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**Two component compositions containing zinc amino acid halide complexes and cysteine**

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(54) Title: TWO COMPONENT COMPOSITIONS CONTAINING ZINC AMINO ACID HALIDE COMPLEXES AND CYSTEINE

(57) Abstract: Provided are compositions, e.g., oral and personal care products, comprising (i) a zinc (amino acid or trialkyl glycine) halide complex, and (ii) cysteine in free or in orally or cosmetically acceptable salt form, together with methods of making and using the same.

## TWO COMPONENT COMPOSITIONS CONTAINING ZINC AMINO ACID HALIDE COMPLEXES AND CYSTEINE

### CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation in part of PCT/US2013/46268, filed on 18 June 2013; PCT/US2012/70489, filed on 19 December 2012; PCT/US2012/70492, filed on 19 December 2012; PCT/US2012/70498, filed on 19 December 2012; PCT/US2012/70506, filed on 19 December 2012; PCT/US2012/70513, filed on 19 December 2012; PCT/US2012/70505, filed on 19 December 2012; PCT/US2012/70501, filed on 19 December 2012; PCT/US2012/70521, filed on 19 December 2012; PCT/US2012/70534, filed on 19 December 2012; and PCT/US2013/50845, filed on 17 July 2013, all of which are incorporated herein by reference.

### BACKGROUND

[0002] Conventional antiperspirants comprising salts of aluminum or aluminum/zirconium are known. These salts function as antiperspirants by forming polymeric complexes which can plug pores, thereby blocking sweat release. There is a need for additional antiperspirant active agents that provide complexes of a size capable of plugging pores to block sweat, that provide deodorant/antibacterial efficacy, and that are less irritating to the skin than the acidic salts in conventional antiperspirants. There is also a need for alternative antibacterial and skin protective agents for use in liquid hand soaps and body washes. Finally, there is a need for agents in oral care products which can whiten and strengthen teeth, retard erosion, and inhibit bacteria and plaque.

[0003] Certain zinc amino-acid complexes can produce zinc-containing precipitates upon dilution with water or other aqueous preparations. Some zinc-containing precipitates are composed of zinc oxide, zinc hydroxide, zinc halides, etc. The precipitates can be deposited onto skin as well as hard and soft dental tissues. Potential benefits related to deposition on the hard tissues include whitening, sensitivity relief, erosion protection and anticavity. Potential benefits related to deposition on the soft tissue include improvement in the host immune response, enhancement in the tissue's barrier function, etc. Zinc ions can be released from the depositions, providing antibacterial, bacteriostatic and other plaque and gingivitis benefits as commonly associated with zinc ions.

**[0004]** Some zinc amino-acid complexes, however, do not have the most optimal precipitation kinetics. In another words, their rate of precipitation upon dilution may be too slow or too fast for typical applications. For example, for oral care typical recommended brushing times range from 1 minute to 3 minutes, but an average person brushes for a significantly shorter duration. Typical recommended rinsing times with a mouthrinse is about a minute, but an average person spends much less time. Some zinc amino-acid complex dilutions typically require more than 3 minutes to precipitate in any substantial quantity, and the amount of precipitation is limited within a typical brushing and rinsing time.

**[0005]** Therefore, there exists a need for optimizing the precipitation times of zinc complexes. In particular, there is a need for reducing the precipitation times associated with the zinc amino-acid complexes with a slow precipitation profile.

**[0005a]** Any discussion of documents, acts, materials, devices, articles or the like which has been included in the present specification is not to be taken as an admission that any or all of these matters form part of the prior art base or were common general knowledge in the field relevant to the present disclosure as it existed before the priority date of each claim of this application.

**[0005b]** Throughout this specification the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated element, integer or step, or group of elements, integers or steps, but not the exclusion of any other element, integer or step, or group of elements, integers or steps.

**[0005c]** In a first aspect, there is provided an oral care or personal care product comprising a container having: (i) a first compartment containing a first component comprising a zinc-(amino acid or trialkyl glycine) halide complex, and (ii) a second compartment containing a second component comprising cysteine in free or in orally or cosmetically acceptable salt form; wherein the first and second compartments maintain the first and second components separate from each other, and wherein the product dispenses a mixture of the first component and the second component for application to the body.

**[0005d]** Another aspect, there is provided the product of claim 1 further comprising glycerol in the first component, in the second component or in both components.

## BRIEF SUMMARY

**[0006]** Provided is a dual component composition to deliver a zinc precipitate to the body which comprises (i) a first component comprising an aqueous solution of zinc X halide complex (“ZXH”, wherein X refers to an amino acid or trialkylglycine, “TAG”), and optionally, glycerol and (ii) a second component comprising acidified cysteine in aqueous solution with, optionally, glycerol; the first and second components being maintained separate from each other until dispensed and combined for application to the body.

**[0007]** The unusual and unexpected properties of this material is that the two components, when mixed, provide a rapid (instant or intentionally delayed) precipitation that allows the delivery of a zinc-containing complex to the body, in particular skin or oral cavity, making it useful in personal care products, e.g., antiperspirant products and liquid hand and body soaps, as well as in oral care products, e.g. mouthwash or dentifrice.

**[0008]** Further areas of applicability of the present invention will become apparent from the detailed description provided hereinafter. It should be understood that the detailed description and specific examples, while indicating the preferred embodiment of the invention, are intended for purposes of illustration only and are not intended to limit the scope of the invention.

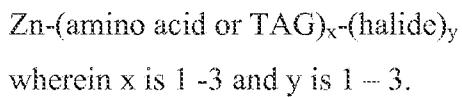
## DETAILED DESCRIPTION

**[0009]** The following description of the preferred embodiment(s) is merely exemplary in nature and is in no way intended to limit the invention, its application, or uses.

[0010] As used throughout, ranges are used as shorthand for describing each and every value that is within the range. Any value within the range can be selected as the terminus of the range. In addition, all references cited herein are hereby incorporated by reference in their entireties. In the event of a conflict in a definition in the present disclosure and that of a cited reference, the present disclosure controls.

[0011] Unless otherwise specified, all percentages and amounts expressed herein and elsewhere in the specification should be understood to refer to percentages by weight. The amounts given are based on the active weight of the material.

[0012] The zinc (amino acid or TAG) halide complex, i.e., ZXH, can be formed by reacting one or more zinc compounds (e.g., zinc oxide, zinc hydroxide, zinc chloride...etc., but tetrabasic zinc chloride is specifically excluded) and a halide salt of a basic amino acid to obtain a complex having the general formula:



[0013] In one embodiment, the ZXH is a zinc amino acid halide complex (“ZAH”) such as a zinc-lysine-chloride complex (“ZLC”), e.g., formed from a mixture of zinc oxide and lysine hydrochloride, having the formula  $[\text{Zn}(\text{C}_6\text{H}_{14}\text{N}_2\text{O}_2)_2\text{Cl}]^+\text{Cl}^-$ . In this complex,  $\text{Zn}^{2+}$  is coordinated by two lysine ligands with two N atoms from  $\text{NH}_2$  groups and two O atoms from carboxylic groups in an equatorial plane. Not wishing to be bound by theory, it is believed that it displays a distorted square-pyramidal geometry with the apical position occupied by a  $\text{Cl}^-$  atom. This structure gives rise to a positive cation moiety, to which a  $\text{Cl}^-$  anion is combined to form an ionic salt.

[0014] In another embodiment, the trialkylglycine (TAG) is  $\text{C}_1\text{-C}_4$  alkylglycine or trimethylglycine.

[0015] ZLC may exist in solution of the cationic ( $[\text{Zn}(\text{C}_6\text{H}_{14}\text{N}_2\text{O}_2)_2\text{Cl}]^+$ ) and the chloride anion, or may be a solid salt, e.g., a crystal, optionally in mono- or dihydrate form, e.g., as a monohydrate crystal having a powder x-ray diffraction pattern with major peaks having a relative intensity and spacing and spacing substantially as depicted in Figure 1 of PCT/US2012/70498.

[0016] Other complexes of zinc and amino acid are possible, and the precise form is dependent in part on the molar ratios of the precursor compounds, e.g., if there is limited halide, halide-free

complexes may form, e.g.  $\text{ZnLys}_2$ , having a pyramid geometry, with the equatorial plane that is same as the above compound (Zn is bound to two oxygen and two nitrogen atoms from different lysines), wherein the top of the pyramid is occupied by a Cl atom. Under particular conditions, zinc oxide can also react with lysine and/or lysine-HCl to form a clear solution of Zn-lysine-chloride complex ( $\text{ZnLys}_2\text{Cl}_2$ ), wherein  $\text{Zn}_2^+$  is located in an octahedral center coordinated with two oxygen and two nitrogen atoms in the equatorial plane coming from two lysine's carboxylic acids and amine groups respectively. The zinc in this complex is also coordinated to the third lysine via its nitrogen and carboxylic oxygen, at the apical position of the metal geometry. The ZXH complexes, e.g. ZLC, have key features (e.g., conductivity, hydrolysis reaction and protein flocculation) which make it competitive with commercial antiperspirant salts. Like conventional aluminum or aluminum-zirconium antiperspirant salts, the ZXH forms precipitates that can plug the pores and block sweat release. As the amount of water increases, the ZXH hydrolyzes to distribute a relatively insoluble zinc-containing precipitate. The precipitate typically contains one or more of zinc oxide, zinc cysteine, zinc hydroxide, or other zinc-containing compounds. This precipitate is unique in that it will allow plugging of pores on the skin. Furthermore, this reaction is atypical since, in most cases, dilution will increase the solubility of an ionic complex. Additionally, zinc is antibacterial, so it provides a precipitate which blocks sweat release from the pores while also providing a deodorant benefit by reducing odor-causing bacteria.

[0017] It is important to note that zinc oxide is soluble at low pH, and as sweat has a pH of 5-6, the sweat can reduce the levels of precipitation of the zinc oxide compared to precipitation levels at neutral pH. Moreover, the sweat can gradually dissolve the depositions, reducing the duration of action of the formulation. This problem can be ameliorated by co-formulating the product with cysteine. The cysteine and the ZHX together form a precipitate. Upon use and dilution with sweat, the precipitate is more resistant to acid than ZHX alone. The formulation comprising ZXH together with cysteine thus has enhanced efficacy as an antiperspirant.

[0018] We have found that when combining cysteine with ZXH at certain pH's, rapid precipitation is the result. The precipitation is prominent even in undiluted formulas which results in storage stability problems in oral care or personal care products. Also, rapid precipitation can result in fewer zinc ions being deposited at desired body sites. We have discovered that this rapid precipitation problem can be solved by physically separating the ZHX from the cysteine until use or application.

[0019] While visible signs of precipitation from some ZLC formulations typically first appear about 30 minutes or more from dilution, the dual component compositions of the invention form visible precipitates from less than 1 second to about 20 seconds after mixing the two components even in undiluted or low-diluted form. The presence of cysteine results in rapid precipitation of zinc complexes. The kinetics or rate of precipitation can vary depending on factors such as pH, cysteine concentration, and amount of dilution (if any). In some embodiments instantaneous precipitation of ZXH complexes is observed upon mixing the two components. For example, if cysteine is present as approximately 0.8 – 1.3 wt% of a cysteine+ZLC solution, an instantaneous precipitate will form. As used herein, “rapid precipitation” means forming a zinc precipitate in 3 minutes or less, “instant precipitation” or “instantaneous precipitation” means forming a zinc precipitate in 1 second or less, and “delayed precipitation” means forming a zinc precipitate between 1 second and up to 3 minutes.

[0020] In preparing the two components of the composition of the invention, typically two stock solutions are prepared, each stock solution containing, respectively ZXH and acidified cysteine. To prepare the two stock solutions, several reagents are necessary. The first component of the stock solution can be prepared by utilization of a standard synthesis procedure for making ZXH. For example, preparing a ZLC stock solution includes reacting zinc oxide with lysine-HCl over water. Then, excess zinc oxide is filtered off to ultimately make a clear solution. This solution is then the stock of ZLC and can be the main active ingredient in component one. Glycerol can be utilized as a co-solvent in component one as well. In the second component, the acidified cysteine stock solution can be prepared by either dissolving cysteine salt in dilute aqueous mineral acid, e.g., hydrochloric acid, or cysteine-HCl can be dissolved in water. Glycerol can also be utilized as a co-solvent in component two.

[0021] A two-component delivery system has been discovered to allow control of zinc complex precipitation times. The first component comprises ZXH, e.g., ZLC. The pH of the first component is alkaline, for example, about 7 to 9, or about 7.25 to about 8.75 or about 7.5 to about 8.5. The pH of the second component is acidic, for example, about 3 to about 6 or about 4 to about 5 or about 4.5 to about 5. The pH of the second component is typically achieved by dissolving the cysteine in an acid, e.g., a mineral acid such as a hydrohalide, e.g., hydrochloric acid, and/or acidification can be achieved by dissolving cysteine monohydrohalide, e.g., monohydrochloride, in water, preferably deionized water.

[0022] It has been discovered that rapid precipitation of zinc complexes occurs at certain pH's, even without dilution. Thus, the pH of the two components when mixed is about 5 to about 8, in another embodiment about 5 to about 6.5, in another embodiment about 6 to about 7, and in another embodiment about 6 to about 6.5. The pH of each component is tailored to achieve the desired pH upon mixing to result the desired rapid rate of precipitation.

[0023] The first and second components are aqueous compositions. Typically the first component will contain about 10 to about 85% water, in another embodiment about 20 to about 85% water, in another embodiment about 20 to about 25% water, and in yet another embodiment about 30 to about 33% water. The second component will typically contain about 10% to about 95% water, in another embodiment about 20 to about 30% water, in another embodiment about 90% to about 95% water. The amount of water in each component will vary depending upon the final product form in order to achieve the desired concentration when the components are mixed. For example, dentifrices typically contain 10 to 25 % total water, mouthwashes typically contain 50 to 90 % total water, personal care products such as antiperspirants typically contain 10 to 20% total water. The precipitation time and pH values of the mixtures are affected by many factors, including water concentration. More water generally leads to more rapid precipitation and higher pH values of the mixture.

[0024] Provided is a dual component composition to deliver zinc to the body which comprises (i) a first component comprising a zinc (amino acid or TAG) halide complex (ZXH) e.g.,  $[Zn(C_6H_{14}N_2O_2)_2Cl]^+Cl^-$  (ZLC) and (ii) a second component comprising cysteine in free or in orally or cosmetically acceptable salt form, the first and second components being maintained separate from each other until dispensed and combined for application to the body. The term "body" includes any site on the body where it is desirable to deposit zinc ions, e.g., skin, in particular pores of sweat glands, and the oral cavity, in particular soft and hard (teeth) tissues. The compositions may be oral care products, e.g., dentifrice or mouthrinse, or personal care products, such as antiperspirants, liquid hand soap or body wash, and skin lotions, creams and conditioners.

[0025] Upon application of the composition of the invention the first component, or component one, containing ZXH is mixed with the second component, or component two, containing acidified cysteine. The weight ratio of component one:component two after mixing is typically about 1:1, but can vary somewhat depending on the compositions of the specific components and

the specific dispensing means used, for example, about 5:1 to about 1:5, in another embodiment about 1:2 to about 2:1.

[0026] The dual component ZXH/cysteine combination is useful in oral care products, for example dentifrice or mouthrinse. A dual component formulation comprising the ZXH/cysteine combination provides an effective concentration of zinc ions to the enamel, thereby protecting against erosion, reducing bacterial colonization and biofilm development, and providing enhanced shine to the teeth. Moreover, upon mixing and use, the formulation is diluted and provides a stabilized precipitate that plugs the dentinal tubules, thereby reducing the sensitivity of the teeth. While providing efficient delivery of zinc in comparison to formulations with insoluble zinc salts, the formulations comprising the ZXH/cysteine combination do not exhibit the poor taste and mouthfeel, poor fluoride delivery, and poor foaming and cleaning associated with conventional zinc-based oral care products using soluble zinc salts.

[0027] Further provided are methods of using such compositions, e.g., methods of reducing sweat comprising applying the composition to skin, methods of killing bacteria comprising contacting the bacteria with the composition, and methods of treating or reducing dental hypersensitivity, erosion, and plaque, comprising applying the composition to the teeth, as well as methods of making such compositions. In the methods of the invention the two components of the composition of the invention are mixed and applied to the body, e.g., skin or oral cavity. The mixing is typically performed just before or during application to the body so that upon application to the body the precipitate is formed at the desired site, e.g., at pores of sweat glands or at the openings of dentinal tubules. In one embodiment the two components are mixed during application, e.g., brushing with a dentifrice where the two components are applied to a toothbrush which are mixed during brushing. The methods of the invention takes advantage of the property of the precipitate being formed in 3 minutes or less after mixing to deliver maximal amount of zinc to the desired body sites.

[0028] In one embodiment, glycerol is added to the first component, second component or both which results in delay of precipitate formation, typically a delay of about 1 to 20 seconds, in one embodiment about 1 to 10 seconds, in another embodiment about 1 to 5 seconds, and in another embodiment about 1 to 3 seconds, as compared to a control formulation without glycerol. In addition to delaying precipitation, the glycerol can also function as a humectant.

[0029] The mixing can result in precipitation without dilution; however, dilution with water or an aqueous fluid such as saliva or sweat generally enhances precipitation. In a particular embodiment, a two component system is provided wherein a first component comprises the ZXH complex and the second component comprises cysteine. In the two-component system, two containers or chambers are provided containing the respective components. The cysteine is present in an amount effective to result in rapid precipitation (instant or delayed) when the two components are mixed together. In the delayed precipitation embodiment, just before or during use and application, the two components are mixed whereby the precipitate does not form while mixing, but does form at the desired body location upon application. The two component system is particularly advantageous to maximize the amount of precipitation at the desired site during use, e.g., at dentinal tubules, tooth surface, pores of sweat glands, and the like.

[0030] The dual component compositions of the present invention, e.g., dentifrices, body washes or mouthrinses, are packaged in a suitable dispensing container in which the components are maintained physically separated and from which the separated components may be dispensed synchronously, e.g., as a combined ribbon for application to a toothbrush. Such containers are known in the art. An example of such a container is a two compartment dispensing container, such as a pump or a tube, having collapsible sidewalls, as disclosed in U.S. Pat. No. 4,487,757 and 4,687,663; wherein, the tube body is formed from a collapsible plastic web such as polyethylene or polypropylene and is provided with a partition within the container body defining separate compartments in which the physically separated components are stored and from which they are dispensed through a suitable dispensing outlet. For mouthwashes or mouthrinses, the two components can be delivered by two separate chambers of a bottle into a mixing cup. Upon mixing, the mixture can be transferred to a human mouth and a rinse can be carried out. When the components are dispensed, they will mix in the mixing cup forming a slightly delayed precipitate that will react with appropriate kinetics as to ensure all precipitation forms within the mouth.

[0031] Provided is, in a first embodiment, a dual component composition (Composition 1) comprising (i) a first component comprising a zinc amino acid halide complex or a zinc-trialkylglycine halide complex and (ii) a second component comprising acidified cysteine in free or in orally or cosmetically acceptable salt form, wherein the two components are maintained separate from each other until dispensed and combined for application to the body, e.g.,

- 1.1. Composition 1 wherein the zinc (amino acid or TAG) halide is formed from precursors, wherein the precursors are a zinc ion source, an amino acid or TAG source, and a halide source, wherein the halide source can be part of the zinc ion source, the amino acid or TAG source, or a halogen acid.
- 1.2. Composition 1 or 1.1 wherein the zinc ion source is at least one of zinc oxide, zinc chloride, zinc carbonate, zinc hydroxide, zinc nitrate, zinc citrate, and zinc phosphate.
- 1.3. Composition 1.1 or 1.3 wherein the amino acid source is at least one of a basic amino acid, lysine, arginine, and glycine.
- 1.4. Any of the foregoing compositions, wherein the trialkyl glycine is a C<sub>1</sub>-C<sub>4</sub> alkyl glycine or trimethyl glycine.
- 1.5. Any of the foregoing compositions wherein the pH of the first component is 3 to 6 or 4 to 5 or 4.5 to 5; and the pH of the second component is 7 to 9 or 7.25 to 8.75 or 7.5 to 8.5.
- 1.6. Any of the foregoing compositions wherein the two components are mixed and the pH of the resulting mixture is 6 to 8 or 7 to 8.
- 1.7. Any of the foregoing compositions wherein the first component contains 0 to 50% or 20 to 40% glycerol; or the second component contains 0 to 50% or 20 to 40% glycerol.
- 1.8. Any of compositions 1.-1.6 wherein the first component contains 0 to 50% or 20 to 40% glycerol; and the second component contains 0 to 50% or 20 to 40% glycerol.
- 1.9. Any of the foregoing Compositions wherein the zinc amino acid halide is made by combining zinc oxide with an amino acid hydrohalide.
- 1.10. Any of the foregoing Compositions wherein the zinc (amino acid or TAG) halide has the formula Zn(Amino Acid or TAG)<sub>2</sub>Hal<sub>2</sub> or Zn(Amino Acid or TAG)<sub>3</sub>Hal<sub>2</sub>, wherein Zn is a divalent zinc ion and Hal is a halide ion.
- 1.11. Any of the foregoing Compositions wherein the zinc amino acid halide complex is [Zn(C<sub>6</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub>)<sub>2</sub>Cl]<sup>+</sup>Cl<sup>-</sup> (sometimes referred to herein as “ZLC”), and wherein when the complex is in crystalline form, e.g. in hydrate form, e.g. a monohydrate or dihydrate, e.g., having a structure wherein the Zn cation is coordinated by two lysine ligands with two nitrogen atoms from alpha NH<sub>2</sub> groups of the two lysine ligands and two oxygen atoms from carboxylic groups of the two lysine ligands in an equatorial plane, having a distorted square-pyramidal geometry with the apical position occupied by a chlorine atom, to form a positive cation moiety, with which a chloride anion is combined to form

an ionic salt Composition 1 or 1.1 wherein the zinc-(amino acid or TAG)-halide complex is  $[Zn(C_6H_{14}N_2O_2)_2Cl]^+Cl^-$  (sometimes referred to herein as “ZLC”), optionally in hydrate form, e.g. a complex formed from a mixture of zinc oxide and lysine hydrochloride, e.g., in a molar ratio of ZnO:Lysine·HCl of 1:1 to 3:1, e.g., 2:1.

- 1.12. Any of the foregoing Compositions which upon dilution with water, provides a precipitate comprising zinc oxide in complex with cysteine, and optionally additionally comprising zinc oxide, zinc carbonate, and mixtures thereof.
- 1.13. Any of the foregoing compositions wherein the total amount of zinc present in the composition when the two components are mixed is about 0.2 to about 9%, or about 0.6% to about 1% or about 2% to about 3% by weight of the total composition.
- 1.14. Any of the foregoing composition the about of zinc present in the first component is about 0.6% to about 2%, or about 0.8% to about 1.5% or about 1% to about 1.2% by weight of the first component.
- 1.15. Any of the foregoing compositions wherein the ratio of zinc to cysteine is from about 5:1 to about 10:1 by weight of the total composition
- 1.16. Any of the foregoing compositions, wherein the cysteine is a cysteine hydrohalide, optionally cysteine hydrochloride.
- 1.17. Any of the foregoing compositions wherein a zinc precipitate forms within 30 seconds, or 1 second to 30 seconds, or 1 to 15 seconds or 1 to 3 seconds after mixing the two components.
- 1.18. Any of the foregoing compositions further comprising an orally or cosmetically acceptable carrier in the first component, second component or both.
- 1.19. Any of the foregoing compositions further comprising an orally or cosmetically acceptable carrier, and which is an oral care product selected from dentifrice or mouthwash, or a personal care product, selected from antiperspirants, deodorants, liquid hand soap, body wash, dermal lotions, dermal creams, and dermal conditioners.
- 1.20. Any of the foregoing compositions wherein the first component contains about 10% to about 85% water, or about 20 to about 85% water, or about 20 to about 25% water, or about 30 to about 33% water; and the second component contains about 10% to about 95% water or about 20 to about 30% water, or about 40% to about 50% water.

[0032] Provided is a method of making composition 1, *et seq.* comprising (i) combining a zinc ion source, an amino acid or TAG source, a halide source (wherein the halide source can be part of the zinc ion source, the amino acid or TAG source, or a halogen acid), in a fluid (e.g., aqueous) medium optionally containing glycerol, optionally isolating the complex thus formed in solid form and placing the material thus formed into a first container, (ii) placing cysteine optionally with glycerol, and optionally with a hydrohalide, in a second container physically separate from the first container. Either or both of the materials in the separate containers can optionally be combined with a cosmetically or orally acceptable carrier.

[0033] Provided is a composition (Composition 2) which is an antiperspirant or deodorant product comprising (i) a first component comprising a zinc (amino acid or TAG) halide complex and (ii) a second component comprising acidified cysteine in free or in orally or cosmetically acceptable salt form, wherein the two components are maintained separate from each other until dispensed and combined for application to the body, and wherein either or both components additionally comprise a cosmetically acceptable carrier, e.g. in accordance with any of the scopes of Composition 1, *et seq.*

- 2.1. Composition 2 which, upon mixing and use, provides a precipitate to the skin, comprising zinc oxide in complex with cysteine, and optionally additionally comprising zinc oxide, zinc carbonate, and mixtures thereof.
- 2.2. Composition 2 or 2.1 wherein zinc (amino acid or TAG) halide complex is  $[\text{Zn}(\text{C}_6\text{H}_{14}\text{N}_2\text{O}_2)_2\text{Cl}]^+\text{Cl}^-$  (sometimes referred to herein as “ZLC”), optionally in hydrate form.
- 2.3. Composition 2 or 2.1 wherein the cosmetically acceptable carrier comprises one or more ingredients selected from water-soluble alcohols (such as C<sub>2-8</sub> alcohols including ethanol); glycols (including propylene glycol, dipropylene glycol, tripropylene glycol and mixtures thereof); glycerides (including mono-, di- and triglycerides); medium to long chain organic acids, alcohols and esters; surfactants (including emulsifying and dispersing agents); additional amino acids; structurants (including thickeners and gelling agents, for example polymers, silicates and silicon dioxide); emollients; fragrances; and colorants (including dyes and pigments).
- 2.4. Composition 2, 2.1, or 2.2 wherein the composition is in the form of an aerosol antiperspirant spray.

[0034] Also provided are methods of reducing perspiration comprising mixing both components and applying an antiperspirant effective amount of any of Composition 2, *et seq.* to the skin, methods of reducing body odor comprising mixing both components and applying a deodorant-effective amount of any of Composition 2, *et seq.* to the skin, and methods of killing bacteria comprising mixing both components and contacting the bacteria with any of Composition 2, *et seq.* For example, provided is (i) a method for controlling perspiration comprising mixing both components and applying to skin an antiperspirant effective amount of a formulation of any embodiment embraced or specifically described herein, e.g., any of Composition 2, *et seq.*; and (ii) a method for controlling odor from perspiration or bacteria on the skin, comprising mixing both components and applying to skin a deodorant effective amount of a formulation of any embodiment embraced or specifically described herein, e.g., any of Composition 2, *et seq.*

[0035] Provided is a method of making an antiperspirant or deodorant comprising (i) a first component comprising a zinc (amino acid or TAG) halide and (ii) a second component physically separate from the first component comprising cysteine in free or cosmetically acceptable salt form, e.g., any of Composition 2, *et seq.* comprising combining a cosmetically acceptable carrier, and optionally glycerol, with zinc amino acid halide in the first component, and/or with cysteine in the second component.

[0036] Also provided is (i) the use of any of Composition 2, *et seq.* to kill bacteria, reduce perspiration, and/or reduce body odor; and (iii) any of Composition 2, *et seq.* for use in killing bacteria, reducing perspiration, and/or reducing body odor.

[0037] Also provided is the use of cysteine in the manufacture of an antiperspirant or deodorant formulation, e.g., a formulation according to any of Composition 2, *et seq.*

[0038] In making Composition 2, *et seq.* the zinc (amino acid or TAG) halide and cysteine in free or cosmetically acceptable salt form can be incorporated into a suitable, cosmetically acceptable base, for example a spray, aerosol, stick, or roll-on for application to the underarm wherein the first and second components mix when forming an aerosol or when contacted through a nozzle or other dispensing means. Following application, in the presence of charged molecules such as proteins found on the skin, the salt will flocculate, forming plugs which block sweat release. Additional water from sweat can moreover dilute the formulation, causing the complex to decompose, resulting in a precipitate composed primarily of zinc oxide in complex with cysteine, which can reduce sweat and odor as described above.

[0039] As used herein, the term antiperspirant can refer generally to any product that can form a plug in a pore to reduce sweating, including those materials classified as antiperspirants by the Food and Drug Administration under 21 CFR part 350. It is understood that antiperspirants may also be deodorants, particularly in the case of the described compositions, as zinc has antibacterial properties and thus inhibits odor-causing bacteria on the skin.

[0040] Also provided is a composition (Composition 3) which is a personal care product selected from liquid hand soap, body wash, dermal lotions, dermal creams, and dermal conditioners comprising (i) a first component comprising a zinc (amino acid or TAG) halide complex and (ii) a second component comprising acidified cysteine in free or in orally or cosmetically acceptable salt form, wherein the two components are maintained separate from each other until dispensed and combined for application to the body, and wherein either or both components additionally comprise a cosmetically acceptable carrier, e.g. in accordance with any of the scopes of Composition 1, *et seq.*, e.g.:

- 3.1. Composition 3 which, upon mixture of both components and use, provides a precipitate to the skin, comprising zinc oxide in complex with cysteine, and optionally additionally comprising zinc oxide, zinc carbonate, and mixtures thereof.
- 3.2. Composition 3 or 3.1 comprising the zinc (amino acid or TAG) halide complex in an amount of 1 to 10 % by weight of the total composition.
- 2.5. Any of the foregoing compositions wherein the zinc amino acid halide complex is  $[\text{Zn}(\text{C}_6\text{H}_{14}\text{N}_2\text{O}_2)_2\text{Cl}]^+\text{Cl}^-$  (sometimes referred to herein as “ZLC”), optionally in hydrate form.
- 3.3. Any of the foregoing compositions, wherein a total amount of zinc present in the total composition is 0.2 to 8 wt.%, 0.1 to 8 wt.%, 0.1 to 2 wt.% or 0.1 to 1 wt.%.
- 3.4. Any of the foregoing compositions, wherein the cysteine is a cysteine hydrohalide, optionally cysteine hydrochloride.
- 3.5. Any of the foregoing compositions wherein the cosmetically acceptable carrier comprises one or more ingredients selected from water-soluble alcohols (such as C<sub>2-8</sub> alcohols including ethanol); glycols (including propylene glycol, dipropylene glycol, tripropylene glycol and mixtures thereof); glycerides (including mono-, di- and triglycerides); medium to long chain organic acids, alcohols and esters; surfactants (including emulsifying and dispersing agents); additional amino acids; structurants (including thickeners and gelling

agents, for example polymers, silicates and silicon dioxide); emollients; fragrances; and colorants (including dyes and pigments).

- 3.6. Any of the foregoing compositions, wherein the cosmetically acceptable carrier comprises one or more nonionic surfactants, for example non-ionic surfactants selected from amine oxide surfactants (e.g., fatty acid amides of alkyl amines, for example lauramidopropyldimethylamine oxide, myristamidopropylamine oxide and mixtures thereof), alcohol amide surfactants (e.g., fatty acid amides of alcohol amines, e.g., cocamide MEA (cocomonoethanolamide)), polyethoxylated surfactants (e.g. polyethoxylated derivatives of esters of fatty acids and polyols (for example glycols, glycerols, saccharides or sugar alcohols), for example polysorbates or PEG-120 methyl glucose dioleate), and combinations thereof.
- 3.7. Any of the foregoing compositions wherein the cosmetically acceptable carrier comprises an anionic surfactant, e.g. selected from sodium lauryl sulfate and sodium ether lauryl sulfate.
- 3.8. Any of the foregoing compositions wherein the cosmetically acceptable carrier comprises water, an anionic surfactant, e.g., sodium laureth sulfate, a viscosity modifying agent, e.g., acrylates copolymer, and a zwitterionic surfactant, e.g., cocamidopropyl betaine.
- 3.9. Any of the foregoing compositions wherein the cosmetically acceptable carrier is substantially free of anionic surfactants.
- 3.10. Any of the foregoing compositions wherein the cosmetically acceptable carrier comprises water, quaternary ammonium agents (e.g. cetrimonium chloride), humectant (e.g. glycerin), and non-ionic surfactant (e.g., selected from amine oxide surfactants (e.g., lauramidopropyldimethylamine oxide myristamidopropylamine oxide and mixtures thereof), alcohol amide surfactants (e.g., cocamide MEA (cocomonoethanolamide)), polyethoxylate surfactants (e.g. PEG-120 methyl glucose dioleate), and combinations thereof).
- 3.11. Any of the foregoing compositions, wherein the cosmetically acceptable carrier comprises an antibacterially effective amount of a non-zinc antibacterial agent, e.g., an antibacterial agent selected from triclosan, triclocarban, chloroxylenol, herbal extracts and essential oils (e.g. rosemary extract, tea extract, magnolia extract, thymol, menthol, eucalyptol, geraniol, carvacrol, citral, hinokitol, catechol, methyl salicylate,

epigallocatechin gallate, epigallocatechin, gallic acid), bisguanide antiseptics (e.g., chlorhexidine, alexidine or octenidine), and quaternary ammonium compounds (e.g., cetylpyridinium chloride (CPC), benzalkonium chloride, tetradecylpyridinium chloride (TPC), N-tetradecyl-4-ethylpyridinium chloride (TDEPC)); and combinations thereof; for example an antibacterially effective amount of benzalkonium chloride.

3.12. Any of the foregoing compositions which has pH of 6-8 when the two components are mixed.

3.13. Any of the foregoing compositions comprising ingredients as follows:

Material	Weight %
Water	80-90%
Quaternary ammonium antibacterial agents, e.g., selected from cetrimonium chloride (cetyl trimethyl ammonium chloride), C <sub>12-18</sub> alkydimethylbenzyl ammonium chloride (BKC), and combinations thereof	0.1-4%
Humectants, e.g., glycerin	1-3%
Non-ionic surfactant, e.g., selected from amine oxide surfactants (e.g., lauramidopropyltrimethylamine oxide myristamidopropylamine oxide and mixtures thereof), alcohol amide surfactants (e.g., cocamide MEA (cocomonooctanolamide)), polyethoxylate surfactants (e.g. PEG-120 methyl glucose dioleate), and combinations thereof	1-5%
Buffering agents and agents to adjust pH	1-3%
Preservatives and/or chelators	0.1-2%
Fragrance and coloring agents	0.1-2%
ZLC	1-5%, e.g., 3-4%
Cysteine	0.1 – 1%, e.g. 0.5%

wherein the formulation is in a container that has a divided chamber; one chamber containing the above base with cysteine and the other containing the above base with ZLC.

[0041] Also provided are methods of killing bacteria comprising mixing both components and contacting the bacteria with an antibacterially effective amount of the mixture, e.g., with any of Composition 3, *et seq.*, for example, methods of treating or reducing the incidence of topical skin infections, for example infections by *Staphylococcus aureus* and/or *Streptococcus pyogenes*, as well as to treat or reduce the incidence of acne, comprising washing the skin with an antibacterially effective amount of a ZLC and cysteine, e.g., with any of Composition 3, *et seq.*, and water.

[0042] Also provided is a method of making a personal care comprising (i) a first component comprising a zinc (amino acid or TAG) halide and (ii) a second component physically separate from the first component comprising cysteine in free or cosmetically acceptable salt form, e.g., any of Composition 3, *et seq.* comprising combining a cosmetically acceptable carrier, and optionally glycerol, with zinc amino acid halide in the first component, and/or with cysteine in the second component.

[0043] Also provided is (i) the use of a dual component composition containing ZXH complex and cysteine, e.g., any of Compositions 1, *et seq.*, to kill bacteria, to protect the skin, e.g., from bacteria or to provide a visual signal when washing; (ii) the use of a ZLC and cysteine in the manufacture of a composition, any of Compositions 1, *et seq.*, to kill bacteria, to protect the skin, or to provide a visual signal when washing; and (iii) ZLC and cysteine, e.g., any of Compositions 1, *et seq.*, for use to kill bacteria, to protect the skin, or to provide a visual signal when washing.

[0044] For example, in one embodiment, either the first component comprising the zinc (amino acid or TAG) complex or the second component comprising the cysteine, or both are mixed with conventional commercial liquid hand soap formulation ingredients comprising surfactants and optionally benzalkonium chloride. Upon mixing both components and dilution a white precipitate is instantaneously formed. Thus, the composition of the invention can provide a visual/sensory trigger for the washing process. The precipitate, composed of ZnO stabilized by cysteine, is deposited on skin and thus enhances the antimicrobial effect of the LHS.

[0045] Also provided is a composition (Composition 4) which is an oral care product, e.g., a dentifrice or mouthrinse, comprising (i) a first component comprising a zinc (amino acid or TAG) halide complex and (ii) a second component comprising acidified cysteine in free or in orally or cosmetically acceptable salt form, wherein the two components are maintained separate from each other until dispensed and combined for application to the oral cavity, and wherein either or both components additionally comprise an orally acceptable carrier, e.g. in accordance with any of the scopes of Composition 1, *et seq.*, e.g.:

- 4.1. Composition 4 in the form of a dentifrice which upon mixing and application to the teeth provides a precipitate to the teeth, comprising zinc oxide in complex with cysteine, and optionally additionally comprising zinc oxide, zinc carbonate, and mixtures thereof.
- 4.2. Composition 4 or 4.1 in the form of a dentifrice wherein the zinc (amino acid or TAG) halide complex is present in an effective amount, e.g., in an amount of 0.5-4% by weight

of zinc, e.g., 1-3% by weight of zinc of the total composition, and wherein the orally acceptable carrier is a dentifrice base.

- 4.3. Any of the foregoing compositions wherein the zinc amino acid halide complex is  $[\text{Zn}(\text{C}_6\text{H}_{14}\text{N}_2\text{O}_2)_2\text{Cl}]^+\text{Cl}^-$  (sometimes referred to herein as “ZLC”), optionally in hydrate form.
- 4.4. Any of the foregoing compositions 4-4.3 in the form of a dentifrice, wherein the orally acceptable carrier is a dentifrice base comprising an abrasive, e.g., an effective amount of a silica abrasive, e.g., 10-30%, e.g., 20%.
- 4.5. Any of the foregoing compositions wherein the zinc amino acid halide complex is present in an effective amount, e.g., in an amount of 0.1-3% by weight of zinc, e.g., 0.2-1% by weight of zinc of the total composition.
- 4.6. Any of the foregoing compositions, wherein the cysteine is a cysteine hydrohalide, optionally cysteine hydrochloride.
- 4.7. Any of the foregoing compositions further comprising an effective amount of a fluoride ion source, e.g., providing 500 to 3000 ppm fluoride based on the total composition.
- 4.8. Any of the foregoing compositions further comprising an effective amount of fluoride, e.g., wherein the fluoride is a salt selected from stannous fluoride, sodium fluoride, potassium fluoride, sodium monofluorophosphate, sodium fluorosilicate, ammonium fluorosilicate, amine fluoride (e.g., N'-octadecyltrimethylendiamine-N,N,N'- tris(2-ethanol)-dihydrofluoride), ammonium fluoride, titanium fluoride, hexafluorosulfate, and combinations thereof.
- 4.9. Any of the preceding compositions comprising an effective amount of one or more alkali phosphate salts, e.g., sodium, potassium or calcium salts, e.g., selected from alkali dibasic phosphate and alkali pyrophosphate salts, e.g., alkali phosphate salts selected from sodium phosphate dibasic, potassium phosphate dibasic, dicalcium phosphate dihydrate, calcium pyrophosphate, tetrasodium pyrophosphate, tetrapotassium pyrophosphate, sodium tripolyphosphate, and mixtures of any of two or more of these, e.g., in an amount of 1-20%, e.g., 2-8%, e.g., ca. 5%, by weight of the composition.
- 4.10. Any of the foregoing compositions comprising buffering agents, e.g., sodium phosphate buffer (e.g., sodium phosphate monobasic and disodium phosphate).

- 4.11. Any of the foregoing compositions comprising a humectant, e.g., selected from sorbitol, propylene glycol, polyethylene glycol, xylitol, and mixtures thereof. Any of the preceding compositions comprising one or more surfactants, e.g., selected from anionic, cationic, zwitterionic, and nonionic surfactants, and mixtures thereof, e.g., comprising an anionic surfactant, e.g., a surfactant selected from sodium lauryl sulfate, sodium ether lauryl sulfate, and mixtures thereof, e.g. in an amount of from 0.3% to 4.5% by weight, e.g. 1-2% sodium lauryl sulfate (SLS); and/or a zwitterionic surfactant, for example a betaine surfactant, for example cocamidopropylbetaine, e.g. in an amount of from 0.1% to 4.5% by weight of the total composition, e.g. 0.5-2% cocamidopropylbetaine.
- 4.12. Any of the preceding compositions further comprising a viscosity modifying amount of one or more of polysaccharide gums, for example xanthan gum or carrageenan, silica thickener, and combinations thereof.
- 4.13. Any of the preceding compositions comprising gum strips or fragments.
- 4.14. Any of the preceding compositions further comprising flavoring, fragrance and/or coloring.
- 4.15. Any of the foregoing compositions comprising an effective amount of one or more antibacterial agents, for example comprising an antibacterial agent selected from halogenated diphenyl ether (e.g. triclosan), herbal extracts and essential oils (e.g., rosemary extract, tea extract, magnolia extract, thymol, menthol, eucalyptol, geraniol, carvacrol, citral, hinokitol, catechol, methyl salicylate, epigallocatechin gallate, epigallocatechin, gallic acid, miswak extract, sea-buckthorn extract), bisguanide antiseptics (e.g., chlorhexidine, alexidine or octenidine), quaternary ammonium compounds (e.g., cetylpyridinium chloride (CPC), benzalkonium chloride, tetradecylpyridinium chloride (TPC), N-tetradecyl-4-ethylpyridinium chloride (TDEPC)), phenolic antiseptics, hexetidine, octenidine, sanguinarine, povidone iodine, delmopinol, salifluor, metal ions (e.g., zinc salts, for example, zinc citrate, stannous salts, copper salts, iron salts), sanguinarine, propolis and oxygenating agents (e.g., hydrogen peroxide, buffered sodium peroxyborate or peroxycarbonate), phthalic acid and its salts, monoperthalic acid and its salts and esters, ascorbyl stearate, oleoyl sarcosine, alkyl sulfate, dioctyl sulfosuccinate, salicylanilide, domiphen bromide, delmopinol, octapinol

and other piperidino derivatives, nicin preparations, chlorite salts; and mixtures of any of the foregoing; e.g., comprising triclosan or cetylpyridinium chloride.

- 4.16. Any of the foregoing compositions comprising an antibacterially effective amount of triclosan, e.g. 0.1 -0.5%, e.g. 0.3% by weight of the total composition.
- 4.17. Any of the preceding compositions further comprising a whitening agent, e.g., a selected from the group consisting of peroxides, metal chlorites, perborates, percarbonates, peroxyacids, hypochlorites, and combinations thereof.
- 4.18. Any of the preceding compositions further comprising hydrogen peroxide or a hydrogen peroxide source, e.g., urea peroxide or a peroxide salt or complex (e.g., such as peroxyphosphate, peroxycarbonate, perborate, peroxy silicate, or persulphate salts; for example calcium peroxyphosphate, sodium perborate, sodium carbonate peroxide, sodium peroxyphosphate, and potassium persulfate);
- 4.19. Any of the preceding compositions further comprising an agent that interferes with or prevents bacterial attachment, e.g., solbrol or chitosan.
- 4.20. Any of the preceding compositions further comprising a source of calcium and phosphate selected from (i) calcium-glass complexes, e.g., calcium sodium phosphosilicates, and (ii) calcium-protein complexes, e.g., casein phosphopeptide-amorphous calcium phosphate
- 4.21. Any of the preceding compositions further comprising a soluble calcium salt, e.g., selected from calcium sulfate, calcium chloride, calcium nitrate, calcium acetate, calcium lactate, and combinations thereof.
- 4.22. Any of the preceding compositions further comprising a physiologically or orally acceptable potassium salt, e.g., potassium nitrate or potassium chloride, in an amount effective to reduce dentinal sensitivity.
- 4.23. Any of the foregoing compositions further comprising an anionic polymer, e.g., a synthetic anionic polymeric polycarboxylate, e.g., wherein the anionic polymer is selected from 1:4 to 4:1 copolymers of maleic anhydride or acid with another polymerizable ethylenically unsaturated monomer; e.g., wherein the anionic polymer is a methyl vinyl ether/maleic anhydride (PVM/MA) copolymer having an average molecular weight (M.W.) of 30,000 to 1,000,000, e.g. 300,000 to 800,000, e.g., wherein the anionic polymer is 1-5%, e.g., 2%, of the weight of the total composition.

4.24. Any of the preceding compositions further comprising a breath freshener, fragrance or flavoring.

4.25. Any of the foregoing compositions, wherein the pH of the total composition is approximately neutral, e.g., from pH 5 to pH 8 e.g., pH 7.

4.26. Any of the foregoing compositions in the form of an oral gel, wherein the amino acid is lysine and the zinc and lysine form a zinc amino acid halide complex having the chemical structure  $[Zn(C_6H_{14}N_2O_2)_2Cl]^+ Cl^-$ , in an amount to provide 0.1 – 8%, e.g., 0.5% zinc by weight, and further comprising humectant, e.g., sorbitol, propylene glycol and mixtures thereof, e.g., in an amount of 45-65%, e.g., 50-60%, thickeners, e.g., cellulose derivatives, e.g., selected from carboxymethyl cellulose (CMC), trimethyl cellulose (TMC) and mixtures thereof, e.g., in an amount of 0.1-2%, sweetener and/or flavorings, and water, e.g., an oral gel comprising

Ingredients	%
Sorbitol	40-60%, e.g., 50-55%
ZLC	to provide 0.1-2%Zn, e.g. 0.5% Zn
Cysteine	0.02 – 0.5%, e.g., 0.1%
Carboxymethyl cellulose (CMC) and Trimethyl cellulose (TMC)	0.5-1%, e.g., 0.7%
Flavoring and/or sweetener	0.01-1%
Propylene Glycol	1-5%, e.g., 3.00%

wherein the formulation is in a tube that has a dual chamber system that separates one side from the other; or, the system has a high enough density difference that allows for almost complete separation of the two stocks or components.

4.27. Any of the forgoing compositions for use to reduce and inhibit acid erosion of the enamel, clean the teeth, reduce bacterially-generated biofilm and plaque, reduce gingivitis, inhibit tooth decay and formation of cavities, and reduce dentinal hypersensitivity.

[0046] The dentifrice of the invention can be placed in a dual chamber tube, each chamber containing one of the respective components. Each component can contain a dentifrice base, e.g., a gel base, as well as either cysteine or ZLC. When the tube is squeezed both reagents will come out at the same time and mixing will take place in-vitro while brushing with the aid of the dentifrice base.

[0047] Also provided are methods to reduce and inhibit acid erosion of the enamel, clean the teeth, reduce bacterially-generated biofilm and plaque, reduce gingivitis, inhibit tooth decay and formation of cavities, and reduce dentinal hypersensitivity, comprising mixing both components and applying an effective amount of a composition, e.g., any of Composition 4, *et seq.* to the teeth, and optionally then rinsing with water or aqueous solution sufficient to enhance precipitation of zinc oxide in complex with cysteine from the composition.

[0048] Also provided is a method of making a an oral care product, e.g., a dentifrice or mouthrinse, comprising (i) a first component comprising a zinc (amino acid or TAG) halide and (ii) a second component physically separate from the first component comprising cysteine in free or cosmetically acceptable salt form, e.g., any of Composition 4, *et seq.* comprising combining an orally acceptable carrier, and optionally glycerol, with zinc amino acid halide in the first component, and/or with cysteine in the second component.

[0049] For example, in various embodiments, provided are methods to (i) reduce hypersensitivity of the teeth, (ii) to reduce plaque accumulation, (iii) reduce or inhibit demineralization and promote remineralization of the teeth, (iv) inhibit microbial biofilm formation in the oral cavity, (v) reduce or inhibit gingivitis, (vi) promote healing of sores or cuts in the mouth, (vii) reduce levels of acid producing bacteria, (viii) to increase relative levels of non-cariogenic and/or non-plaque forming bacteria, (ix) reduce or inhibit formation of dental caries, (x), reduce, repair or inhibit pre-carious lesions of the enamel, e.g., as detected by quantitative light-induced fluorescence (QLF) or electrical caries measurement (ECM), (xi) treat, relieve or reduce dry mouth, (xii) clean the teeth and oral cavity, (xiii) reduce erosion, (xiv) whiten teeth; (xv) reduce tartar build-up, and/or (xvi) promote systemic health, including cardiovascular health, e.g., by reducing potential for systemic infection via the oral tissues, comprising mixing both components and applying any of Compositions 4, *et seq.* as described above to the oral cavity of a person in need thereof, e.g., one or more times per day. Also provided are Compositions 4, *et seq.* for use in any of these methods.

[0050] Also provided is the use of (i) a ZXH complex, and (ii) cysteine in free or orally acceptable salt form in the manufacture of an oral care composition, e.g., in accordance with any of Compositions 4, *et seq.*

[0051] Also provided is the use of (i) a ZXH complex, and (ii) cysteine in free or orally acceptable salt form, to reduce and inhibit acid erosion of the enamel, clean the teeth, reduce

bacterially-generated biofilm and plaque, reduce gingivitis, inhibit tooth decay and formation of cavities, and/or reduce dentinal hypersensitivity.

[0052] In one embodiment, the ZXH complex is prepared at room temperature by mixing the precursors in an aqueous solution. The *in situ* formation provides ease of formulation. The precursors can be used instead of first having to form the salt. In another embodiment, the water permitting formation of the salt from the precursor comes from water (e.g., rinsing water, saliva or sweat, depending on the application) that comes into contact with the composition in the course of use.

[0053] In some embodiments, the total amount of zinc in the composition is 0.05 to 8 % by weight of the total composition. In other embodiments, the total amount of zinc is at least 0.1, at least 0.2, at least 0.3, at least 0.4, at least 0.5, or at least 1 up to 8% by weight of the total composition. In other embodiments, the total amount of zinc in the composition is less than 5, less than 4, less than 3, less than 2, or less than 1 to 0.05% by weight of the total composition. For example, the zinc content may be 2-3%.

[0054] In certain embodiments, the ZHX complex is anhydrous for dentifrice compositions that contain less than 10% water by weight. By anhydrous, there is less than 5% by weight water, optionally less than 4, less than 3, less than 2, less than 1, less than 0.5, less than 0.1 down to 0% by weight water. When provided in an anhydrous form, precursors of zinc amino acid halide complex, e.g., zinc oxide and lysine hydrochloride, will not significantly react. When contacted with a sufficient amount of water, the precursors will then react to form the desired salt, e.g., ZLC, which upon further dilution with use forms the desired precipitate on the skin or teeth.

[0055] X moiety:

[0056] The X moiety in the ZXH complex can be an amino acid or trialkylglycine, preferably glycine betaine. The amino acid in the zinc amino acid halide complex can be a basic amino acid. By “basic amino acid” is meant the naturally occurring basic amino acids, such as arginine, lysine, and histidine, as well as any basic amino acid having a carboxyl group and an amino group in the molecule, which is water-soluble and provides an aqueous solution with a pH of 7 or greater. Accordingly, basic amino acids include, but are not limited to, arginine, lysine, citrulline, ornithine, creatine, histidine, diaminobutanoic acid, diaminopropionic acid, salts thereof or combinations thereof. In a particular embodiment, the basic amino acid is lysine. The

basic amino acids for use in making zinc amino acid halide complex are generally provided in the form of the halide acid addition salt, e.g., a hydrochloride.

[0057] Trialkyl glycine possesses a quaternary ammonium structure. The alkyl groups are, independently, C<sub>1-4</sub> straight chain or branched alkyl groups. A preferred trialkyl glycine is *N,N,N*-trimethylglycine (also known as TMG, glycine betaine, or trimethylglycine). At neutral pH, the compound exists as a zwitterion, forming an inner salt between the quaternary ammonium and the carboxy portions of the molecule. In the presence of strong acids, it will form acid addition salts, e.g., hydrochloride. The compound is originally isolated from sugar beets, and is used as a dietary supplement in animal feed and as a laboratory reagent stabilizer, e.g., in polymerase chain reactions.

[0058] *Glycerol*

[0059] Glycerol or glycerin is an optional ingredient in the first and/or second component of the composition. It has been found that the presence of glycerol can delay the precipitation of the ZXH complex when the two components are mixed. Glycerol can also act as a humectant.

[0060] *Cysteine*

[0061] The compositions also comprise cysteine in free or orally or cosmetically acceptable salt form. By “orally or cosmetically acceptable salt form” is meant a salt form which is safe for administration to the oral cavity or skin respectively in the concentrations provided, and which does not interfere with the biological activity of the zinc. In a particular embodiment, the cysteine is administered in free form. Wherever weights are given for amounts of amino acids in formulations herein, the weights are generally provided in terms of the weight of the free acid unless otherwise noted. In certain embodiments, the cysteine is a cysteine hydrohalide, such as cysteine hydrochloride.

[0062] In compositions comprising an orally or cosmetically acceptable carrier, the carrier represents all other materials in the composition other than zinc amino acid halide complex (including precursors) and the cysteine. The amount of carrier is thus the amount to reach 100% by adding to the weight of zinc amino acid halide complex (including precursors) and the protein. By “orally acceptable carrier” is meant a carrier which is suitable for use in an oral care product, consisting of ingredients which are generally recognized as safe for use in amounts and concentrations as provided in a dentifrice or mouthrinse, for example. By “cosmetically acceptable carrier” is meant a carrier which is suitable for use in a product for topical use on the

skin, consisting of ingredients which are generally recognized as safe for use in amounts and concentrations as provided in a liquid hand soap or body wash, or in an antiperspirant product, for example. Excipients for use in the compositions thus may include for example excipients which are "Generally Recognized as Safe" (GRAS) by the United States Food and Drug Administration.

*Personal Care Formulations:*

[0063] The term "cosmetically acceptable carrier" thus refers to any formulation or carrier medium that provides the appropriate delivery of an effective amount of the complex as defined herein, does not interfere with the effectiveness of the biological activity of the zinc, and is suitable and nontoxic for topical administration to the skin. Representative carriers include water, oils, both vegetable and mineral, soap bases, cream bases, lotion bases, ointment bases and the like, particularly aqueous detergent carriers, for example liquid hand soaps or body washes. In one embodiment, the aqueous soap bases are free of or contain less than one percent of anionic surfactants. In another embodiment, the cosmetically acceptable carrier contains topically acceptable quaternary ammonium compounds. They may additionally include buffers, preservatives, antioxidants, fragrances, emulsifiers, dyes and excipients known or used in the field of drug formulation and that do not unduly interfere with the effectiveness of the biological activity of the active agent, and that is sufficiently non-toxic to the host or patient. Additives for topical formulations are well-known in the art, and may be added to the topical composition, as long as they are pharmaceutically acceptable and not deleterious to the epithelial cells or their function. Further, they should not cause deterioration in the stability of the composition. For example, inert fillers, anti-irritants, tackifiers, excipients, fragrances, opacifiers, antioxidants, gelling agents, stabilizers, surfactant, emollients, coloring agents, preservatives, buffering agents, and other conventional components of topical formulations as are known in the art.

[0064] In some cases, the personal care compositions comprise oils or moisturizers, which may not be water soluble and may be delivered in an emulsion system, wherein the zinc-lysine complex would be in the water phase of the emulsion. Surfactants for the emulsion formulations may comprise a combination of nonionic surfactants, for example, one or more surfactants selected from the group consisting of: (i) lipophilic surfactants, e.g., having an HLB value of 8 or lower, for example sorbitan-fatty acid esters, such as sorbitan oleates, for example, sorbitan sesquioleate; and (ii) hydrophilic surfactants, e.g., having an HLB of greater than 8, particularly

a. di- or tri-alkanol amines, such as triethanol amine; b. polyethoxylated surfactants, for example polyethoxylated alcohols (esp. polyethoxylated polyols), polyethoxylated vegetable oils, and polyethoxylated silicones, e.g., polysorbate 80, dimethicone polyethylene oxide, and dimethylmethyl (polyethylene oxide) siloxane. For a water-in-oil emulsion, the overall HLB of the surfactant mixture is preferably 2-8, i.e., there is typically a higher proportion of lipophilic surfactant; whereas for an oil-in-water emulsion, the overall HLB of the surfactant mixture is preferably 8-16.

[0065] The personal care compositions may also comprise suitable antioxidants, substances known to inhibit oxidation. Antioxidants suitable for use in the compositions include, but are not limited to, butylated hydroxytoluene, ascorbic acid, sodium ascorbate, calcium ascorbate, ascorbic palmitate, butylated hydroxyanisole, 2,4,5- trihydroxybutyrophene, 4-hydroxymethyl-2,6-di-fert-butylphenol, erythorbic acid, gum guaiac, propyl gallate, thiodipropionic acid, dilauryl thiodipropionate, tert-butylhydroquinone and tocopherols such as vitamin E, and the like, including pharmaceutically acceptable salts and esters of these compounds. Preferably, the antioxidant is butylated hydroxytoluene, butylated hydroxyanisole, propyl gallate, ascorbic acid, pharmaceutically acceptable salts or esters thereof, or mixtures thereof. Most preferably, the antioxidant is butylated hydroxytoluene. These materials are available from Ruger Chemical Co, (Irvington, NJ). When the topical formulations contain at least one antioxidant, the total amount of antioxidant present is from 0.001 to 0.5 wt%, preferably 0.05 to 0.5 wt%, more preferably 0.1%.

[0066] The pesonal care compositions may also comprise suitable preservatives. Preservatives are compounds added to a formulation to act as an antimicrobial agent. Among preservatives known in the art as being effective and acceptable in parenteral formulations are benzalkonium chloride, benzethonium, chlorohexidine, phenol, m-cresol, benzyl alcohol, methylparaben, propylparaben, chlorobutanol, o-cresol, p-cresol, chlorocresol, phenylmercuric nitrate, thimerosal, benzoic acid, and various mixtures thereof. See, e.g., Wallhausser, K.-H., Develop. Biol. Standard, 24:9-28 (1974) (S. Krager, Basel). Preferably, the preservative is selected from methylparaben, propylparaben and mixtures thereof. These materials are available from Inolex Chemical Co (Philadelphia, PA) or Spectrum Chemicals. When the topical formulations contain at least one preservative, the total amount of preservative present is from 0.01 to 0.5 wt%, preferably from 0.1 to 0.5%, more preferably from 0.03 to 0.15. Preferably the preservative is a

mixture of methylparaben and propylparaben in a 5/1 ratio. When alcohol is used as a preservative, the amount is usually 15 to 20%.

[0067] The personal care compositions may also comprise suitable chelating agents to form complexes with metal cations that do not cross a lipid bilayer. Examples of suitable chelating agents include ethylene diamine tetraacetic acid (EDTA), ethylene glycol-bis(beta- aminoethyl ether)-N,N,N',N"-tetraacetic acid (EGTA) and 8-Amino-2-[(2-amino-5-methylphenoxy)methyl]-6-methoxyquinoline-N<sub>5</sub>N,N',N"-tetraacetic acid, tetrapotassium salt (QUIN-2). Preferably the chelating agents are EDTA and citric acid. These materials are available from Spectrum Chemicals. When the topical formulations contain at least one chelating agent, the total amount of chelating agent present is from 0.005% to 2.0% by weight, preferably from 0.05% to 0.5 wt%, more preferably 0.1 % by weight. Care must be taken that the chelators do not interfere with the zinc complex, for example by binding zinc, but in the formulations tested, low levels of EDTA, for example, have not presented problems.

[0068] The personal care compositions may also comprise suitable pH adjusting agents and/or buffers to adjust and maintain the pH of the formulation to a suitable range, e.g., pH 6-8 or approximately neutral pH.

[0069] The personal care compositions may also comprise suitable viscosity increasing agents. These components are diffusible compounds capable of increasing the viscosity of a polymer-containing solution through the interaction of the agent with the polymer. CARBOPOL ULTREZ 10 may be used as a viscosity-increasing agent. These materials are available from Noveon Chemicals, Cleveland, OH. When the topical formulations contain at least one viscosity increasing agent, the total amount of viscosity increasing agent present is from 0.25% to 5.0% by weight, preferably from 0.25% to 1.0 wt%, and more preferably from 0.4% to 0.6% by weight.

[0070] Liquid forms, such as lotions suitable for topical administration or suitable for cosmetic application, may include a suitable aqueous or nonaqueous vehicle with buffers, suspending and dispensing agents, thickeners, penetration enhancers, and the like. Solid forms such as creams or pastes or the like may include, for example, any of the following ingredients, water, oil, alcohol or grease as a substrate with surfactant, polymers such as polyethylene glycol, thickeners, solids and the like. Liquid or solid formulations may include enhanced delivery technologies such as liposomes, microsomes, microsponges and the like.

[0071] Topical treatment regimens can comprise applying the composition directly to the skin at the application site, from one to several times daily, and washing with water to trigger precipitation of the zinc oxide on the skin.

[0072] Formulations can be used to treat, ameliorate or prevent conditions or symptoms associated with bacterial infections, acne, inflammation and the like.

Oral Care Formulations:

[0073] The oral care compositions, e.g., Composition 4, *et seq.* may comprise various agents which are active to protect and enhance the strength and integrity of the enamel and tooth structure and/or to reduce bacteria and associated tooth decay and/or gum disease, including or in addition to the zinc–amino acid–halide complexes. Effective concentration of the active ingredients used herein will depend on the particular agent and the delivery system used. It is understood that a toothpaste for example will typically be diluted with water upon use, while a mouthrinse typically will not be. Thus, an effective concentration of active in a toothpaste will ordinarily be 5-15x higher than required for a mouthrinse. The concentration will also depend on the exact salt or polymer selected. For example, where the active agent is provided in salt form, the counterion will affect the weight of the salt, so that if the counterion is heavier, more salt by weight will be required to provide the same concentration of active ion in the final product. Arginine, where present, may be present at levels from, e.g., 0.1 to 20 wt % (expressed as weight of free base), e.g., 1 to 10 wt % for a consumer toothpaste or 7 to 20 wt % for a professional or prescription treatment product. Fluoride where present may be present at levels of, e.g., 25 to 25,000 ppm, for example 750 to 2,000 ppm for a consumer toothpaste, or 2,000 to 25,000 ppm for a professional or prescription treatment product. Levels of antibacterial agents will vary similarly, with levels used in toothpaste being e.g., 5 to 15 times greater than used in mouthrinse. For example, a triclosan toothpaste may contain 0.3 wt % triclosan.

[0074] The oral care compositions may further include one or more fluoride ion sources, e.g., soluble fluoride salts. A wide variety of fluoride ion-yielding materials can be employed as sources of soluble fluoride in the present compositions. Examples of suitable fluoride ion-yielding materials are found in U.S. Pat. No. 3,535,421, to Briner et al.; U.S. Pat. No. 4,885,155, to Parran, Jr. et al. and U.S. Pat. No. 3,678,154, to Widder et al. Representative fluoride ion sources include, but are not limited to, stannous fluoride, sodium fluoride, potassium fluoride, sodium monofluorophosphate, sodium fluorosilicate, ammonium fluorosilicate, amine fluoride,

ammonium fluoride, and combinations thereof. In certain embodiments the fluoride ion source includes stannous fluoride, sodium fluoride, sodium monofluorophosphate as well as mixtures thereof. In certain embodiments, the oral care composition may also contain a source of fluoride ions or fluorine-providing ingredient in amounts sufficient to supply 25 ppm to 25,000 ppm of fluoride ions, generally at least 500 ppm, e.g., 500 to 2000 ppm, e.g., 1000 to 1600 ppm, e.g., 1450 ppm. The appropriate level of fluoride will depend on the particular application. A toothpaste for general consumer use would typically have 1000 to 1500 ppm, with pediatric toothpaste having somewhat less. A dentifrice or coating for professional application could have as much as 5,000 or even 25,000 ppm fluoride. Fluoride ion sources may be added to the compositions at a level of 0.01 wt. % to 10 wt. % in one embodiment or 0.03 wt. % to 5 wt. %, and in another embodiment 0.1 wt. % to 1 wt. % by weight of the composition in another embodiment. Weights of fluoride salts to provide the appropriate level of fluoride ion will obviously vary based on the weight of the counterion in the salt.

[0075] *Abrasives*: The oral care compositions, e.g. Composition 4 *et seq.* may include silica abrasives, and may comprise additional abrasives, e.g., a calcium phosphate abrasive, e.g., tricalcium phosphate ( $\text{Ca}_3(\text{PO}_4)_2$ ), hydroxyapatite ( $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$ ), or dicalcium phosphate dihydrate ( $\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$ , also sometimes referred to herein as DiCal) or calcium pyrophosphate; calcium carbonate abrasive; or abrasives such as sodium metaphosphate, potassium metaphosphate, aluminum silicate, calcined alumina, bentonite or other siliceous materials, or combinations thereof.

[0076] Other silica abrasive polishing materials useful herein, as well as the other abrasives, generally have an average particle size ranging between 0.1 and 30 microns, between 5 and 15 microns. The silica abrasives can be from precipitated silica or silica gels, such as the silica xerogels described in U.S. Pat. No. 3,538,230, to Pader et al. and U.S. Pat. No. 3,862,307, to Digiulio. Particular silica xerogels are marketed under the trade name Syloid® by the W. R. Grace & Co., Davison Chemical Division. The precipitated silica materials include those marketed by the J. M. Huber Corp. under the trade name Zeodent®, including the silica carrying the designation Zeodent 115 and 119. These silica abrasives are described in U.S. Pat. No. 4,340,583, to Wason. In certain embodiments, abrasive materials useful in the practice of the oral care compositions include silica gels and precipitated amorphous silica having an oil absorption value of less than 100 cc/100 g silica and in the range of 45 cc/100 g to 70 cc/100 g

silica. Oil absorption values are measured using the ASTA Rub-Out Method D281. In certain embodiments, the silicas are colloidal particles having an average particle size of 3 microns to 12 microns, and 5 to 10 microns. Low oil absorption silica abrasives particularly useful in the compositions are marketed under the trade designation Sylodent XWA® by Davison Chemical Division of W.R. Grace & Co., Baltimore, Md. 21203. Sylodent 650 XWA®, a silica hydrogel composed of particles of colloidal silica having a water content of 29% by weight averaging 7 to 10 microns in diameter, and an oil absorption of less than 70 cc/100 g of silica is an example of a low oil absorption silica abrasive useful in the composition.

**[0077] Foaming agents:** The oral care compositions also may include an agent to increase the amount of foam that is produced when the oral cavity is brushed. Illustrative examples of agents that increase the amount of foam include, but are not limited to polyoxyethylene and certain polymers including, but not limited to, alginate polymers. The polyoxyethylene may increase the amount of foam and the thickness of the foam generated by the oral care carrier component of the composition. Polyoxyethylene is also commonly known as polyethylene glycol ("PEG") or polyethylene oxide. The polyoxyethylenes suitable for this composition will have a weight average molecular weight of 200,000 to 7,000,000. In one embodiment the weight average molecular weight will be 600,000 to 2,000,000 and in another embodiment, 800,000 to 1,000,000. Polyox® is the trade name for the high molecular weight polyoxyethylene produced by Union Carbide. The polyoxyethylene may be present in an amount of 1% to 90%, in one embodiment 5% to 50% and in another embodiment 10% to 20% by weight of the oral care carrier component of the oral care compositions. Where present, the amount of foaming agent in the oral care composition (i.e., a single dose) is 0.01 to 0.9 % by weight, 0.05 to 0.5% by weight, and in another embodiment 0.1 to 0.2 % by weight.

**[0078] Surfactants:** The compositions may contain anionic, cationic, nonionic and/or zwitterionic surfactants, for example:

- i. water-soluble salts of higher fatty acid monoglyceride monosulfates, such as the sodium salt of the monosulfated monoglyceride of hydrogenated coconut oil fatty acids such as sodium N-methyl N-cocoyl taurate, sodium cocomonoglyceride sulfate,
- ii. higher alkyl sulfates, such as sodium lauryl sulfate,

- iii. higher alkyl-ether sulfates, e.g., of formula  $\text{CH}_3(\text{CH}_2)_m\text{CH}_2(\text{OCH}_2\text{CH}_2)_n\text{OSO}_3\text{X}$ , wherein m is 6-16, e.g., 10, n is 1-6, e.g., 2, 3 or 4, and X is Na or K, for example sodium laureth-2 sulfate ( $\text{CH}_3(\text{CH}_2)_{10}\text{CH}_2(\text{OCH}_2\text{CH}_2)_2\text{OSO}_3\text{Na}$ ).
- iv. higher alkyl aryl sulfonates such as sodium dodecyl benzene sulfonate (sodium lauryl benzene sulfonate)
- v. higher alkyl sulfoacetates, such as sodium lauryl sulfoacetate (dodecyl sodium sulfoacetate), higher fatty acid esters of 1,2 dihydroxy propane sulfonate, sulfocolaurate (N-2-ethyl laurate potassium sulfoacetamide) and sodium lauryl sarcosinate.

[0079] By “higher alkyl” is meant, e.g.,  $\text{C}_{6-30}$  alkyl. In particular embodiments, the anionic surfactant is selected from sodium lauryl sulfate and sodium ether lauryl sulfate. The anionic surfactant may be present in an amount which is effective, e.g.,  $> 0.01\%$  by weight of the formulation, but not at a concentration which would be irritating to the oral tissue, e.g.,  $< 10\%$ , and optimal concentrations depend on the particular formulation and the particular surfactant. For example, concentrations used or a mouthwash are typically on the order of one tenth that used for a toothpaste. In one embodiment, the anionic surfactant is present in a toothpaste at 0.3% to 4.5% by weight, e.g., 1.5%. The compositions may optionally contain mixtures of surfactants, e.g., comprising anionic surfactants and other surfactants that may be anionic, cationic, zwitterionic or nonionic. Generally, surfactants are those which are reasonably stable throughout a wide pH range. Surfactants are described more fully, for example, in U.S. Pat. No. 3,959,458, to Agricola et al.; U.S. Pat. No. 3,937,807, to Haefele; and U.S. Pat. No. 4,051,234, to Gieske et al. In certain embodiments, the anionic surfactants useful herein include the water-soluble salts of alkyl sulfates having 10 to 18 carbon atoms in the alkyl radical and the water-soluble salts of sulfonated monoglycerides of fatty acids having 10 to 18 carbon atoms. Sodium lauryl sulfate, sodium lauroyl sarcosinate and sodium coconut monoglyceride sulfonates are examples of anionic surfactants of this type. In a particular embodiment, the composition, e.g., Composition 4, *et seq.*, comprises sodium lauryl sulfate.

[0080] The surfactant or mixtures of compatible surfactants can be present in the composition in 0.1% to 5%, in another embodiment 0.3% to 3% and in another embodiment 0.5% to 2% by weight of the total composition.

[0081] Note that care must be taken that the anionic surfactants do not interfere with zinc amino acid halide complex or with the activity of the zinc. At relatively low levels and in a relatively

low water formulation, the surfactants generally would not have major impact, but higher levels of anionic surfactant, particularly in aqueous formulations, anionic surfactants can be excluded. Cationic and/or nonionic surfactants may be utilized instead.

[0082] In general, the optional ingredients described herein can be present in the first component, the second component or both.

[0083] *Tartar control agents:* In various embodiments, the compositions comprise an anticalculus (tartar control) agent. Suitable anticalculus agents include without limitation phosphates and polyphosphates (for example pyrophosphates), polyaminopropanesulfonic acid (AMPS), hexametaphosphate salts, zinc citrate trihydrate, polypeptides, polyolefin sulfonates, polyolefin phosphates, diphosphonates. The composition thus may comprise phosphate salts. In particular embodiments, these salts are alkali phosphate salts, i.e., salts of alkali metal hydroxides or alkaline earth hydroxides, for example, sodium, potassium or calcium salts. "Phosphate" as used herein encompasses orally acceptable mono- and polyphosphates, for example,  $P_{1-6}$  phosphates, for example monomeric phosphates such as monobasic, dibasic or tribasic phosphate; dimeric phosphates such as pyrophosphates; and multimeric phosphates, e.g., sodium hexametaphosphate. In particular examples, the selected phosphate is selected from alkali dibasic phosphate and alkali pyrophosphate salts, e.g., selected from sodium phosphate dibasic, potassium phosphate dibasic, dicalcium phosphate dihydrate, calcium pyrophosphate, tetrasodium pyrophosphate, tetrapotassium pyrophosphate, sodium tripolyphosphate, and mixtures of any of two or more of these. In a particular embodiment, for example the compositions comprise a mixture of tetrasodium pyrophosphate ( $Na_4P_2O_7$ ), calcium pyrophosphate ( $Ca_2P_2O_7$ ), and sodium phosphate dibasic ( $Na_2HPO_4$ ), e.g., in amounts of ca. 3-4% of the sodium phosphate dibasic and ca. 0.2-1% of each of the pyrophosphates. In another embodiment, the compositions comprise a mixture of tetrasodium pyrophosphate (TSPP) and sodium tripolyphosphate (STPP) ( $Na_5P_3O_{10}$ ), e.g., in proportions of TSPP at 1-2% and STPP at 7% to 10%. Such phosphates are provided in an amount effective to reduce erosion of the enamel, to aid in cleaning the teeth, and/or to reduce tartar buildup on the teeth, for example in an amount of 2-20%, e.g., ca. 5-15%, by weight of the composition.

[0084] *Flavoring Agents:* The oral care compositions may also include a flavoring agent. Flavoring agents which can be used in the composition include, but are not limited to, essential oils as well as various flavoring aldehydes, esters, alcohols, and similar materials. Examples of

the essential oils include oils of spearmint, peppermint, wintergreen, sassafras, clove, sage, eucalyptus, marjoram, cinnamon, lemon, lime, grapefruit, and orange. Also useful are such chemicals as menthol, carvone, and anethole. Certain embodiments employ the oils of peppermint and spearmint. The flavoring agent may be incorporated in the oral composition at a concentration of 0.1 to 5% by weight e.g. 0.5 to 1.5% by weight.

[0085] *Polymers*: The oral care compositions may also include additional polymers to adjust the viscosity of the formulation or enhance the solubility of other ingredients. Such additional polymers include polyethylene glycols, polysaccharides (e.g., cellulose derivatives, for example carboxymethyl cellulose, or polysaccharide gums, for example xanthan gum or carrageenan gum). Acidic polymers, for example polyacrylate gels, may be provided in the form of their free acids or partially or fully neutralized water soluble alkali metal (e.g., potassium and sodium) or ammonium salts.

[0086] Silica thickeners, which form polymeric structures or gels in aqueous media, may be present. Note that these silica thickeners are physically and functionally distinct from the particulate silica abrasives also present in the compositions, as the silica thickeners are very finely divided and provide little or no abrasive action. Other thickening agents are carboxyvinyl polymers, carrageenan, hydroxyethyl cellulose and water soluble salts of cellulose ethers such as sodium carboxymethyl cellulose and sodium carboxymethyl hydroxyethyl cellulose. Natural gums such as karaya, gum arabic, and gum tragacanth can also be incorporated. Colloidal magnesium aluminum silicate can also be used as component of the thickening composition to further improve the composition's texture. In certain embodiments, thickening agents in an amount of 0.5% to 5.0% by weight of the total composition are used.

[0087] The compositions may include an anionic polymer, for example in an amount of from 0.05 to 5%. Such agents are known generally for use in dentifrice, although not for this particular application, useful in composition are disclosed in U.S. Pat. Nos. 5,188,821 and 5,192,531; and include synthetic anionic polymeric polycarboxylates, such as 1:4 to 4:1 copolymers of maleic anhydride or acid with another polymerizable ethylenically unsaturated monomer, preferably methyl vinyl ether/maleic anhydride having a molecular weight (M.W.) of 30,000 to 1,000,000, most preferably 300,000 to 800,000. These copolymers are available for example as Gantrez, e.g., AN 139 (M.W. 500,000), AN 119 (M.W. 250,000) and preferably S-97 Pharmaceutical Grade (M.W. 700,000) available from ISP Technologies, Inc., Bound Brook, N.J. 08805. The

enhancing agents when present are present in amounts ranging from 0.05 to 3% by weight. Other operative polymers include those such as the 1:1 copolymers of maleic anhydride with ethyl acrylate, hydroxyethyl methacrylate, N-vinyl-2-pyrollidone, 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. Suitable generally, are polymerized olefinically or ethylenically unsaturated carboxylic acids containing an activated carbon-to-carbon olefinic double bond and at least one carboxyl group, that is, an acid containing an olefinic double bond which readily functions in polymerization because of its presence in the monomer molecule either in the alpha-beta position with respect to a carboxyl group or as part of a terminal methylene grouping. Illustrative of such acids are acrylic, methacrylic, ethacrylic, alpha-chloroacrylic, crotonic, beta-acryloxy propionic, sorbic, alpha-chlorsorbic, cinnamic, beta-styrylacrylic, muconic, itaconic, citraconic, mesaconic, glutaconic, aconitic, alpha-phenylacrylic, 2-benzyl acrylic, 2-cyclohexylacrylic, angelic, umbellic, fumaric, maleic acids and anhydrides. Other different olefinic monomers copolymerizable with such carboxylic monomers include vinylacetate, vinyl chloride, dimethyl maleate and the like. Copolymers contain sufficient carboxylic salt groups for water-solubility. A further class of polymeric agents includes a composition containing homopolymers of substituted acrylamides and/or homopolymers of unsaturated sulfonic acids and salts thereof, in particular where polymers are based on unsaturated sulfonic acids selected from acrylamidoalkane sulfonic acids such as 2-acrylamide 2 methylpropane sulfonic acid having a molecular weight of 1,000 to 2,000,000, described in U.S. Pat. No. 4,842,847, Jun. 27, 1989 to Zahid. Another useful class of polymeric agents includes polyamino acids containing proportions of anionic surface-active amino acids such as aspartic acid, glutamic acid and phosphoserine, e.g. as disclosed in U.S. Pat. No. 4,866,161 Sikes et al.

[0088] Water: The oral compositions may comprise significant levels of water. Water employed in the preparation of commercial oral compositions should be deionized and free of organic impurities. The amount of water in the compositions includes the free water which is added plus that amount which is introduced with other materials.

[0089] Humectants: Within certain embodiments of the oral compositions, it is also desirable to incorporate a humectant to prevent the composition from hardening upon exposure to air.

Certain humectants can also impart desirable sweetness or flavor to dentifrice compositions. Suitable humectants include edible polyhydric alcohols such as glycerine, sorbitol, xylitol, propylene glycol as well as other polyols and mixtures of these humectants. In one embodiment, the principal humectant is glycerin, which may be present at levels of greater than 25%, e.g. 25-35% 30%, with 5% or less of other humectants.

[0090] *Other optional ingredients:* In addition to the above-described components, the oral care embodiments can contain a variety of optional dentifrice ingredients some of which are described below. Optional ingredients include, for example, but are not limited to, adhesives, sudsing agents, flavoring agents, sweetening agents, additional antiplaque agents, abrasives, and coloring agents. These and other optional components are further described in U.S. Pat. No. 5,004,597, to Majeti; U.S. Pat. No. 3,959,458 to Agricola et al. and U.S. Pat. No. 3,937,807, to Haefele, all being incorporated herein by reference.

Other forms

[0091] The form of the dual component system can take the form of a dual chamber form or any other means to separate the components which include, but is not limited to beads, capsules, and films.

[0092] Unless stated otherwise, all percentages of composition components given in this specification are by weight based on a total composition or formulation weight of 100%. The term "total composition" or just "composition" means the total final product form, i.e., the combination of the first and second components.

[0093] The compositions and formulations as provided herein are described and claimed with reference to their ingredients, as is usual in the art. As would be evident to one skilled in the art, the ingredients may in some instances react with one another, so that the true composition of the final formulation may not correspond exactly to the ingredients listed. Thus, it should be understood that the composition extends to the product of the combination of the listed ingredients.

[0094] As used throughout, ranges are used as shorthand for describing each and every value that is within the range. Any value within the range can be selected as the terminus of the range. In addition, all references cited herein are hereby incorporated by reference in their entireties. In the event of a conflict in a definition in the present disclosure and that of a cited reference, the present disclosure controls.

[0095] Unless otherwise specified, all percentages and amounts expressed herein and elsewhere in the specification should be understood to refer to percentages by weight. The amounts given are based on the active weight of the material.

[0096] Embodiments of the present invention are further described in the following examples. The examples are merely illustrative and do not in any way limit the scope of the invention as described and claimed.

## EXAMPLES

**[0097] Example A – ZLC Stock Solution**

18.2650g (0.1mole) of L-LysineHCl is dissolved in 100ml of Deionized water at room temperature under stirring. After all L-LysineHCl dissolves, 4.1097g (0.0505mole) of ZnO is slowly added into the solution under stirring. The suspension is continued mixing at room temperature for at least 30 minutes to 24 hours. Then, the suspension solution is centrifuged at 7000rpm for 20 minutes and filtered through filter membrane with 0.45um pore size to remove unreacted ZnO. The clear supernatant is recovered as stock solution.

**[0098] Example 1**

A solution 1 was prepared by dissolving 0.05 g of cysteine in 1mL of 1M HCl solution and 10.7 g of water. A solution 2 was prepared by mixing 4.95 g of ZLC stock solution with 14.85 g of glycerol.

[0099] When the two solutions were mixed, precipitation occurred with a 8 seconds delay. The mixture had a final pH of 6.03.

[0100] The 8 seconds delay, as well as the delays discussed with the following examples, is very beneficial, because it allows ample time for the transfer of the mixture from the mixing cup to the mouth of the user before the onset of the precipitation, and the precipitation occurs within the time period a typical user would brush or rinse.

**[0101] Example 2**

[0102] A solution 1 was prepared by dissolving 0.05 g of cysteine in 1mL of 1M HCl solution and 10.7 g of water. A solution 2 was prepared by mixing 4.95 g of ZLC stock solution with 24.75 g of glycerol.

[0103] When the two solutions were mixed, precipitation occurred with a 8 seconds delay. The mixture had a final pH of 6.17.

**[0104] Example 3**

[0105] A solution 1 was prepared by dissolving 0.05 g of cysteine in 1mL of 1M HCl solution and 21.4 g of water. A solution 2 was prepared by mixing 4.95 g of ZLC stock solution with 14.85 g of glycerol.

[0106] When the two solutions were mixed, precipitation occurred with a 3 seconds delay. The mixture had a final pH of 6.31.

**[0107] Example 4**

[0108] A solution 1 was prepared by dissolving 0.05 g of cysteine in 1mL of 1M HCl solution without added water. A solution 2 was prepared by mixing 4.95 g of ZLC stock solution with 14.85 g of glycerol.

[0109] When the two solutions were mixed, precipitation occurred within 10 seconds delay. The mixture had a final pH of 5.88.

**[0110] Example 5**

[0111] A solution 1 was prepared by mixing 0.05 g of cysteine in 1 mL of 0.0001 M HCl solution, resulting in complete dissolution. The pH value of the solution 1 was about 5.13. A solution 2 was prepared by mixing 4.95 g of ZLC stock solution and 14.85 g of glycerol.

[0112] When the two solutions were mixed, precipitation occurred in about 7 seconds.

[0113] The system using 0.0001M HCl solution is preferred over the above-mentioned systems involving 1M HCl, because the solution 1 prepared from 1mL of 1M HCl is substantially lower in pH value from that prepared using 1mL of 0.0001M HCl solution. For example, a solution of 0.05g of cysteine in 1 mL of 1M HCl has a pH of about 1.15. If the acid strength is reduced to 0.1 M, the pH is 2.44. If the acid is at 0.01M, the pH is 3.62. If the acid is supplied at 0.001 M, the pH is 4.89. Although preparations using these acid levels will work in delaying the precipitation times, they are less safe as compared to the preparation using 0.0001M HCl, with a pH of 5.13.

**[0114] Example 6**

[0115] A solution 1 was prepared by mixing 0.05 g of cysteine, 1mL of 0.0001 M HCl solution, and glycerol so that the total mass of the solution 1 was 19.8 g. A solution 2 was prepared by mixing 4.95 g of ZLC stock solution and 14.85 g of glycerol.

[0116] When the two solutions were mixed, precipitation took place after a significant delay. Cloudiness occurred about 12 second after mixing, and the mixture stopped turning more cloudy about 20 seconds after mixing.

**a. Surface deposition and occlusion of dentine tubules using systems containing ZLC, cysteine, HCL and glycerol.**

[0117] The dual-component system proved effective in occluding dentine tubules in in-vitro assays.

[0118] A first solution was prepared by mixing 0.05 g of cysteine with 1mL of 0.0001 M HCl solution. A second solution was prepared by mixing 4.95 g of ZLC stock solution with 14.85 g of glycerol. The two stock solutions were mixed in the presence of dentine slices. The dentine slices were prepared by cutting human tooth into thin dentine sections of about 800 microns in thickness, choosing a test side, sanding said test side using a sandpaper of about 600 grit, polishing said test side using a Buehler polishing cloth and 5 micron Buehler aluminum oxide, acid-etching said dentine section in 1 % (by weight) citric acid solution for about 20 seconds, sonicating said dentine section for 10 minutes, and storing said dentine section in phosphate buffered saline (PBS, pH 7.4).

[0119] The dentine slices were examined under confocal microscope in XYZ and XZY mode for surface deposition and occlusions of tubules at their openings.

[0120] It was discovered that during six consecutive treatments and examinations, there was progressively more deposition of particles on the dentine surface, and progressively more accumulation of particles within tubules and around the tubule openings.

[0121] The surface deposition leads to benefits such as erosion protection, as well as providing a reservoir of zinc ions for controlled release.

[0122] The occlusion of tubules leads to benefits such as sensitivity relief, as well as providing the same reservoir.

[0123] The dentine section is dried and examined under a Spectroshade™ spectrophotometer (Handy Dental Type 71,3000). The treated dentinal area is included and the enamel rim is excluded from the examination and subsequent data processing. The CIELAB color reading is obtained. It is commonly understood that, by definition, L\*=0 means black and L\*=100 indicates diffuse white, negative a\* value indicates green while positive values indicate magenta, and

negative  $b^*$  values indicate blue and positive values indicate yellow. It is noted that the successive surface deposition led to a slight increase in  $L^*$  values of the surface (from 69.1 at baseline to about 71.8 after 6 treatments), an indication of slight increase in whiteness.

**b. Ineffectiveness of methionine in changing precipitation time of ZLC chelates.**

[0124] Among the sulfur-containing amino acids, cysteine is the only one that is capable of adjusting precipitation time of ZLC. Methionine has no effect.

[0125] In a first example, a solution 1 was prepared from 0.05g methionine and 1 mL of 0.0001M HCl solution. A solution 2 was prepared from 4.95 g of ZLC stock solution and 14.85g of glycerol. When the two solutions were mixed, no precipitation occurred. The same system using cysteine instead of methionine resulted in precipitation.

[0126] In a second example, a solution 1 was prepared from 0.05g of methionine, and 1 mL of 1M HCl solution. A solution 2 was prepared from 4.95g of ZLC stock solution and 14.85g of glycerol. When the two solutions were mixed, no precipitation occurred.

[0127] In a third example, a solution 1 was prepared from 0.05 g of methionine, and 1 mL of 0.0001M HCl solution. A solution 2 was prepared from 4.95 g of ZLC stock solution with no glycerol, so that the rate of the reaction can be enhanced. No precipitation occurred upon mixing.

[0128] It is contemplated that any other compounds with an available terminal –SH functional group may be used in place or in combination with cysteine for the present invention. Such compounds include amino acid dimers, trimers, oligomers, or polymers, i.e., peptides and proteins that contain at least one terminal –SH functional group.

**[0129] Example 7 – Liquid hand soap with ZLC**

[0130] 1g of ZLC-Cys solution of Example 4 (prior to dilution to form the “stock” solution) is combined with 4g of a commercial liquid hand soap (LHS) having a formulation as set forth in Table 6, to provide a formulation having 0.7% zinc.

Table 1

Material	Weight %
Cetrimonium chloride (cetyl trimethyl ammonium chloride)	2.4
Glycerin	2
Lauramidopropyl dimethylamine oxide	1.2

Cocamide MEA (cocomonoethanolamide)	1
PEG-120 methyl glucose dioleate	0.6
Myristamidopropylamine oxide	0.4
C <sub>12-18</sub> alkydimethylbenzyl ammonium chloride (BKC)	0.13
Water and optional ingredients	Q.S.

In a soap container, the bottle is divided by a of barrier. Both sides of the barrier contain the standard soap base in the table immediately above. One side contains the appropriate amount of cysteine and the other side contains the appropriate amount of ZLC. When dispensed, the two stocks will mix in the nozzle forming an instantaneous precipitation directly to the skin's surface without having a reaction occur within the bottle that may expend all the desired benefits.

[0131] **Example 8** – Gel formulations comprising Zinc-Lysine

[0132] An oral gel toothpaste with ZLC / cysteine as active ingredient is formulated. The precipitation property of ZLC gel phase is also investigated by hydrolysis reaction study, to determine whether when the teeth are being brushed with toothpaste containing ZLC / cysteine, the insoluble particles formed during brushing can penetrate into the dentin tubules and block the tubules resulting in an anti-sensitivity effect and signal for the consumer.

[0133] A gel with ZLC / cysteine as active ingredient is formulated with the ingredients shown in Table 2. The clarity and the precipitation by dilution is evaluated. Zinc ion concentration in the following batches is at 0.5% (w/w) zinc level.

Table 2 – Oral gel with ZLC / cysteine

Ingredients	%	Loading (g)
Sorbitol 70% sol	76.03%	380.15
Aqueous ZLC solution 2.53%Zn plus 0.5% cysteine	20.00%	100
Carboxymethyl cellulose (CMC) and Trimethyl cellulose (TMC)	0.70%	3.5
Na Saccharin	0.27%	1.35
Propylene Glycol	3.00%	15
Total	100.00%	500
%Zn	0.506%	

The ingredients are placed in a tube. The tube is separated by means of either a physical divider resulting in two chambers, one chamber containing cysteine and the other containing ZLC. When dispensed, the formulation does not react due to the appropriate desired delay. Upon mixing and brushing a precipitate forms to occlude tubules and provides zinc ion benefits to the oral surfaces.

## CLAIMS

1. An oral care or personal care product comprising a container having: (i) a first compartment containing a first component comprising a zinc-(amino acid or trialkyl glycine) halide complex, and (ii) a second compartment containing a second component comprising cysteine in free or in orally or cosmetically acceptable salt form; wherein the first and second compartments maintain the first and second components separate from each other, and wherein the product dispenses a mixture of the first component and the second component for application to the body.
2. The product of claim 1 further comprising glycerol in the first component, in the second component or in both components.
3. The product according to any of the foregoing claims wherein the pH of the first component is 7 to 9 and the pH of the second component is 3 to 6.
4. The product according to any of the foregoing claims, wherein the zinc (amino acid or trialkyl glycine) halide is formed from precursors, wherein the precursors are a zinc ion source, an amino acid or trialkyl glycine source, and a halide source, wherein the halide source can be part of the zinc ion source, the amino acid or trialkyl glycine source, or a halogen acid.
5. The product according to claim 2, wherein the zinc ion source is at least one of zinc oxide, zinc chloride, zinc carbonate, zinc nitrate, zinc citrate, and zinc phosphate.
6. The product according to any of the foregoing claims, wherein the amino acid source is at least one of a basic amino acid, lysine, arginine, and glycine.
7. The product according to any of the foregoing claim, wherein the trialkyl glycine is a C<sub>1</sub>-C<sub>4</sub> alkyl glycine or trimethyl glycine.
8. The product according to any of the foregoing claims wherein the zinc amino acid halide is made by combining zinc oxide with an amino acid hydrohalide.
9. The product according to any of the foregoing claims wherein the zinc (amino acid or trialkyl glycine) halide has the formula Zn(amino acid or trialkyl

glycine)<sub>2</sub>Hal<sub>2</sub> or Zn(amino acid or trialkyl glycine)<sub>3</sub>Hal<sub>2</sub>, wherein Zn is a divalent zinc ion and Hal is a halide ion.

10. The product according to any of the foregoing claims wherein the zinc (amino acid or trialkyl glycine) halide complex is  $[\text{Zn}(\text{C}_6\text{H}_{14}\text{N}_2\text{O}_2)_2\text{Cl}]^+\text{Cl}^-$ .
11. The product according to any of the foregoing claims wherein the amount of cysteine is 0.1% to 1%.
12. The product according to any of the foregoing claims, wherein the cysteine is cysteine hydrohalide, optionally cysteine hydrochloride.
13. The product according to any of the foregoing claims which upon mixing the two components, provides a precipitate comprising zinc oxide in complex with cysteine, and optionally additionally comprising zinc oxide, zinc carbonate, and mixtures thereof.
14. The product according to any of the foregoing claims which upon mixing the two components, forms a precipitate in about 1 to about 20 seconds after mixing.
15. The product according to any of the foregoing claims wherein the total amount of zinc present in the composition is selected from the ranges of 0.2 to 8% by weight, 0.1 to 8 weight %, 0.1 to 2 and 0.1 to 1 weight % of the total composition.
16. The product according to any of the foregoing claims which is an antiperspirant or deodorant product, further comprising a cosmetically acceptable carrier.
17. A method of killing bacteria, reducing perspiration, and/or reducing body odor comprising mixing the two components of claim 16 and applying to skin an effective amount of the mixed components.
18. The product of any of claims 1-15 which is a personal care product selected from liquid hand soap, body wash, dermal lotions, dermal creams, and dermal conditioners further comprising a cosmetically acceptable carrier in the first component, the second component, or in both components.

19. A method of killing bacteria, treating or reducing the incidence of acne or topical skin infections, or to provide a visual signal when washing, comprising mixing the two components of claim 18 and then washing the skin with water and an effective amount of the mixed components.
20. The product of any of claims 1-15 which is an oral care product, further comprising an orally acceptable carrier in the first component, the second component, or in both components.
21. A method to reduce and inhibit acid erosion of the enamel, clean the teeth, reduce bacterially-generated biofilm and plaque, reduce gingivitis, inhibit tooth decay and formation of cavities, and/or reduce dentinal hypersensitivity comprising mixing the components of claim 20 and applying an effective amount of the mixed components to the oral cavity of a person in need thereof.
22. Use of a zinc (amino acid or trialkyl glycine) halide complex together with cysteine in free or orally acceptable salt form in the manufacture of a composition for use in any of the methods of claims 17, 19, or 21.