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ABSTRACT

5 Provided are compositions comprising an orally-acceptable carrier and a cationic copolymer derived from the polymerization of n-vinyl pyrrolidone (VP) with cationic monomers containing amines or by copolymerization of n-vinyl pyrrolidone (VP) monomers with cationic monomers comprising amides followed by deprotection to amines. Also provided are uses of such compounds in the oral cavity to inhibit demineralization of a tooth.

Oral Care Composition

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a divisional of Australian Patent Application No. 2024204312, filed 24 June 2024, which is a divisional of Australian Patent Application No. 2018381169, filed 29 November 2018, is related to PCT/US2018/063000, and claims priority from U.S. Provisional Application No. 15/834,160, filed 7 December 2017, all of which are incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

The present invention relates to compositions comprising cationic PVP copolymers for use in oral care composition to prevent demineralization. In certain embodiments, the present invention relates to amine-containing copolymers of vinyl pyrrolidone used to deliver demineralization prevention benefits.

BACKGROUND OF THE INVENTION

Caries is one of the most prevalent diseases affecting individuals globally. It is caused by the complex relationship between dental biofilms (plaque), the host and fermentation of dietary sugars to organic acids. Essentially, the acids produced effectively decrease the pH of the microenvironment below 5.5 resulting in enamel dissolution or demineralization. Rapid adjustment to near neutral pH occurs due to the high buffer capacity of saliva resulting in remineralization at the surface of enamel. An imbalance in de- and remineralization cycles, with more time spent in the demineralization, result in caries.

Fluoride, renowned for prevention and repair of tooth decay, has been considered as a possible solution to regulated dental erosion. Recently, different types of micro-/nanoparticles (hydroxyapatite, bioglass, silica particles, etc.) have also been explored for their anti-erosion properties. Some divalent cations, such as calcium, zinc and stannous, have also been used to prevent demineralization.

While fluoride has been widely used in consumer products, almost half of the population still suffers from caries. Micro-/nanoparticles show some efficacy in remineralization, but they are very challenging to formulate in mouth rinse and the efficacy highly depends on the retention time on enamel surface. For example, bioglass, such as that trademarked under the name NOVAMIN, can only be prepared in anhydrous formulations. Divalent cations also have limitations in either formulation or consumer experience, for example, zinc has a bitter after taste and stannous is known for causing teeth staining issue.

Preventing the demineralization of teeth is rapidly gaining attention as a valid strategy to reduce occurrence and/or progression of dental decay. Hence, there is always a need to develop oral care compositions to prevent demineralization.

SUMMARY OF THE INVENTION

According to one aspect are described compositions comprising an orally-acceptable carrier and a cationic copolymer derived from the polymerization of n-vinyl pyrrolidone (VP) with cationic monomers containing amines or by copolymerization of n-vinyl pyrrolidone (VP) monomers with cationic monomers comprising amides followed by deprotection to amines. Another aspect is related to uses of such compounds in the oral cavity to inhibit demineralization of a tooth.

DETAILED DESCRIPTION OF THE INVENTION

The compositions of the present invention can comprise, consist of, or consist essentially of the essential elements and limitations of the invention described herein, as well any of the additional or optional ingredients, components, or limitations described herein. The term “comprising” (and its grammatical variations) as used herein is used in the inclusive sense of “having” or “including” and not in the exclusive sense of “consisting only of.”

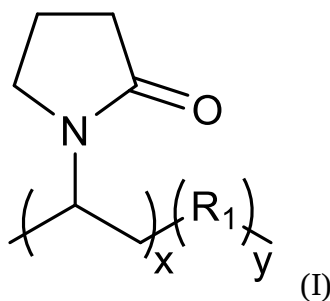
The terms “a” and “the” as used herein are understood to encompass the plural as well as the singular.

Unless otherwise indicated, all documents cited are, in relevant part, incorporated herein by reference; the citation of any document is not to be construed as an admission that it is prior art with response to the present invention. Furthermore, all documents incorporated herein by reference in their entirety are only incorporated herein to the extent that they are not inconsistent with this specification.

All percentages listed in this specification are percentages of solids/active amounts by weight (wt%), unless otherwise specifically mentioned.

The present invention relates to cationic copolymers of vinyl pyrrolidone used to deliver benefits including mineralization and anti-erosion benefits in oral care formulations.

In certain embodiments, the cationic copolymers used in the present invention are described by the formula I:



wherein R_1 is a repeat unit containing an amine group, wherein “x” represents the number of VP units and is an integer; “y” represents the number of R_1 units and is an integer; and the ratio of “x” to “y” is from about 1:99 to about 99:1. The repeat units x and y may be randomly distributed in the copolymer of the present invention.

The cationic copolymers of vinyl pyrrolidone (Cationic PVP-copolymers) are prepared via copolymerization of n-vinyl pyrrolidone (VP) monomers with cationic monomers containing amines, or by copolymerization of n-vinyl pyrrolidone (VP) monomers with cationic monomers comprising amides followed by deprotection to amines. Examples of suitable monomers containing amines include, for example, n-vinyl phthalimide (VPA), 2-N-morpholinoethyl acrylate, methacryloylcholine methyl sulfate, 2-N-morpholinoethyl methacrylate, 2-diisopropylaminoethyl methacrylate, 2-aminoethyl methacrylate, Methacryloyl-L-lysine, N-[3-(N,N-dimethylamino)propyl] methacrylamide, N-(2-aminoethyl) methacrylamide, 2-(N,N-Dimethylamino)ethyl acrylate, 2-(N,N-Diethylamino)ethyl methacrylate, 2-(tert-Butylamino)ethyl methacrylate, 2-(N,N-Dimethylamino)ethyl methacrylate, 2-Acryloxyethyltrimethylammonium, and the like. Examples of suitable monomers containing amides including n-vinyl formamide (VF), N-(3-aminopropyl)methacrylamide, N-(3-BOC-aminopropyl)methacrylamide, N-[2-(N,N-dimethylamino)ethyl]methacrylamide, N-[3-(N,N-Dimethylamino)propyl] acrylamide and the like.

Other examples of monomers containing amines include, for example, guanidinium containing monomers, 3-guanidinopropyl methacrylate, N-(3-

guanidinopropyl)methacrylamide, Arginine methacrylamide, N-(Diaminomethylene)-2-methylprop-2-enamide, 1-(2-aminoethyl)-1H-pyrrole-2,5-dione, and 1-(2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)ethyl)guanidine, combinations of two or more thereof and the like.

Yet another examples of monomers include, for example, monomers which can be modified post-polymerization to display an amine or guanidine functional group, such as maleic anhydride followed by a condensation reaction with a primary amine and/or a primary amine displaying the guanidine functional group, for example spermidine and 1-(4-aminobutyl)guanidine) respectively. Specifically, for the monomers containing multiple amines, one amine would be available for reactivity, while the other would be protected to prevent cross-linking. Here, after the post-polymerization is completed the protected amine would be deprotected to display a primary amine. This approach could also be applied to other amine containing functional groups.

Some of monomers and the post-polymerization modifications may result in displaying both a positive and negative charge, or zwitterionic.

According to certain preferred embodiments, the cationic copolymers of vinyl pyrrolidone are prepared via copolymerization of n-vinyl pyrrolidone (VP) monomers with monomers comprising amine groups such as n-vinyl phthalimide. In other preferred embodiments, the cationic copolymers of vinyl pyrrolidone are prepared via copolymerization of n-vinyl pyrrolidone (VP) monomers with cationic monomers comprising amides, such as n-vinyl formamide, followed by deprotection to amines. As will be understood by those of skill in the art, with respect to Formula I, the repeat unit R_1 may be described as being derived from a cationic monomer containing amine or a cationic monomer containing amide which has been deprotected to form an amine as described herein. For example, wherein R_1 is a repeat unit derived from n-vinyl phthalimide, or from n-vinyl formamide which has been deprotected.

The cationic copolymers for use in the present invention may be heterogenous in the distribution of the R_1 monomers and can vary in the percent by weight of each repeat unit and ratio of the respective monomers/repeat units. For example, in certain embodiments, the repeat units derived from vinyl pyrrolidone and cationic monomers (R_1) are independently from about 5 to about 95% by weight of the polymer, including from about 10 to about 90%, 20 to about 80%, 20 to about 50%, 30 to about 50%, 30 to about 40%, 50 to about 90%, 50 to

about 70%, 50 to about 60%, 60 to about 70% by weight of the polymer. In certain preferred embodiments, the repeat units derived from vinyl pyrrolidone is from about 60 to about 80 %, including about 65 weight percent, by weight of the polymer, or from about 70 to about 90%, including about 85%, by weight of the polymer.

5 The ratio of repeat units derived from vinyl pyrrolidone to repeat units derived from cationic monomers (R_1) is from about 10:90 to about 90:10, including from about 20:80 to about 80:20, about 30:70 to about 70:30, about 40:60 to about 60:40, and about 50:50. In certain preferred embodiments, the ratio of repeat units derived from vinyl pyrrolidone to repeat units derived from cationic monomers (R_1) is from about 50:50 to about 70:30, including about 60:30 to about 70:30. In certain preferred embodiments, the ratio of repeat units derived from vinyl pyrrolidone to repeat units derived from cationic monomers (R_1) is from about 70:30 to about 90:10, including about 85:15.

10 The copolymers of the present invention may be of any suitable molecular weight. In certain embodiments, the polymers have a weight average molecular weight of from about 10,000 to about 1,000,000 including from about 10,000 to about 750,000, about 10,000 to about 500,000, about 10,000 to about 250,000, and about 150,000. In certain preferred embodiments, the average molecular weight is from about 10,000 to about 500,000, including about 10,000 to about 250,000. In certain preferred embodiments, the average molecular weight is from about 10,000 to about 250,000, including about 150,000.

20 The copolymers may comprise cross-linking agents. Cross-linking agents suitable for use in the present invention comprise at least two reactive sites which are electrophiles designed to react easily with amines. When the cross-linker has two reactive sites it is bifunctional and can thus react with two amino groups e.g. two cationic units in different polymer chains. The distance between the reactive groups may be increased by a spacer moiety. This spacer is often an aliphatic chain or a polyether construct like poly- or oligoethylene glycols. Preferably the cross-linking agent is bi-, tri- or tetrafunctional, although bi- or trifunctional is preferred and bifunctional is most preferred. Typical examples of such cross-linking functionalities are reactive esters, Michael acceptors and epoxides. Suitable cross-linking agents are known and include glycosaminoglycans such as hyaluronic acid and chondroitin sulfate, glutaraldehyde, glyoxal, diethyl squarate, diepoxides such as diglycidyl ether, genipin, formaldehyde. Preferred cross-linking molecules are ester

derivatives of squaric acid, diepoxides and derivatives of acrylamides, diethyl squarate (3,4-diethoxy-3-cyclobutene-1,2-dione) and its structurally closely related analogues, 1,4-butanediol diglycidylether, derivatives of acrylamide and their structurally closely related analogues. Most preferred cross-linking molecules are phosphate-containing molecules such as tripolyphosphate, pyrophosphate, hexametaphosphate, phytic acid, inositol phosphate and the like. Other suitable cross-linking agents may include, but it is not limited to, sulfate-containing molecules, citric acid the like. These cross-linking agents may be used individually or in combination with each other. In general, it is preferred to have higher polymer concentrations and lower concentrations of cross-linking agent to achieve a composition of the desired nature. It is preferable to minimize the amount of cross-linker used. The molar ratio of cross-linking agent to polymer based on the number of functional groups in the cross-linking agent and the number of accessible amino groups in the polymer is preferably 0.2:1 or less, more preferably 0.1:1 or less and most preferably 0.05:1 or less. The molar ratio is based on the number of groups available for cross-linking on the cross-linker and on the polymer. For the cross-linker it will depend on the functionality (bi-, tri-, tetrafunctional etc.) and on the polymer to the accessibility of the cationic groups.

The compositions of the present invention may comprise from about 0.01~10% of the cationic polymers of the present invention. In certain preferred embodiments, the compositions comprise from about 0.01 to about 5%, from about 0.01 to about 3%, from about 0.01 to about 2%, from about 0.01 to about 1%, or from about 0.01 to about 0.5% or from about 0.01 to about 0.05% by weight of the cationic polymer of Formula I. In certain preferred embodiments, the composition comprises from about 0.01 to about 5%, preferably from about 0.01 to about 3%, or from about 0.01 to about 1% by weight of the cationic polymer of Formula I.

Any of a wide variety of orally-acceptable vehicles may be used in the present compositions. The vehicle can be aqueous or non-aqueous. The aqueous vehicle is generally water, although water/alcohol mixtures may also be employed. In certain embodiments, water is added to q.s. (Quantum Sufficit, Latin for "as much as needed") the composition. In certain embodiments, the aqueous phase comprises from about 60% to about 95%, or from about 75% to about 90%, by weight of the composition. In certain compositions, water is present in an amount of from about 60% to about 95%, or from about 75% to about 90%.

Alternatively, the compositions of the present invention may be formulated in a dry powder, chewing gum, film, semi-solid, solid or liquid concentrate form. In such embodiments, for example, water is added to q.s. as necessary in the case of liquid concentrates or powdered formulations, or water may be removed using standard evaporation procedures known in the art to produce a composition in dry powder form. Evaporated, or freeze dried forms are advantageous for storage and shipping.

In some embodiments, alcohol may be added to the composition. Any of a variety of alcohols represented by the formula $R_3\text{—OH}$, wherein R_3 is an alkyl group having from 2 to 6 carbons, may be used in the present invention. Examples of suitable alcohols of formula $R_3\text{—OH}$ include ethanol; n-propanol, iso-propanol; butanols; pentanols; hexanols, and combinations of two or more thereof, and the like. In certain embodiments, the alcohol is, or comprises, ethanol.

In some embodiments, the alcohol may be present in the composition in an amount of about 10.0% v/v or greater of the total composition, or from about 10.0% to about 35.0% v/v of the total composition, or from about 15.0% to about 30.0% v/v of the total composition and may be from about 20.0% to about 25.0% v/v of the total composition.

In some embodiments, the compositions may comprise a reduced level of alcohol. The phrase “reduced level” of alcohol means an amount of a $R_3\text{—OH}$ alcohol of about 10% v/v or less, or about 5% v/v or less, or about 1.0% v/v or less, or about 0.1% v/v or less by volume of the total composition. In certain embodiments, the compositions of the present invention are free of $R_3\text{—OH}$ alcohols.

The compositions of the present invention preferably have a pH of about 11 or less. In certain embodiments, the composition have a pH of from about 3 to less than 7, or from about 3.5 to less than 7, or from about 3.5 to about 6.5, or from about 3.5 to about 5.5, or from about 3.5 to about 5.0.

As will be recognized by those of skill in the art, the pH of the composition may be adjusted or achieved using a buffer in an amount effective to provide the composition with a pH below 11. The composition can optionally comprise at least one pH modifying agents among those useful herein include acidifying agents to lower pH, basifying agents to raise pH, and buffering agents to control pH within a desired range. For example, one or more compounds selected from acidifying, basifying and buffering agents can be included to

provide a pH of about 2 to about 7, or in various embodiments from about 3 to about 6, or from about 4 to about 5. Any orally acceptable pH modifying agent can be used including without limitation carboxylic and sulfonic acids, acid salts (e.g., monosodium citrate, disodium citrate, monosodium malate, etc.), alkali metal hydroxides such as sodium hydroxide, borates, silicates, imidazole and mixtures thereof. One or more pH modifying agents are optionally present in a total amount effective to maintain the composition in an orally acceptable pH range. In certain embodiments, inorganic acids may be used as the buffer added to the composition.

In certain embodiments, organic acids may be used as the buffer added to the composition. Organic acids suitable for use in the compositions of the present invention include, but are not limited to, ascorbic acid, sorbic acid, citric acid, glycolic acid, lactic acid and acetic acid, benzoic acid, salicylic acid, phthalic acid, phenolsulphonic acid, and mixtures thereof, optionally, the organic acid is selected from the group consisting of benzoic acid, sorbic acid, citric acid and mixtures thereof, or optionally, the organic acid is benzoic acid.

In some embodiments, useful buffer systems have been found to be sodium benzoate/benzoic acid, sodium citrate/citric acid, phosphoric acid/sodium/potassium phosphate.

Generally, the amount of buffer is between about 0.001% (or about 0.001% w/v) to about 5.0% (or about 5.0% w/v) of the composition. In certain embodiment, the buffer is present in amounts of from 0.001% (or about 0.001% w/v) to 1.0% w/v (or about 1.0% w/v) of the composition, or between about 0.100% (or about 0.100% w/v) to about 1.0% (or about 1.0% w/v) of the composition.

The compositions of the present invention may further comprise any of a variety of optional ingredients therein, including, but not limited to oily components, active ingredients, additional surfactants, humectants, solvents, flavors, sweeteners, colorants, preservatives, and the like.

Any of a variety of oily components may be used in the present compositions. The oily component may comprise any one or more oils, or other materials that are water insoluble, or substantially water-insoluble, meaning that its solubility is less than about 1% by weight in water at 25°C or, optionally, less than about 0.1%. In certain embodiments, the

oily component of the present invention comprises, consists essentially of, or consists of, at least one essential oil, i.e. a natural or synthetic (or combination thereof) concentrated hydrophobic material of vegetable origin, generally containing volatile compounds, at least one flavor oil, or a combination of two or more thereof. Examples of suitable essential oils, 5 flavor oils, and their amounts are described below. In certain embodiments, the composition comprises a total amount of oily component of about 0.05% w/w or more, about 0.1% w/w or more, or about 0.2% w/w or more of oily component.

In certain embodiments, compositions of the present invention comprise essential oils. Essential oils are volatile aromatic oils which may be synthetic or may be derived from 10 plants by distillation, expression or extraction, and which usually carry the odor or flavor of the plant from which they are obtained. Useful essential oils may provide antiseptic activity. Some of these essential oils also act as flavoring agents. Useful essential oils include but are not limited to citra, thymol, menthol, methyl salicylate (wintergreen oil), eucalyptol, carvacrol, camphor, anethole, carvone, eugenol, isoeugenol, limonene, osimen, n-decyl 15 alcohol, citronel, a-salpineol, methyl acetate, citronellyl acetate, methyl eugenol, cineol, linalool, ethyl linalol, safrola vanillin, spearmint oil, peppermint oil, lemon oil, orange oil, sage oil, rosemary oil, cinnamon oil, pimento oil, laurel oil, cedar leaf oil, gerianol, verbenone, anise oil, bay oil, benzaldehyde, bergamot oil, bitter almond, chlorothymol, cinnamic aldehyde, citronella oil, clove oil, coal tar, eucalyptus oil, guaiacol, tropolone 20 derivatives such as hinokitiol, avender oil, mustard oil, phenol, phenyl salicylate, pine oil, pine needle oil, sassafras oil, spike lavender oil, storax, thyme oil, tolu balsam, terpentine oil, clove oil, and combinations thereof.

In certain embodiments, the essential oils are selected from the group consisting of thymol ($((\text{CH}_3)_2\text{CHC}_6\text{H}_3(\text{CH}_3)\text{OH}$, also known as isopropyl-m-cresol), eucalyptol ($\text{C}_{10}\text{H}_{18}\text{O}$, 25 also known as cineol), menthol ($\text{CH}_3\text{C}_6\text{H}_9(\text{C}_3\text{H}_7)\text{OH}$), also known as hexahydrothymol), methyl salicylate ($\text{C}_6\text{H}_4\text{OHCOOCH}_3$, also known as wintergreen oil), isomers of each of these compounds, and combinations of two or more thereof. In some embodiments, the compositions of the present invention contain thymol. In some embodiments, the compositions of the present invention contain menthol. In some embodiments, the 30 composition contains all four of these essential oils.

In certain embodiments, thymol is employed in amounts of from about 0.0001% to about 0.6% w/v, or from about 0.005% to about 0.07% w/v of the composition. In certain embodiments, eucalyptol may be employed in amounts of from about 0.0001% to about 0.51% w/v, or from about 0.0085% to about 0.10% w/v of the composition. In certain
5 embodiments, menthol is employed in amounts of from about 0.0001% to about 0.25% w/v, or from about 0.0035% to about 0.05% w/v of the composition. In certain embodiments, methyl salicylate is employed in amounts of from about 0.0001% to about 0.28% w/v, or from about 0.004% to about 0.07% w/v of the composition. In certain embodiments, the total amount of all of such essential oils present in the disclosed compositions can be from about
10 0.0004% to about 1.64% w/v, or from about 0.0165% to about 0.49% w/v of the composition.

In certain embodiments, fluoride providing compounds may be present in the mouth rinse compositions of this invention. These compounds may be slightly water soluble or may be fully water soluble and are characterized by their ability to release fluoride ions or fluoride
15 containing ions in water. Typical fluoride providing compounds are inorganic fluoride salts such as soluble alkali metal, alkaline earth metal, and heavy metal salts, for example, sodium fluoride, potassium fluoride, ammonium fluoride, cupric fluoride, zinc fluoride, stannic fluoride, stannous fluoride, barium fluoride, sodium hexafluorosilicate, ammonium hexafluorosilicate, sodium fluorozirconate, sodium monofluorophosphate, aluminum mono-
20 and difluorophosphate and fluorinated sodium calcium pyrophosphate. Amine fluorides, such as N'-octadecyltrimethylendiamine-N,N,N'-tris(2-ethanol)-dihydrofluoride and 9-octadecenylamine-hydrofluoride), may also be used. In certain embodiments, the fluoride providing compound is generally present in an amount sufficient to release up to about 5%, or from about 0.001% to about 2%, or from about 0.005% to about 1.5% fluoride by weight
25 of the composition.

In certain embodiments, sensitivity reducing agents, such as potassium salts of nitrate and oxalate in an amount from about 0.1% to about 5.0% w/v of the composition may be incorporated into the present invention. Other potassium releasing compounds are feasible (e.g. KCl). High concentrations of calcium phosphates may also provide some added
30 sensitivity relief. These agents are believed to work by either forming an occlusive surface mineral deposit on the tooth surface or through providing potassium to the nerves within the

teeth to depolarize the nerves. A more detailed discussion of suitable sensitivity reducing agents can be found in US 2006/0013778 to Hodosh and U.S. Pat. No. 6,416,745 to Markowitz et al., both of which are herein incorporated by reference in their entirety.

In certain embodiments, compounds with anti-calculus benefits (e.g. various carboxylates, polyaspartic acid, etc.) may be incorporated into the present invention. Also, useful as an anticalculus agent are the anionic polymeric polycarboxylates. Such materials are well known in the art, being employed in the form of their free acids or partially or preferably fully neutralized water soluble alkali metal (e.g. potassium and preferably sodium) or ammonium salts. Preferred are 1:4 to 4:1 by weight copolymers of maleic anhydride or acid with another polymerizable ethylenically unsaturated monomer, preferably methyl vinyl ether (methoxyethylene) having a molecular weight (M.W.) of about 30,000 to about 1,000,000. These copolymers are available, for example, as Gantrez 25 AN 139 (M.W. 500,000), AN 119 (M.W. 250,000) and preferably S-97 Pharmaceutical Grade (M.W. 70,000), of GAF Chemicals Corporation.

Additional anti-calculus agents may be selected from the group consisting of polyphosphates (including pyrophosphates) and salts thereof polyamino propane sulfonic acid (AMPS) and salts thereof; polyolefin sulfonates and salts thereof; polyvinyl phosphates and salts thereof; polyolefin phosphates and salts thereof; diphosphonates and salts thereof; phosphonoalkane carboxylic acid and salts thereof; polyphosphonates and salts thereof; polyvinyl phosphonates and salts thereof; polyolefin phosphonates and salts thereof; polypeptides; and mixtures thereof; carboxy-substituted polymers; and mixtures thereof. In one embodiment, the salts are alkali metal or ammonium salts. Polyphosphates are generally employed as their wholly or partially neutralized water-soluble alkali metal salts such as potassium, sodium, ammonium salts, and mixtures thereof. The inorganic polyphosphate salts include alkali metal (e.g. sodium) tripolyphosphate, tetrapolyphosphate, dialkyl metal (e.g. disodium) diacid, trialkyl metal (e.g. trisodium) monoacid, potassium hydrogen phosphate, sodium hydrogen phosphate, and alkali metal (e.g. sodium) hexametaphosphate, and mixtures thereof. Polyphosphates larger than tetrapolyphosphate usually occur as amorphous glassy materials. In one embodiment the polyphosphates are those manufactured by FMC Corporation, which are commercially known as Sodaphos ($n \approx 6$), Hexaphos ($n \approx 13$), and Glass H ($n \approx 21$, sodium hexametaphosphate), and mixtures thereof. The pyrophosphate

salts useful in the present invention include, alkali metal pyrophosphates, di-, tri-, and mono-potassium or sodium pyrophosphates, dialkali metal pyrophosphate salts, tetraalkali metal pyrophosphate salts, and mixtures thereof. In one embodiment the pyrophosphate salt is selected from the group consisting of trisodium pyrophosphate, disodium dihydrogen pyrophosphate ($\text{Na}_2\text{H}_2\text{P}_2\text{O}_7$), dipotassium pyrophosphate, tetrasodium pyrophosphate ($\text{Na}_4\text{P}_2\text{O}_7$), tetrapotassium pyrophosphate ($\text{K}_4\text{P}_2\text{O}_7$), and mixtures thereof. Polyolefin sulfonates include those wherein the olefin group contains 2 or more carbon atoms, and salts thereof. Polyolefin phosphonates include those wherein the olefin group contains 2 or more carbon atoms. Polyvinylphosphonates include polyvinylphosphonic acid. Diphosphonates and salts thereof include azocycloalkane-2,2-diphosphonic acids and salts thereof, ions of azocycloalkane-2,2-diphosphonic acids and salts thereof, azacyclohexane-2,2-diphosphonic acid, azacyclopentane-2,2-diphosphonic acid, N-methyl-azacyclopentane-2,3-diphosphonic acid, EHDP (ethane-1-hydroxy-1,1,-diphosphonic acid), AHP (azacycloheptane-2,2-diphosphonic acid), ethane-1-amino-1,1-diphosphonate, dichloromethane-diphosphonate, etc. Phosphonoalkane carboxylic acid or their alkali metal salts include PPTA (phosphonopropane tricarboxylic acid), PBTA (phosphonobutane-1,2,4-tricarboxylic acid), each as acid or alkali metal salts. Polyolefin phosphates include those wherein the olefin group contains 2 or more carbon atoms. Polypeptides include polyaspartic and polyglutamic acids.

In certain embodiments, zinc salts such as zinc chloride, zinc acetate or zinc citrate may be added as an astringent for an "antiseptic cleaning" feeling, as a breath protection enhancer or as anti-calculus agent in an amount of from about 0.0025% w/v to about 0.75% w/v of the composition.

Any of a variety of additional surfactants may be used in the present invention.

Suitable surfactants may include anionic, non-ionic, cationic, amphoteric, zwitterionic surfactants, and combinations of two or more thereof. Examples of suitable surfactants are disclosed, for example, in U.S. Pat. No. 7,417,020 to Fevola, et al which is incorporated in its entirety herein by reference.

In certain embodiments, the compositions of the present invention comprise a non-ionic surfactant. Those of skill in the art will recognize that any of a variety of one or more non-ionic surfactants include, but are not limited to, compounds produced by the

condensation of alkylene oxide groups (hydrophilic in nature) with an organic hydrophobic compound which may be aliphatic or alkyl-aromatic in nature. Examples of suitable nonionic surfactants include, but are not limited to, alkyl polyglucosides; alkyl glucose amines, block copolymers such as ethylene oxide and propylene oxide copolymers e.g. Poloxamers; 5 ethoxylated hydrogenated castor oils available commercially for example under the trade name CRODURET (Croda Inc., Edison, N.J.); alkyl polyethylene oxide e.g. Polysorbates, and/or; fatty alcohol ethoxylates; polyethylene oxide condensates of alkyl phenols; products derived from the condensation of ethylene oxide with the reaction product of propylene oxide and ethylene diamine; ethylene oxide condensates of aliphatic alcohols; long chain tertiary 10 amine oxides; long chain tertiary phosphine oxides; long chain dialkyl sulfoxides; and mixtures thereof.

Exemplary non-ionic surfactants are selected from the group known as poly(oxyethylene)-poly(oxypropylene) block copolymers. Such copolymers are known commercially as poloxamers and are produced in a wide range of structures and molecular 15 weights with varying contents of ethylene oxide. These non-ionic poloxamers are non-toxic and acceptable as direct food additives. They are stable and readily dispersible in aqueous systems and are compatible with a wide variety of formulations and other ingredients for oral preparations. These surfactants should have an HLB (Hydrophilic-Lipophilic Balance) of between about 10 and about 30 and preferably between about 10 and about 25. By way of 20 example, non-ionic surfactants useful in this invention include the poloxamers identified as poloxamers 105, 108, 124, 184, 185, 188, 215, 217, 234, 235, 237, 238, 284, 288, 333, 334, 335, 338, 407, and combinations of two or more thereof. In certain preferred embodiments, the composition comprises poloxamer 407.

In certain embodiments, the compositions of the claimed invention comprise less than 25 about 9% of non-ionic surfactant, less than 5%, or less than 1.5%, or less than 1%, or less than 0.8, less than 0.5%, less than 0.4%, or less than .3% of non-ionic surfactants. In certain embodiments, the composition of the present invention is free of non-ionic surfactants.

In certain embodiments, the compositions of the present invention also contain at least one alkyl sulfate surfactant. In certain embodiments, suitable alkyl sulfate surfactants 30 include, but are not limited to sulfated C₈ to C₁₈, optionally sulfated C₁₀ to C₁₆ even numbered carbon chain length alcohols neutralized with a suitable basic salt such as sodium carbonate

or sodium hydroxide and mixtures thereof such that the alkyl sulfate surfactant has an even numbered C₈ to C₁₈, optionally C₁₀ to C₁₆, chain length. In certain embodiments, the alkyl sulfate is selected from the group consisting of sodium lauryl sulfate, hexadecyl sulfate and mixtures thereof. In certain embodiments, commercially available mixtures of alkyl sulfates are used. A typical percentage breakdown of alkyl sulfates by alkyl chain length in commercially available sodium lauryl sulfate (SLS) is as follows:

	Alkyl Component
	Chain Percentage
10	Length in SLS
	C ₁₂ >60%
	C ₁₄ 20%-35%
	C ₁₆ <10%
	C ₁₀ <1%
15	C ₁₈ <1%

Another suitable surfactant is one selected from the group consisting of sarcosinate surfactants, isethionate surfactants and taurate surfactants. Preferred for use herein are alkali metal or ammonium salts of these surfactants, such as the sodium and potassium salts of the following: lauroyl sarcosinate, myristoyl sarcosinate, palmitoyl sarcosinate, stearyl sarcosinate and oleoyl sarcosinate. The sarcosinate surfactant may be present in the compositions of the present invention from about 0.1% to about 2.5%, or from about 0.5% to about 2% by weight of the total composition.

In certain embodiments, the compositions of the present invention are substantially free of sodium lauryl sulfate. As used herein the term substantially free means less than 2% by weight of the composition, preferably less than 1%, less than 0.5%, less than 0.1%, less than 0.05% by weight of the composition. In certain embodiments, the composition of the present invention are free of sodium lauryl sulfate.

Zwitterionic synthetic surfactants useful in the present invention include derivatives of aliphatic quaternary ammonium, phosphonium, and sulfonium compounds, in which the aliphatic radicals can be straight chain or branched, and wherein one of the aliphatic substituents contains from about 8 to 18 carbon atoms and one contains an anionic water-solubilizing group, e.g., carboxy, sulfonate, sulfate, phosphate or phosphonate.

The amphoteric surfactants useful in the present invention include, but are not limited to, derivatives of aliphatic secondary and tertiary amines in which the aliphatic radical can be a straight chain or branched and wherein one of the aliphatic substituents contains from about 8 to about 18 carbon atoms and one contains an anionic water-solubilizing group, e.g.,
5 carboxylate, sulfonate, sulfate, phosphate, or phosphonate. Examples of suitable amphoteric surfactants include, but are not limited to alkyliminodipropionates, alkylamphoglycinates (mono or di), alkylamphopropionates (mono or di), alkylamphoacetates (mono or di), N-alkyl [3-aminopropionic acids, alkylpolyamino carboxylates, phosphorylated imidazolines, alkyl betaines, alkylamido betaines, alkylamidopropyl betaines, alkyl sultaines, alkylamido
10 sultaines, and mixtures thereof. In certain embodiments, the amphoteric surfactant is selected from the group consisting of alkylamidopropyl betaines, amphoacetates such as sodium auroamphoacetate and mixtures thereof. Mixtures of any of the above mentioned surfactants can also be employed. A more detailed discussion of anionic, nonionic and amphoteric surfactants can be found in U.S. Pat. No. 7,087,650 to Lennon; U.S. Pat. No. 7,084,104 to
15 Martin et al.; U.S. Pat. No. 5,190,747 to Sekiguchi et al.; and U.S. Pat. No. 4,051,234, Gieske, et al., each of which patents are herein incorporated by reference in their entirety.

In certain embodiments, the compositions of the claimed invention comprise less than about 9% of amphoteric surfactant, less than 5%, or less than 1.5%, or less than 1%, or less than 0.8, less than 0.5%, less than 0.4%, or less than .3% of amphoteric surfactants. In certain
20 embodiments, the composition of the present invention is free of amphoteric surfactants.

Additional surfactants may be added with the alkyl sulfate surfactant to aid in solubilization of the essential oils provided such surfactants do not affect the bioavailability of the essential oils. Suitable examples include additional anionic surfactants, nonionic surfactants, amphoteric surfactants and mixtures thereof. However, in certain embodiments,
25 the total surfactant concentration (including the alkyl sulfate surfactant alone or in combination with other surfactants) for mouth rinses of the present invention should not exceed or should be about 9% or less, optionally, the total surfactant concentration should be about 5% or less, optionally about 1% or less, optionally about 0.5% or less w/w% of active surfactant by weight of the composition.

30 In certain embodiments, a sugar alcohol (humectant) is also added to the oral compositions of the present invention. The sugar alcohol solvent(s) may be selected from

those multi-hydroxy-functional compounds that are conventionally used in oral and ingestible products. In certain embodiments, the sugar alcohol (s) should be nonmetabolized and non-fermentable sugar alcohol (s). In specific embodiments, the sugar alcohols include, but are not limited to sorbitol, glycerol, xylitol, mannitol, maltitol, inositol, allitol, altritol, dulcitol, galactitol, glucitol, hexitol, iditol, pentitol, ribitol, erythritol and mixtures thereof. Optionally, the sugar alcohol is selected from the group consisting of sorbitol and xylitol or mixtures thereof. In some embodiments, the sugar alcohol is sorbitol. In certain embodiments, the total amount of sugar alcohol (s), which are added to effectively aid in the dispersion or dissolution of the mouth rinse or other ingredients, should not exceed about 50% w/ of the total composition. Or, total amount of sugar alcohol should not exceed about 30% w/v of the total composition. Or, total amount of sugar alcohol should not exceed 25% w/v of the total composition. The sugar alcohol can be in an amount of from about 1.0% to about 24% w/v, or from about 1.5% to about 22% w/v, or from about 2.5% to about 20% w/v of the total composition.

In certain embodiments, a polyol solvent is added to the composition. The polyol solvent comprises a polyol or polyhydric alcohol selected from the group consisting of polyhydric alkanes (such as propylene glycol, glycerin, butylene glycol, hexylene glycol, 1,3-propanediol); polyhydric alkane esters (dipropylene glycol, ethoxydiglycol); polyalkene glycols (such as polyethylene glycol, polypropylene glycol) and mixtures thereof. In certain embodiments, the polyol solvent can be present in an amount of from 0% to about 40% w/v, or from about 0.5% to about 20% w/v, or from about 1.0% to about 10% w/v of the composition.

Sweeteners such as aspartame, sodium saccharin (saccharin), sucralose, stevia, acesulfame K and the like may be added for better taste in amounts of from about 0.0001% w/v to about 1.0% w/v. In certain preferred embodiments, the sweetener comprises sucralose.

In certain embodiments, the composition further comprises flavors or flavorants to modify or magnify the taste of the composition, or reduce or mask the sharp “bite” or “burn” of ingredients such as thymol. Suitable flavors include, but are not limited to, flavor oils such as oil of anise, anethole, benzyl alcohol, spearmint oil, citrus oils, vanillin and the like may be incorporated. Other flavors such as citrus oils, vanillin and the like may be incorporated to provide further taste variations. In these embodiments, the amount of flavor oil added to the

composition can be from about 0.001% to about 5% w/v, or from about 0.01% to about 0.3% w/v of the total composition. The particular flavors or flavorants, and other taste improving ingredients, employed will vary depending upon the particular taste and feel desired. Those skilled in the art can select and customize these types of ingredients to provide the desired results.

In certain embodiments, acceptably approved food dyes may be used to provide a pleasing color to the compositions of the invention. These may be selected from, but not limited to, the long list of acceptable food dyes. Suitable dyes for this purpose include FD&C yellow #5, FD&C yellow #10, FD&C blue #1 and FD&C green #3. These are added in conventional amounts, typically in individual amounts of from about 0.00001% w/v to about 0.0008% w/v, or from about 0.000035% w/v to about 0.0005% w/v of the composition.

Other conventional ingredients may be used in the liquid or mouth rinse compositions of this invention, including those known and used in the art. Examples of such ingredients include thickeners, suspending agents and softeners. Thickeners and suspending agents useful in the compositions of the present invention can be found in U.S. Pat. No. 5,328,682 to Pullen et al., herein incorporated by reference in its entirety. In certain embodiments, these are incorporated in amounts of from about 0.1% w/v to about 0.6% w/v, or about 0.5% w/v of the composition.

In some embodiments, antimicrobial preservatives may be added to the composition. Some antimicrobial preservatives which may be used include, but are not limited to cationic antibacterials, such as sodium benzoate, polyquaternium polycationic polymers (i.e. polyquaternium-42: Poly[oxyethylene(dimethylimino)ethylene (dimethylimino)ethylene dichloride]), quaternary ammonium salts or quaternary ammonium compounds, parabens (i.e. parahydroxybenzoates or esters of parahydroxybenzoic acid), hydroxyacetophenone, 1,2-Hexanediol, Caprylyl Glycol, chlorhexidine, alexidine, hexetidine, benzalkonium chloride, domiphen bromide, cetylpyridinium chloride (CPC), tetradecylpyridinium chloride (TPC), N-tetradecyl-4-ethylpyridinium chloride (TDEPC), octenidine, bisbiguanides, zinc or stannous ion agents, grapefruit extract, and mixtures thereof. Other antibacterial and antimicrobial agents include, but are not limited to: 5-chloro-2-(2,4-dichlorophenoxy)-phenol, commonly referred to as triclosan; 8-hydroxyquinoline and its salts, copper II compounds, including, but not limited to, copper(II) chloride, copper(II) sulfate, copper(II)

acetate, copper(II) fluoride and copper(II) hydroxide; phthalic acid and its salts including, but not limited to those disclosed in U.S. Pat. No. 4,994,262, including magnesium monopotassium phthalate; sanguinarine; salicylanilide; iodine; sulfonamides; phenolics; delmopinol, octapinol, and other piperidino derivatives; niacin preparations; nystatin; apple
5 extract; thyme oil; thymol; antibiotics such as augmentin, amoxicillin, tetracycline, doxycycline, minocycline, metronidazole, neomycin, kanamycin, cetylpyridinium chloride, and clindamycin; analogs and salts of the above; methyl salicylate; hydrogen peroxide; metal salts of chlorite; pyrrolidone ethyl cocoyl arginate; lauroyl ethyl arginate monochlorohydrate; and mixtures of all of the above. In another embodiment, the composition comprises phenolic
10 antimicrobial compounds and mixtures thereof. Antimicrobial components may be present from about 0.001% to about 20% by weight of the oral care composition. In another embodiment the antimicrobial agents generally comprise from about 0.1% to about 5% by weight of the oral care compositions of the present invention.

Other antibacterial agents may be basic amino acids and salts. Other embodiments
15 may comprise arginine.

In certain embodiments, the compositions may include whitening agents, oxidizing agents, anti-inflammatories, chelating agents, abrasives, combinations thereof, and the like.

A whitening agent may be included as an active in the present compositions. The actives suitable for whitening are selected from the group consisting of alkali metal and
20 alkaline earth metal peroxides, metal chlorites, polyphosphates, perborates inclusive of mono and tetrahydrates, perphosphates, percarbonates, peroxyacids, and persulfates, such as ammonium, potassium, sodium and lithium persulfates, and combinations thereof. Suitable peroxide compounds include hydrogen peroxide, urea peroxide, calcium peroxide, carbamide peroxide, magnesium peroxide, zinc peroxide, strontium peroxide and mixtures thereof. In
25 one embodiment the peroxide compound is carbamide peroxide. Suitable metal chlorites include calcium chlorite, barium chlorite, magnesium chlorite, lithium chlorite, sodium chlorite, and potassium chlorite. Additional whitening actives may be hypochlorite and chlorine dioxide. In one embodiment the chlorite is sodium chlorite. In another embodiment the percarbonate is sodium percarbonate. In one embodiment the persulfates are oxones. The
30 level of these substances is dependent on the available oxygen or chlorine, respectively, that the molecule is capable of providing to bleach the stain. In one embodiment the whitening

agents may be present at levels from about 0.01% to about 40%, in another embodiment from about 0.1% to about 20%, in another embodiment form about 0.5% to about 10%, and in another embodiment from about 4% to about 7%, by weight of the oral care composition.

The compositions of the invention may contain an oxidizing agent, such as a peroxide source. A peroxide source may comprise hydrogen peroxide, calcium peroxide, carbamide peroxide, or mixtures thereof. In some embodiments, the peroxide source is hydrogen peroxide. Other peroxide actives can include those that produce hydrogen peroxide when mixed with water, such as percarbonates, e.g., sodium percarbonates. In certain embodiments, the peroxide source may be in the same phase as a stannous ion source. In some embodiments, the composition comprises from about 0.01% to about 20% of a peroxide source, in other embodiments from about 0.1% to about 5%, in certain embodiments from about 0.2% to about 3%, and in another embodiment from about 0.3% to about 2.0% of a peroxide source, by weight of the oral composition. The peroxide source may be provided as free ions, salts, complexed, or encapsulated. It is desirable that the peroxide in the composition is stable. The peroxide may provide a reduction in staining, as measured by the Cycling Stain Test, or other relevant methods.

Anti-inflammatory agents can also be present in the compositions of the present invention. Such agents may include, but are not limited to, non-steroidal anti-inflammatory (NSAID) agents, oxicams, salicylates, propionic acids, acetic acids and fenamates. Such NSAIDs include but are not limited to ketorolac, flurbiprofen, ibuprofen, naproxen, indomethacin, diclofenac, etodolac, indomethacin, sulindac, tolmetin, ketoprofen, fenoprofen, piroxicam, nabumetone, aspirin, diflunisal, meclofenamate, mefenamic acid, oxyphenbutazone, phenylbutazone and acetaminophen. Use of NSAIDs such as ketorolac are claimed in U.S. Pat. No. 5,626,838. Disclosed therein are methods of preventing and/or treating primary and reoccurring squamous cell carcinoma of the oral cavity or oropharynx by topical administration to the oral cavity or oropharynx of an effective amount of an NSAID. Suitable steroidal anti-inflammatory agents include corticosteroids, such as flucinolone, and hydrocortisone.

The present compositions may optionally contain chelating agents, also called chelants or sequestrants, many of which also have anticalculus activity or tooth substantive activity. Use of chelating agents in oral care products is advantageous for their ability to

complex calcium such as found in the cell walls of bacteria. Chelating agents can also disrupt plaque by removing calcium from the calcium bridges which help hold this biomass intact. 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. In addition, chelants can in principle remove stains by binding to teeth surfaces thereby displacing color bodies or chromagens. The retention of these chelants can also prevent stains from accruing due to disruption of binding sites of color bodies on tooth surfaces. Therefore, chelants can aid in helping to mitigate stain and improve cleaning. A chelant may help to improve the cleaning as fused silica and abrasives clean in a mechanical mechanism while the chelant may help to provide chemical cleaning. Because the fused silica is a good mechanical cleaner, there may be more stain removed so a chelant may be desired to hold, suspend, or complex with the stain so it is not able to restrain the tooth surface. Additionally, the chelant may coat the surface of the tooth to help prevent new stain. Chelants may be desired to be added to formulations containing cationic antibacterial agents. It may be desired to add chelants to stannous containing formulations. The chelant is able to help stabilize the stannous and keep a higher amount of the stannous bioavailable. The chelant may be used in stannous formulations which have a pH above about 4.0. In some formulations, the stannous may be stable without the need for a chelant as the stannous is more stable with fused silica as compared to precipitated silica.

Suitable chelating agents include soluble phosphate compounds, such as phytates and linear polyphosphates having two or more phosphate groups, including tripolyphosphate, tetrapolyphosphate and hexametaphosphate, among others. Preferred polyphosphates are those having the number of phosphate groups n averaging from about 6 to about 21, such as those commercially known as Sodaphos ($n \approx 6$), Hexaphos ($n \approx 13$), and Glass H ($n \approx 21$). 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. The amount of chelating agent in the compositions will depend on the chelating agent used and typically will be from at least about 0.1% to about 20%, preferably from about 0.5% to about 10% and more preferably from about 1.0% to about 7%.

Still other phosphate compounds that are useful herein for their ability to bind, solubilize and transport calcium are the surface active organophosphate compounds described above useful as tooth substantive agents including organic phosphate mono-, di- or triesters.

Other suitable agents with chelating properties for use in controlling plaque, calculus and stain include polyphosphonates described in U.S. Pat. No. 3,678,154 to Widder et al., U.S. Pat. No. 5,338,537 to White, Jr.; carbonyl; acrylic acid polymer or copolymer in U.S. Pat. No. 4,847,070, Jul. 11, 1989 to Pyrz et al. and in U.S. Pat. No. 4,661,341, Apr. 28, 1987 to Benedict et al.; sodium alginate in U.S. Pat. No. 4,775,525, issued Oct. 4, 1988, to Pera; polyvinyl pyrrolidone in GB 741,315, WO 99/12517 and U.S. Pat. No. 5,538,714 to Pink et al.; and copolymers of vinyl pyrrolidone with carboxylates in U.S. Pat. No. 5,670,138 to Venema et al.

Still other chelating agents suitable for use in the present invention are the anionic polymeric polycarboxylates. Such materials are well known in the art, being employed in the form of their free acids or partially or preferably fully neutralized water soluble alkali metal (e.g. potassium and preferably sodium) or ammonium salts. Examples are 1:4 to 4:1 copolymers of maleic anhydride or acid with another polymerizable ethylenically unsaturated monomer, preferably methyl vinyl ether (methoxyethylene) having a molecular weight (M.W.) of about 30,000 to about 1,000,000. These copolymers are available for example as Gantrez® AN 139 (M.W. 500,000), AN 119 (M.W. 250,000) and S-97 Pharmaceutical Grade (M.W. 70,000), of GAF Chemicals Corporation. Other operative polymeric polycarboxylates include the 1:1 copolymers of maleic anhydride with ethyl acrylate, hydroxyethyl methacrylate, N-vinyl-2-pyrrolidone, or ethylene, the latter being available for example as Monsanto EMA No. 1103, M.W. 10,000 and EMA Grade 61, and 1:1 copolymers of acrylic acid with methyl or hydroxyethyl methacrylate, methyl or ethyl acrylate, isobutyl vinyl ether or N-vinyl-2-pyrrolidone. Additional operative polymeric polycarboxylates are

disclosed in U.S. Pat. No. 4,138,477, Feb. 6, 1979 to Gaffar and U.S. Pat. No. 4,183,914, Jan. 15, 1980 to Gaffar et al. and include copolymers of maleic anhydride with styrene, isobutylene or ethyl vinyl ether; polyacrylic, polyitaconic and polymaleic acids; and sulfoacrylic oligomers of M.W. as low as 1,000 available as Uniroyal ND-2. Other suitable
5 chelants include polycarboxylic acids and salts thereof described in U.S. Pat. No. 5,015,467 to Smitherman U.S. Pat. Nos. 5,849,271 and 5,622,689 both to Lukacovic; such as tartaric acid, citric acid, gluconic acid, malic acid; succinic acid, disuccinic acid and salts thereof, such as sodium or potassium gluconate and citrate; citric acid/alkali metal citrate combination; disodium tartrate; dipotassium tartrate; sodium potassium tartrate; sodium hydrogen tartrate;
10 potassium hydrogen tartrate; acid or salt form of sodium tartrate monosuccinate, potassium tartrate disuccinate, and mixtures thereof. In some embodiments, there may be mixtures or combinations of chelating agents.

Suitable abrasives for use in the present invention may include, but are not limited to: perlite, silica such as sand or quartz, ground glass, silicon carbide, ilmenite (FeTiO_3), zircon
15 oxide, zircon silicate, topaz, TiO_2 , precipitated lime, chalk, flour of pumice, zeolites, talcum, kaolin, kieselguhr, aluminum oxide, silicates, zinc orthophosphate, sodium bicarbonate (baking soda), plastic particles, alumina, hydrated alumina, calcium carbonate, calcium pyrophosphate, and mixtures thereof. The silica abrasive may be natural amorphous silica including diatomaceous earth; or a synthetic amorphous silica such as a precipitated silica; or
20 a silica gel, such as a silica xerogel; or mixtures thereof.

Generally, an amount of abrasive suitable for use in the composition of the invention will be empirically determined to provide an acceptable level of cleaning and polishing, in accordance with the techniques well known in the art. In one embodiment, a composition of the present invention includes an abrasive. In one embodiment, a composition includes a
25 silica abrasive. In one embodiment, a silica abrasive is present in an amount of from 0.001 wt. % to 30 wt. %. In one embodiment, a silica abrasive is present in an amount of from 1 wt. % to 15 wt. %. In one embodiment, a silica abrasive is present in an amount of from 4 wt. % to 10 wt. %

Other useful oral care actives and/or inactive ingredients and further examples thereof
30 can be found in U.S. Pat. No. 6,682,722 to Majeti et al. and U.S. Pat. No. 6,121,315 to Nair et al., each of which are herein incorporated by reference in its entirety.

The compositions of the present invention may be made according to any of a variety of methods disclosed herein and known in the art. In general, the described compositions may be prepared by combining the desired components in a suitable container and mixing them under ambient conditions in any conventional mixing means well known in the art, such as a mechanically stirred propeller, paddle, and the like.

The compounds and compositions of the present invention may be used in the oral cavity. According to certain embodiments, the present invention comprises inhibiting, preventing, and/or treating the demineralization of teeth by contacting the tooth surface with a composition of the present invention. In certain embodiments, the present invention comprises inhibiting or preventing the demineralization of teeth by contacting the tooth surface with a composition of the present invention.

In each of the above methods, the composition of the claimed method may be introduced to the tooth surface via any of a variety of methods. In certain embodiments, the composition is introduced into the oral cavity and applied to the tooth surface by a user as a mouthwash or mouth rinse. In certain embodiments, the composition is introduced to the oral cavity and applied to the tooth surface as toothpaste on an article for cleaning the teeth, e.g. a toothbrush. The compositions of the present invention may be further introduced via the mouth and applied to the tooth surface as a gum, lozenge, dissolvable strip, or the like.

Furthermore, the contacting step of the methods of the present invention may comprise contacting the tooth surface with the composition for any suitable amount of time. In certain embodiments, the contacting step comprises contacting the surface for less than thirty seconds. In certain embodiments, the contacting step comprises contacting the surface with the composition for thirty seconds or more, for example, for about thirty seconds, for about forty seconds, for about one minute, or for greater than one minute.

EXAMPLES

EXAMPLE 1

A cationic copolymer of vinyl pyrrolidone (cationic PVP-copolymer) was prepared via copolymerization of n-vinyl pyrrolidone (VP) monomer with n-vinyl phthalimide (VPA)

monomer followed by hydrazinolysis of VPA to vinyl amine. The resultant copolymer is referred to as PVP-PVAmine.

Briefly, a mixture of isopropyl alcohol (IPA, 105 g) and acetic acid (0.05 g) was heated to approximately 82°C in a round bottom flask under nitrogen atmosphere and gentle agitation. An initiator solution consisting of IPA (125 g) and a mix of VPA (30 g), VP (70 g) and VAZO 67 (0.4 g, Chemours Inc.) was added gradually over 90 minutes. The reaction temperature was allowed to rise during the polymerization to 85-86°C and maintained at this temperature for an additional hour before cooling to 80°C. Hydrazine hydrate (200 g) was then added to the reaction mixture and the temperature was held at 80°C for an additional 2.5 hours. The solution was diluted with methanol (600 g) and phthalhydrazine solids were removed by vacuum filtration. The extract was distilled to concentrate the final solution to approximately 100g. The polymer was then precipitated from tetrahydrofuran, filtered, and vacuum dried for several hours. The predicted composition of the polymer is 64.8 wt% VP/35.2 wt% VPA based on titration to pH endpoint of 5.0 (2.03 meq/g Titer). All chemicals were purchased from Sigma-Aldrich unless otherwise noted.

EXAMPLE 2

The anti-erosion efficacy of PVP-PVAmine synthesized in Example 1 was compared to commercially available PVP homopolymers (Sigma Aldrich – Cat.# PVP10, PVP4, PVP360) by measuring the pH change due to the dissolution of hydroxyapatite (HAP) powder in citric acid solution. Treatment solutions were prepared by dissolving the PVP homopolymers or PVP-PVAmine copolymer in water and adjusting the pH using hydrochloric acid or sodium hydroxide.

In brief, prior to treatment, 100 mg of Ceramic Hydroxyapatite, Type I, 20 µm (Bio-Rad Laboratories, Inc. – Cat. # 158-2000) was incubated for 2 hours at 37°C in artificial saliva (Northeast Laboratory, Waterville, ME – Cat. # T0300) to allow formation of salivary pellicle. Pellicle-coated HAP powder was subjected to one ten-minute treatment mixing end over end with 10 mL of assigned treatment solution. Treated particles were subsequently filtered using a 5 µm pore size, 25 mm diameter, polycarbonate membrane filter (Whatman® Nuclepore™ Track-Etched Membranes – Cat. # 110613) and rinsed with DI water before dispersing into 25 mL of 1 wt% citric acid solution at pH 3.8. The bulk pH value of the citric

acid solution was recorded every 30 seconds for 10 minutes. Erosion prevention efficacy was measured from the magnitude of the pH increase from baseline, with lower pH increases indicative of slower dissolution and greater efficacy.

Tables 1 and 2 show the compositions of the various treatment solutions. Table 1 lists solutions with PVP homopolymers, while Table 2 lists solutions with PVP-PVAmine copolymers. In some of the solutions, sodium fluoride (NaF), or Sodium Tripolyphosphate (PPi) were added to determine if synergistic effects could be found when fluoride or phosphate ions were in the treatment solution. The tables also show positive controls (100 ppm NaF in water) and negative controls (water).

Table 1: Prototype formulas of PVP homopolymers used in the manual erosion prevention study. Concentrations are listed in % wt/wt.

Ingredient	A2	B2	C2	D2	E2	F2	G2	H2
PVP (average mol wt 10,000)	-	-	2.000	2.000	-	-	-	-
PVP (average mol wt 40,000)	-	-	-	-	2.000	2.000	-	-
PVP (average mol wt 360,000)	-	-	-	-	-	-	2.000	2.000
Sodium Fluoride	-	0.0221	-	-	-	-	-	-
Water, pH adjuster	100	QS	QS	QS	QS	QS	QS	QS
pH	N/A	4.2	4.2	7.0	4.2	7.0	4.2	7.0

Note: concentration converted to %w/w assuming bulk product density of 1.000 g/mL.

A2 = Water (negative control)

B2 = 100 ppm F, pH=4.2 (positive control)

C2 = PVP-10K, pH 4.2

D2 = PVP-10K, pH 7.0

E2 = PVP-40K, pH 4.2

F2 = PVP-40K, pH 7.0

G2 = PVP-360K, pH 4.2

H2 = PVP-360K, pH 7.0

Table 2. Prototype formulas of PVP-PVAmine used in the manual erosion prevention study.

Concentrations are listed in % wt/wt.

Ingredient	A2	B2	I2	J2	K2	L2	M2
PVP-PVAmine	-	-	3.086	3.086	-	3.086	3.086
Sodium Tripolyphosphate (PPi)	-	-	-	-	1.266	1.266	1.266
Sodium Fluoride	-	0.0221	-	0.0221	-	-	0.0221
Water, pH adjuster	100	QS	QS	QS	QS	QS	QS
pH	N/A	4.2	6.8	6.8	-	6.8	6.8

Note: concentration converted to %w/w assuming bulk product density of 1.000 g/mL.

5

A2 = Water (negative control)

B2 = 100 ppm F, pH 4.2 (positive control)

I2 = PVP-PVAmine, pH 6.8

J2 = PVP-PVAmine + 100 ppm F, pH 6.8

10 K2 = PPi

L2 = PVP-PVAmine + PPi, pH 6.8

M2 = PVP-PVAmine + PPi + 100 ppm F, pH 6.8

15 Table 3 summarized the erosion prevention efficacy of the treatment solutions from
Tables 1 and 2.

Table 3: Results of manual erosion prevention study of prototype formulas of PVP homopolymers and PVP-PVAmine copolymers, given as the increase in pH of the bulk solution from baseline (ΔpH).

Formulation	ΔpH
A2	0.29
B2	0.09
C2	0.26
D2	0.29
E2	0.28
F2	0.28
G2	0.30
H2	0.28
I2	0.23
J2	0.04
K2	0.22
L2	0.13
M2	0.04

5

Table 3 shows that the treatment solutions containing only PVP (C2 thru H2) offer insignificant erosion prevention when compared to water alone (ΔpH of 0.29 for water versus 0.26 to 0.30 for PVP treatment solutions). The treatment solution with PVP-PVAmine alone (I2) was superior in erosion prevention to water alone, while the solution of PVP-PVAmine with Sodium Tripolyphosphate (PPi), solution L2, was superior in erosion prevention to PPi alone. The treatment solutions showing the highest erosion prevention efficacy were those where PVP-PVAmine combined with fluoride (J2) or with both fluoride and phosphate ions (M2). These treatment solutions outperformed the positive control (B2).

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So, in summary, treatment solutions comprising cationic PVP-copolymer PVP-PVAmine are better in erosion prevention than solutions comprising PVP polymers.

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EXAMPLE 3

A second cationic copolymer of vinyl pyrrolidone (cationic PVP-copolymer) was prepared via copolymerization of n-vinyl pyrrolidone (VP) monomer with n-vinyl formamide (VF) monomer followed by deprotection by aqueous caustic hydrolysis. The resultant copolymer is also referred to as PVP-PVAmine.

Briefly, a solution of isopropyl alcohol (IPA, 80 g) and water (360 g) was heated to approximately 82°C in a round bottom flask under nitrogen atmosphere and gentle agitation. An initial solution of the initiator VAZO 56 (1 g, Chemours Inc.) in water (20 g) was added. Next, a monomer/initiator solution consisting of VF (60 g), VP (340 g), VAZO 56 (3 g) and water (36 g) was added gradually over 120 minutes. The pH of the solution was checked periodically and a solution of mono sodium phosphate (~20% in water) was added as needed to maintain a pH of 6-6.5. During the polymerization the temperature was allowed to rise to 83-84 C and maintained at this temperature for an additional 30 minutes before cooling to 73 °C. A promoter solution of FeSO₄ heptahydrate (0.01g) in water (5 g) was then added, followed by an initiator chase solution of 70% T-butyl hydroperoxide (0.75 g) diluted in water (5 g). The reaction temperature maintained at 77°C for 20 min. A second initiator chase solution was then added, followed by an activator solution of isoascorbic acid (1 g) in water (10 g). The temperature maintained for an additional 20 min and then allowed to cool. The polymer solution was then diluted with water (900g) and purified by overnight dialysis (Slide-A-Lyzer G2 dialysis cassette, MWCO = 2k) against an equal weight of water. VF was hydrolyzed by addition of sodium bisulfite (2 g dissolved in 5 g of water) and heating to 80° C for 4 hours in a round bottom flask. The polymer solution was then cooled, and purified again by overnight dialysis. The final polymer was isolated by precipitation in acetone and vacuum drying at 50°C overnight. The theoretical composition of the polymer was 85 wt% VP/15wt% VF, corresponding to 2.11 meq/g of titer for titration to a pH endpoint of 5.0. The actual titer required was 1.2 meq/g. All chemicals were purchased from Sigma-Aldrich unless otherwise noted.

EXAMPLE 4

The influence of the PVP-PVAmine synthesized in Example 3 on hydroxyapatite remineralization was assessed using a constant-composition based auto-titration method.

Treatment solutions comprising PVP-PVAmine were compared to treatment solutions comprising a commercially available PVP homopolymer. Treatment solutions were prepared by dissolving the PVP homopolymer or PVP-PVAmine copolymer in water and adjusting the pH to 4.2 using hydrochloric acid or sodium hydroxide.

In brief, prior to treatment 50 mg of Ceramic Hydroxyapatite, Type I, 20 μ m (Bio-Rad Laboratories, Inc. – Cat. # 158-2000) was soaked overnight in 10 mL of artificial complete saliva (Northeast Laboratory, Waterville, ME – Cat. # T0300) to form a pellicle layer. The pellicle coated hydroxyapatite was then subjected to one ten-minute treatment, filtered, rinsed, and added to a solution of artificial saliva solution (1 mM CaCl_2 , 0.6 mM KH_2PO_4 , pH = 7.4). The pH and calcium activity were measured and maintained at a constant level by auto-titration (Metrohm Titrando). Greater remineralization efficacy was correlated with greater volumes of titrant added to maintain constant composition.

Table 4 shows the compositions of the various treatment solutions. In some of the solutions, sodium fluoride (NaF) was added to determine if synergistic effects could be found when fluoride ions were in the treatment solution. The tables also show positive controls (0.0221 NaF in water) and negative controls (water).

Table 4. Prototype formulas of PVP-PVAmine used in constant composition experiments. Concentrations are listed in % wt/wt. *Plasdone K-29/32 polymer from Ashland, a commercially available water-soluble homopolymer of N-vinyl-2-pyrrolidone with a typical molecular weight of 58,000 daltons.

Ingredient	A2	B2	C4	D4	E4	F4	G4	H4
PVP-PVAmine	-	-	-	-	1.000	1.000	5.000	5.000
PVP*	-	-	0.850	0.850	-	-	-	-
Sodium Fluoride	-	0.0221	-	0.0221	-	0.0221	-	0.0221
Water, pH adjuster	100	QS	QS	QS	QS	QS	QS	QS
pH	N/A	4.2	4.2	4.2	4.2	4.2	4.2	4.2

Table 5 summarized the results of the constant composition experiments for the treatment solutions from Table 4.

Table 5: Results of constant composition experiments given as the final titrant volume (in mls) after 30 min of auto-titration.

Formulation	Final Titrant Volume (mean $\pm$ SE, mls)
A2	8.3 $\pm$ 0.6
B2	25.0 $\pm$ 2
C4	9.4 $\pm$ 0.09
D4	26.8 $\pm$ 0.6
E4	12.2 $\pm$ 0.4
F4	31.0 $\pm$ 2
G4	12.1 $\pm$ 0.7
H4	25.3 $\pm$ 0.7

The table shows that Final Titrate Volume of treatment solutions containing only PVP (C4) offer insignificant remineralization efficacy when compared to water alone (8.3 mL for water versus 9.4 mL for PVP treatment solutions). For treatment solutions with PVP-PVAmine alone (E4, G4), the Final Titrate Volume rises to about 12 mL. When fluoride is added to the PVP-PVAmine treatment solutions, remineralization efficacy increases by as much as 24% relative to treatment with fluoride alone (B2).

EXAMPLE 5

In vitro remineralization efficacy of PVP-PVAmine prototype formulas was evaluated based on five-day remineralization-demineralization cycling. The PVP-PVAmine used in this example was that synthesized in Example (3).

Briefly, twenty-four ground and polished human enamel specimens were demineralized to create non-cavitated artificial lesions. Artificial lesions were formed through immersion of specimens in a demineralization solution and the baseline lesion surface ranged 25-45 in units of Vickers hardness number (VHN). Initial surface microhardness was measured for each specimen using a Shimadzu Micro Hardness Tester. The twenty-four specimens were divided into four groups of six, with the four groups being balanced by the initial surface microhardness of the specimens.

The four treatment groups were subjected to a series of treatments followed by remineralization and demineralization steps. The four treatment groups used formulations C4, D4, E4 and F4 from Table 4 of Example 4. In brief, C4 was 0.85% PVP homopolymer, D4 was 0.85% PVP with 100 ppm F, E4 was 1% PVP-PVAmine, and F4 was 1% PVP-PVAmine with 100 ppm F.

The remineralization step used artificial saliva (130 mM KCl, 1.5 mM CaCl₂, 0.9 mM KH₂PO₄, 25 mM BTP buffer, 2.2 g/L Porcine Mucin, pH =7), while the demineralization step used lactic acid (0.1 M lactic acid, 0.2 wt% Carbopol, 50% saturated with hydroxyapatite, pH = 5.0). The daily regimen, followed for five days, is given in Table 6.

Table 6: Daily regimen for five-day remineralization-demineralization cycling study. *At the start of the study the first treatment is preceded by one hour soak in artificial saliva. ** On day five of the study the final treatment is followed by one hour soak in artificial saliva.

00:02	Treatment*
01:28	Artificial Saliva Soak
00:02	Treatment
01:28	Artificial Saliva Soak
02:00	Lactic Acid Challenge
01:30	Artificial Saliva Soak
00:02	Treatment
01:28	Artificial Saliva Soak
00:02	Treatment
15:58	Overnight Artificial Saliva Soak**

After five days, specimens were evaluated for change in surface microhardness (Δ SMH) measured using a Shimadzu Micro Hardness Tester, in units of Vickers hardness number (VHN). Higher remineralization efficacy was correlated with a greater increase in surface microhardness. Table 7 shows the change in surface microhardness following five days of treatment.

Table 7: Change in surface microhardness following five-day remineralization/demineralization cycling.

Treatments	Δ SMH (VHN)
C4	1 ± 2
D4	13 ± 11
E4	2 ± 2
F4	36 ± 10

Table 7 shows that following 20 treatments over five days, an increase in the surface microhardness of the enamel specimens treated with PVP-Amine with 100 ppm F was observed. Treatment with 1 wt% PVP-PVAmine and fluoride (F4) resulted in a Δ SMH 1.8x higher than treatment with the PVP homopolymer and fluoride (D4).

EXAMPLE 6

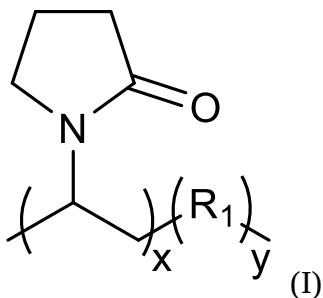
Solutions of 1 wt% PVP-PVAmine synthesized in Example 3 and diluted in commercially available or experimental mouthwash formulations were prepared and their stability tested following (i) equilibrium at room temperature, (ii) equilibrium at 40°C, and (iii) freeze-thaw cycling. The formulations tested are given in Table 8, and represent both fluoride and non-fluoride containing formulations, alcohol and alcohol-free formulations, and alcohol-free formulations with and without anionic surfactants. All solutions were initially homogenous throughout. Failed stability was identified as the loss of this homogeneity, for example due to the formation of a precipitate. After at least 22-week storage at room temperature or 40°C, only formulations containing sodium lauryl sulfate surfactant had failed stability. Additionally, all solutions prepared from commercially available formulations, including those containing an anionic surfactant, had passing stability after three freeze-thaw cycles of 24 hours at -10°C and 24 hours at 25°C.

Table 8: Commercially available mouthwash formulation used to test the stability of PVP-PVAmine

Product Name	Country of Origin	Contains Alcohol	Contains Fluoride	Contains Sodium Lauryl Sulfate Surfactant
LISTERINE ZERO mouthwash	United States	No	No	Yes
LISTERINE ZERO mouthwash	Germany	No	Yes	Yes
LISTERINE COOL MINT mouthwash	United States	Yes	No	No
LISTERINE TOTAL CARE ENAMEL GUARD mouthwash	United Kingdom	Yes	Yes	No
Experimental mouthwash	NA	No	No	No

What is claimed is:

1. A composition comprising an orally-acceptable carrier and a cationic copolymer having repeat units derived from n-vinyl pyrrolidone (VP) and repeat units derived from monomers containing amines or guanidine.
2. The composition of claim 1 wherein said copolymer is described by Formula I below:



wherein x and y are integers in a ratio of from 1:99 to about 99:1, the repeat units x and y are randomly distributed, and R₁ is a repeat unit containing an amine group.

3. The composition of claim 2 wherein R₁ is derived from a monomer compound selected from the group consisting of n-vinyl phthalimide, 2-N-morpholinoethyl acrylate, methacryloylcholine methyl sulfate, 2-N-morpholinoethyl methacrylate, 2-diisopropylaminoethyl methacrylate, 2-aminoethyl methacrylate, Methacryloyl-L-lysine, N-[3-(N,N-dimethylamino)propyl] methacrylamide, N-(2-aminoethyl) methacrylamide, 2-(N,N-Dimethylamino)ethyl acrylate, 2-(N,N-Diethylamino)ethyl methacrylate, 2-(tert-Butylamino)ethyl methacrylate, 2-(N,N-Dimethylamino)ethyl methacrylate, 2-Acryloxyethyltrimethylammonium, and the like.

4. The composition of claim 3 wherein R₁ is derived from n-vinyl phthalimide.

5. The composition of claim 2 wherein R₁ is a repeat unit derived from a cationic monomer comprising an amide followed by deprotection of the amide to an amine.

- 5 6. The composition of claim 5 wherein said cationic monomer comprising an amide is selected from the group consisting of n-vinyl formamide, N-(3-aminopropyl)methacrylamide, N-(3-BOC-aminopropyl)methacrylamide, N-[2-(N,N-dimethylamino)ethyl]methacrylamide, N-[3-(N,N-Dimethylamino)propyl] acrylamide and the like.
- 10 7. The composition of claim 7 wherein aid cationic monomer comprising an amide is n-vinyl formamide.
- 10 8. The composition of claim 1 comprising from about 0.01 to about 5% of said cationic copolymer.
- 15 9. The composition of claim 1 further comprising fluoride.
- 15 10. The composition of claim 1 further comprising sodium tripolyphosphate.
- 20 11. The composition of claim 1 wherein said composition is in a form selected form the group consisting of a mouthwash, mouth rinse, mouth spray, toothpaste, tooth gel, sub-gingival gel, mousse, foam, denture care product, dentifrice, lozenge, concentrate and chewable tablet.
- 25 12. The composition of claim 11 wherein said composition is a mouthwash comprising water, and at least one surfactant selected from the group consiting of anionic, cationic, non-ionic, zwitterionic surfactants and combinations of two or more thereof.
- 25 13. The composition of claim 11 further comprising at least one essential oil selected from the group consiting of menthol, thymol, eucalyptol, methyl salicylate, and combinations of two or more thereof.
- 30 14. The composition of claim 13 further comprising fluoride.
- 30 15. The composition of claim 13 further comprising sodium tripolyphosphate.

16. The composition of claim 1 wherein said copolymer has a weight average molecular weight of from about 10,000 to about 1,000,000.
- 5 17. The composition of claim 6 wherein said copolymer has a weight average molecular weight of from about 10,000 to about 1,000,000.
18. The composition of claim 17 wherein said copolymer has a weight average molecular weight of from about 10,000 to about 500,000.
- 10 19. The composition of claim 1 said composition being substantially free of sodium lauryl sulfate.
20. The composition of claim 12 said composition being substantially free of sodium lauryl sulfate.
- 15 21. A method of inhibiting demineralization of a tooth by contacting a tooth surface with a composition of claim 1.
22. A method of inhibiting demineralization of a tooth by contacting a tooth surface with a composition of claim 13.
- 20 23. A method of inhibiting demineralization of a tooth by contacting a tooth surface with a composition of claim 14.