifically anionic polymers. The PMSA's contain anionic groups, e.g., phosphate, phosphonate, carboxy, or mixtures thereof, and thus, have the capability to interact with cationic or positively charged entities. The "mineral" descriptor is intended to convey that the surface activity or substantivity of the polymer is toward mineral surfaces such as calcium phosphate minerals in teeth.

[0052] PMSA's are useful in the present compositions because of their stain prevention benefit. It is believed the PMSA's provide a stain prevention benefit because of their reactivity or substantivity to mineral surfaces, resulting in desorption of portions of undesirable adsorbed pellicle proteins, in particular those associated with binding color bodies that stain teeth, calculus development and attraction of undesirable microbial species. The retention of these PMSA's on teeth can also prevent stains from accruing due to disruption of binding sites of color bodies on tooth surfaces.

[0053] The ability of PMSA's to bind stain promoting ingredients of oral care products, for example, stannous ions and cationic antimicrobials, is also believed to be helpful. The PMSA will also provide tooth surface conditioning effects which produce desirable effects on surface thermodynamic properties and surface film properties, which impart improved clean feel aesthetics both during and most importantly, following rinsing or brushing. Many of these polymeric agents are also known or expected to provide tartar control benefits when applied in oral compositions, hence providing improvement in both the appearance of teeth and their tactile impression to consumers.

[0054] Suitable examples of such polymers are polyelectrolytes such as condensed phosphorylated polymers; polyphosphonates; copolymers of phosphate- or phosphonate-containing monomers or polymers with other monomers such as ethylenically unsaturated monomers and amino acids or with other polymers such as proteins, polypeptides, polysaccharides, poly(acrylate), poly(acrylamide), poly(methacrylate), poly(ethacrylate), poly(hydroxyalkylmethacrylate), poly(vinyl alcohol), poly(maleic anhydride), poly(maleate) poly(amide), poly(ethylene amine), poly(ethylene glycol), poly(propylene glycol), poly(vinyl acetate) and poly(vinyl benzyl chloride); polycarboxylates and carboxy-substituted polymers; and mixtures thereof. Suitable polymeric mineral surface active agents include the carboxy-substituted alcohol polymers described in U.S. Pat. Nos. 5,292,501; 5,213,789, 5,093,170; 5,009,882; and 4,939,284; all to Degenhardt et al. and the diphosphonate-derivatized polymers in U.S. Pat. No. 5,011,913 to Benedict et al. the synthetic anionic polymers including polyacrylates and copolymers of maleic anhydride or acid and methyl vinyl ether (e.g., Gantrez), as described, for example, in U.S. Pat. No. 4,627,977, to Gaffar et al. A preferred polymer is diphosphonate modified polyacrylic acid. Polymers with activity must have sufficient surface binding propensity to desorb pellicle proteins and remain affixed to enamel surfaces. For tooth surfaces, polymers with end or side chain phosphate or phosphonate functions are preferred although other polymers with mineral binding activity may prove effective depending upon adsorption affinity.

[0055] Additional examples of suitable phosphonate containing polymeric mineral surface active agents include the geminal diphosphonate polymers disclosed as anticalculus agents in U.S. Pat. No. 4,877,603 to Degenhardt et al. phosphonate group containing copolymers disclosed in U.S. Pat. No. 4,749,758 to Dursch et al. and in GB 1,290,724 (both assigned to Hoechst) suitable for use in detergent and cleaning compositions; and the copolymers and cotelomers disclosed as useful for applications including scale and corrosion inhibition, coatings, cements and ion-exchange resins in U.S. Pat. No. 5,980,776 to Zakikhani et al. and U.S. Pat. No. 6,071,434 to Davis et al. Additional

polymers include the water-soluble copolymers of vinylphosphonic acid and acrylic acid and salts thereof disclosed in GB 1,290,724 wherein the copolymers contain from about 10% to about 90% by weight vinylphosphonic acid and from about 90% to about 10% by weight acrylic acid, more particularly wherein the copolymers have a weight ratio of vinylphosphonic acid to acrylic acid of 70% vinylphosphonic acid to 30% acrylic acid; 50% vinylphosphonic acid to 50% acrylic acid; or 30% vinylphosphonic acid to 70% acrylic acid. Other suitable polymers include the water soluble polymers disclosed by Zakikhani and Davis prepared by copolymerizing diphosphonate or polyphosphonate monomers having one or more unsaturated C-C bonds (e.g., vinylidene-1,1-diphosphonic acid and 2-(hydroxyphosphinyl)ethylidene-1,1-diphosphonic acid), with at least one further compound having unsaturated C-C bonds (e.g., acrylate and methacrylate monomers). Suitable polymers include the diphosphonate/acrylate polymers supplied by Rhodia under the designation ITC 1087 (Average MW 3000-60,000) and Polymer 1154 (Average MW 6000-55,000).

[0056] A preferred PMSA is a polyphosphate. A polyphosphate is generally understood to consist of two or more phosphate molecules arranged primarily in a linear configuration, although some cyclic derivatives may be present. Although pyrophosphates (n=2) are technically polyphosphates, the polyphosphates desired are those having around three or more phosphate groups so that surface adsorption at effective concentrations produces sufficient non-bound phosphate functions, which enhance the anionic surface charge as well as hydrophilic character of the surfaces. The inorganic polyphosphate salts desired include tripolyphosphate, tetrapolyphosphate and hexametaphosphate, among others. Polyphosphates larger than tetrapolyphosphate usually occur as amorphous glassy materials. Preferred in this invention are the linear polyphosphates having the formula:
[0000]
XO(XPO3)nX

[0000] wherein X is sodium, potassium or ammonium and n averages from about 3 to about 125. Preferred polyphosphates are those having n averaging from about 6 to about 21, such as those commercially known as Sodaphos (n 6), Hexaphos (n 13), and Glass H (n 21) and manufactured by FMC Corporation and Astaris. These polyphosphates may be used alone or in combination. Polyphosphates are susceptible to hydrolysis in high water formulations at acid pH, particularly below pH 5. Thus it is preferred to use longer-chain polyphosphates, in particular Glass H with an average chain length of about 21. It is believed such longer-chain polyphosphates when undergoing hydrolysis produce shorter-chain polyphosphates which are still effective to deposit onto teeth and provide a stain preventive benefit.

[0057] Other polyphosphorylated compounds may be used in addition to or instead of the polyphosphate, in particular polyphosphorylated inositol compounds such as phytic acid, myo-inositol pentakis(dihydrogen phosphate); myo-inositol tetrakis(dihydrogen phosphate), myo-inositol trikis(dihydrogen phosphate), and an alkali metal, alkaline earth metal or ammonium salt thereof. Preferred herein is phytic acid, also known as myo-inositol 1,2,3,4,5,6-hexakis (dihydrogen phosphate) or inositol hexaphosphoric acid, and its alkali metal, alkaline earth metal or ammonium salts. Herein, the term "phytate" includes phytic acid and its salts as well as the other polyphosphorylated inositol compounds.

[0058] The amount of tooth substantive agent will typically be from about 0.1% to about 35% by weight of the total oral composition. In dentifrice formulations, the amount is preferably from about 2% to about 30%, more preferably from about 5% to about 25%, and most preferably from about 6% to about 20%. In mouthrinse compositions, the amount of tooth substantive agent is preferably from about 0.1% to 5% and more preferably from about 0.5% to about 3%.

[0059] In addition to creating the surface modifying effects, the tooth substantive agent may also function to solubilize insoluble salts. For example, Glass H has been found to solubilize insoluble stannous salts. Thus, in compositions containing stannous fluoride for example, Glass H contributes to decreasing the stain promoting effect of stannous.

Chelating Agents

[0060] Another optional agent is a chelating agent, also called sequestrants, such as gluconic acid, tartaric acid, citric acid and pharmaceutically-acceptable salts thereof. Chelating agents are able to complex calcium found in the cell walls of the bacteria. Chelating agents can also disrupt plaque by removing calcium from the calcium bridges which help hold this biomass intact. However, it is not desired to use a chelating agent which has an affinity for calcium that is too high, as this may result in tooth demineralization, which is contrary to the objects and intentions of the present invention. Suitable chelating agents will generally have a calcium binding constant of about 10<1 > to 10<5 > to provide improved cleaning with reduced plaque and calculus formation. Chelating agents also have the ability to complex with metallic ions and thus aid in preventing their adverse effects on the stability or appearance of products. Chelation of ions, such as iron or copper, helps retard oxidative deterioration of finished products.

[0061] Examples of suitable chelating agents are sodium or potassium gluconate and citrate; citric acid/alkali metal citrate combination; disodium tartrate; dipotassium tartrate; sodium potassium tartrate; sodium hydrogen tartrate; potassium hydrogen tartrate; sodium, potassium or ammonium polyphosphates and mixtures thereof. The chelating agent may be used from about 0.1% to about 2.5%, preferably from about 0.5% to about 2.5% and more preferably from about 1.0% to about 2.5%.

TABLE 2
Toothpaste Formulations

Ingredients	A	B	C	D	E	F	G	H	I	J	K
USP Water	11.0	11	11.0	11.0	11.0	11.0	11.0	11.0	11.0	11.0	11.0
Silica, dental type	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0
NaF USP	0.243	0.243	0.243	0.243	0.243	0.243	0.243	0.243	0.243	0.243	0.243
MAP L210<5>	-	5.0	-	-	-	-	-	-	5.0	-	
Foamphos L-3<3>	-	-	5.0	-	-	-	-	-	-		
Foamphos L-9<7>	-	-	-	5.0	-	-	-	-	-	-	
DLP-10<8>	-	-	-	-	5.0	-	-	-	-	-	
KL340D<6>	-	-	-	-	-	-	-	-	-	5.0	
MAP 230K<2>	-	-	-	-	-	5.0	5.0	-	-	-	-
Crodaphos SG<4>	-	-	-	-	-	-	-	-	5.0	-	-
MAP 230T<9>	-	-	-	-	-	-	-	-	5.0	-	-
Sodium saccharin	0.13	0.13	0.13	0.13	0.13	0.13	0.13	0.13	0.13	0.13	0.13
NaOH (50% soln)	0.5	0.5	1.0	0.5	1.0	1.0	1.0	1.0	1.0	0.5	1.0
CMC sodium	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75
Titanium dioxide	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Carbomer 956	0.30	0.30	0.30	0.30	0.30	0.30	0.30	0.30	0.30	0.30	0.30
Flavor	0.80	0.80	0.80	0.80	0.80	0.80	0.80	0.80	0.80	0.80	0.80
Na lauryl sulfate (28% soln)	4.0	4.0	-	-	-	-	-	-	-	-	-
Cocamidopropyl Betaine (30% soln.)	-	-	-	-	-	3.3	-	-	-	3.3	-
Sorbitol solution	67.0	62.0	66.0	66.0	66.0	62.7	66.0	66.0	66.0	62.7	66.0
FD&C Blue #1	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Total	100	100	100	100	100	100	100	100	100	100	100

<2> Potassium C12/13 phosphate supplied by Croda
<3> Laureth-3 phosphate supplied by Alzo, neutralized with base such as NaOH
<4> PPG5 Ceteareth-10 phosphate supplied by Croda, neutralized with base such as NaOH
<5> Laureth-1 phosphate supplied by Rhodia, neutralized with NaOH
<6> Trilaureth-4 phosphate supplied by Clariant
<7> Laureth-9 phosphate supplied by Alzo, neutralized with base such as NaOH
<8> Sodium diLaureth-10 phosphate supplied by Nikkol Chemical
<9> Triethanolamine C12/13 phosphate supplied by Croda

[0000]

CALCIUM PEROXYPHOSPHATES AND USE THEREOF IN DENTAL COMPOSITIONS US2011142768

BACKGROUND OF THE INVENTION

[0003] A tooth is comprised of an outer hard enamel protective layer and an inner dentin layer. The outer enamel layer is naturally either opaque white or slightly off-white in color. It is composed of apatite mineral crystals that are somewhat porous. Without being bound by theory, it is believed that the porous nature of the enamel layer permits staining agents and discoloring substances to permeate into the enamel and discolor a tooth.

[0004] Dentin, the inner bony part of the tooth, contains thousands of microscopic tubules. On the crown end of the tooth, the dentin tubule ends are normally sealed by the enamel. These dentin tubules pass all the way through the dentin from the enamel-sealed crown end to the pulp chamber. On the root end of the tooth, these tubules are also sealed by a bony material called cementum. However, if either the enamel-sealed crown ends or the cementum-sealed root ends of the dentin tubules become exposed, fluid easily travels through the tubules, causing hypersensitivity and/or pain. Undesirable exposure of dentin tubules may result from mechanical abrasion, caries, chemical treatment (e.g., whitening agents), and other factors.

[0005] Plaques are a major cause of both dental decay and inflammatory periodontal disease. These plaques can contain 250 or more separate microbial species. They use sugars and other fermentable carbohydrates to produce acids, which cause demineralization of the tooth surface, and polymers, with which the microbial organisms bind themselves to the tooth surface...

SUMMARY OF THE INVENTION

[0014] The present invention is directed to calcium peroxyphosphate compounds and methods for the preparation of these compounds. The present invention is also directed to dental compositions comprising calcium peroxyphosphate compounds and methods for using such compositions that combine tooth whitening/stain removal with remineralization to hinder and/or prevent degradation of the tooth structure, normally associated with whitening.

[0015] In one embodiment, therefore, the present invention is a calcium peroxyphosphate compound or a hydrate or a peroxyhydrate thereof. In another embodiment, the compound further comprises hydrogen ions and/or hydroxide ions.

[0016] In another embodiment, the calcium peroxyphosphate compound is a calcium peroxymonophosphate or calcium diperoxymonophosphate having Formula (I):...

DETAILED DESCRIPTION OF THE INVENTION

[0024] Calcium peroxyphosphates represent a class of compounds capable of releasing active oxygen, calcium ions, and phosphate ions from a single molecule. Such compounds provide both whitening and remineralizing components for oral use. In particular, without being bound by theory, it is believed that as active oxygen removes tooth stains and leaves behind a void, the calcium and phosphate ions that are in close proximity and released from the same parent molecule precipitate to form tooth mineral (i.e., calcium phosphate) and repair the void by such remineralization. Such calcium peroxyphosphates should be provided in sufficient concentration in the oral environment to effect the desired whitening and remineralizing of teeth without toxicity or other undesirable effects. Such compositions may additionally contain a source of fluoride ions to enhance further remineralization. In this manner, compositions of the present invention advantageously achieve both whitening and remineralization of teeth.

[0025] Exemplary calcium peroxyphosphate compounds of the present invention include calcium peroxyphosphates, which embrace calcium peroxymonophosphates, calcium peroxydiphosphates, calcium peroxytriphosphates, etc. Other exemplary compounds of the present invention also include calcium diperoxyphosphates, which embrace calcium diperoxymonopho sphates, calcium diperoxydipho sphates, calcium diperoxytriphosphates, etc. Overall, compounds of the present invention include the calcium salts of phosphate monomers, dimers, and polymers, provided that at least one of the phosphate structural units is oxidized to a peroxyphosphate group (e.g., PO5<-3>), comprising one peroxy substituent, or to a diperoxyphosphate group (e.g., PO6 <-3>), comprising two peroxy substituents. These peroxyphosphate and diperoxyphosphate groups may also be in their respective hydrogen or dihydrogen forms. Thus, calcium peroxyphosphates and calcium diperoxyphosphates include calcium compounds having hydrogen peroxyphosphate groups (HPO5<-2>), dihydrogen peroxyphosphate (H2PO5<-1>), hydrogen diperoxyphosphate groups (HPO6<-2>), and/or dihydrogen diperoxyphosphate groups (H2PO6<-1>). Furthermore, the calcium peroxyphosphate and calcium diperoxyphosphate compounds of the present invention may also include hydroxyl (OH<->) groups that, in addition to the negatively charged peroxyphosphate and peroxydiphosphate groups (whether or not in their hydrogen forms) must be charge-balanced by the positive oxidation state of calcium.

[0026] Other exemplary compounds of the present invention include calcium peroxymonopho sphates, calcium peroxydipho sphates, calcium diperoxymonopho sphates, and calcium diperoxydiphosphates. Preferred are calcium peroxymonophosphate or calcium diperoxymonophosphate compounds having Formula (I):

[0000]
CaqHx(PHOS)y(OH), (I)

[0027] wherein q is [1/2].(3y+z-x); x is from 0 to 8; y is an integer from 1 to 3; z is from 0 to 1; x<3y; and PHOS is peroxymonophosphate having the formula PO5 or diperoxymonophosphate having the formula PO6, or calcium peroxydiphosphate or calcium diperoxydiphosphate compounds having Formula (II):

[0000]
CaqHx(DIPHOS) (II)

[0000] wherein q is [1/2].(4-x); x is from 0 to 3; and DIPHOS is peroxydiphosphate having the formula P2O8 or diperoxydiphosphate having the formula P2O9.

[0028] Exemplary peroxymonophosphates of the above-defined Formula (I) include CaHPO5, Ca(H2PO5)2, Ca3(PO5)2, Ca4H(PO5)3, and Ca5(PO5)3OH. Exemplary peroxydiphosphates of the above-defined Formula (II) include CaH2(P2O8) and Ca2(P2O8).

[0029] In one synthesis route in preparing calcium peroxymonophosphate compounds of the present invention, an initial step involves the preparation of peroxymonophosphoric acid. The synthesis of peroxymonophosphoric acid may be carried out as described, for example, by Schmidlin and Massini (Ber., 43, 1910, page 1162) according to the reaction

[0000]
P2O5+2H2O2+H2O->2H3PO5 (i)

[0000] However, due to the inherent safety risk of the above highly exothermic reaction (1), improvements in this basic synthesis route to peroxymonophosphoric acid were developed and are described, for example, in Can. J. Chem. 81:156-160 (2003) and U.S. Pat. Nos. 3,036,887 and 3,085,856. Alternative methods for preparing this acid are described, for example, by J. E. Such, "Peroxophosphoric Acid & Peroxophosphates" in MELLOR'S COMPREHENSIVE TREATISE ON INORGANIC AND THEORETICAL CHEMISTRY, Vol. VIII (Supp III), Longmana, London (1971). These methods include (i) the hydrolysis of peroxydiphosphate in a strong acid solution, (ii)

the reaction of H4P2O7 with aqueous hydrogen peroxide, and (iii) the anodic oxidation of PO4<-3 >or P2O7<-4>.

[0030] Diperoxyphosphoric acid, H3PO6, a starting material in the preparation of calcium diperoxymonophosphate, is less well known than H3PO5. However, this peroxy acid may be prepared, for example, in a manner similar to that for preparation of H3PO5, namely by the action of hydrogen peroxide on either P2O5 or pyrophosphoryl chloride (PO3Cl4). In general, the use of a peroxygenated phosphoric acid starting material allows for the preparation of various types of calcium peroxyphosphate compounds described herein.

[0031] Preferably, peroxymonophosphoric acid is prepared according to the above-noted reaction (1) in a water-immiscible liquid medium, such as carbon tetrachloride, that is inert to both the reactants and the reaction product under the conditions of use. The resulting peroxymonophosphoric acid may thereafter be separated from the organic diluent phase by, for example, decantation or equivalent methods. The recovered peroxymonophosphoric acid is then reacted with a calcium compound, preferably selected from the group consisting of calcium carbonate, calcium bicarbonate, calcium hydroxide, and mixtures thereof. The calcium compound may be added as a solid or a solution (e.g., an aqueous solution). The reaction between the peroxy acid and the calcium compound is preferably carried out at low temperature, preferably from about -10[deg.] C. to about 20[deg.] C., to avoid excessive loss of active oxygen through decomposition. The calcium peroxymonophosphates generated from this reaction typically precipitate rapidly upon mixing of the reactants. When a solid calcium carbonate reactant is used, the rate of dissolution of this compound and the rate of evaporation of carbon dioxide both influence the rate of product precipitation.

[0032] The solid product can be recovered from the liquid medium described above by separation methods that include, but are not limited to, evaporation, filtration, and freeze-drying. Product purity can be increased by recrystallization or fractional crystallization, with either of these methods preferably employing water or a mixture of water and a water-soluble organic solvent. Preferred organic solvents having some water solubility and that are appropriate for this purpose include saturated aliphatic ketones (e.g., acetone) and aliphatic alcohols (e.g., methanol, ethanol, and glycerol). The various calcium peroxyphosphate compounds described herein (e.g., calcium peroxydiphosphates, and calcium diperoxydiphosphates) may be prepared following analogous procedures, using the appropriate starting peroxy acid.

[0033] While the above-noted procedures may generate a single calcium peroxyphosphate compound, generally a mixture of compounds is obtained. For example, a mixture of the peroxygenated forms Ca(H2PO5)2 and CaHPO5 may be obtained in the preparation of calcium peroxymonophosphates. The procedures described above may also yield non-peroxygenated calcium phosphates such as mono- and di-calcium phosphates. Preferably, however, the peroxygenated forms will be present, in either the impure or purified reaction products described above, in an amount of at least about 10% by weight, and more preferably in an amount from about 10% to about 90% by weight, relative to the total amount of peroxygenated and non-peroxygenated calcium phosphates. Mixtures of calcium peroxyphosphates and calcium phosphates may be characterized according to their overall relative amounts of calcium, phosphate, and peroxide and/or according to other analytically identifiable criteria, in order to help assess the types and relative amounts of the calcium phosphate species present. In case a mixture of various calcium peroxyphosphates or a mixture of calcium peroxyphosphates and calcium phosphates is obtained, the molar average calcium to phosphate molar ratio (Ca/P ratio) of the various these calcium compounds ranges preferably from about 0.25 to about 1.67, depending on the relative amounts of calcium compounds and peroxymonophosphoric acid used in the reaction described above. Importantly, both the peroxygenated and non-peroxygenated calcium phosphates, obtained from the synthesis procedures described above, may also be incorporated into dental compositions or restoratives as described herein without the need to segregate the peroxygenated forms. It is also possible to employ precursors of calcium peroxyphosphates (e.g., components comprising sources of calcium and peroxyphosphate that react to form the desired calcium peroxyphosphates) in these

restorative compositions, for example in separate compositions that are mixed before or during use. In this manner, the calcium peroxyphosphate compound may be generated in situ within, and/or on the surfaces of, the teeth.

[0034] Any of the calcium peroxyphosphates and calcium diperoxyphosphates described above may be in their respective hydrated or peroxyhydrated forms without adversely affecting their ability to release calcium ions, phosphate ions, and peroxide. As is known in the art, hydrated or peroxyhydrated forms refer to the parent molecules having one or more water molecules or hydrogen peroxide molecules, respectively, in their structures. Thus, as an example, a hydrated form of tricalcium peroxymonophosphate may be represented as Ca3(PO5)2.m H2O, indicating the association of "m" water molecules per molecule of calcium peroxymonophosphate. Likewise, a peroxyhydrated form of tricalcium peroxymonophosphate may be represented as Ca3(PO5)2.n H2O2, indicating the association of "n" hydrogen peroxide molecules per molecule of calcium peroxymonophosphate. Typically, "m" is an integer from 0 to 5.

[0035] Advantageously, when used in dental compositions the calcium peroxyphosphate compounds described above can readily provide both tooth whitening and remineralizing activity, as they comprise both peroxyphosphate ions and calcium ions in a single molecule of an ionic salt. Thus, these compounds are capable of releasing calcium ions, phosphate ions, and active oxygen simultaneously, in close proximity, and in amounts sufficient and effective for these purposes. By "active oxygen" is meant atomic oxygen (O) that may be generated by the decomposition or hydrolysis of peroxyphosphate ions. As illustrated below, peroxymonophosphate ion, for example, may decompose to yield phosphate and active oxygen according to the following reaction (2):

[0000]
PO5<-3>->PO4<-3>+O (2)

[0036] Alternatively, and generally to a lesser extent, peroxymonophosphate ion may react with water (i.e., hydrolyze) to form hydrogen peroxide, which in turn degrades to form active oxygen, as illustrated in the following reactions (3):

[0000]
PO5<-3>+H2O->PO4<-3>+H2O2H2O2->H2O+O (3)

[0037] Without being bound by theory, it is believed that, as active oxygen is generated according to the reactions (2) and (3) above, a free perhydroxyl radical (HOO.) forms for brief periods of time sufficient to oxidize dental stains. At the same time, calcium ions and phosphate ions deposit or precipitate, as calcium orthophosphate, in the void left behind, thereby remineralizing the tooth, strengthening it, inhibiting its decay, and/or attenuating its sensitivity. Additionally, remineralization, effected by the calcium and phosphate sources, can decrease tooth porosity resulting from the stain removal process. This in turn may prevent or slow the re-formation of a new stain within the void and also prolong the whitening effect. Because the deposited calcium orthophosphate is itself white, remineralization may further enhance whitening. Also, the precipitation of calcium orthophosphate onto and/or into the tooth surface can close pores in enamel and plug dentin tubules (e.g., at root ends) to reduce or eliminate post-treatment tooth sensitivity. The accompanying reduced porosity and/or plugging of dentin tubules can also generally reduce tooth surface permeability and consequently minimize the undesired effect of peroxide diffusion into the tooth pulp.

[0038] Associated with the present invention is the determination that sufficiently high concentrations of calcium ions and phosphate ions are particularly effective for tooth remineralization as a means to compensate for the reduction in tooth surface integrity that may result from whitening or bleaching with active oxygen, generated according to above-noted reactions (2) and/or (3).

[0039] Compounds of the present invention typically decompose in aqueous media (e.g., upon

exposure to saliva) to provide tooth whitening and remineralizing at combined effective amounts or concentrations of calcium ions, phosphate ions, and active oxygen. By "whitening and remineralizing at combined effective amounts" is meant that the amounts of calcium ion, phosphate ion, and active oxygen together are sufficient to whiten teeth and compensate, through precipitation (i.e., remineralization) of calcium phosphate, for some or all of the void that typically accompanies the whitening or stain removal process. The remineralization that is effected by compounds of the present invention also refers to the strengthening of pre-existing tooth weaknesses that are not associated with contemporaneous whitening or stain removal.

[0040] Preferably, when used in dental compositions, compounds of the present invention are present, on an anhydrous basis, in the composition in an amount of at least about 1% and preferably from about 3% to about 32% by weight, to provide generally effective amounts of calcium ions, phosphate ions, and active oxygen to effect the dual purposes of tooth whitening and remineralization discussed above. Also additional sources of peroxide, calcium salts, and phosphate salts can be included...

[0041] The decomposition of peroxymonophosphates according to reaction (2) above, which promotes the effects of tooth whitening and remineralization when used in dental compositions or restoratives, increases in rate with increasing pH, until a maximum decomposition rate is achieved in a pH range of 12-13. In order to inhibit decomposition prior to use, however, these compounds are preferably stabilized by maintaining them either at a neutral pH or at a slightly acidic pH and optionally in the presence of a stabilizer. While low pH favors the hydrolysis of peroxyphosphate according to reaction (3) above, it is believed that the extent of hydrolysis becomes appreciable only under strongly acidic conditions, which are easily avoided.

[0042] Stabilizers for use in dental compositions comprising compounds of the present invention include chelating agents that can scavenge and inactivate trace metals that could otherwise catalyze the decomposition process. Suitable chelating agents are described, for example, in U.S. Pat. No. 6,221,341. Metals, such as iron, manganese, and copper, and their oxides are known in the art to promote the degradation of peroxide through Fenton-type reactions. This particular degradation mechanism is undesirable in that the hydroxyl free radical (HO.) is created and is not as effective as active oxygen generated according to reactions (2) and (3) above, in attacking chromogens that stain the teeth.

[0043] Stabilizers therefore include, but are not limited to, pharmaceutically acceptable chelating agents such as the various amino carboxylate compounds that have the capacity to form metal-ligand complexes with one or more transition metal ions in solution. Such amino carboxylates include ethylenediaminetetraacetic acid (EDTA) and diethyltriaminepentaacetic (DTPA), 1,2-bis(2-aminophenoxy)ethane-N,N,N',N'-tetraacetic acid (BAPTA), ethylene glycol-bis(2-aminoethyl)-N,N,N',N'-tetraacetic acid (EGTA), and other amino carboxylate compounds having one or multiple carboxylate groups. Any derivative salt form of these amino carboxylate chelating agents, for example the disodium salt form, may be also used, provided that some capacity remains for the chelating agent to complex with free transition metal ions present. Forms of these chelating agents other than salt forms are also effective and include the various ester, anhydride, and halogenated forms of these compounds. A preferred stabilizer is EDTA.

[0044] As stated, calcium peroxyphosphate compounds of the present invention may be stabilized under neutral to slightly acidic pH conditions. When used in dental compositions, these compounds can be conveniently decomposed at the time of use to effect the beneficial release of (i) active oxygen for tooth whitening and (ii) calcium phosphate for tooth remineralization. Peroxyphosphate decomposition according to reaction (2) above is achieved, for example, by increasing pH or introducing activators such as catalytic amounts of trace metal ions into the calcium peroxyphosphate composition. A further advantage associated with effecting decomposition by increasing pH is the simultaneous promotion, at elevated pH, of the precipitation of calcium phosphate as tooth mineral. As described previously, calcium phosphate is a decomposition product of calcium peroxymonophosphates.

[0045] Based on the above, a kit comprising two separate compositions represents a possible vehicle for employing compounds of the present invention, allowing for long-term storage of these compounds prior to use and activation of these compounds at the point of use. In such an embodiment, for example, the first composition may be a pH-control composition having an alkaline pH and the second composition may comprise a compound of the present invention. In this embodiment, an alkaline pH of the first composition refers to a pH value preferably above 8, and more preferably from about 8 to about 12, and even more preferably from about 9 to about 11. The second composition comprising the calcium peroxyphosphate preferably has a neutral pH or a slightly acidic pH value (e.g., from about 3 to about 7).

[0046] Alternatively, the first composition may comprise an activator (e.g., a transition metal ion such as Zn<+2>) to catalyze or accelerate the decomposition of calcium peroxyphosphate upon contact therewith prior to or during use. The first composition may also optionally comprise a soluble calcium salt to provide an additional source of calcium. Soluble calcium salts include, but are not limited to, calcium sulfate (e.g., plaster of paris), calcium chloride, calcium nitrate, calcium acetate, calcium bromide, calcium gluconate, calcium benzoate, calcium glycerophosphate, calcium formate, calcium fumarate, calcium lactate, calcium butyrate, calcium isobutyrate, calcium malate, calcium propionate, and calcium valerate. Preferred soluble calcium salts include calcium chloride, calcium nitrate, calcium sulfate, and calcium acetate. Calcium orthophosphates include, but are not limited to, amorphous calcium phosphate (ACP), amorphous calcium phosphate fluoride (ACPF), and amorphous calcium carbonate phosphate (ACCP), which are described, for example, in U.S. Pat. No. 5,037,639.

[0047] Upon increasing the pH of the second composition and/or activating it by combining or mixing it with the first pH-control composition having an alkaline pH and/or an activator, not only is active oxygen made available for whitening, but also the released calcium ions and phosphate ions are precipitated as calcium phosphate for remineralization. Another means of realizing the goals of long-term storage of compounds of the present invention and their activation upon use may be through the provision of a layered composition, with separate layers (e.g., gel layers) being maintained under separate conditions and/or having separate compositions as described above. A further alternative method of stabilizing a calcium peroxyphosphate compound prior to use is to maintain it as a solid (either crystalline or amorphous) or a solid suspended in an inert carrier, such as a polyol. The solid form can then be either dissolved in a composition comprising an aqueous carrier at the point of use or applied directed to the surfaces of the teeth. Yet another alternative for stabilization involves lyophilization of the calcium peroxymonophosphate, coupled with reconstitution prior to use.

[0048] In the kit embodiment described previously, comprising two compositions, these compositions may be mixed or combined prior to application to the tooth surface, such that the combination/application steps are performed sequentially. In a preferred method of sequential application, for example, the compositions may be mixed and thereafter applied to the teeth in a tray and/or mouth guard. Alternatively, the compositions may be mixed on the teeth at the time of application (i.e., use) to the teeth in a simultaneous manner. Thus, simultaneous mixing and application includes methods wherein the first composition is applied onto the surface of the teeth (e.g., applying a solution with a cotton tip) and the second composition is then applied and combined with the applied first composition.

[0049] Simultaneous mixing and application represents a preferred method of teeth whitening and remineralization, particularly when a first composition that comprises a soluble calcium salt is first applied to the surface of the teeth, allowing the applied calcium to diffuse into the teeth. After application of the first composition, a second composition comprising a compound of the present invention (i.e., a calcium peroxyphosphate) is thereafter applied to the teeth. In this manner, both within the teeth as well as on the surface of the teeth, active oxygen (obtained from the second composition) is generated for whitening or bleaching and the calcium ions (obtained from both compositions) and phosphate ions (obtained from the second composition) are activated for precipitation or remineralization as calcium phosphate tooth mineral. Preferably, the first

composition is an aqueous solution. In another preferred embodiment, the second composition is in a gel form and is applied using a tray. In other embodiments, the calcium peroxyphosphate of the second composition may either be suspended as a solid in a non-aqueous medium or otherwise dissolved therein. In yet other embodiments, the second composition may comprise a peroxyphosphate and optionally a non-peroxygenated phosphate, such that the soluble calcium salt of the first composition reacts with the peroxyphosphate of the second composition to generate a calcium peroxyphosphate compound in situ. Without being bound by theory, it is believed that the calcium peroxymonophosphate compounds of the present invention, whether supplied in a single composition, in a kit comprising two or more compositions, or in the form of precursor components that are reacted at the point of use, can cause calcium orthophosphate (or tooth mineral) to precipitate, both on the surfaces of the dental tissues as well as in their interiors.

[0050] Whether a single composition, or, as described above, two or more separate compositions are employed, the pH of the compositions of the present invention may be maintained or controlled using any pH-control agents and buffer systems known in the art to be suitable for oral compositions. For example, compositions for oral use may be adjusted and maintained at an alkaline pH, preferably at a pH from about 8 to about 12, using hydroxide compounds (e.g., sodium hydroxide) and/or carbonate compounds (e.g., sodium carbonate). Likewise, compositions may be adjusted and maintained for stabilization purposes at approximately neutral or slightly acidic conditions, preferably at a pH from about 3 to about 7 using, for example, inorganic or organic acids including phosphoric acid, benzoic acid, and/or citric acid. Alternatively, dissolved carbon dioxide, for example in a carbonated solution under pressure, may also function as a pH-control agent as well as a carrier for calcium peroxymonophosphate compounds...

EXAMPLE 1
Preparation of Calcium Peroxymonophosphate

[0060] A 9.9 gram sample of phosphorus pentoxide powder was suspended in 68 g of carbon tetrachloride and cooled in an ice bath under vigorous stirring. To this suspension, 5.3 ml of 70% aqueous hydrogen peroxide was added dropwise at rate of 3 drops per second. The mixture was stirred for 3 hrs after the hydrogen peroxide addition. The mixture over time formed separate organic and aqueous peroxymonophosphoric acid layers. Five milliliters of the acid layer was obtained by decanting. To half of this inorganic concentrated peroxymonophosphoric acid, calcium carbonate slurry was added slowly in an ice bath and under stirring, until the pH of the solution was 1.7. This solution was then lyophilized. The resulting solid comprised calcium peroxymonophosphates with a Ca/P ratio of 0.28 and possibly additionally contained non-peroxygenated calcium phosphate compounds. The prepared calcium peroxymonophosphate had a distinct x-ray powder diffraction pattern, different from that corresponding to calcium phosphate. The d-space for 010 was in the range of 12.5 to 12.9 A, compared to 11.7 A corresponding to calcium phosphate. The calcium peroxymonophosphates also exhibited a peroxide IR peak of 785 cm<-1>, which was absent from the corresponding calcium phosphates.

EXAMPLE 2

[0061] Calcium carbonate slurry was added slowly, under stirring, to the other half of the inorganic concentrated peroxymonophosphoric acid layer as described in the Example 1, until the pH of solution was 3.5. This solution was then lyophilized. The solid comprised calcium peroxymonophosphates with a Ca/P ratio of 0.5 and possibly additionally contained non-peroxygenated calcium phosphate compounds. such as dicalcium phosphate dihydrate and monocalcium phosphate monohydrate. The prepared calcium peroxymonophosphate has a distinct x-ray powder diffraction pattern different from that corresponding to calcium phosphate. The d-space for 010 was 12 A, compared to 11.7 A for calcium phosphate. The calcium peroxymonophosphates also exhibited a peroxide IR peak of 785 cm<-1>, which was absent from the corresponding simple calcium phosphates.

EXAMPLE 3

Alternate Preparation of Calcium Peroxymonophosphate

[0062] Suspend 2.22 grams of calcium hydroxide in 50 ml of water. To this suspension, slowly add 2.28 grams of concentrated peroxymonophosphoric acid, to be prepared as described in Example 1, in order to precipitate calcium peroxymonophosphate. Filter the resulting slurry and wash it with distilled water. The solid to be recovered is a basic calcium peroxymonophosphate, possibly also containing one or more calcium phosphate compounds.

EXAMPLE 4
Preparation of Calcium Peroxydiphosphate

[0063] Dissolve 3.46 grams of potassium peroxydiphosphate in 10 ml of water. To this solution, add 2.94 grams of calcium chloride dihydrate under stirring, in order to precipitate calcium peroxydiphosphate. Filter the resulting slurry and wash it with distilled water. The solid to be recovered contains calcium peroxydiphosphate.

EXAMPLE 5
Preparation of Calcium Diperoxymonophosphate

[0064] Prepare diperoxymonophosphoric acid by the action of hydrogen peroxide on pyrophosphoryl chloride. Maintain this inorganic diperoxymonophosphoric acid in an ice bath under stirring and slowly add a calcium carbonate slurry until the pH of the resulting solution is 3.3 and calcium diperoxymonophosphate precipitates. Filter the resulting slurry and then wash it with distilled water. The solid to be recovered contains calcium diperoxymonophosphates and possibly also contains one or more calcium phosphate compounds.

Dentifrice compositions
US4327079

According to the present invention, there is provided a dentifrice composition containing synthetic hydroxyapatite powder and being neutral or weakly alkaline.

It has been found that the dentifrice composition of the present invention is very effective in fortifying a surface of a tooth, promoting remineralization of the surface of the tooth and eliminating plaque (a colony of bacteria).

In general, a conventional dentifrice contains, as a tooth-cleaning and abrading agent, a mineral, such as colloidal silica, calcium phosphate, calcium carbonate, magnesium carbonate, etc. While these abrading agents are used to remove contaminants on teeth, it is essential that they do not harm the teeth.

Since the dentifrice composition of the present invention contains a suitable amount of synthetic hydroxyapatite powder, plaque as well as substances contaminating teeth can be removed very effectively. We presume this is due to the fact that the synthetic hydroxyapatite has a hardness similar to that of the enamel portion of the tooth and it can impart an appropriate abrading effect on the enamel portion of the tooth in brushing the teeth. We further presume this is also due to the fact that the synthetic hydroxyapatite has a large surface area and an excellent absorptivity. We have further found that the synthetic hydroxyapatite powder has the effect of strengthening the coating on and remineralization the surface of the enamel of the tooth.

In accordance with the present invention, there is further provided a dentifrice composition containing synthetic hydroxyapatite powder and, based on the weight of the composition, 0.1 to 20% by weight of NaCl and/or KCl and 0.003 to 3% by weight of $MgCl_2$.

It has also been found that the presence of a mixture of NaCl and/or KCl with $MgCl_2$ in a dentifrice composition containing synthetic hydroxyapatite powder can effectively promote the elimination of

plaque from teeth and the fortification and remineralization of the surfaces of the teeth.

More specifically, the latter dentifrice composition of the present invention can effectively deposit and coat crystals of hydroxyapatite on the surfaces of the teeth. We presume this is due to the fact that the solubility of hydroxyapatite in water is increased in the presence of the chlorides as specified above. More particularly, since hydroxyapatite is a salt which only slightly soluble in water, the ion products of ions such as [Ca@++], [HPO4@--], etc. ionized in the dentifrice are small. This means that the ion products for promoting coating on the surfaces of the teeth, i.e. deposition of the crystals of hydroxyapatite on the surfaces of the teeth are small. However, if NaCl and/or KCl and MgCl2 are added to the dentifrice containing hydroxyapatite, it is presumed that the solubilities of Ca@++ and HPO4@-- are increased very much and the coating on the teeth is enhanced.

In cases where the amounts of NaCl and/or KCl and MgCl2 contained in the dentifrice composition of the present invention are smaller than those specified above, a sufficient coating effect cannot be obtained, while in cases where such amounts are larger than those specified above, it becomes difficult to give a comfortable feeling in the use of the dentifrice composition.

To obtain a suitable abrading effect and desired plaque elimination, the average particle size of the hydroxyapatite powder is preferably about 2.mu. and the maximum particle size thereof is preferably 10.mu. or less.

The dentifrice composition of the present invention may include various additives which are commonly employed in dentifrices and may further include, if desired, citric acid, lactic acid, acetic acid, pyrrolic acid, glutamine, proline, serine, glycine, etc.

EXAMPLE 1
Tooth Paste

Apatite Powder 13.2
Calcium phosphate 25.0
CMC sodium salt 0.3
Carrageenan 1.2
Glycerin 10.0
Solbitol 15.0
Sodium lauryl sulfate 2.0
Flavor 1.2
Sodium saccharinate
0.1
Silicon dioxide 2.0
Water 30.0

EXAMPLE 2
Tooth Paste

Apatite powder 7.2
Calcium phosphate 10.0
Calcium pyrophosphate 20.0
CMC Sodium salt 1.0
Sodium alginate 0.1
Glycerin 10.0
Solbitol 10.0
Sodium lauryl sulfate 1.5
Sodium lauryl sarcosinate 0.5
Flavor 0.5
Sodium saccharinate 0.1

Silicon dioxide 2.5
Sodium phosphate 1.0
Water 35.0

EXAMPLE 3
Tooth Paste

Apatite powder 22.3
Calcium pyrophosphate 10.0
CMC sodium salt 0.5
Carrageenan 0.6
Glycerin 20.0
Solbitol 10.0
Sodium lauryl sulfate 2.0
Flavor 1.0
Sodium saccharinate 0.1
Silicon dioxide 2.0
Sodium phosphate 0.5
Water 30.0

EXAMPLE 4
Tooth Paste

Apatite powder 38.1
CMC sodium salt 1.0
Carrageenan 0.3
Glycerin 35.0
Sodium lauryl sulfate 2.0
Flavor 1.0
Sodium saccharinate 0.1
Silicon dioxide 2.5
Water 20.0

EXAMPLE 5
Tooth Powder

Apatite powder 96.3
Sodium lauryl sulfate 2.0
Flavor 1.5
Sodium saccharinate0.2

EXAMPLE 6
Tooth Powder

Apatite powder 40.7
Calcium pyrophosphate 50.0
Silicon dioxide 5.0
Sodium lauryl sulfate 2.0
Flavor 2.0
Sodium saccharinate 0.3

EXAMPLE 7
Wet Tooth Powder

Apatite powder 65.38
Calcium phosphate 10.0

Solbitol 10.0
Sodium lauryl sulfate 2.0
Flavor 1.5
Calcium phosphate 1.0
Water 10.0
Sodium saccharinate 0.12

EXAMPLE 11
Tooth Paste

Apatite powder 10.0
Calcium phosphate 25.0
CMC sodium salt 0.3
Carrageenan 1.2
Glycerin 10.0
Solbitol 15.0
Sodium lauryl sulfate 2.0
Flavor 1.2
Sodium saccharinate 0.1
Silicon dioxide 2.0
NaCl 0.27
MgCl2 0.01
Water 32.92

EXAMPLE 12
Tooth Paste

Apatite powder 5.0
Calcium phosphate 10.0
Calcium pyrophosphate 20.0
CMC sodium salt 1.0
Sodium alginate 0.1
Glycerin 10.0
Solbitol 10.0
Sodium lauryl sulfate 1.5
Sodium lauryl sarcosinate 0.5
Flavor 0.5
Sodium saccharinate 0.1
Silicon dioxide 2.5
NaCl 3.0
MgCl2 0.2
Water 35.0

EXAMPLE 13

Tooth Paste

Apatite powder 20.0
Calcium pyrophosphate 10.0
CMC sodium salt 0.5
Carrageenan 0.6
Glycerin 20.0
Solbitol 10.0
Sodium lauryl sulfate 2.0
Flavor 1.0
Sodium saccharinate 0.1

Silicon dioxide 2.0
KCl 2.0
$MgCl_2$ 0.3
Sodium phosphate 0.5
Water 30.0

EXAMPLE 14
Tooth Paste

Apatite powder 35.0
CMC sodium salt 1.0
Carrageenan 0.3
Glycerin 35.0
Sodium lauryl sulfate 2.0
Flavor 1.0
Sodium saccharinate 0.1
Silicon dioxide 2.5
NaCl 2.0
$MgCl_2$ 0.1
KCl 1.0
Water 20.0

EXAMPLE 15

Tooth Powder

Apatite powder 90.8
Sodium lauryl sulfate 2.0
Flavor 1.5
Sodium saccharinate 0.2
NaCl 5.0
$MgCl_2$ 0.5

EXAMPLE 16

Tooth Powder

Apatite powder 38.0
Calcium pyrophosphate 50.0
Silicon dioxide 5.0
Sodium lauryl sulfate2.0
Flavor 2.0
Sodium saccharinate 0.3
NaCl 1.8
$MgCl_2$ 0.2
Potassium phosphate 0.7

EXAMPLE 17
Wet Tooth Powder

Apatite powder 63.0
Calcium phosphate 10.0
Solbitol 10.0
Sodium lauryl sulfate 2.0
Flavor 1.5
NaCl 3.3

MgCl2 0.08
Water 10.0
Sodium saccharinate 0.12

EXAMPLE 18

1 g of hydroxyapatite powder was introduced into 100 ml of 37 DEG C. distilled water and NaCl and MgCl2 were added in various concentrations. The calcium ion concentrations of the respective solutions were measured and it was confirmed that the solubility of hydroxyapatite was increased by adding NaCl and MgCl2. The calcium ion concentrations 10 days after the preparation of the solutions were as follows:

NaCl concentration;
0 0.3 0.3 3.0 3.0 (%)

MgCl2 concentration;
0 0.03 0.3 0.03 0.3 (%)

Ca@++ concentration;
4.9 26.0 31.2 31.5 36.7 (ppm)

EXAMPLE 19

An adult's permanent tooth was sliced in two using a prisma adamantinum to prepare a section about 200 .mu.m thick. The enamel portion was removed to expose the dentin portion. A hydroxyapatite-saturated solution in distilled water containing 0.001% of MgCl2 and 0.9% of NaCl was passed over the so prepared section at a flow rate of 0.6 ml/min. The section was continuously observed using a polarization microscope and it was confirmed that all over the surfaces of the section were coated with analogous apatite crystals at a thickness of about 5 .mu.m.

DENTAL FORMULATION
WO9319728

This invention concerns inhibiting tooth enamel demineralization.

More specifically it relates to the use of a water soluble phosphate, particularly a **pyrophosphate or tripolyphosphate**, to inhibit demineralization while not negatively impacting remineralization. This provides a means for preventing or reducing dental caries.

It has been found that certain water soluble phosphates exemplified by the alkali metal pyrophosphates and tripolyphosphates inhibit demineralization of enamel and they do not interfere with the remineralization phenomena of the fluoride ion in subsurface caries-like lesions. This finding makes it possible to provide an anti-caries dental preparation which **does not use fluoride.**..

Specific Embodiments

In the broadest embodiment, this invention utilizes certain phosphates as a means for inhibiting tooth enamel demineralization and thus reducing or preventing dental caries. It has been found that the presence of a orally acceptable water soluble phosphate is the critical factor, not the acid or salt form in which it is presented. Such a phosphate may be an orthophosphate, a pyrophosphate, a polyphosphate (chain phosphates) or a metaphosphate (cyclic phosphates). The preferred phosphates are pyrophosphate and tripolyposphate. So far as the ionic form of the phosphate is concerned, the acid form of each of these phosphates should not be used. That is acid phosphates such as Hop3010 or H4P207 should not be used. But the partially neutralized forms may be used, though the fully neutralized forms are usually preferred.The salts of Group Ia alkali metals of periods 2, 3 and 4 are preferred, particularly the sodium and potassium forms and mixtures thereof.

Most preferred is Nags3010 alone or mixtures of Na4P2O7 and K4P207. Notwithstanding this preference, several phosphate types and ionic forms may be incorporated into a single preparation. The phosphate may be anhydrous or hydrated.

Many commercial sources sell suitable phosphate preparations. In particular sodium and potassium pyrophosphate and sodium tripolyphosphate are available from a number of companies. Or the salts may be custom prepared to define standards by a commercial source or by the one who is doing the formulation work by using published techniques and processes. Pure phosphate preparations meeting local regulatory requirements should be used in these dental preparations.

Effective concentrations of phosphate will vary with the type of phosphate selected, its water solubility, the type of product (i.e., toothpastes, mouthwashes, chewing gums) and may be influenced by the nature and chemical or physical characteristics of the carrier and coformulated excipients. Some ingredients or formulations may have a higher available phosphate content. In any event, an effective amount is that amount which will reduce enamel demineralization to an extent that dental caries will be reduced in a statistically significant manner over a phosphate-free control which is also free of any other demineralization inhibiting agent or remineralizing agent.

As a practical matter, though not intending to be bound by such lower limit, about 2% by weight, or more, of a phosphate ion should provide an effective anti-caries preparation when used incorporated into orally acceptable preparations and when used in a normal, routine fashion. A preferred baseline for toothpastes, gels and liquids is 5% by weight. As regards sodium tripolyphosphate concentrations, 5% wlw is a preferred amount. As for pyrophosphates, a preferred amount is about 1.8% tetrasodium pryophosphate and 4.0% tetrapotassium pyrophosphate. These amounts, when combined with the excipients normally used to confect pastes and gels, should provide sufficient available phosphate to inhibit enamel demineralization to a point where dental caries will be usefully reduced.Variations and refinements in the level of phosphates can be carried out as required or as appropriate to maximize the effectiveness of the phosphate in a given formulation.

Phosphates may represent a higher percentage of the overall ingredient profile in dry formulations such as dental tablets, lozenges and chewing gums.

These phosphates can be presented in any orally acceptable carrier. The only limitation is that the phosphate must be available to interact with tooth enamel and the formulation must not have any deleterious or untoward affects on the teeth or the oral cavity when used within approved guidelines.

Many orally acceptable formulations are known in the dental arts.

Broadly speaking, these include dentifrices (pastes, gels and liquids), tooth powders, mouth rinses, dental tablets, dental lozenges, and dental care chewing gums, for example. Three of the most preferred formulations are toothpastes, gels, and mouthwashes. These will be specifically illustrated below as of orally acceptable formulations contemplated in the use of this invention.

Toothpastes, gels and liquid formulations may be prepared with conventional ingredients, keeping in mind that certain abrasives may not be compatible with certain water soluble phosphates. These potential limitations are detailed below. Aside from this one limitation, one can use pretty much any combination of dentally acceptable abrasive, humectant, detergent, sweetening agent, flavor, antimicrobial agent, coloring agent and pigment and the like. A preferred toothpaste or gel will contain about 5% of the pyrophosphate salt or tripolyphosphate salt, about 10 to 80% of a humectant, about 0.25 to 5% of a detergent, up to 2% sweetening and flavoring agents (in combination), coloring agents, binders and thickening agents, and water in amounts sufficient to make a stable, flowable paste or gel.

The abrasive polishing material contemplated for use in the present invention can be any material

which does not excessively abrade dentin. These include, for example, silicas including gels and precipitates, calcium pyrophosphate, calcium polymetaphosphate, insoluble sodium polymetaphosphate, hydrated alumina, and resinous abrasive materials such as particulate condensation products of urea and formaldehyde, and others such as disclosed by in U.S. Pat. No. 3,070,510 incorporated herein by reference. Mixtures of abrasives may also be used. Certain abrasives may not be compatible with the metioned phosphates. For example calcium carbonate, dicalcium orthophosphate dihydrate, and tricalcium phosphate are best avoided if the maximum effect of the water soluble phosphates are to be realized.

Silica dental abrasives, of various types, can provide the unique benefits of exceptional dental cleaning and polishing performance without unduly abrading tooth enamel or dentin. Silica abrasive materials are also exceptionally compatible with many ionic materials including the phosphates which are the subject of this invention. For these reasons they are preferred for use herein.

The silica abrasive polishing materials useful herein, as well as the other abrasives, generally have an average particle size ranging between about 0.1 and 30 microns, preferably 5 and 15 microns. The silica abrasive can be precipitated silica or silica gels such as the silica, xerogels described in U.S. Pat. No. 3,538,230 and U.S. Pat. No. 3,862,207, both incorporated herein by reference. Preferred are the silica xerogels marketed under the trade name "Syloid" by the W.R. Grace & BR Company, Davison Chemical Division. Preferred precipitated silica materials include those marketed by the J.M. Huber Corporation under the trade name, "Zeodent." These silica abrasives are described in U.S.Pat. No. 4,340,583, incorporated herein by reference.

The abrasive in the dentifrice compositions described herein is present at a level of from about 6% to about 70%, preferably from about 15% to about 25% when the dentifrice is a toothpaste. Higher levels, as high as 90%, may be used if the composition is a tooth powder...

Water is also present in the toothpaste compositions of this invention. Water employed in the preparation of commercially suitable compositions should preferably be deionized and free of organic impurities. Water generally comprises from about 10% to 70%, preferably from about 20% to 40%, by weight of a toothpaste. These amounts of water include the free water which is added plus that which is introduced with other materials such as when sorbitol or other polyhydric alcohols which are manufactured as dilutions where water is the diluent...

It is also desirable to include a humectant in a toothpaste to keep it from hardening. Suitable humectants include glycerin, sorbitol, and other edible polyhydric alcohols such as PEGs, at a level of from about 10% to about 70%.

Antibacterial agents may be added to these pastes and gels (and mouthwashes). Any one of a number of antibacterial drugs or agents may be used. Triclosan, 5-chloro-2-(2,4-dichlorpphenoxy)phenol, is one example. A group of useful antibacterials is the cationic antibacterial agent. Suitable cationic antibacterial agents for use in dentifrices include:

(i) quaternary ammonium compounds, for instance those in which one or two of the subsistent on the quaternary nitrogen has between 8 and 20, preferably 10 and 18 carbon atoms and is preferably an alkyl group, which may optionally be interrupted by an amine, ester, oxygen, sulphur, or heterocyclic ring The remaining nitrogen substituents will have a lower number of carbon atoms, for instance between 1 and 7, and are preferably alkyl, for instance methyl or ethyl, or benzyl. The anion will be an orally acceptable salt forming group.

Examples of such compounds include benzalkonium chloride, dodceyl trimethyl ammonium chloride, benzyl dimethyl stearyl ammonium chloride, cetyl trimethyl ammonium bromide, benzethonium chloride Cdiisobutyl phenoxyethoxyethyl dimethylbenzyl ammonium chloride), and methyl benzethonium chloride;
ii) pyridinium and isoquinolinium compounds, exemplified by hexadecylpyridinium chloride, cetyl

pyridinium chloride, and alkyl isoquinolinium bromide;
(iii) pyrimidine derivatives such as hexetidine (5-amino-1,3 Bi(2-ethylhexylS5-methylhexahydropyrimidine);
(iv) aniline derivatives such as hexamidine isothionate (4,4'diamonding-a,w-diphenoxyhexane isothionate); ;
(v) bispyridine derivatives such as octenidine(N,N'[1,10- decanediyldi-1(4H)-pyridinyl-4-ylidine]bs(l-o ctanamine dihydrochloride); and
(vi) biguanides including:
(a) mono-biguanides such as p-chlorobenzyl biguanide and N' (4-chlorobenzyl)-N"-(2,4-dichlorobenzyl)biguanide.

(b) bis-biguanides of the general formula (I):
EMI7.1
wherein:
A1 and A2 are independently a phenyl group optionally substituted by (C1,4)alkyl, (C1-4)alkoxy, nitro, halogen, C1 l2)alkyl group, or (C4 12)alicylclic;
X1 and X2 are independently (C1 3)alkylene;
R and R1 are independently hydrogen, (C112)alkyl, or aryl(C 6)alkyl;
Z1 and Z2 are independently 0 or 1;
Q is CH2, oxygen, sulfur, or aryl;
n in teach (CH2)n group is independently an integer from 1 to 12 but the total of both n groups may not exceed 12;
aryl is phenyl, naphthyl or another aromatic ring; and orally acceptable acid addition salts thereof. Preferred compounds are chlorhexidine and alexidine.

(c) poly(biguanides) such as polyhexamethylene biguanide hydrochloride.

An effective amount of a antibacterial agent is in the range of about 0.005 to 10% weight/weight (w/w), preferably 0.005 to 5%, more preferably 0.005 to 2.5% and most preferably 1.0% w/w...

Generally, on a weight basis, the mouthwashes of the invention comprise 0.5% to 5% of the phosphate, 5% to 30% (preferably 5% to 20%) ethyl alcohol, 0% to 25% (preferably 3% to 20%) of a humectant, 0% to 25% (preferably 0.01% to 2.0%) surfactant, 0% to 5% (preferably 0.005% to 0.3%) sweetening agent, 0% to 0.3% (preferably 0.03% to 0.3%) flavoring agent, about 0.1% of a preservative, pH adjusting agent as needed, and the balance water.

The pH of a mouthwash and/or its pH in the mouth can be any pH which is safe for the mouth's hard and soft tissues. Generally the pH will be adjusted to about 3 to about 10, preferably from about 4 to about 8...

Example 1
Toothpaste Formulation
A toothpaste can be prepared using the following ingredients and two different phosphates.

Table 1 - Tube Formulations

Ingredient	% W/W (triDolvDhos)	% W/W (ovrophos)
PEG-8, FCC (PEG 400)	3.00	3.00
Xanthan Gum	0.700	0.6000
Sorbitol USP (70%)	29.9322	28.4761
Hydrated silicia (Zeofree 153)	8.000	7.000
Hydrated silicia (Zeofree 113)	14.000	14.000
Sodium tripolyphosphate	5.000	
Sodium pyrophosphate	1.810	
Ptassium pyrophosphate	4.000	
Sodium Hydroxide (50% solution)	0.900	
Glycerin	10.000	10.000

Flavor 0.800 0.800
Sodium lauryl sulfate 1.150 1.150
Sodium saccharin 0.214 0.214
D & Red * 30 Aluminum lake 0.025 0.025
FD & Blue #1 (0.2%) 0.2478 0.2478
D & Yellow *10 (0.2%) 0.2015 0.2015
Titanium dioxide 0.7235 0.7235
Sodium benzoate 0.100 0.100
Deionized water qs 100.00% qs 100.00%
In these two formulations, PEG-8 is a polyethylene glycol. It, along with the sorbitol and glycerin, is a humectant. Xanthan gum and the Zeofree 153 are binders and thickening agents. Three dyes are recited in this formulation as it is to be presented as a tri-colored product much like that sold under the Aquafresh brand name of SmithKline
Beehcam Consumer Brands.

Because of the presence of pyrophosphates and tripolyphosphates, clear gel-like formulations cannot be prepared. But one can prepare gellike toothpastes, albeit opaque gels, by eliminating the three dyes from the foregoing formulations.

Pump dispensers have gained favor with many toothpaste users.

The following formulation can be used with a pump dispenser system.

Table 2 - Pump Dispenser Formulation
Ingredient % WIW (trinolvnbos) % WIW (pyronbos)
PEG-8, FCC (PEG 400) 3.00 3.00 XanthanGum 0.700 0.6000
Sorbitol USP (70%) 29.609 28.253
Hydrated silicia (Zeofree 153) 8.000 7.000
Hydrated silica (Zeofree 113) 14.000 14.000
Sodium tripolyphosphate 5.000
Sodium pyrophosphate 1.810
Potassium pyrophosphate 4.000
Sodium Hydroxide (50it solution) 0.900
Glycerin 10.000 10.000
Flavor 0.800 0.800
Sodium lauryl sulfate 1.150 1.150
Sodium saccharin 0.214 0.214
D & Red # 30 Aluminum lake 0.025 0.025
FD & Blue #1 (0.2%) 0.2478 0.2478
D & Yellow #10 (0.2%) 0.2015 0.2015
Titanium dioxide 0.9560 0.9560 Sodium benzoate 0.100 0.200
Purified Water qs 100.00% qs 100.00%
Example 2
Mouthwash Formulations
An anti-caries mouthwash employing the pyrophosphates of this invention is illustrated by the following formulation.

Table 3 - Pvrophosphate-containing Mouthwash
Ingredients % W/W
Ethyl Alcohol, 190 proof 8.00
Glycerin, 99% U.S.P. 8.000
Sodium pyrophosphate 2.060
Potassium pyrophosphate 0.710
Flavor 0.200
Menthol 0.007
Cremophor RH-60 0.200

Pluronic F-108 (surfactant) 0.100
Pluronic F-127 (surfactant) 0.100
Benzoic acid 0.100
Sodium saccharin 0.060
FD & #1 (0.2% solution) 0.140
FD & yellow #5 (0.2% solution) 0.900
Phosphoric acid 25% solution
to adjust pH As needed
Deionized water qs 100.00%
These ingredients, expect the phosphoric acid and a small amount of the water are mixed together, the pH is adjusted to the desired figure, then the solution is brought to volume with water. This mouthwash may be packaged in any conventional bottle or container.

A similar mouthwash, but using a tripolyphosphate, is prepared as per the following formulation.

Table 4
Tripolvphosphate-containing Mouthwash Ingredients % W/W %W/W
Ethyl Alcohol, 190 proof 8.00
Glycerin, 99% U.S.P. 8.000
Sodium tripolyphosphate 0.50
Flavor 0.200
Menthol 0.007
Cremophor RH-60 0.200
Pluronic F-108 (surfactant) 0.100
Pluronic F-127 (surfactant) 0.100
Benzoic acid 0.100
Sodium saccharin 0.060
FD & #1 (0.2% solution) 0.140
FD & yellow #5 (0.2% solution)0.900
Phosphoric acid 25% solution
to adjust pH As needed
Deionized water qs 100.00%
Example 3
Method for Testing the Efficacv of Phosphates
The efficacy of these phosphates was determined using the following protocol:
Dentifrices (toothpastes) were prepared in plain color-coded tubes.

All had the same base to which was added a tripolyphosphate, pyrophosphate, or one of these phosphates with NaF. The control was the dentifrice base. The following table gives the concentrations of actives in each formulation.

Product Description
(Fluoride as NaF. 1100 ppm F-- where shown)
Sodium tripolyphosphate (5%) without F
Sodium/potassium pyrophosphate (1.8/4.0%) without F
Toothpaste base
Sodium tripolyphosphate with F
Sodium/potassium pyrophosphate with F
The identity of the products was withheld from the technician until all experiments were completely assessed and data assembled. All experiments were conducted with color-coded tubes and all experimental racks and tubes similarly coded to keep the operatives blind. The only partial breaking of the code was when it became necessary to instruct the operative which was the correct radiotracer to add in the "hot" experiments.

The pH cycling (demineralization/remineralization) model for the in vitro study of fluoride-containing products and fluoride products containing anticalculus agents was that of Featherstone et

al, Caries
Res. 1988; 22:337-341. This model has previously been shown to simulate results found by us in vivo around orthodontic brackets (O'Reilly and Featherstone, Am. J. Orthod. 1987; 92:33-40). Each test cell consisted of ten human tooth crowns which were removed from the roots, cleaned and painted with acid resistant varnish to leave test windows as described in detail previously (Featherstone et al, Caries Res.

1988; 22:337-341).

The study was divided into "cold" legs and "hot" legs. The "cold" legs, with no radiotracer added, were used in order to determine whether the test anticalculus agents (pyrophosphate and tripolyphosphate) individually had a detrimental outcome on the net effect of demineralization/remineralization. In this case two windows, designated "upper" (towards occlusal) and "lower" (towards cervical) were placed on the enamel surface of each tooth crown. In the "hot" legs where 32p labelled potassium pyrophosphate or sodium tripolyphosphate was added, one window approximately 3 x 7 mm was placed on each test surface.

The test regimen in each 24 hour period was as follows:
1. Demineralization. Teeth were immersed individually for 6 hours daily at 37 OC in 40 mli of a buffer containing 0.075 mol/L acetate, 2.0 mmol/L CaHP04 at pH 4.3.

2. Product immersion. The crowns were removed from solution, thoroughly rinsed with double deionized water (DDW), and immersed individually in 4 mL of a 1:3 slurry of dentifrice (one of the test or placebo products, see below) in DDW, and stirred on an orbital shaker for 5 minutes. The slurries were made fresh daily within 30 minutes of immersion, and where appropriate, radiotracers were added and dispersed by vortexing. After the product immersion, the samples were again thoroughly washed in DDW and transferred to the remineralizing solution.

3. Remineralization. Each tooth was then immersed individually for 17 hours at 37 "C in 20 mL of a mineralizing solution containing 1.5 mmol/L calcium, 0.9 mmol/L phosphate, 150 mmoVL KCI (to maintain ionic strength), 20 mmol/L cacodylate to buffer to pH 7.0. This solution simulates the remineralizing phase (ten Cate and Duijsters, Caries Res.

1982; 16:201-210) of the caries process (by salivary minerals).

Duration of pH cvcling. The above pH cycling was repeated for 3 weeks, consisting of 14 cycling days and two weekend periods in mineralizing solution. The test scheme was designed to model, a total daily demineralization challenge of 6 hours, a once per day fluoride (or non fluoride) treatment, and 17 hours daily of repair (remineralization).

Test Groups. The experiments were carried out in duplicate, one group of each pair using sodium tripolyphosphate and one using pyrophosphate salts The groups were designed to give four "cold" legs (A1, A2, B1, B2, below) which were assessed by cross-sectional microhardness testing (see below) to determine the degree of demineralization, and four identical "hot" legs (C1, C2, D1, D2) using radiolabeled sodium tripolyphosphate or pyrophosphate salts to determine the degree of penetration of the tripolyphosphate or pyrophosphate into the enamel during treatment with and without fluoride present. A fifth "cold" leg (E below) served as the baseline control and used a placebo dentifrice with no fluoride, no tripolyphosphate, and no pyrophosphate ions.

A1. Demineralization/remineralization cycling as above with 5 minutes daily immersion prior to remineralization in a 1:3 slurry of a sodium tripolyphosphate/sodium fluoride dentifrice (4 mL of solution per tooth individually).

A2. In the duplicate experiment a pyrophosphate salt/NaF dentifrice was used.

B1. Demineralization/remineralization cycling with 5 minutes daily immersion prior to

remineralization in a 1:3 slurry of an sodium tripolyphosphate non-fluoride dentifrice (sodium tripolyphosphate present as in A but with no added sodium fluoride) (4 mL of solution per tooth individually).

B2. In the duplicate experiment pyrophosphate salts containing dentifrice without an added fluoride ion was similarly used.

C1. Demineralization/remineralization cycling with 5 minutes daily immersion prior to remineralization in a 1:3 slurry of an sodium tripolyphosphate/sodium fluoride dentifrice (4 mL of solution per tooth individually). In this group the sodium tripolyphosphate slurry was labeled with 32P as sodium tripolyphosphate added as a radiotracer prior to immersion of the teeth.

C2. In the duplicate experiment pyrophosphate salts were used and similarly radiolabeled with 32P as pyrophosphate salts.

D1. Demineralization/remineralization cycling with 5 minutes daily immersion prior to remineralization in a 1:3 slurry of sodium tripolyphosphate (as in C, but with no added sodium fluoride) dentifrice (4 mL of solution per tooth individually) and with 32P labeled sodium tripolyphosphate added as described above.

D2. In the duplicate experiment pyrophosphate salts were used, similarly radiolabeled.

E. Demineralization/remineralization cycling with 5 minutes daily immersion prior to remineralization in a 1:3 slurry of a placebo dentifrice (no added sodium fluoride, no added sodium tripolyphosphate or pyrophosphate salts, 4 mL per tooth individually).

All groups used freshly made treatment slurries daily.

Demineralization and remineralization solutions were replaced weekly.

Assessment Methodology
Chemical analvses: All demineralization and remineralization solutions were analyzed for fluoride ion by specific ion electrode before use. Each individual test tube was analyzed for F- after 7 and 14 days of cycling. Changes in F- solution were calculated by subtracting the starting values.

Phvsical analvses: Groups A1, A2, B1, B2, and E were assessed by cross-sectional microhardness profiles, as described below. The duplicate radiotracer groups (C1, C2, D1, and D2) obviously could not be assessed in this manner. They were assessed by radiotracer counting as described separately below.

At the end of the cycling period, teeth from groups A, B, and E were thoroughly rinsed in DDW, sectioned longitudinally through the center of the lesions produced, and embedded in epoxy resin with the cut face exposed as described in detail previously (ten Cate et al, Caries Res.

1985: 19:335-341). After serially polishing the embedded teeth, each lesion was assessed by cross-sectional microhardness, according to the published methods in the references above. Indents were commenced at 25 pm from the anatomical surface and repeated at 25 pm intervals to a depth of 300 Fun, across the sectioned lesion and into the sound underlying enamel. This method has been shown to give results comparable with microradiography (White and Featherstone, Caries Res.

1987; 21:502-512).

The indentation lengths were converted as per our published formula to volume percent, mineral and mineral loss (AZ) values (jim x vol % mineral) were calculated using Simpson's rule for each profile, for each lesion on each tooth, as described previously (White and Featherstone, Caries Res. 1987; 21:502-512). Mean values of AZ for each group were calculated,

and mineral loss profiles were plotted as vol % mineral vs. depth from the outer surface.

Radiotracer analvses: Teeth from groups C and D were thoroughly washed in DDW and the varnish was removed individually from each tooth by acetone. Eight stepwise abrasions were made for each sample using small preweighed circles of silicon carbide paper (600 grade) to remove layers approximately 5 jim thick Each sample was weighed, dissolved into a scintillation cocktail and the radioactivity counted in a Searle scintillation counter.

Results for sodium tripolyphosphate and pyrophosphate salt products, with and without fluoride present, were compared. The amount of lesion formation was measured by the duplicate "cold" legs (A and B) described above as radiotracer material cannot be used in the other laboratories.

Uptake of tripolyphosphate or pvrophosphate into caries-like lesions.

This assay assessed the amount of uptake of sodium tripolyphosphate or pyrophosphate salts into preformed caries-like lesions in human enamel in vitro:
Test material: Human dental enamel from molars with caries free (by stereo microscope) buccal or lingual surfaces. Teeth were cleaned and prepared as described above for the pH cycling study.

Artificial caries lesion formation: Artificial caries-like lesions were produced in one window (3 x 7 mm) on one enamel surface of molars prepared in our standard manner by immersion for 5 days in a pH 5.0 buffer (0.05 mol/L lactate), 50 percent saturated with hydroxyapatite, and with 0.2% carbopol, as per the method of White (Caries Res. 1987: 21:228-242). This system produced lesions approximately 100 pm deep in 5 days.

Immersion in tripolvuhosphate or pvrophosphate salts: Teeth with preformed caries-like lesions were individually immersed in 20m1 of a 1:3 slurry of sodium tripolyphosphate or pyrophosphate salts dentifrice with 32P labeled sodium tripolyphosphate or pyrophosphate salts added at similar concentration as used in the pH cycling experiments above. Groups of 10 teeth each were used. The first group was immersed for one hour and the second group for 4 hours for each of sodium tripolyphosphate and pyrophosphate salts. At the end of the immersion period the teeth were removed, rinsed in DDW and immediately air dried. They were assessed for radiotracer uptake using the abrasion method as described above.

Table 6
Relative mineral loss, AZ (volume % x pm) as mean values
(SD = standard deviation) for each group for upper and lower
windows. Values are arranged in ascending order of AZ
values for the upper window.

Test Group	Product Description	Mean AZ (vol % x pm) Upper Window	Lower Window
A2	PPir Toothpaste, with NaF3	292 (346)	318 (368)
A1	STPP2 toothpaste, with NaF	597 (425)	273 (638)
B1	STPP without NaF	1300 (814)	1996 (834)
B2	PPi without NaF	1399 (652)	2671 (1643)
E	Placebo, no NaF, no STPP,no PPi	3809 (584)	5069 (1092)

1 PPi means potassium pyrophosphate/sodium pyrophosphate (4.0%l1.81to)
2 STPP means sodium tripolyphosphate (5%).

3 NaF at a concentration sufficient to give 1100 ppm F-.

Both sodium tripolyphosphate and potassium/sodium pyrophosphate mix demonstrated significant reduction in caries as compared with the placebo, and approaching that demonstrated by the combination of these phosphates and NaF.

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CHEWING GUM WITH DENTAL HEALTH BENEFITS EMPLOYING CALCIUM LACTATE
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SPECIFICATION
TITLE
"CHEWING GUM WITH DENTAL HEALTH BENEFITS
EMPLOYING CALCIUM LACTATE"
BACKGROUND OF THE INVENTION
The present invention relates generally to chewing gums. More specifically, the present invention relates to chewing gums that can provide dental benefits.

Except for the common cold, dental caries (tooth decay) is the most prevalent human disorder. See, The Merck Manual, Sixteenth Edition, p. 2480. Even though, many steps have been taken to reduce dental caries and tooth decay, such as fluoridation and improved dental care, tooth decay continues to be a significant problem. This is especially true in the adult population; 80% of the tooth decay occurs in 20% of the population. See Featherstone, An Updated Understanding of the Mechanism of Dental Decay and its Prevention, Nutrition Quarterly, Vol. 14, No. 1,1990, pp. 5-11.

To protect a normal tooth, a thin layer of dental enamel forms a protective coating over the tooth. This coating consists mainly of calcium, phosphate, and other ions in a hydroxyapatite-like structure. The enamel contains 2 to 5 percent carbonate; this carbonate content makes the enamel susceptible to acid dissolution. See, Featherstone, id. at 6.

The interaction of three factors is believed to result in dental caries: a susceptible tooth surface; the proper microflora; and a suitable substrate for the microflora. Although several acidogenic micro-organisms that are present in the mouth can initiate carious lesions, Streptococcus mutans is believed to be the primary pathogen. See, The Merck
Manual, supra.

It is known that foods containing fermentable carbohydrates can promote dental caries. Tooth decay begins when the Streptococcus mutans, that reside principally in the plaque that adheres to a tooth surface, metabolize the fermentable carbohydrates consumed by the host. During the metabolism of the fermentable carbohydrates by the bacteria, lactic acid and other organic acids are secreted as a by-product. These acids reduce the pH of the surrounding plaque/tooth environment.

When the pH of the plaque/tooth environment drops below a critical level of 5.5 to 5.7, hydroxyapatite (calcium phosphate hydroxide, Cal0 (PO4) 6 (OH) 2), the key component of tooth enamel, begins to dissolve. This critical pH can change depending on the concentration of the key ions. Typically, the dissolution begins below the tooth's porous surface.

With repeated acid attacks, caused by the further metabolism of fermentable carbohydrates by the bacteria, subsurface lesions expand. The body's natural remineralization mechanism, however, at this point, can still reverse the decay process.

But, if the lesions expand to the point that the enamel surface breaks, a cavity is formed and the process is no longer reversible.

The natural remineralization process involves, in part, the flow of saliva over the plaque. The saliva can raise the pH of the environment. Additionally, calcium and phosphate ions in the saliva precipitate out to replace the hydroxyapatite that was dissolved by the organic acids created during the metabolism of the fermentable carbohydrates.

However, typically, this remineralization process only occurs at significant levels when the pH is above the critical level. Therefore, if the saliva does not sufficiently raise the pH, significant remineralization will not occur. But, the remineralization process may be enhanced by fluoride in the oral cavity that speeds up new crystal growth and makes a flurorapatite-like material that is precipitated on the surface of the crystals inside the caries lesion. See, Featherstone, id. at 7.

A number of salts have been reported in certain experiments to counteract demineralization. One of the difficulties is providing a viable vehicle for delivering the salts. Still further, a number of safety issues are raised by some of the salts.

Furthermore, sensory problems with respect to some of the salts prevent these salts from being taken on a regular basis by a patient to provide prophylactic benefits.

U. S. Patent No. 5,378,171 discloses a sugar chewing gum with dental health benefits that includes calcium glycerophosphate.

SUMMARY OF THE INVENTION

The present invention provides a composition and method for the remineralization of enamel. Pursuant to the present invention, sugar free chewing gum is provided that includes a therapeutically effective amount of calcium lactate.

It has been found that calcium lactate counteracts the decaying process. Calcium lactate is believed to function by promoting remineralization of the tooth enamel caused by dental caries. Calcium lactate has been found to be an effective enamel remineralization agent that is acceptable from sensory and safety standpoints.

Pursuant to the present invention, calcium lactate can be used in chewing gum.

Chewing gum is an especially good vehicle for delivering calcium lactate because it can deliver the ingredient over prolonged periods of time. Additionally, chewing gum can be conveniently used almost anywhere, at anytime, as opposed to a rinse or dentifrices.

To this end, a method for remineralizing enamel is provided comprising the step of providing a chewing gum that includes a therapeutically effective amount of calcium lactate.

In an embodiment, two pieces of chewing gum are chewed at a time.

In an embodiment of the method, the gum is chewed at least twice a day.

In an embodiment of the method, the chewing gum produces a calcium ion concentration in the saliva of the mouth of the chewer of at least 200 ppm.

In an embodiment of the method, the gum is chewed for at least two minutes.

The present invention also provides a chewing gum for reducing the generation of dental caries comprising a water insoluble base, water soluble portion and flavor, and calcium lactate.

In an embodiment, the chewing gum is sugarless.

In an embodiment, the chewing gum is wax-free.

In an embodiment, the chewing gum is a low calorie chewing gum.

In an embodiment, the chewing gum contains other therapeutic agents.

In an embodiment, the chewing gum includes at least 40 mg of calcium lactate.

In an embodiment, the chewing gum is in the form of a stick.

In an embodiment, the chewing gum is in the form of a pellet.

In an embodiment, the chewing gum includes an additional therapeutic agent.

An advantage of the present invention is to provide a method for preventing, or reducing the risk of, dental caries of the remineralization of enamel.

Another advantage of the present invention is to treat dental caries.

Additionally, an advantage of the present invention is to provide a chewing gum that can be used to improve dental health.

Further, an advantage of the present invention is to provide a chewing gum that does not have the sensory drawbacks of other sources of calcium.

Moreover, an advantage of the present invention is to provide an easy and enjoyable way to improve dental health.

Still further, an advantage of the present invention is to provide a composition and method for delivering a therapeutic agent over a prolonged period of time to the oral region.

Additional features and advantages of the present invention are described in, and will be apparent from, the detailed description of the presently preferred embodiments.

DETAII, ED DESCRIPTION OF THE PRESENTLY PREFERRED EMBODIMENTS

The present invention provides a method and composition for remineralizing tooth enamel and thereby preventing and/or treating dental caries. Pursuant to the present invention, a chewing gum is provided that includes a therapeutically effective amount of calcium lactate. The chewing gum of the present invention, by including a therapeutically effective amount of calcium lactate, can improve dental health when chewed.

Calcium lactate is believed to function by the remineralization of tooth enamel.

Calcium lactate when provided in a chewing gum can produce a calcium ion concentration in the saliva during chewing which is effective to remineralized carious lesions in teeth. For example, it has been found that 80 mg of calcium lactate in chewing gum will produce saliva calcium levels greater than 500 parts per million, this level has been shown to remineralize teeth.

It is believed that the calcium ion concentration in the saliva should be above 200 ppm in order to initiate the remineralization process. Preferably the calcium ion concentration should be above 350 ppm and most preferably above 500 ppm. These levels should be provided for at least one minute, preferably more than two minutes, and most preferably more than four minutes upon chewing the gum.

It has been found that these levels can be accomplished by the inclusion of at least 40 mg, preferably at least 60 mg and most preferably at least 80 mg of calcium lactate in a piece of chewing gum. In some cases, it may be desirable to divide the prescribed dosage among two or

more smaller pieces of gum which are intended to be chewed together.

In another embodiment of the invention, a method for the remineralization of carious lesions in teeth is provided that comprises providing a sugarless chewing gum comprising calcium lactate. The gum is chewed for at least two minutes (preferably at least 5 minutes and most preferably at least 20 minutes) whereby the calcium is released by the gum in a quantity sufficient to produce a calcium concentration which is effective to remineralized the carious lesions. This treatment is repeated at least twice, preferably at least three times, and most preferably at least five times daily until the lesion has been remineralized.

The chewing gum composition may be any chewing gum formula and most preferably a sugarless formulation. Such formulas typically contain a major amount of a sugar alcohol bulking agent, a substantial portion of gum base, minor amounts of syrups, softeners, flavors, color and high intensity sweeteners. Low calorie gums which contain reduced levels of sugar alcohols and increased levels of base and/or low calorie or calorie-free bulking agents are also anticipated. The product may be formed into tabs, sticks, chunks or coated pellets. A piece size of 1 to 4 grams is preferred. As previously mentioned, with smaller pieces sizes, it may be desirable to split the calcium lactate dosage between two or more pieces to reduce the concentration for improved sensory acceptability.

Chewing gum generally consists of a water insoluble gum base, a water soluble portion, and flavors. The water soluble portion dissipates with a portion of the flavor over a period of time during chewing. The gum base portion is retained in the mouth throughout the chew.

The insoluble gum base generally comprises elastomers, resins, fats and oils, softeners, and inorganic fillers. The gum base may or may not include wax. The insoluble gum base can constitute approximately 5 to about 95 percent, by weight, of the chewing gum, more commonly, the gum base comprises 10 to about 50 percent of the gum, and in some preferred embodiments, 20 to about 35 percent, by weight, of the chewing gum.

In an embodiment, the chewing gum base of the present invention contains about 20 to about 60 weight percent synthetic elastomer, 0 to about 30 weight percent natural elastomer, about 5 to about 55 weight percent elastomer plasticizer, about 4 to about 35 weight percent filler, about 5 to about 35 weight percent softener, and optional minor amounts (about one percent or less) of miscellaneous ingredients such as colorants, antioxidants, etc.

Synthetic elastomers may include, but are not limited to, polyisobutylene with GPC weight average molecular weight of about 10,000 to about 95,000, isobutyleneisoprene copolymer (butyl elastomer), styrene-butadiene copolymers having styrenebutadiene ratios of about 1: 3 to about 3: 1, polyvinyl acetate having GPC weight average molecular weight of about 2,000 to about 90,000, polyisoprene, polyethylene, vinyl acetate-vinyl laurate copolymer having vinyl laurate content of about 5 to about 50 percent by weight of the copolymer, and combinations thereof.

Preferred ranges are, for polyisobutylene, 50,000 to 80,000 GPC weight average molecular weight, for styrene-butadiene, 1: 1 to 1: 3 bound styrene-butadiene, for polyvinyl acetate, 10,000 to 65,000 GPC weight average molecular weight with the higher molecular weight polyvinyl acetates typically used in bubble gum base, and for vinyl acetate-vinyl laurate, vinyl laurate content of 10-45 percent.

Natural elastomers may include natural rubber such as smoked or liquid latex and guayule as well as natural gums such as jelutong, lechi caspi, perillo, sorva, massaranduba balata, massaranduba chocolate, nispero, rosindinha, chicle, gutta hang kang, and combinations thereof. The preferred synthetic elastomer and natural elastomer concentrations vary depending on whether the chewing gum in which the base is used is abhesive or conventional, bubble gum or regular gum, as discussed below. Preferred natural elastomers include jelutong, chicle, sorva and massaranduba

balata.

Elastomer plasticizers may include, but are not limited to, natural rosin esters such as glycerol esters of partially hydrogenated rosin, glycerol esters polymerized rosin, glycerol esters of partially dimerized rosin, glycerol esters of rosin, pentaerythritol esters of partially hydrogenated rosin, methyl and partially hydrogenated methyl esters of rosin, pentaerythritol esters of rosin; synthetics such as terpene resins derived from alphapinene, beta-pinene, and/or d-limonene; and any suitable combinations of the foregoing. the preferred elastomer plasticizers will also vary depending on the specific application, and on the type of elastomer which is used.

Fillers/texturizers may include magnesium and calcium carbonate, ground limestone, silicate types such as magnesium and aluminum silicate, clay, alumina, talc, titanium oxide, mono-, di-and tri-calcium phosphate, cellulose polymers, such as wood, and combinations thereof.

Softeners/emulsifiers may include tallow, hydrogenated tallow, hydrogenated and partially hydrogenated vegetable oils, cocoa butter, glycerol monostearate, glycerol triacetate, lecithin, mono-, di-and triglycerides, acetylated monoglycerides, fatty acids (e. g. stearic, palmitic, oleic and linoleic acids), and combinations thereof.

Colorants and whiteners may include FD & C-type dyes and lakes, fruit and vegetable extracts, titanium dioxide, and combinations thereof.

The base may or may not include wax. An example of a wax-free gum base is disclosed in U. S. Patent No. 5,286,500, the disclosure of which is incorporated herein by reference.

In addition to a water insoluble gum base portion, a typical chewing gum composition includes a water soluble bulk portion and one or more flavoring agents. The water soluble portion can include bulk sweeteners, high intensity sweeteners, flavoring agents, softeners, emulsifiers, colors, acidulants, fillers, antioxidants, and other components that provide desired attributes.

Softeners are added to the chewing gum in order to optimize the chewability and mouth feel of the gum. The softeners, which are also known as plasticizers and plasticizing agents, generally constitute between approximately 0.5 to about 15% by weight of the chewing gum. The softeners may include glycerin, lecithin, and combinations thereof. Aqueous sweetener solutions such as those containing sorbitol, hydrogenated starch hydrolysates, corn syrup and combinations thereof, may also be used as softeners and binding agents in chewing gum.

Bulk sweeteners include both sugar and sugarless components. Bulk sweeteners typically constitute 5 to about 95% by weight of the chewing gum, more typically, 20 to 80% by weight, and more commonly, 30 to 60% by weight of the gum.

Sugar sweeteners generally include saccharide-containing components commonly known in the chewing gum art, including, but not limited to, sucrose, dextrose, maltose, dextrin, dried invert sugar, fructose, levulose, galactose, corn syrup solids, and the like, alone or in combination.

Sugarless sweeteners include, but are not limited to, sugar alcohols such as sorbitol, mannitol, xylitol, hydrogenated starch hydrolysates, maltitol, and the like, alone or in combination.

High intensity artificial sweeteners can also be used, alone or in combination with the above. Preferred sweeteners include, but are not limited to sucralose, aspartame, salts of acesulfame, alitame, saccharin and its salts, cyclamic acid and its salts, glycyrrhizin, dihydrochalcones, thaumatin, monellin, and the like, alone or in combination. In order to provide longer lasting sweetness and flavor perception, it may be desirable to encapsulate or otherwise control the release of at least a portion of the artificial sweetener. Such techniques as wet granulation, wax granulation, spray drying, spray chilling, fluid bed coating, coacervation, and fiber extension may be used to achieve the desired release characteristics.

Usage level of the artificial sweetener will vary greatly and will depend on such factors as potency of the sweetener, rate of release, desired sweetness of the product, level and type of flavor used and cost considerations. Thus, the active level of artificial sweetener may vary from 0.02 to about 8%. When carriers used for encapsulation are included, the usage level of the encapsulated sweetener will be proportionately higher.

Combinations of sugar and/or sugarless sweeteners may be used in chewing gum.

Additionally, the softener may also provide additional sweetness such as with aqueous sugar or alditol solutions.

If a low calorie gum is desired, a low caloric bulking agent can be used. Example of low caloric bulking agents include: polydextrose; Raftilose, Raftilin;
Fructooligosaccharides (NutraFlora); Palatinose oligosaccharide; Guar Gum Hydrolysate (Sun Fiber); or indigestible dextrin (Fibersol). However, other low calorie bulking agents can be used.

A variety of flavoring agents can be used. The flavor can be used in amounts of approximately 0.1 to about 15 weight percent of the gum, and preferably, 0.2 to 5%.

Flavoring agents may include essential oils, synthetic flavors or mixtures thereof including, but not limited to, oils derived from plants and fruits such as citrus oils, fruit essences, peppermint oil, spearmint oil, other mint oils, clove oil, oil of wintergreen, anise and the like. Artificial flavoring agents and components may also be used. Natural and artificial flavoring agents may be combined in any sensorially acceptable fashion.

Additional oral health ingredients may be added including but not limited to, antiplaque/anti-gingivitis agents (such as chlorhexidine, CPC, triclosan), pH control agents (including Urea and buffers,) other inorganic components for tarter or caries control (phosphates, fluoride) and biological agents (antibodies, enzymes). The only requirement is that the agents be safe and effective and that they do not react undesirably with each other such as may happen with phosphate salts.

Preferably the calcium lactate is mixed into the chewing gum mass but it may also be added to a coating syrup or used as a dry charge in a coating process in the case of a coated chewing gum.

The following examples, which as of this time have not been made, illustrate some embodiments of the invention. Of course, many others are possible.

EXAMPLES 2 3 4
Gum Base 30.0% 32.60% 30.0% 70.0%
Sorbitol 40.0-25.4 10.4
Maltitol-30.00
Xylitol 0.5 15.00 30.0
Mannitol 7.0 5.00 2.0 2.0
Calcium Lactate 3.0 4.00 4.0 6.0
Aspartame 0.5-0.2 Acesulfame K-0.15 0.1
Sucralose-0.15-0.2
Alitame--0.1 Neotame---0.1
Sorbitol Solution 15.0-5.0 (70% solids)
HydrogenatedStarch-9.00-5.0
Hydrolysate Syrup (85% solids)
Glycerin 3.0 3.00 2.0 5.0
Color-0.10 0.2 0.3
Flavor 1.0 1. 00 1.0 1.0
(Spearmint) (Cinnamon) (Peppermint) (Wintergreen)
Total 100% 100% 100% 100%

Form 3g stick 3g stick 2g tab lg tab
EXAMPLES
7 8 9 10
Gum Base 25.0% 35.00% 35.0% 30.0%
Sorbitol 31.9-35.0 39.50%
Polydextrose-40.88
Xylitol 15.0-5.0 5.00
Mannitol 5.0 5.00 5.0 4.00
Calcium Lactate 3.0 2.00 4.0 4.00
Aspartame 0.5 0.50 0.3 0.50
Chlorhexidine-0.17
Triclosan-0.25
Urea 3.5--0.50
S. Mutans Monclonal---0.50
Antibodies
Glycerin 5.0 5.00 5.0 15.00
Hydrogenated Starch 10.0 10.00 9.9
Hydrolysate Syrup (85% solids)
Color 0.1 0.20 0.1 0.15
Flavor 1.0 1. 00 0.7 0.85
(Sweet Fruit) (Peppermint) (Menthol) (Spearmint)
Total 100.0% 100.00% 100.0% 100.00%
Form 3g stick 3g stick lg pellet 3g stick
center
Notes on Examples:
Examples 4 and 8 are low caloric chewing gums.
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Oral and dental care product
Description of US2007154411

[0030] Protein hydrolysates mean for the purposes of the present invention degradation products of proteins such as, for example, collagen, elastin, casein, keratin, almond, potato, wheat, rice and soybean protein which are obtained by acidic, alkaline and/or enzymatic hydrolysis of the proteins themselves or their degradation products such as, for example, gelatin. Suitable for the enzymatic degradation are all enzymes having hydrolytic activity, such as, for example, alkaline proteases. Further suitable enzymes and enzymatic hydrolysis methods are described for example in K. Drauz and H. Waldmann, Enzyme Catalysis in Organic Synthesis, VCH-Verlag, Weinheim 1975. In the degradation, the proteins are split into smaller subunits, and the degradation may proceed via the stages of polypeptides to oligopeptides and on to the individual amino acids. Protein hydrolysates with little degradation include for example the gelatin which is preferred for the purposes of the present invention and which may have molecular masses in the range from 15 000 to 250 000 D. Gelatin is a polypeptide which is obtained principally by hydrolysis of collagen under acidic (type A gelatin) or alkaline (type B gelatin) conditions. The gel strength of the gelatin is proportional to its molecular weight, i.e. gelatin which has been hydrolyzed to a greater extent yields a solution of lower viscosity. The gel strength of gelatin is indicated in Bloom numbers. The polymer size is greatly reduced in the enzymatic cleavage of gelatin, leading to very low Bloom numbers.
[0036] For the preparation of the composite material, reference is expressly made to the disclosure in WO 01/01930 A1.
lower when the chosen calcination temperature is higher and the chosen duration of calcination is longer. Slightly calcined aluminas differ from pure [gamma]-Al2O3 by the agglomerates being less hard, the specific area being larger and the pore volumes being larger.

[0055] Examples of water-insoluble metaphosphates of the invention are in particular sodium metaphosphate, calcium phosphate such as, for example, tricalcium phosphate, calcium hydrogen phosphate, calcium hydrogen phosphate dihydrate and calcium pyrophosphate.

[0056] A further possibility according to the invention is to employ magnesium carbonate, magnesium hydrogen phosphate, trimagnesium phosphate or sodium hydrogen carbonate as polishing agents, especially mixed with other polishing agents.

[0057] A further polishing agent which is suitable for use in the oral and dental hygiene products of the invention is calcium phosphate dihydrate ($CaHPO_4*2H_2O$). Calcium phosphate dihydrate occurs naturally as brushite and is obtainable commercially in suitable particle sizes of from 1 to 50 [mu]m as polishing agent.

[0062] The remineralization-promoting component in the products of the invention promotes the remineralization of the enamel and the sealing of dental lesions and is selected from fluorides, microparticulate phosphate salts of calcium such as, for example, calcium glycerol phosphate, calcium hydrogen phosphate, hydroxyapatite, fluoroapatite, F-doped hydroxyapatite, dicalcium phosphate dihydrate and calcium fluoride. However, magnesium salts such as, for example, magnesium sulfate, magnesium fluoride or magnesium monofluorophosphate also have remineralizing effects.

[0063] In a preferred embodiment of the invention, a magnesium salt is employed as remineralization-promoting agent.

Tartar Inhibitors

[0105] Tartar comprises mineral deposits which are very similar to natural enamel. In order to inhibit tartar formation, substances which intervene specifically in crystal nucleation and prevent nuclei which are already present from growing further are added to the dental cleaning compositions of the invention. Examples thereof are condensed phosphates which are preferably chosen from the group of tripolyphosphates, of pyrophosphates, of trimetaphosphates or mixtures thereof. They are employed in the form of their alkali metal or ammonium salts, preferably in the form of their sodium or potassium salts. Aqueous solutions of these phosphates typically have an alkaline reaction, so that the pH of the dental hygiene products of the invention is adjusted where appropriate to values of 7.5-9 by adding acid. Examples of acids which can be used in this connection are citric acid, phosphoric acid or acidic salts, e.g. NaH_2PO_4. The desired pH of the dental hygiene product can, however, also be adjusted by adding acidic salts of the condensed phosphates, e.g. $K_2H_2P_2O_7$.

[0106] It is also possible to employ according to the invention mixtures of various condensed phosphates and/or hydrated salts of the condensed phosphates. Tartar inhibitors are normally employed in amounts of 0.1-5% by weight, preferably 0.1-3% by weight and in particular 0.1-2% by weight in the products of the invention.

[0107] Further suitable tartar inhibitors are organophosphonates such as 1-azacycloheptane-2,2-diphosphonate (Na salt), 1-hydroxyethane-1,1-diphosphonate (Na salt) and zinc citrate.

Active Substances to Counter Hypersensitive Teeth

[0108] The products of the invention preferably further comprise active substances to counter hypersensitive teeth, they are selected from potassium and strontium salts such as potassium chloride, potassium sulfate, potassium bicarbonate, potassium citrate, potassium acetate, potassium nitrate, strontium chloride, strontium nitrate, strontium citrate, strontium acetate and strontium lactate and eugenol.

[0109] The eugenol may be present mixed with aromatic oils in the oral and dental hygiene products. It is preferably present in the compositions in the
form of clove bud oil.

[0110] The oral and dental hygiene products of the invention preferably comprise at least 0.5% by weight of potassium or strontium ions in the form of a dissolved salt and at least 0.01% by weight of eugenol in pure form or in the form of the clove bud oil...

US2006079467
Formulation of dual eicosanoid system and cytokine system inhibitors for use in the prevention and treatment of oral diseases and conditions

FIELD OF THE INVENTION

[0002] This invention relates generally to a novel composition of matter comprised of a mixture of a blend of two specific classes of compounds-Free-B-Ring flavonoids and flavans-which target the eicosanoid and cytokine pathways for use in the prevention and treatment of diseases and conditions of the mouth, teeth and gums.

BACKGROUND OF THE INVENTION

[0003] Periodontal disease is a combination of inflammation and infection of some or all of the tooth support structures (gingiva, cementum, periodontal ligament, alveolar bone and other tissues surrounding the teeth). Gingivitis (gums) and periodontitis (gums and bone) are the two main forms of periodontal disease. According to National Oral Information distributed by the National Institute of Dental and Craniofacial Research, an estimated 80 percent of American adults currently have some form of periodontal disease. Periodontal disease is initiated when a pellicle forms on a clean tooth or teeth. This pellicle attracts aerobic gram-positive bacteria (mostly actinomyces and streptococci), which adhere to the tooth forming plaque. Within days the plaque thickens, the underlying bacteria run out of oxygen and anaerobic motile rods and spirochetes begin to populate the subgingival area. Endotoxins released by the anaerobic bacteria cause inflammation, gum tissue destruction and even bone loss. There are four primary stages of periodontal disease that can be characterized as indicated below. The destructive impact of periodontal disease goes beyond dental hygiene and health, in that microscopic lesions resulting from periodontal disease have been found in the liver, kidneys, and brain of some affected persons.

Four Stages of Periodontal Disease

Grade 1 Inflammation

Grade 2 Inflammation, edema, gingival bleeding upon probing

Grade 3 Inflammation, edema, gingival bleeding upon probing, pustular

discharge - slight to moderate bone loss

Grade 4 Inflammation, edema, gingival bleeding upon probing, pustular

discharge, mobility - severe bone loss

[0004] The inflammation resulting from periodontal disease is mainly related to two biological systems:-the eicosanoid system and the cytokine system. The release and metabolism of arachidonic acid (AA) from the cell membrane results in the generation of pro-inflammatory metabolites by several different pathways. Two of the most important pathways to inflammation are mediated by the enzymes lipoxygenase (LOX) and cyclooxygenase (COX). These are parallel pathways that result in the generation of leukotrienes and prostaglandins, respectively, which play important roles in the initiation and progression of the inflammatory response. These vasoactive compounds are chemotaxins, which both promote infiltration of inflammatory cells into gum tissue and serve to prolong the inflammatory response that may lead to bone loss. Consequently, the

enzymes responsible for generating these mediators of inflammation can be targeted to develop therapeutic agents to prevent and treat diseases and conditions related to the mouth, teeth and gums.

[0005] The cytokine system is a very potent force in homeostasis when activation of the network is local and the cytokines act vicinally in surface-bound or diffusible form. But when cytokine production is sustained and/or systemic, cytokines contribute to the signs, symptoms, and pathology of inflammatory, infectious, autoimmune, and malignant diseases. TNF-[alpha] is a potent pleiotropic cytokine produced by macrophages, neutrophiles, fibroblasts, keratinocytes, NK cells T and B cell and tumor cells. IL-1[beta], together with TNF-[alpha], plays a central role in inflammatory responses. Administration of antagonists, such as IL-1ra (IL-1 receptor antagonist), soluble fragment of IL-1 receptor, or monoclonal antibodies to TNF-[alpha] and soluble TNF receptor, all block various acute and chronic responses in animal models of inflammatory diseases. Nuclear factor kappa B (NF[kappa]B) is a transcription factor that controls gene expression of interleukin-1 beta (IL-1[beta]), tumor necrosis factor-alpha (TNF[alpha]), interleukin-6 (IL-6) and many other proteins. Some of these antagonists are beginning to be utilized as anti-inflammatory agents in diseases such as sepsis, periodontal diseases and rheumatoid arthritis. (Dinarello (2004) Curr Opin Pharmacol. 4:378-385). Anti-TNF-[alpha] antibodies were not only found to induce striking remissions in rheumatoid arthritis, but also to reduce tissue inflammation in Crohn's disease, an inflammatory bowel disease (Maini and Feldmann. (2002) Arthritis Res. 4 Suppl 2: S22-8).

[0006] Periodontal ligament (PDL) cells exhibit osteoblast-like features and are capable of differentiating into cells of either cementogenic or osteogenic lineage. These cells are crucial for the maintenance of the integrity and regeneration of the periodontium (Somerman et al. (1990) Arch Oral Biol. 35: 241-47; Pitaru et al. (1994) J Periodontal Res. 29:81-94). Chronic infections in the periodontium, initiated by bacterial colonization, induce synthesis of pro-inflammatory cytokines, which can potentially affect PDL cell phenotype and function. These cytokines not only activate and recruit immune cells to the site of infection (Le and Vilcek (1987) J. Immunol. 139: 3330; Kunkel et al (1994) Ann. N.Y. Acad. Sci. 730:134), but also induce loss of supporting bone and ligamentous attachment (Pitaru et al. (1994) J Periodontal Res. 29:81-94). TNF[alpha], for example, has been shown to modulate the PDL cell osteoblast-like phenotype and functions (Agarwal et al. (1998) Infect. Immun. 66:932-937). Additionally, TNF[alpha] and IL-1[beta] change the phenotypic characteristics of osteoblasts by down-regulation of alkaline phosphatase (Kuroki et al. (1994) Rheumatology 33:224) and by the modulation of collagen, collagenase, proteoglycan, and prostaglandin syntheses (Agarwal et al. (1998) Infect. Immun. 66:932-937).

[0007] In the isolated PDL cells, IL-1[beta] induces phenotypic changes (Agarwal et al. (1998) Infect. Immun. 66:932-937). PDL cells from healthy periodontium do not recognize bacterial lipopolysaccharide (LPS) nor do they elicit pro-inflammatory cytokines in response to LPS. Following IL-1[beta] treatment, PDL cells lose their osteoblast-like characteristics while assuming a new LPS-responsive phenotype. Thus, IL-1[beta] is an important regulator of PDL cell function and directs these cells to participate actively in an immune response during infections. IL-1[beta] stimulates bone resorption and inhibits bone formation (Stashenko et al. (1987) J Bone Miner Res. 2:559-65; Nguyen et al. (1991) Lymphokine Cytokine Res. 10:15-21; Tatakis (1993) J Periodontol (1991) 64:416-31). In addition, IL-1[beta] synergizes the bone-resorptive actions of TNF-[alpha] (Bertolini et al. (1986) Nature 319:516-18; van der Pluijm et al. (1991) Endocrinology 129:1596). Another important activity of IL-1[beta] in the pathological process of periodontitis is to induce the production of matrix metalloproteinases (MMPs) (Havemose-Poulsen and Holmstrup (1997) Crit. Rev. Oral. Biol. Med 8:217). IL-1[beta] gives rise to an elevated level of procollagenase in both gingival fibroblasts and PDL cells (Meikle et al. (1989) J Periodontal Res. 24:207-13; Lark et al. (1990) Connect Tissue Res. 25:49-65; Tewari et al. (1994) Arch Oral Biol. 39 657-64). In addition, IL-1[beta] stimulates plasminogen activator in gingival fibroblasts, resulting in the generation of plasmin, which is an activator of several matrix metalloproteinases (Mochan et al. (1988) J Periodontal Res. 23:28-32). Furthermore, Stashenko and co-workers reported a positive correlation between IL-1[beta] levels in gingival tissues and recent attachment loss (Stashenko et al. (1991) J Clin Periodontol 18:548-54).

[0008] TNF[alpha] is another key mediator of immune and inflammatory responses and has been found in measurable quantities in the areas of active periodontal inflammation (Rossomando et al. (1990) Arch Oral Biol. 35:431-34; Stashenko et al. (1991) J Clin Periodontol 18:548-54). TNF[alpha] changes the osteoblastic features of PDL cells (Quintero et al. (1995) J. Dent. Res.74:1802). This is substantiated by their ability to express other pro-inflammatory cytokines, such as IL-1[beta], IL-6, and IL-8, in response to LPS. TNF[alpha] induces the secretion of collagenase by fibroblasts, resorption of cartilage and bone, and has been implicated in the destruction of periodontal tissue in periodontitis (Elias et al. (1987) J. Immunol. 138:3812; Meikle et al. (1989) J Periodontal Res. 24:207-13; Chaudhary et al. (1992) Endocrinology 130:2528). In resting macrophages, TNF[alpha] induces the synthesis of IL-1[beta] and prostaglandin E2. TNF-[alpha] also activates osteoclasts and thus induces bone resorption. TNF-[alpha] has synergistic effects with the bone-resorptive actions of IL-1[beta] ((van der Pluijm et al. (1991) Endocrinology 129:1596; Bertolini et al. (1986) Nature 319:516-8; Johnson et al. (1989) Endocrinology 124:1424).

[0009] In inflammatory periodontal lesions, a variety of cell types-such as T-cells, macrophages, endothelial cells, and fibroblasts-were shown to have increased IL-6 expression at both the mRNA and protein levels (Kono et al. (1991) J. Immunol. 146:1812; Matsuki et al (1992) Immunology 76:42-47; Fujihashi et al. (1993) Am. J. Pathol. 142:1239; Yarnazaki et al. (1994) J Oral Pathol Med. 23:347-53). Since IL-6 is of particular importance in human B cell responses, it has been speculated that the expansion of B-cells/plasma cells seen in periodontitis lesions may result from an increased production of IL-6 at diseased sites (Fujihashi et al (1993) J Periodontol 64:400-406). Additionally, IL-6 plays an important role in the local regulation of bone turnover (Lowik et al. (1989) Biochem Biophys Res Commun. 162:1546-52; Ishimi et al. (1990) J. Immunol. 145:3297; Kurihara et al. (1990) J. Immunol. 144:4226) and appears to be essential for bone loss caused by estrogen deficiency (Horowitz (1993) J Bone Miner Res. 8:1163-71). In vitro studies also demonstrated that simultaneous treatment of mouse osteoblastic cells and bone marrow cells with IL-6 and soluble IL-6 receptor strikingly induced osteoclast formation (Tamura et al. (1993) PNAS 90:11924) . Furthermore, it was also suggested that IL-6 may act as an autocrine and/or paracrine factor in bone resorption in pathologic states by stimulating the formation of osteoclasts and the activation of osteoclastic bone resorption (Ohsaki et al. (1992) Endocrinology 131: 2229). These findings imply the involvement of IL-6 in the pathogenesis of periodontal tissue destruction in periodontitis.

[0010] Inhibition of the COX enzyme is the mechanism of action attributed to most non-steroidal anti-inflammatory drugs (NSAIDS). There are two distinct isoforms of the COX enzyme (COX-1 and COX-2), which share approximately 60% sequence homology, but differ in expression profiles and function. COX-1 is a constitutive form of the enzyme that has been linked to the production of physiologically important prostaglandins, which help regulate normal physiological functions, such as platelet aggregation, protection of cell function in the stomach and maintenance of normal kidney function. (Dannhardt and Kiefer (2001) Eur. J. Med. Chem. 36:109-26). The second isoform, COX-2, is a form of the enzyme that is inducible by pro-inflammatory cytokines, such as interleukin-1[beta] D(IL-1[beta]) and other growth factors. (Herschmann (1994) Cancer Metastasis Rev. 134:241-56; Xie et al. (1992) Drugs Dev. Res. 25:249-65). This isoform catalyzes the production of prostaglandin E2 (PGE2) from arachidonic acid (AA). Inhibition of COX is responsible for the anti-inflammatory activity of conventional NSAIDs.

[0011] Inhibitors that demonstrate dual specificity for COX and LOX would have the obvious benefit of inhibiting multiple pathways of arachidonic acid metabolism. Such inhibitors would block the inflammatory effects of prostaglandins (PG), as well as, those of multiple leukotrienes (LT) by limiting their production. This includes the vasodilation, vasopermeability and chemotactic effects of PGE2, LTB4, LTD4 and LTE4, also known as the slow reacting substance of anaphalaxis. Of these, LTB4 has the most potent chemotactic and chemokinetic effects. (Moore (1985) in Prostanoids: pharmacololical physiological and clinical relevance, Cambridge University Press, N.Y., pp. 229-230).

[0012] Because the mechanism of action of COX inhibitors overlaps that of most conventional NSAID's, COX inhibitors are used to treat many of the same symptoms, including pain and swelling associated with inflammation in transient conditions and chronic diseases in which inflammation plays a critical role. However, most of the known NSAIDs are not suitable for periodontal diseases due to their poor solubility and bioavailability.

...Applicant is unaware of any reports of a formulation combining Free-B-Ring-Flavonoids and flavans as the primary biologically active components targeting the eicosanoid and cytokine pathways for the treatment of oral diseases and conditions.

[0014] Flavonoids or bioflavonoids are a widely distributed group of natural products, which have been reported to have antibacterial, anti-inflammatory, antiallergic, antimutagenic, antiviral, antineoplastic, anti-thrombic and vasodilatory activity. The structural unit common to this group of compounds includes two benzene rings on either side of a 3-carbon ring as illustrated by the following general structural formula:
EMI1.0
Various combinations of hydroxyl groups, sugars, oxygen and methyl groups attached to this general three ring structure create the various classes of flavonoids, which include flavanols, flavones, flavan-3-ols (catechins), anthocyanins and isoflavones.

[0015] Free-B-Ring flavones and flavonols are a specific class of flavonoids, which have no substituent groups on the aromatic B ring (referred to herein as Free-B-Ring flavonoids), as illustrated by the following general structure:
EMI2.0

[0020] Free-B-Ring flavonoids are relatively rare. Out of 9,396 flavonoids synthesized or isolated from natural sources, only 231 Free-B-Ring flavonoids are known (The Combined Chemical Dictionary, Chapman & Hall/CRC, Version 5:1 June 2001). Free-B-Ring flavonoids have been reported to have diverse biological activity...

[0022] The Chinese medicinal plant, Scuttellaria baicalensis contains significant amounts of Free-B-Ring flavonoids, including baicalein, baicalin, wogonin and baicalenoside. Traditionally, this plant has been used to treat a number of conditions including clearing away heat, purging fire, dampness-warm and summer fever syndromes; polydipsia resulting from high fever; carbuncle, sores and other pyogenic skin infections; upper respiratory infections, such as acute tonsillitis, laryngopharyngitis and scarlet fever; viral hepatitis; nephritis; pelvitis; dysentery; hematemesis and epistaxis. This plant has also traditionally been used to prevent miscarriage. (Encyclopedia of Chinese Traditional Medicine, ShangHai Science and Technology Press, ShangHai, China, 1998). Clinically Scutellaria is now used to treat conditions such as pediatric pneumonia, pediatric bacterial diarrhea, viral hepatitis, acute gallbladder inflammation, hypertension, topical acute inflammation, resulting from cuts and surgery, bronchial asthma and upper respiratory infections. (Encyclopedia of Chinese Traditional Medicine, ShangHai Science and Technology Press, ShangHai, China, 1998). The pharmacological efficacy of Scuttellaria roots for treating bronchial asthma is reportedly related to the presence of Free-B-Ring flavonoids and their suppression of eotaxin associated recruitment of eosinophils. (Nakajima et al. (2001) Planta Med. 67(2):132-135).

[0023] To date, a number of naturally occurring Free-B-Ring flavonoids have been commercialized for varying uses. For example, liposome formulations of Scutellaria extracts have been utilized for skin care (U.S. Pat. Nos. 5,643,598; 5,443,983). Baicalin has been used for preventing cancer, due to its inhibitory effects on oncogenes (U.S. Pat. No. 6,290,995). Baicalin and other compounds have been used as antiviral, antibacterial and immunomodulating agents (U.S. Pat. No. 6,083,921 and WO98/42363) and as natural anti-oxidants (WO98/49256 and Poland Pub. No. 9,849,256). Flavonoids formulates with terpenoids have been used as inhibitors of surface-bound glusosyltransferase for treating and inhibiting dental caries (US#20040057908). Japanese Pat. No. 63027435 describes the extraction, and enrichment of baicalein and Japanese Pat. No. 61050921

describes the purification of baicalin.

[0024] U.S. application Ser. No. 10/091,362, filed Mar. 1, 2002, entitled "Identification of Free-B-Ring Flavonoids as Potent COX-2 Inhibitors," and U.S. application Ser. No. 10/427,746, filed Jul. 22, 2003, entitled "Formulation of a Mixture of Free-B-Ring Flavonoids and Flavans as a Therapeutic Agent" disclose a method for inhibiting the cyclooxygenase enzyme COX-2 by administering a composition comprising a Free-B-Ring flavonoid or a composition containing a mixture of Free-B-Ring flavonoids to a host in need thereof. This is the first report of a link between Free-B-Ring flavonoids and COX-2 inhibitory activity. These applications are specifically incorporated herein by reference in their entirety.

[0031] Catechin is a flavan, found primarily in green tea, having the following structure:
EMI4.0
Catechin works both alone and in conjunction with other flavonoids found in tea, and has both antiviral and antioxidant activity. Catechin has been shown to be effective in the treatment of viral hepatitis. It also appears to prevent oxidative damage to the heart, kidney, lungs and spleen and has been shown to inhibit the growth of stomach cancer cells...

[0033] Acacia is a genus of leguminous trees and shrubs. The genus Acacia includes more than 1000 species belonging to the family of Leguminosae and the subfamily of Mimosoideae. Acacias are distributed worldwide in tropical and subtropical areas of Central and South America, Africa, parts of Asia, as well as, Australia, which has the largest number of endemic species. To date, approximately 330 compounds have been isolated from various Acacia species. Flavonoids are the major class of compounds isolated from Acacias. Approximately 180 different flavonoids have been identified, 111 of which are flavans. Terpenoids are second largest class of compounds isolated from species of the Acacia genus, with 48 compounds having been identified. Other classes of compounds isolated from Acacia include, alkaloids (28), amino acids/peptides (20), tannins (16), carbohydrates (15), oxygen heterocycles (15) and aliphatic compounds (10). (Buckingham, The Combined Chemical Dictionary, Chapman & Hall CRC, version 5:2, December 2001)...

[0035] The Uncaria genus, includes 34 species many of which are well known as medicinal plants. Uncaria plants have been utilized by different cultures for treatment of wounds, and ulcers, fevers, headaches, gastrointestinal illnesses and microbial/gungal infections. Uncaria plants contain significant amounts of catechin and other flavones. Other components that have been reported in Uncaria genus include alkaloids, terpenes, quinovic acid glycosides, coumarins, and flavonoids. Uncaria gambir is a species common in Malaysia, Singapore, India and other South East Asian countries. Catechins are major components in the whole plant of Uncaria gambir.

SUMMARY OF THE INVENTION

[0036] The present invention includes methods that are effective in simultaneously inhibiting both the eicosanoid system and the cytokine system for use in the prevention and treatment of diseases and conditions related to the mouth, teeth and gums. The method for the simultaneous dual modulation of both the eicosanoid system and the cytokine system is comprised of administering, systemically or locally, a composition comprised of a mixture of Free-B-Ring flavonoids and flavans synthesized and/or isolated from a single plant or multiple plants to a host in need thereof. This composition of matter is referred to herein as UP676. The efficacy and safety of this method is demonstrated with purified enzymes, in different cell lines, in multiple animal models and eventually in a human clinical study. The ratio of the Free-B-Ring flavonoids to flavans in the composition is in the range of 99.9:0.1 of Free-B-Ring flavonoids:flavans to 0.1:99.9 Free-B-Ring flavonoids:flavans. In specific embodiments of the present invention, the ratio of Free-B-Ring flavonoids to flavans is selected from the group consisting of approximately 90:10, 80:20, 70:30, 60:40, 50:50, 40:60, 30:70, 20:80 and 10:90. In a preferred embodiment of this invention, the ratio of Free-B-Ring flavonoids:flavans in the composition of matter is 80:20. In a preferred embodiment, the Free-B-Ring flavonoids are isolated from a plant or plants in the Scutellariagenus of plants and the flavans are isolated from a plant or plants in the Acacia or Uncaaria genus of

plants.

[0037] The present invention also includes methods for the prevention and treatment of diseases and conditions of the mouth, teeth and gums. The method for preventing and treating said diseases and conditions of the mouth, teeth and gums is comprised of administering, systemically or topically, to a host in need thereof an effective amount of a composition comprising a mixture of Free-B-Ring flavonoids and flavans synthesized and/or isolated from a single plant or multiple plants and a pharmaceutically acceptable carrier. The ratio of the Free-B-Ring flavonoids to flavans in the composition is in the range of 99.9:0.1 of Free-B-Ring flavonoids:flavans to 0.1:99.9 Free-B-Ring flavonoids:flavans. In specific embodiments of the present invention, the ratio of Free-B-Ring flavonoids to flavans is selected from the group consisting of approximately 90:10, 80:20, 70:30, 60:40, 50:50, 40:60, 30:70, 20:80 and 10:90. In a preferred embodiment of this invention, the ratio of Free-B-Ring flavonoids:flavans in the composition of matter is 80:20. In a preferred embodiment, the Free-B-Ring flavonoids are isolated from a plant or plants in the Scutellaria genus of plants and the flavans are isolated from a plant or plants in the Acacia or Uncaria genus of plants...

[0044] The Free-B-Ring flavonoids of this invention may be obtained by synthetic methods or extracted from the family of plants including, but not limited to Annonaceae, Asteraceae, Bignioniaceae, Combretaceae, Compositae, Euphorbiaceae, Labiatae, Lauranceae, Leguminosae, Moraceae, Pinaceae, Pteridaceae, Sinopteridaceae, Ulmaceae and Zingiberacea. The Free-B-Ring flavonoids can be extracted, concentrated, and purified from the following genus of high plants, including but not limited to Demos, Achyrocline, Oroxylum, Buchenavia, Anaphalis, Cotula, Gnaphalium, Helichrysum, Centaurea, Eupatoriuin, Baccharis, Sapium, Scutellaria, Molsa, Colebrookea, Stachys, Origanum, Ziziphora, Lindera, Actiniodaphne, Acacia, Derris, Glycyrrhiza, Millettia, Pongamia, Tephrosia, Artocarpus, Ficus, Pityrogramma, Notholaena, Pinus, Ulmus and Alpinia.

[0051] The flavans of this invention may be obtained from a plant or plants selected from the genus of Acacia or Uncaria. In a preferred embodiment, the plant is selected from the group consisting of Acacia catechu, Acacia concinna, Acacia farinesiana, Acacia Senegal, Acacia speciosa, Acacia arabica, A. caesia, A. pennata, A. sinuata. A. mearnsii, A. picnantha, A. dealbata, A. auriculiformis, A. holoserecia and A. mangium; and Uncaria gambir, Uncaria lanosa, Uncaria hirsute, Uncaria africana, Uncaria elliptica, Uncaria orientalis, Uncaria attenuate, Uncaria acida, Uncaria homomalla, Uncaria sessilifructus, Uncaria sterrophylla, Uncaria bernaysii, Uncaria sinensis, Uncaria callophylla, Uncaria rhychophylla, Uncaria tomeentosa, Uncaria longiflora, Uncaria hirsute, Uncaria cordata, and Uncaria borneensis.

...The combination of Free-B-Ring-flavonoids with flavans to produce the composition of matter referred to herein as UP676, offers a synergistic and potent modulator of both the eicosanoid system and the cytokine system that will help to control inflammation of the periodontal tissues, including inflammation in all four stages of periodontal disease. Additionally, due to the different biological availability, i.e. rate and percentage of biologically active compounds penetrating the epithelial cell membrane and the local concentrations of biologically active compounds in periodontal tissues, the combination of the two different type of compounds (higher polarity flavans vs. lower polarity Free-B-Ring flavonoids) offers both quick, on-site pain and acute-inflammatory relief by the biologically active flavans, as well as, longer lasting modulation of chronic inflammation in periodontal tissues by the biologically active Free-B-Ring flavonoids. Finally, in the preferred embodiment formulation of significant amounts of free-B-Ring flavonoids (80% by weight) with comparatively lower concentration of flavans (20% by weight), the more potent anti-oxidative flavans will function both as natural preservatives against oxidative degradation of the Free-B-Ring flavonoids and to neutralize and buffer the composition allowing delivery of the major active components-the Free-B-Ring flavonoids at the optimum pH and ionization conditions.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

...The Free-B-Ring flavonoids of this invention may be obtained by synthetic methods or may be isolated from the family of plants including, but not limited to Annonaceae, Asteraceae, Bignoniaceae, Combretaceae, Compositae, Euphorbiaceae, Labiatae, Lauranceae, Leguminosae, Moraceae, Pinaceae, Pteridaceae, Sinopteridaceae, Ulmaceae, and Zingiberacea. The Free-B-Ring flavonoids can be extracted, concentrated, and purified from the following genus of high plants, including but not limited to Desmos, Achyrocline, Oroxylum, Buchenavia, Anaphalis, Cotula, Gnaphalium, Helichrysum, Centaurea, Eupatorium, Baccharis, Sapium, Scutellaria, Molsa, Colebrookea, Stachys, Origanum, Ziziphora, Lindera, Actinodaphne, Acacia, Derris, Glycyrrhiza, Millettia, Pongamia, Tephrosia, Artocarpus, Ficus, Pityrogramma, Notholaena, Pinus, Ulmus and Alpinia. The flavonoids can be found in different parts of plants, including but not limited to stems, stem barks, twigs, tubers, roots, root barks, young shoots, seeds, rhizomes, flowers and other reproductive organs, leaves and other aerial parts.

[0111] Methods for the isolation and purification of Free-B-Ring flavonoids are described in U.S. application Ser. No. 10/091,362, filed Mar. 1, 2002, entitled "Identification of Free-B-Ring Flavonoids as Potent Cox-2 Inhibitors," and U.S. application Ser. No. 10/469,275, filed Aug. 27, 2003, entitled "Identification of Free-B-Ring Flavonoids as Potent Cox-2 Inhibitors," each of which is incorporated herein by reference in its entirety.

[0112] The flavans that can be used in accordance with the method of this invention include compounds illustrated by the general structure set forth above. The flavans of this invention are isolated from a plant or plants selected from the Acacia or Uncaria genus of plants. In a preferred embodiment, the plant is selected from the group consisting of Acacia catechu (A. catechu), A. concinna, A. farnesiana, A. Senegal, A. speciosa, A. arabica, A. caesia, A. pennata, A. sinuata. A. mearnsii, A. picnantha, A. dealbata, A. auriculiformis, A. holoserecia and A. mangium; or Uncaria gambir, Uncaria lanosa, Uncaria hirsute, Uncaria africana, Uncaria elliptica, Uncaria orientalis, Uncaria attenuate, Uncaria acida, Uncaria homomalla, Uncaria sessilifructuts, Uncaria sterrophylla, Uncaria bernaysii, Uncaria sinensis, Uncaria callophylla, Uncaria rhychophylla, Uncaria tomentosa, Uncaria longiflora, Uncaria hirsute, Uncaria cordata, and Uncaria borneensis. The flavans can be found in different parts of plants, including but not limited to stems, stem barks, trunks, trunk barks, twigs, tubers, roots, root barks, young shoots, seeds, rhizomes, flowers and other reproductive organs, leaves and other aerial parts.

[0113] Methods for the isolation and purification of flavans are described in U.S. application Ser. No. 10/104,477, filed Mar. 22, 2002, entitled "Isolation of a Dual Cox-2 and 5-Lipoxygenase Inhibitor from Acacia," which is incorporated herein by reference in its entirety.

EXAMPLES

Example 1

Preparation of Organic and Aqueous Extracts from Acacia and Scuttellaria Plants

[0136] Plant material from Acacia catechu (L) Willd. barks, Scutellaria orthocalyx roots, Scutellaria baicalensis roots or Scutellaria lateriflora whole plant and various Oroxylum and Uncaria species was ground to a particle size of no larger than 2 mm. Dried ground plant material 60 g) was then transferred to an Erlenmeyer flask and methanol:dichloromethane (1: 1) (600mL) was added. The mixture was shaken for one hour, filtered and the biomass was extracted again with methanol: dichloromethane (1:1) (600 mL). The organic extracts were combined and evaporated under vacuum to provide the organic extract (see Table 1 below). After organic extraction, the biomass was air dried and extracted once with ultra pure water (600 mL). The aqueous solution was filtered and freeze-dried to provide the aqueous extract (see Table 1 below).

TABLE 1
Yield of Organic and Aqueous Extracts from Plant Species
Plant Source Plant Part Organic Extract Aqueous Extract

Acacia catechu barks 27.2 g 10.8 g
Scutellaria orthocalyx roots 4.04 g 8.95 g
Scutellaria baicalensis roots 9.18 g 7.18 g
Scutellaria lateriflora whole plant 6.54 g 4.08 g
Oroxylum indicum seeds 6.58 g 4.04 g
Uncaria hirsuta arerial parts 2.41 g 0.90 g
Uncaria sinensis arerial parts 3.94 g 1.81 g
Uncaria tomentosa bark 6.47 g 2.31 g

Example 2
Inhibition of COX-2 and COX-1 Peroxidase Activity by Plant Extracts from A. catechu, Various Scutellaria Species and Other Plants

TABLE 2
Inhibition of COX-2 Peroxidase Activity by Various Species
Inhibition of COX-2 Inhibition of COX-2
Plant Source by organic extract by aqueous extract
Acacia catechu (bark) 75% 30%
Scutellaria orthocalyx (root) 55% 77%
Scutellaria baicalensis (root) 75% 0%

TABLE 3
IC50 Values of Organic Extracts for Human and Ovine COX-2 and COX-1
IC50 Human IC50 Ovine IC50 Ovine
COX-2 COX-2 COX-1
Plant Source ([mu]g/mL) ([mu]g/mL) ([mu]g/mL)
Acacia catechu (bark) 3 6.25 2.5
Scutellaria orthocalyx (root) Not tested 10 10
Scutellaria baicalensis (root) 30 20 20
Scutellaria lateriflora (whole plant) 20 30 80
Uncaria sinensis (whole plant) Not tested 2.2 72.0
Oroxylum indicum (seeds) Not tested 2.48 8.4

TABLE 4
Inhibition of COX Enzyme Activity by Purified Free-B-Ring Flavonoids
Inhibition Inhibition
Free-B-Ring Flavonoids of COX-1 of COX-2
Baicalin 95% 97%
Baicalein 107% 109%
5,6-Dihydroxy-7-methoxyflavone 75% 59%
7,8-Dihydroxyflavone 74% 63%
Wogonin 16% 12%

Example 4
Inhibition of 5-Lipoxygenase by Catechin isolated from A. catechu

TABLE 5
Free-B-Ring Flavonoid Content in Active Plant Extracts
% Weight Total amount Free-B-Ring Active of % Extractible of Free-B-Ring Flavonoids Extracts Extract from BioMass Flavonoids in Extract
S. orthocalyx 8.95 g 14.9% 0.2 mg 0.6%

(aqueousextract)
S. orthocalyx 3.43 g 5.7% 1.95 mg 6.4% (organicextract)
S. baicalensis 7.18 g 12.0% 0.03 mg 0.07% (aqueous extract)
S. baicalensis 9.18 g 15.3% 20.3 mg 35.5% (organic extract)

TABLE 6
Catechin Content in Active Plant Extracts
Active Extracts from Weight of % Extractible % Flavans
bark of A. catechu Extract from BioMass in Extract
Aqueous Extract 10.8 g 18.0% 0.998%
Organic Extract 27.2 g 45.3% 30.37%

Example 7
Preparation of a Standardized Extract from A. catechu

[0146] A. catechu (500 mg of ground root) was extracted twice with 25 mL (2*25 mL) of the following solvent systems. (1) 100% water, (2) 80:20 water:methanol, (3) 60:40 water:methanol, (4) 40:60 water:methanol, (5) 20:80 water:methanol, (6) 100% methanol, (7) 80:20 methanol:THF, (8) 60:40 methanol:THF. The two extracts from each individual extraction were combined concentrated and dried under low vacuum. The identification of the chemical components in each extract was achieved by HPLC using a PhotoDiode Array detector (HPLC/PDA) and a 250 mm*4.6 mm C18 column. The chemical components were quantified based on retention time and PDA data using catechin and epicatechin as standards. The results are set forth in Table 7. As shown in Table 7, the flavan extract generated from solvent extraction with 80% methanol/water provided the highest concentration of flavan components.

TABLE 7
Solvents for Generating Standardized Flavan Extracts from A. catechu
Extraction Weight of % Extractible Total amount % Catechins
Solvent Extract from BioMass of Catechins in Extract
100% water 292.8 mg 58.56% 13 mg 12.02%
water:methanol 282.9 mg 56.58% 13 mg 11.19%
(80:20) water:methanol 287.6 mg 57.52% 15 mg 13.54%
(60:40) water:methanol 264.8 mg 52.96% 19 mg 13.70%
(40:60) water:methanol 222.8 mg 44.56% 15 mg 14.83%
(20:80)100% methanol 215.0 mg 43.00% 15 mg 12.73%
methanol:THF 264.4 mg 52.88% 11 mg 8.81%
(80:20) methanol:THF 259.9 mg 51.98% 15 mg 9.05%
(60:40)

[0147] A standardized extract was obtained from whole plant of Uncaria gambir by extracting the biomass with alcohol/water solvent. The flavan content in the standardized extract from Uncaria gambir were quantified using the same method. The results are set forth in Table 8. The flavans were quantified based on retention time and PDA data using catechin as standards.

[0148] Higher purity material can be obtained by recrystallization of extracts having a catechin content of between 8%-15% using an alcohol/water and/or aqueous solvents as the recrystallization solvent. It may be necessary to decolorize prior to recrystallization by adding active charcoal or other decolorization agent to a heated saturated solution of the extract. The high purity catechins then crystallized upon cooling of the heated saturated solution. The crystals were then filtered to remove solvent, dried and ground into a fine powder. Recrystallization can be repeated as necessary to achieve the desired level of purity (60%-100% of catechin flavans).

Example 8

Preparation of Standardized Free-B-Ring Flavonoid Extracts from various Scutellaria species

[0149] S. orthocalyx (500 mg of ground root) was extracted twice with 25 mL of the following solvent systems. (1) 100% water, (2) 80:20 water:methanol, (3) 60:40 water:methanol, (4) 40:60 water:methanol, (5) 20:80 water:methanol, (6) 100% methanol, (7) 80:20 methanol:THF, (8) 60:40 methanol:THF. The extracts were combined, concentrated and dried under low vacuum. Identification of chemical components in each extract was performed by HPLC using a PhotoDiode Array detector (HPLC/PDA) and a 250 mm*4.6 mm C18 column. The chemical components were quantified based on retention time and PDA data using baicalein, baicalin, scutellarein, and wogonin as standards. The results are set forth in Table 9.

TABLE 9

Quantification of Free-B-Ring Flavonoids Extracted from S. orthocalyx

Solvent	Total Extract from BioMass	% Flavo-noids	Extraction Weight of Flavonoids	% Extractible amount of Flavonoids in Extract
100% water	96 mg	19.2%	0.02 mg	0.20%
Water:methanol (80:20)	138.3 mg	27.7%	0.38 mg	0.38%
Water:methanol (60:40)	169.5 mg	33.9%	0.78 mg	8.39%
Water:methanol (40:60)	142.2 mg	28.4%	1.14 mg	11.26%
Water:methanol (20:80)	104.5 mg	20.9%	0.94 mg	7.99%
100% methanol	57.5 mg	11.5%	0.99 mg	10.42%
methanol:THF (80:20)	59.6 mg	11.9%	0.89 mg	8.76%
methanol:THF (60:40)	58.8 mg	11.8%	1.10 mg	10.71%

[0150] S. baicalensis (1000 mg of ground root) was extracted twice using 50 mL of a mixture of methanol and water as follows: (1) 100% water, (2) 70:30 water:methanol, (3) 50:50 water:methanol, (4) 30:70 water:methanol, (5) 100% methanol. The extracts were combined, concentrated and dried under low vacuum. Identification of the chemical components was performed by HPLC using a PhotoDiode Array detector (HPLC/PDA), and a 250 mm*4.6 mm C18 column. The chemical components in each extract were quantified based on retention time and PDA data using baicalein, baicalin, scutellarein, and wogonin standards. The results are set forth in Table 10.

TABLE 10

Quantification of Free-B-Ring Flavonoids Extracted from S. baicalensis

Solvent	Total Extract from BioMass	% Flavo-noids	Extraction Weight of Flavonoids	% Extractible amount of Flavonoids in Extract
100% water	277.5 mg	27.8%	1 mg	0.09%
Water:methanol (70:30)	338.6 mg	33.9%	1.19 mg	11.48%
Water:methanol (50:50)	304.3 mg	30.4%	1.99 mg	18.93%
Water:methanol (30:70)	293.9 mg	29.4%	2.29 mg	19.61%
100% methanol	204.2 mg	20.4%	2.73 mg	24.51%

[0151] Higher purity Free-B-Ring flavonoids can be obtained by recrystallization of extracts having a Free-B-Ring flavonoid content of between 8-15% using alcohol/water as a recrystallization solvent. It may be necessary to decolorize prior to recrystallization by adding active charcoal or other decolorization agent to a heated saturated solution of the extract. The Free-B-Ring flavonoids

crystallized upon cooling. The crystals were filtered, dried and ground into a fine powder. Recrystallization can be repeated as necessary to achieve the desired level of purity (60%-100% of Free-B-Ring flavonoids).

Example 9

Preparation of a Formulation with a Standardized Free-B-Ring Flavonoid Extract from the Roots of S. baicalensis and a Standardized Flavan Extract from the Bark of A. catechu

[0152] A novel composition of matter, referred to herein as UP676 was formulated using two standardized extracts isolated from Acacia and Scutellaria, respectively, together with one or more excipients. A general example for preparing such a composition is set forth below. The Acacia extract used in this example contained >80% total flavans, as catechin and epicatechin, and the Scutellaria extract contained >80% Free-B-Ring flavonoids, which was primarily baicalin. The Scutellaria extract also contained other minor amounts of Free-B-Ring flavonoids as set forth in Table 11. One or more excipients/preservatives was also added to the composition of matter. The ratio of flavans and Free-B-Ring flavonoids can be adjusted based on the indications and the specific requirements with respect to inhibition of COX vs. LO, requirements of skin penetration, and potency requirements of the product, such as duration of potency required, etc. The quantity of the excipients can be adjusted based on the actual active content of each ingredient. A blending table for each individual batch of product must be generated based on the product specification and QC results for individual batch of ingredients. Additional amounts of active ingredients in the range of 2-5% are recommended to meet the product specification.

[0153] S. baicalensis root extract (38.5 kg) (lot # RM052302-01) having a Free-B-Ring flavonoid content of 82.2% (baicalin); Acacia catechu bark extract (6.9 kg) (lot # RM052902-01) with total flavan content of 80.4%; and excipient (5.0 kg of Candex) were combined to provide a UP676 formulation (50.4 kg) having a blending ratio of 85:15 by weight of the active Free-B-Ring flavonoids and flavans. Table 11 provides the quantification of the active Free-B-Ring flavonoids and flavans of this specific batch of UP676 (Lot#G 1702-COX-2), determined using the methods provided in Examples 6 and 8. With reference to Table 11, this specific batch of UP676 contains 86% total active ingredients, including 75.7% Free-B-Ring flavonoids and 10.3% flavans. FIG. 10 illustrates the HPLC chromatogram of a representative UP676 sample, which had a blending ratio of 80:20 by weight of the active Free-B-Ring flavonoids and flavans.

TABLE 11

Free-B-Ring Flavonoid and Flavan Content of a UP676 Formulation

Active Components	% Content
1. Flavonoids	
a. Baicalin	62.5%
b. Minor Flavonoids	
i. Wogonin-7-glucuronide	6.7%
ii. Oroxylin A 7-glucuronide	2.0%
iii. Baicalein	1.5%
iv. Wogonin	1.1%
v. Chrysin-7-glucuronide	0.8%
vi. 5-Methyl-wogonin-7-glucuronide	0.5%
vii. Scutellarin	0.3%
viii. Norwogonin	0.3%
ix. Chrysin	<0.2%
x. Oroxylin A	<0.2%
c. Total Free-B-ring Flavonoids	75.7%
2. Flavans	
a. Catechin	9.9%
b. Epicatechin	0.4%
c. Subtotal Flavans	10.3%
3. Total Active Ingredients	86%

[0154] Using the same approach, the following batches of UP676 were prepared using a combination of a standardized Free-B-Ring flavonoid extract from S. baicalensis roots and a standardized flavan extract from Acacia catechu bark having a blending ratio of 12:88 and 15:85, respectively.
[0155] S. baicalensis root extract (58.0 g) (lot # RM021203-01) having a Free-B-Ring flavonoid content of 87.9% (as baicalin) and Acacia catechu bark extract (442.0 g) (lot # RM050603-01) with total flavan content of 84.9% were blended to provide a UP676 composition (500 g, lot#QJ205-19) having a blending ratio of 12:88 by weight. Utilizing the methods provided in Examples 6 and 8, the Free-B-Ring flavonoid content of (baicalin) was 9.65% and flavan content (total catechin and epicatechin) was 73.2% in this specific batch of UP676 (lot#QJ205-19).
[0156] S. baicalensis root extract (300 g) (lot # RM060403-01) having a Free-B-Ring flavonoid content of 82.9% (as baicalin) and Acacia catechu bark extract (1700 g) (lot # RM050603-01) with total flavan content of 90.8% were blended to provide a UP676 composition (2000 g, lot#A1904) having a blending ratio of 15:85 by weight. Utilizing the methods provided in Examples 6 and 8, the Free-B-Ring flavonoid content (baicalin) was 15.6% and flavan content (total catechin and epicatechin) was 75.0% in this specific batch of UP676 (lot#A1904).

Example 14
Formulation of the UP676 Composition into a Cream

[0164] UP676 (0.5% by weight of UP676) (lot#A1904 as described in Example 9) was formulated as a cream as illustrated in the following procedure and in Table 13.

[0165] UP676 (Lot#A1904) was dissolved in water at room temperature and homogenized with a blender until it was fully dispersed in solution (approximately 5 minutes). At room temperature and without stirring or agitating the solution, Ultrez-21 carbomer was added by sprinkling onto the surface of the solution and allowing it to fully wet (no white areas visible) and fall into the solution. With gentle stirring, the solution was then heated to 40[deg.] C. and glycerin was added (Part A). The mixture was then stirred for an additional 5 minutes. The remaining components (Part B) were weighed and heated to 40[deg.] C. while mixing. At 40[deg.] C., the remaining components (Part B) were added to Part A and the resulting composition was mixed well until homogenous (approximately 5 minutes). The emulsion was cooled to 30[deg.] C. and the pH was adjusted to approximately 5.5 (5.3 to 5.7) by titrating with neutralizer while stirring with a stir bar and/or spatula. The emulsion became highly viscous due to neutralization-induced conformational change of the carbomer. The emulsion eventually achieved a suitable viscosity for an emulsion cream. The emulsion cream was then mixed until uniform after which it was poured into a clean storage vessel and stored at 2[deg.] C. to 8[deg.] C. for one month.

TABLE 13
Ingredient list for a 0.5% UP676 Cream

Phase	Ingredient	% (w/w)	Weight (g)
Aqueous	Water, Purified	85.00	1275.0
	UP676 (Lot#A1904)	0.50	7.5
	Ultrez 21 Carbomer	0.50	7.5
	Glycerin	8.00	120.0
Oil	PEG-7 Glyceryl Cocoate	3.00	45.0
	Caprylic/Capric Triglyceride	2.67	40.0
PH	Sodium Hydroxide (18% w/v),	0.00	0.0
Neutralizer	Molecular Biology Grade		
SUM	7 Ingredients	99.7	1495.0

Example 15
Evaluation of the Stability of Catechin in Solution

[0166] Pure catechin was dissolved in 70% MeOH in water to a final concentration of 0.05% (W/V) after mixing with the solutions detailed below. A total of 6 different conditions (not

including control solution) were chosen for this stability investigation at 45[deg.] C. Aqueous K2HPO4 (0.5 M) or KH2PO4 (0.5 M) was utilized to make buffered solutions at pH 5 or 8, respectively. H2O2, SnCl2, FeCl3 or EDTA was added to the catechin solution to a concentration of 0.6% H2O2, or 0.05% SnCl2, or 0.05% FeCl3 or 0.05% EDTA, respectively. All seven solutions were stored in sealed bottles at 45[deg.] C. Each sample was tested for catechin content by HPLC as described in the Example 6 at day 0, 1, 3, 6, 8, 10, 13, 20, and 28. The results are set forth in FIG. 15.

[0167] The following preservatives: BHA, BHT, diammonium citrate (DAC), H2O2, propyl gallate (PG), sodium gluconate (SG), and sodium bisulfate/metabisulfite (SBS), were added into a buffered (pH 7.5) 0.05% catechin MeOH/H2O solution to yield a concentration of 0.05%. All eight solutions were stored in sealed bottles at 45[deg.] C. Each sample was tested by HPLC as described in Example 6 for catechin content at day 0, 1, 3, 6, 8, 10, 13, 20, and 28. The results are set forth in FIG. 16.

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CALCIUM BINDING PEPTIDES

[0004] BACKGROUND

[0005] [0002] Compounds that bind specifically to calcified surfaces include small fluorescent molecules such as tetracycline, calcein, and alizarin, and large calcium-binding proteins such as dentin phosphoprotein (DPP, often referred to as phosphophoryn) and amelogenin. DPP is one of the major noncollagenous proteins found in the dentin extracellular matrix and has long been implicated in the nucleation of hydroxyapatite (HA) during dentin mineralization (Lee 1980; Lussi 1988; Veis 1998; Hao 2004). Human DPP is derived from proteolytic cleavage of dentin sialophosphoprotein (DSPP). Human DPP is a highly flexible (Cross 2005), highly phosphorylated (Lee 1980) protein consisting primarily of a large number of Asp-Ser-Ser amino acid repeats (Gu 2000). The biochemical characteristics of DPP have been extensively investigated. These investigations have revealed that immobilized DPP causes marked increases in the rate of hydroxyapatite nucleation, though this effect is not seen with DPP in solution or with dephosphorylated DPP. In addition, high concentrations of DPP have been shown to inhibit HA crystal growth (Lussi 1988; Veis 1998; Saito 2000).

[0006] SUMMARY

[0007] [0003] In certain embodiments, a composition is provided that includes one or more calcium binding peptides. These calcium binding peptides comprise the three amino acid repeat sequence (X-Y-Z)n, wherein X is aspartic acid, glutamic acid, asparagine, alanine or glutamine, Y and Z alanine, serine, threonine, phosphoserine, or phosphothreonine, and n is a number from 1 and 40, and wherein said calcium binding peptides bind calcium phosphate. In certain of these embodiments, the calcium binding peptides comprise about 1 to about 40 three amino acid repeats (i.e., n=1-40), and have a length from about 3 to about 120 amino acids. In certain of these embodiments, n is a number from 2 to 8. In certain embodiments, X is aspartic acid and Y and Z are serine. In certain of these embodiments, the calcium binding peptides may have the amino acid sequence set forth in any of SEQ ID NOs:12-15.

[0023] DETAILED DESCRIPTION

[0025] Abbreviations

[0026] [0024] The following abbreviations are used herein: BE, basal enamel; CE, cortical enamel; CL, carious lesion; CLSM, confocal laser scanning microscopy; CPD, circumpulpal dentin; D, dentin; DEJ, dentin-enamel junction; DPP, dentin phosphoprotein; E, enamel; DSPP, dentin sialophosphoprotein; HA, hydroxyapatite; MD, mantle dentin; MIC, minimum inhibitory

concentration; P, pulp cavity wall; PB, periodontal bone; SEM, scanning electron microscopy; RTD, root tip dentin; [lambda], excitation wavelength.

[0027] [0025] Amino acids are abbreviated using the standard system set forth below.

[0028] Amino acid One letter Three letter abbreviation abbreviation
[0029] Alanine A Ala
[0030] Arginine R Arg
[0031] Asparagine N Asn
[0032] Aspartic acid D Asp
[0033] Cysteine C Cys
[0034] Glutamic acid E GIu
[0035] Glutamine Q GIn
[0036] Glycine G GIy
[0037] Histidine H His lsoleucine I Ne
[0038] Leucine L Leu
[0039] Lysine K Lys
[0040] Methionine M Met
[0041] Phenylalanine F Phe
[0042] Phosphoserine SP Sep
[0043] Proline P Pro
[0044] Serine S Ser
[0045] Threonine T Thr
[0046] Tryptophan W Trp
[0047] Tyrosine Y Tyr
[0048] Valine V VaI Unless indicated otherwise by a "D" prefix, e.g., D-AIa, the stereochemistry of the alpha-carbon of the amino acids and aminoacyl residues in peptides described herein is the natural or "L" configuration.

[0049] Calcium binding peptides

[0050] [0026] Compounds currently available for the direct remineralization of decalcified tissues consist mainly of various formulations of free or protein-bound calcium phosphate and/or sodium fluoride. Enhancement of calcification in biological tissues is generally achieved by manipulating cell signaling in bone and tooth precursor cells, or by increasing the global calcium concentration using calcium-fortified foods, dietary supplements, or other treatments rich in free or protein-bound calcium. Previous studies have described a formulation that recruits calcium phosphate to the tooth surface to enhance remineralization (see U.S. Pat. No. 6,780,844). However, enhancement of calcification by directly and specifically targeting calcium to surfaces has not been demonstrated. [0027] Disclosed herein are a series of small calcium binding peptides made up of variations of the Asp-Ser-Ser motif found in DPP. These peptides have been shown to bind tightly and specifically to calcium phosphate surfaces. In addition, these peptides have been shown to recruit calcium phosphate to such surfaces and to serve as binding moieties for the attachment of fluorescent labels to calcified surfaces regardless of their phosphorylation state. [0028] The peptides disclosed herein, referred to generally as DSS peptides, are composed of various numbers and/or combinations of the three amino acid Asp-Ser-Ser motif of DPP or variations thereof. Examples of three amino acid repeats that may be utilized include, but are not limited to, Asp-Ser-Ser (DSS, SEQ. ID NO. 1), Glu-Ser-Ser (ESS, SEQ. ID NO. 2), Asp-Thr-Thr (DTT, SEQ. ID NO. 3), Glu-Thr-Thr (ETT, SEQ. ID NO. 4), Asn-Ser-Ser (NSS, SEQ. ID NO. 5), Asn-Thr-Thr (NTT, SEQ. ID NO. 6), Gln-Ser-Ser (QSS, SEQ. ID NO. 7), Gln-Thr- Thr (QTT, SEQ. ID NO. 8), and variations thereof. Alternatively or in addition to these repeat sequences, the peptides disclosed herein may Include minor variations of these repeats, including but not limited to Asp-Ser-Thr (DST, SEQ. ID NO. 9), Asp-Ala-Ala (DAA, SEQ. ID NO. 10), or Ala-Ser-Thr (AST, SEQ. ID NO. 11). One or more amino acid residues within a three amino acid repeat may be chemically modified. For example, the peptides may contain one or more Ser or Thr residues in which a hydroxyl group has been modified by the addition of a phosphate group. The peptides may vary in length from three to greater than fifty

amino acids.

[0051] [0029] The binding affinity of the peptides disclosed herein for calcified surfaces may be controlled by altering the composition and number of repeats. For example, inclusion of one or more Asp-Ser-Ser (SEQ. ID NO. 1) repeats will increase the binding affinity of the peptide, because this sequence exhibits the highest affinity of any of the repeats tested. The binding affinity of the peptide may also be increased by increasing the number of three amino acid repeats. Peptides containing more than six repeats generally exhibit greater binding affinity than those with fewer repeats. In certain embodiments, the peptides disclosed herein may have a binding affinity (KA) for hydroxyapatite of greater than 15,000 M<"1>. In certain embodiments, this binding affinity may be greater than 50,000 M<"1>, in other embodiments greater than 100,000 M<"1>, in other embodiments greater than 200,000 M<'1>, and in other embodiments greater than 300,00O M<"1>. [0030] In certain embodiments, the peptides may contain one or more additional amino acids that are not part of a three amino acid repeat sequence. For example, in certain embodiments, the repeat portion of the peptide may be fused to an amino acid sequence having an additional functionality, such as for example an antimicrobial peptide sequence such as the 2c-4, PL135, or b-34 peptide sequences. In certain of these embodiments, the repeat portion of the peptide may be fused to the additional amino acid sequence via a linker sequence, such as for example a triglycine sequence. [0031] In certain embodiments, the peptides disclosed herein comprise the sequence (X-Y-Z)n, wherein X is an amino acid selected from aspartic acid, glutamic acid, asparagine, alanine and glutamine, Y and Z are amino acids selected from alanine, serine, threonine, phosphoserine, phosphothreonine, and their derivatives, and n is a number between 1 and 20. In certain embodiments, n is between 1 and 15, in other embodiments, n is between 1 and 10, and in certain embodiments n is between 3 and 8.

[0052] [0032] The calcium binding peptides disclosed herein have been shown to induce calcium phosphate crystal growth on demineralized enamel and on both demineralized and nondemineralized dentin, depending on treatment conditions. Likewise, the peptides have been shown to induce remineralization of bone. Thus, in certain embodiments, compositions comprising the calcium binding peptides disclosed herein may be used to enhance mineralization by recruiting free-floating calcium phosphate particles to calcified surfaces. These peptides may bind to calcified surfaces and/or free-floating calcium phosphate aggregates. Concurrent binding of calcified surfaces and free-floating aggregates results in increased calcium phosphate concentration near the calcified surface, which leads to enhanced remineralization of the surface. By modulating the size and binding affinity of the peptides, it is possible to alter the amount of calcium bound to the surface. In certain embodiments, remineralization of teeth results in complete or partial occlusion of dentinal tubules.

[0087] 2005), these results suggest that DSS peptides may be used to target kidney stones in diagnostic or therapeutic applications, and that they may be able to modulate the growth of kidney stones.

US6602490

SUMMARY OF THE INVENTION

[0006] The principal and secondary objects of the inventions are to provide a dental hygiene preparation that can effectively remove plaque and food debris from teeth, braces and prosthetic devices, remineralize tooth enamel over long periods between meals and avoid the toxicity of fluoridation compounds so that it can be effectively used by elderly or handicapped persons as well as those persons affected by mouth ulcers and irritations.

[0007] These and other valuable objects are achieved by the preparation that uses in solution, a sequestrant such as Potassium Citrate, a chelating agent such as Dissodium Edetate and a nonfermentable sweetener such as Xylitol in combination with an emulsifying, wetting and

solubizing agent such as Polysorbate. The preparation also contains Calcium Ascorbate as antioxidant as well as flavoring agents such as Spearmint and Peppermint. **The preparation does not contain any effective amount of Sodium Fluoride, Sodium monoflurophosphate, Stanous Fluoride or any other source of Fluoride.**

DESCRIPTION OF THE PREFERRED EMBODIMENT OF THE INVENTION

[0008] The dental hygiene preparation according to the invention includes a sequestran such as Sodium Tripolyphospate, Sorbitol, Sodium Citrate and, preferably, Potassium Citrate in a proportion of approximately 0.0013 to 0.032 percent per weight;

[0009] a saturated solution of Disodium Edetate in proportion of approximately 0.0003 to 0.04 percent per volume;

[0010] Xylitol in a proportion of approximately 0.008 to 0.08 percent per weight;

[0011] one or more emulsifying, wetting and solubizing agent such as Polysorbate in a proportion of approximately 0.0132 to 0.32 percent per volume, and Poloxamer in a proportion of 0.0013 to 0.0317 percent per weight; and

[0012] an antioxidant, preferably Calcium Ascorbate Dihydrate in a proportion of approximately 0.003 to 0.02 percent per weight.

[0013] The preparation also, preferably, includes an additional sweetener such as Aspartane and Sodium Saccharin Dihydrate in a proportion of approximately 0.026 to 0.66 percent per weight, as well as some flavoring agent such as Spearmint and Peppermint. Natural glycerin is preferably added as a humectant, plasticizer and tonicity agent. A small amount of alcohol and a coloring agent may also be included.

[0014] The preparation does not contain any effective amount of Fluoride compound that could provide free Fluoride as a caries-preventive agent.

[0015] The composition of a preferred example of the dental hygiene preparation is provided in Table 1.

TABLE 1

Water (purified) 3.785 l (one gallon)
Ethanol 200 Proof U.S.P./N.F. 15 ml
Rectified F.C.C. Oil of Spearmint 2 ml
Natural F.C.C. Oil of Peppermint 2 ml
DL-Menthol Crystal U.S.P./N.F. 400 mg
(Crystals are Mixed into the alcohol solution).
Calcium Ascorbate Dihydrate F.C.C. 400 mg (Powder is mixed into the water).
Potassium Citrate F.C.C. (Granules are 400 mg mixed into water).
Polysorbate 20 U.S.P./N.F. 3 ml
Poloxamer 338 U.S.P./N.F. 400 mg
Natural Glycerin U.S./N.F. 6 ml
Xylitol F.C.C. 1.33 g
Disodium Edetate U.S.P./N.F. (100 mg of 1.25 ml
this powder is mixed in 10 ml of warm purified water to obtain a saturated solution and 1.25 ml of this saturated solution is mixed into the main solution of other ingredients).
Aspartane (Nutrasweet) U.S.P./N.F. 2.6 g
Blue Coloring F.D. & C. #1 1 drop (about 0.13 ml)
Sodium Carbonate, Anhydrous U.S.P./N.F. to adjust pH to 7.0

[0016] In the example, **Xylitol, derived from the cell walls of plants, as been proven to inhibit the growth of bacteria, in particular Strep Mutans**, the main bacteria responsible for dental caries. Contrary to Fluoride, Xylitol can be safely ingested. Potassium Citrate is preferred as a sequestrant due to its solubizing and pH-stablilizing properties.

[0017] The preparation in the example was obtained according to the following steps:

[0018] Heating the water to approximately 66 degrees Celsius (150[deg.] F.);

[0019] Dissolving the oil of Spearmint, oil of Peppermint, Menthol and Glycerin in the Ethanol, and stirring the mixture into the heated water. The Polysorbate 20, Poloxamer 338 and Potassium Citrate were then sequentially dissolved into the heated water. Next, the Disodium Edetate solution was added within a range of 200 mg to 800 mg, i.e., from 2 to 8 mg of pure Disodium. After letting the preparation cool to approximately 49 degrees Celsius (120[deg.] F.), the Xylitol was added. After letting the preparation cool to approximately 43 degrees Celsius (110[deg.] F.), the approximately 38 degrees Celsius (100[deg.] F.), the blue coloring agent is added.

[0020] The pH was then adjusted to 7.0 with Sodium Carbonate.

[0021] It should be noted that the preparation was continuously stirred during the entire process. Finally, the preparation was filtered through a 616-20 paper.

[0022] Before bottling for commerical distribution, the preparation is passed through an ultra-violet disinfection unit then further filtered through a 5 micron filter prior to bottling.

PROCESSES AND COMPOSITIONS FOR REMINERALIZATION OF DENTAL ENAMEL
GB1452125

It is well known in the dental art that dental caries begins as a subsurface demineralization ("white spot") of the dental enamel and that remineralization may be of importance in retarding or arresting dental caries. U.S. Patent 3,679,360, July 25, 1972, to Rubin et al., discloses a method, the purpose of which is to deposit calcium phosphate from a gel medium onto the surface of a tooth. But this method of remineralizing has several disadvantages. Remineralization occurs only on the surface of the tooth whereas the initial cause of dental caries is subsurface demineralization. The surface on which apatite growth is desired must be prepared (as by roughening), and the tooth and coatings must be covered by a suitable cap for several days while the mineralization of the tooth surface occurs.

The disadvantages of the method disclosed in the Rubin et al. patent are overcome by the present invention which provides for subsurface remineralization rather than surface remineralization. Since dental caries begins as a subsurface demineralization of the dental enamel, subsurface remineralization arrests and repairs the carious lesion before any permanent structural damage to the tooth occurs. The present invention does not require preparation of the enamel surface, capping of the tooth, or removal of decay products. Further, the present invention may be conveniently practiced by the public without substantially changing their dental care habits.

The present invention provides an oral treatment pack comprising as components adapted for sequential application (in either order) to dental tissue:

(A) a first component which comprises application in water-soluble form, which cation is capable of forming an insoluble precipitate; and

(B) a second component which comprises an anion in water-soluble form, which anion is capable of forming with said cation an insoluble precipitate adapted to remineralize subsurface dental

enamel, wherein one or both of the components contains a flavouring agents, the components being compatible with the oral environment and being such as to have a pH from 3 to 10 solution.

Concentrations of cationic and anionic solutions for use as the components of the invention may generally be from 0.005% to 10% (or the limit of solubility of the salt), with from 0.05 % to 5 % being preferred.

(These percentages are by weight). More than one cation may be employed in the cationic solution. Similarly, more than one anion may be employed in the anionic solution.

The application of the oral treatment pack of the invention involves:

(1) applying one of the components to the surface of a tooth having a demineralized subsurface for a period of time sufficient to allow the said ion of
that component to diffuse into the demineralized subsurface, and thereafter

(2) applying the other component to the surface of the tooth whereby the said ion of that other component is diffused into the demineralized subsurface and the said insoluble precipitate is thereby formed.

The remineralizing precipitate formed is less susceptible to demineralization than original enamel if heavy metal cations and fluoride anions are employed.

There is a-visible effect on "white spots" after as few as eight sequential applications, and it is contemplated that several sequential applications will be employed to achieve the most beneficial results.

The present invention involves the discovery that subsurface dental enamel may be remineralized by the sequential application of certain soluble salts yielding ions which will react to form a remineralizing precipitate.

The sequential application consists of two steps which may be performed in either order, although the following order is slightly preferred. In the first step, one com- ponent is placed in contact with the tooth surface nearest to the demineralized subsurface. This, first component preferably contains the stated cations, and they diffuse through the tooth surface to its demineralized subsurface.

In the second step, the other component containing the stated anions is placed in contact with the tooth surface nearest the demineralized subsurface. The anions diffuse through the tooth surface to the demineralized subsurface where they come in contact with the cations previously deposited and form a precipitate which is bound to the tooth structure. As a result, the tooth's subsurface is remineralized.

Concentrations of the salt solutions are generally from 0.005 % to 10% or the limit of solubility of the salt, as stated above.

Excess salt can be present, if desired. Con centrations from about 0.05Oó to about 5 0/s are preferred. The concentrations of the soluble salts containing the desired anions are essentially the same as those for the watersoluble salts containing the desired cations.

If the remineralization contemplated by this invention is carried out in the presence of e:ther a heavy metal ion or fluoride ion, the remineralized enamel is more resistant to demineralization than was the original enamel.

If both ions are present, the remineralized enamel is even more resistant to demineralization. The concentration of salt containing heavy metal ion and fluoride ion in their respective solutions may be from 0.005% to 10%, in accordance with the limits given above, but from 0.005% to 0.1:d is

preferred.

Examples of suitable heavy metal ions are barium, lanthanum, manganese, lead, tin, zinc, indium, zirconium, iron, titanium, vanadium, and cadmium. Indium is preferred.

In the most preferred embodiment of the present invention, the remineralizing cationic solution contains from about 0.005 % to about 10%, preferably about 1%, of a soluble calcium salt yielding calcium ions and from about 0.005% to about 10%, preferably from about 0.005% to 0.1% of a soluble indium salt yielding indium ions. The remineralizing anionic solution contains from about 0.005% to about 10%, preferably about 1%, of soluble phosphate salt yielding phosphate ions and from about 0.005% to about 10%, preferably from about 0.005% to about 0.1% of a soluble fluoride salt yielding fluoride ions.

The resulting precipitate is a calcium phosphate or hydroxylapatite, the natural constituent of tooth enamel, with incorporated indium and fluoride ions. Not only does this process result in remineralized enamel, but the remineralized enamel is more resistant to subsequent demineralization than was the original enamel.

Soluble fluoride and indium salts which are suitable for use in solutions of the present invention include, but are not limited to, indium chloride, indium sulfate, and indium nitrate. Suitable salts for other desired cations and anions would be obvious to one skilled in the art
The anions which give desirable insoluble precipitates include phosphate, C,--C1, fatty acyl groups, fluoride, fluorophosphate, silica fluoride, molybdate, sulfate, tungstate, ,,8 hydroxyquinolate, tartrate, sorbate, C,;Ci8 alkyl sulfonates, carbonates, iodates, etc.

Mixtures of these anions are desirable.

Cations which give desirable insoluble precipitates are calcium, zinc, indium, rare earth metals, magnesium, manganese, cadmium, aluminum, barium, lanthanum, zirconium, strontium, cesium, etc. Mixtures of these cations are desirable.

EXAMPLE I

Cationic Mouthwash
Ingredient % by wight
Indium trichloride (2.89%
solution in H2O) 1.000
Bolic acid, U.S.P. 0.075
Glacial acetic acid, A.C.S.
0.200 NaOH (10 ,ó solution in H O) 0.400

Anionic Mouth Rinse
Ingredient % by weight

Disodium phosphate 0.847
Boric acid, U.S.P. 0.075
Distilled water 81.210%

EXAMPLE II

Anionic Dentifrice
Ingredient Ó by weight
Disodium phosphate 3.820
Abrasive (precipitated silicagel) 19.000

Cationic Dentifrice

Ingredient e,,') by weight
Calcium chloride 5.000
Indium trichloride (2.89% solution in H2O) 6.000

EXAMPLE IV

Toothp owder
Cationic Portion
Ingredient o,Ó by weight
Indium trichloride 0.0289
Sodium citrate 1.50

Anionic Portion
Ingredient % by weight
Disodium phosphate 3.82
Sodium citrate 1.50

EXAMPLE V

Chewing Gum
Cationic Portion
Ingredient % by weight

InCI, 0.0289 CaCl2 5.00
Citric acid 1.00
Anionic Portion
Ingredient oÓ by weight
Gum base
30 parts Estergum
45 parts Coumarone resin
15 parts dry Latex
10 parts Paraffin wax
(M.P.=180 F.) 30.00

Na2HPO4 3.82
Citric acid 1.00
Flavor balance

The concentration of the combination of the calcium and indium salts and the combinations of the phosphate and fluoride salts in the human mouth in use are respectively about 2% and about 1%.

As an Example of the use of the oral treatment packs of the Examples a subject rinses his mouth with the cationic mouthwash of Example I and then rinses his mouth with the anionic mouthwash of Example I. Each rinse is performed for about 30 seconds.

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It has also already been proposed to add compounds containing calcium ions and phosphate ions to dental cosmetics which are used topically, and thus to achieve a remineralization of the dental enamel. In this way, however, no more satisfactory results, that is to say adequate remineralization of the dental enamel by the incorporation of calcium ions and phosphate ions, were achievable than in the case of using water-insoluble calcium phosphates, for example dicalcium phosphate, which has also already been described (British Patent Specification No. 1,102,024), for example in chewing gum. This is presumably due to the fact that as a result of the low solubility in water of these calcium phosphates and of the consequent inadequate dissociation, calcium ions and phosphate ions are not available in sufficient amount to effect satisfactory incorporation of these

ions into the demineralized dental enamel.

British Patent Specification No. 1,090,340 describes a process for the re-hardening of dental enamel which is characterized in that a supersaturated solution of an apatite material, which is stabilized with an isotonic sodium chloride solution, is produced in the presence of teeth by reaction of a mixture of a water-soluble calcium salt, a water-soluble phosphate salt and a water-soluble fluoride salt. This material is intended to be incorporated into the demineralized dental enamel. In this process, no real absorption of calcium ions, phosphate ions and fluoride ions by the dental enamel occurs, and hence no remineralization of the softened dental enamel, a deposit of fluorohydroxyapatite being merely produced on the surface of the dental enamel. In addition, the requisite presence of sodium chloride presents considerable problems in the manufacture of a dental

As calcium compound it is in principle possible to employ, in the preparations of the invention, all water-soluble toxicologically harmless calcium compounds. A compound is considered to be water-soluble when at least 0.25 gram thereof dissolves in 100 ml of H2 O at 20 DEG C.

Suitable water-soluble calcium compounds are, for example, calcium chloride, calcium nitrate, calcium acetate, calcium gluconate, calcium benzoate, calcium citrate, calcium formate, calcium fumarate, calcium lactate, calcium butyrate and calcium isobutyrate, calcium malate, calcium maleate, calcium propionate, calcium valerate or mixtures of water-soluble calcium compounds. In the compositions of the invention for the remineralization of human dental enamel, at least about 50 ppm of calcium ions should be present; the upper limit is about 35,000 ppm of calcium ions.

Suitable water-soluble inorganic phosphates within the scope of the present invention are, for example, the alkali salts and ammonium salts of orthophosphoric acid, such as potassium, sodium or ammonium orthophosphate, water-soluble alkali metaphosphates or alkali polyphosphates or mixtures of these substances.

Particular water-soluble organic phosphates are sugar esters of orthophosphoric acid and esters of phosphoric acid and polyhydric alcohols. As examples there may be mentioned fructose phosphate, sorbitol phosphate, glucose phosphate, sucrose phosphate, glycerophosphate, mannitol phosphate and inositol phosphate and their water-soluble salts. The concentration of the PO4 ions is preferably about 50 to 40,000 ppm; solubility in water is defined as in the case of the calcium compounds.

Toothpaste
A B

Calcium chloride.2 H2 O 1.80 --
Disodium hydrogen phosphate -- 1.00
Phytic acid -- 0.35

EXAMPLE 2

Two pastes A and B were prepared, of which paste A consists of a customary paste base and contains a calcium compound. In contrast, paste B, which contains water-soluble phosphates, is in the form of a transparent gel. The teeth are first cleaned with paste A and subsequently with paste B.

Toothpaste A:
Calcium gluconate 5.60 % by weight
Water 32.80 "

Toothpaste B, in the form of a gel:
Sodium glycerophosphate 0.85
Potassium dihydrogen phosphate 0.50

Disodium hydrogen phosphate 0.70 "
Precipitated silica 21.00
Water 13.12
Calcium chloride, anhydrous
1.10 KH2 PO4
0.01 Na2 HPO4.2 H2 O

EXAMPLE 4

A two-layer (I and II) chewing gum was produced as follows (data in % by weight):

1.82 of Ca Cl2.2H2 O and
(II) a mixture of 0.65 of Na2 HPO4.2H2 O, 0.55 of KH2 PO4 and 0.82 of sodium glycerophosphate,

EXAMPLE 5

13.00% by weight of gum arabic
13.00 gelatin
(I) 49.94% by weight of or
(II) 51.47% by weight of water,

were incorporated, in (I) 2.50% by weight of calcium gluconate, and in II
0.32% by weight of Na2 HPO4,
0.35% by weight of KH2 PO4 and
0.30% by weight of sodium glycerophosphate