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(21) International Application Number: PCT/US91/09487 (22) International Filing Date: 17 December 1991 (17.12.91) (30) Priority data: 633,043 24 December 1990 (24.12.90) US (60) Parent Application or Grant (63) Related by Continuation US 633,043 (CIP) Filed on 24 December 1990 (24.12.90) (71)(72) Applicant and Inventor: EBY, George, A., III [US/US]; 2109 Paramount Avenue, Austin, TX 78704 (US).		(74) Agent: PARKER, David, L.; Arnold, White & Durkee, P.O. Box 4433, Houston, TX 77210 (US). (81) Designated States: AT, AT (European patent), AU, BB, BE (European patent), BF (OAPI patent), BG, BJ (OAPI patent), BR, CA, CF (OAPI patent), CG (OAPI patent), CH, CH (European patent), CI (OAPI patent), CM (OAPI patent), CS, DE, DE (European patent), DK, DK (European patent), ES, ES (European patent), FI, FR (European patent), GA (OAPI patent), GB, GB (Eu- ropean patent), GN (OAPI patent), GR (European pa- tent), HU, IT (European patent), JP, KP, KR, LK, LU, LU (European patent), MC (European patent), MG, ML (OAPI patent), MN, MR (OAPI patent), MW, NL, NL (European patent), NO, PL, RO, SD, SE, SE (European patent), SN (OAPI patent), SU ⁺ , TD (OAPI patent), TG (OAPI patent), US. Published <i>With international search report.</i>
(54) Title: FLAVOR STABLE ZINC ACETATE COMPOSITIONS FOR ORAL ABSORPTION (57) Abstract Instant invention is a flavor stable, pleasant tasting zinc acetate composition that shortens the duration of common colds in humans. The composition is used in the oral cavity of a human suffering from a common cold. The composition comprises highly ionizable zinc acetate and a pharmaceutically acceptable carrier such as fructose or sucrose with various additions. Compositions are unique in that they are pleasant tasting and do not have an offensive aftertaste, yet deliver zinc ions into saliva. Composition is thermally, chemically and flavor stable. The composition may be prepared in the form of a compressed tablet, lozenge, powder, liquid or chewing gum. Instant composition delivers strongly antirhinoviral zinc ions to the oral mucosa of a human. <i>in vitro</i>, zinc⁺² is as antirhinoviral and as protective of cell monolayers as interferon and is a potent interferon inducer. Said pleasant tasting composition is an improvement upon a slow-release candy composition comprising a hard candy base, zinc acetate and an amino acid; and said composition is an improvement upon a medicinal composition for release of zinc ion consisting essentially of a suitable pharmaceutical carrier, zinc acetate and anethole.		

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**Flavor Stable Zinc Acetate Compositions
For Oral Absorption**

This invention relates to medicinal or nutritional compositions containing zinc acetate for oral absorption by humans. More particularly, this invention relates to chemically, thermally and flavor stable compositions containing zinc acetate and pharmaceutically acceptable carriers, preferably those that are sweet such as fructose, sucrose and the like. Other necessary ingredients are described such as extra sweeteners, flavors, stabilizers and lubricants, when making compressed tablets; gum bases, sugars and flavors, when making chewing gum, water and sugars when making syrups and so forth. Such compositions, when applied to oral and oral pharyngeal membranes of a human, are palatable and without undesirable taste or aftertaste yet allow absorption of zinc ions into oral and oral pharyngeal tissues. Said absorption of zinc ions into the oral and oral pharyngeal tissues is of particular benefit in shortening the duration of common colds.

The art of managing metallic ions in food products has received much attention by the food industry. Metallic ions of iron, copper and zinc can be present in some food products with adverse effects on food integrity. If they are allowed to remain in some food products even in low concentrations, such metallic ions can greatly reduce shelf life of some fats, oils and other foods that are subject to spoiling and oxidization. However, that zinc ions must be present in some medicinal oral compositions is new and is of importance in compositions intended to be of use in common cold treatment. Such presents problems in preserving a pleasant taste of said compositions.

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Chemical Sequestration of Metallic Ions

Sequestrants are chemicals that deactivate or stabilize these metallic ions by chemically tying up positively charged metal ions through chemical reactions to form stable, neutrally or negatively charged complexes that do not adversely affect integrity or quality of such food products. Sequestrants are also known as sequestering agents, stabilizers, chelators, chelating agents and metal scavengers. Sequestrants help to establish, maintain, and enhance integrity of many food products. From a food manufacturing viewpoint, strong sequestrants serve to stabilize or enhance numerous properties identified with wholesome food including color, flavor and texture. Usually, sequestrants chemically react with metallic ions to form complexes which tend to alter properties and effects of metals in substrates.

Many sequestrants employed in food production occur naturally in nature. They include as monocarboxylic acids, gluconic and acetic acids which weakly sequester zinc ions; as hydroxycarboxylic acids, citric and tartaric acids which strongly chelate zinc ions; and as amino acids such as sweet tasting lysine, glycine, leucine, alanine, and valine. Other sweeteners, including saccharin, sorbitol, mannitol and a constituent of aspartame, phenylalanine, have also been shown to sequester metals strongly. For sequestration, chelation, to occur, two general conditions must be met: (a) ligands must have proper steric and electronic configuration in relation to metal ions being complexed and (b) the surrounding milieu (pH, ionic strength, solubility, etc.) must likewise be conducive to complex formation. That strong sequestration of metal ions is a desirable goal of food manufacturers is well known in the art.

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Desirability of Weak Sequestration in Common Cold Treatment

The desirability of strongly sequestering metal ions in all cases must be challenged in view of nature of some metal chelators relative to environments in which their use is intended. For example, use of zinc gluconate in throat lozenges, troches and similar oral means has been described as a method for reducing duration of common cold symptoms (U.S. Patent 4,503,070, March 5, 1985 and its reissue RE 33465, November 27, 1990). In such usage, zinc ions are only weakly bound by the gluconate moiety. The first stability constant of zinc gluconate is $\log K_1 = 1.70$. Thirty percent or more of zinc appears as positively charged zinc ions with remaining zinc being positively charged zinc gluconate in all acidic to neutral pHs normally found in the human mouth. Such ions are readily available for those biochemical activities in oral and oral pharyngeal mucous membranes that result in a reduction in duration of common cold symptoms.

Although the exact nature of biochemical activities of zinc ions in reducing duration of common cold symptoms remains to be determined, it is conclusive that zinc must be ionized and positively charged. That the zinc ion acts to reduce common cold duration by an antiviral mechanism must be understood. Published articles, describe the *in vitro* antirhinoviral activity of zinc⁺² from highly ionizable zinc chloride and zinc acetate. Said articles include:

- B.D. Korant, et al. (1974), "Zinc Ions Inhibit Replication of Rhinoviruses", *Nature*, 248:588-590.
- B. D. Korant and B. E. Butterworth, (1976), "Inhibition by Zinc of Rhinovirus Protein Cleavage:

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Interaction of Zinc with Capsid Polypeptides",
Journal of Virology, 18:298-306.

- 5 • B. E. Butterworth, et al. (1976), "Replication of Rhinoviruses", *Archives of Virology*, 51:169-189.
- B. D. Korant, (1976), *Chemical Abstracts*, 85:76, Abst. No. 814y.
- 10 • B. D. Korant, (1979), "Role of Cellular and Viral Proteases in the Processing of Picornavirus Proteins", in *The Molecular Biology of Picornaviruses*, pp. 149-173, R. Perez Bercoff, ed., Plenum Publishing.
- 15 • B. D. Korant, (1979), "Inhibition of Viral Protein Cleavage", in *Design of Inhibitors of Viral Functions*, I. Gauri, ed., Academic Press.
- 20 • V. J. Merluzzi et al., (1989), "Evaluation of Zinc Complexes on the Replication of Rhinovirus 2 In Vitro", *Research Communications in Chemical Pathology and Pharmacology*, 66:425-440.

25 The Korant and Butterworth articles describe the antirhinoviral activity of zinc⁺² from zinc chloride and zinc acetate, not from tightly bound or highly chelated zinc. The Merluzzi article shows in figure one that zinc⁺² is as protective of rhinovirus infected monolayer
30 cells as interferon. Merluzzi shows that the antirhinoviral activity of zinc complexes tested in the rhinovirus cytopathogenic effect (CPE) assay was directly related to the amount of unbound zinc ion available, and not to the total amount of zinc available.

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Other possible mechanisms for the effect of zinc on

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common colds are the mitogenic effect of zinc ions on human lymphocytes and interferon induction. Zinc chloride, a totally ionizable zinc compound, induces gamma-interferon at 0.05 to 0.5 mM concentration according to M. Salas and H. Kirchner, 1987, "Induction of Interferon-Gamma in Human Leukocyte Cultures Stimulated by Zn^{2+} ", *Clinical Immunology and Immunopathology*, 45(1):139-142. Such concentration is same as that required for antirhinoviral effects.

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Published articles show beneficial *in vivo* effects of zinc gluconate lozenges against common colds when zinc compounds having available zinc ions are present. Articles showing positive effects include:

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- G. A. Eby et al., (1984), "Reduction in Duration of Common Cold Symptoms by Zinc Gluconate Lozenges in a Double Blind Study", *Antimicrobial Agents and Chemotherapy*, 25:20-24.

20

- W. Al-Nakib et al., (1987), "Prophylaxis and Treatment of Rhinovirus Colds with Zinc Gluconate Lozenges", *Journal of Antimicrobial Chemotherapy*, 20:893-901.

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Each article reported the effect of zinc gluconate with no additional metal sequestrants added, and each showed a marked reduction in duration of common cold symptoms.

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Adverse Effects of Sequestration in Common Cold Research

Conversely, in a similar 1987 study "Two Randomized Controlled Trials of Zinc Gluconate Lozenge Therapy of Experimentally Induced Rhinovirus Colds", *Antimicrobial Agents and Chemotherapy*, 31:1183-1187, by Barry M. Farr

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et al., citric acid, a strong zinc chelator, was used in lozenges in extramolar amounts sufficient to eliminate taste of zinc, resulting in no reduction in duration of common colds. The first stability constant of citric acid for zinc ions is generally accepted to be $\log K_1$ --
5 4.5. In oral use in lozenge form, zinc gluconate rapidly ionizes. It is known in the art that if such occurs in the presence of sufficient amount of a chelator having a high stability constant for zinc ions such as equimolar
10 citric acid, a new, vastly stronger equilibrium may occur.

Such equilibrium may result in neutrally or negatively charged compounds having little or no
15 bioavailability at salivary pH and normal oral tissue pH. In the case of lozenges containing zinc gluconate with extramolar citric acid, soluble zinc complexes were shown to be tasteless and were proposed to be sufficiently biologically available to be effective in reducing
20 duration of common colds. However, with addition of extramolar citric acid, there occurs in saliva such powerful binding of zinc ions that neutral or negatively charged zinc species predominate. A complete loss of positively charged zinc ions occurs in saliva and in
25 oral tissues. There is no metallic taste. No localized activity occurs, and no reduction in common cold duration occurs from zinc tightly bound by citrate.

Recently, J. E. Zarembo et al., (1991), reported in
30 "Zinc (II) in Saliva: Determination of Concentrations Produced by Several Different Formulations of Zinc Gluconate Lozenges containing Common Excipients", *Journal TBD*, __: __-__, that laboratory tests using exact copies of the Farr zinc gluconate lozenges with extramolar
35 citric acid demonstrated an insignificant amount of the contained zinc as zinc^{+2} in fresh human saliva.

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Similarly, no availability of zinc ions in saliva was reported when lozenges were formulated with a tablet base of mannitol or sorbitol. According to the original authors and tablet manufacturers for the following two reports, said sugar-alcohols were used as tablet bases without common cold treatment efficacy:

- D. S. Smith, et al., (1989), "Failure of Zinc Gluconate in Treatment of Acute Upper Respiratory Tract Infections", *Antimicrobial Agents and Chemotherapy*, 33:646-648.
- R. M. Douglas, et al., "Failure of Effervescent Zinc Acetate Lozenges to Alter the Course of Upper Respiratory Tract Infections in Australian Adults", *Antimicrobial Agents and Chemotherapy*, 31:1263-1265.

Conversely, Zarembo found that addition of sucrose and corn syrup to zinc gluconate lozenges did not interfere with ionization of zinc to produce zinc⁺². A.E. Martell shows in his six-volume reference set entitled, *Critical Stability Constants*, that extra molar amounts of metal chelators always result in negatively charged metal complexes.

Flavor Stability of Compositions Containing Ionizable Zinc

There are additional requirements of composition ingredients. For product shelf-life, all ingredients must not adversely affect the taste of the composition. Said ingredients so constituted into said composition must not degrade in taste when aged or thermally stressed. Compositions must be thermally, chemically and flavor stable under all normal and near normal conditions over long periods of time. All ingredients should be

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inexpensive, readily available and Generally Regarded As Safe (GRAS).

The inventor conducted multi-year stability tests of
5 hundreds of pleasant tasting, flavor-masked zinc
compositions containing highly ionizable zinc compounds
including zinc gluconate and zinc acetate. Several
flavor masks of zinc gluconate, including anethole and
glycine, in various sweet bases were tested for flavor
10 stability over long periods of time and under thermally
stressful conditions. Glycine-treated zinc gluconate
under U.S. Patent 4,684,528 was provided by the inventor.
Anethole is an aromatic flavor mask and aftertaste mask
for zinc compounds and is disclosed and claimed as such
15 by George A. Eby, III in U.S. Patent 5,002,970, issued
March 26, 1991. All available sweet pharmaceutically
acceptable tablet bases including sugars such as sucrose,
dextrose, fructose, lactose, Sugartab®, Emdex®,
Sweetrex®; sugar-alcohols such as mannitol, sorbitol, and
20 xylitol, and other commercial products specifically
designed for pharmaceutical tablets were tested with zinc
compounds with and without flavor masks. Compositions
were exposed to seasonal temperatures reaching 45 to 55 C.
degrees during summer months for long term storage
25 testing and to similar temperatures in accelerated aging
tests. The inventor found that:

- Glycine flavor masked zinc gluconate compositions in
Mendell's Sugartab® turned deep brown after several
30 months exposure to high summer-time temperatures.
Similar composition in a hard candy base (sucrose and
corn syrup) turned from pale tan to an orange color
although there was little degradation of composition
flavor. Similar compositions in pure fructose, or in
35 ground fructose agglomerated with polyethylene
glycol-8000 did not show a color change.

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- Compressed tablets containing zinc gluconate in various tablet bases of sucrose, dextrose, lactose, maltodextrin, xylitol, sorbitol, mannitol and various direct compression tableting combinations developed objectionable tastes and aftertastes after storage for a few days to a few weeks with or without anethole.
- Aeromatic anethole usually evaporated from solid compositions suggesting that plating anethole on silica gel is inadequate for a flavor stable unsealed product. Spray dried flavors or flavor oil incorporated within cyclodextrins remained stable. Many people do not like the taste of anethole when present in sufficient amounts to flavor mask the taste and aftertaste of zinc gluconate.
- Compressed tablets, containing zinc gluconate in a tablet base of ground fructose agglomerated with polyethylene glycol 8000 (PEG-8000) to about 10%, and flavor masked with anethole and flavored with menthol and eucalyptol hermetically sealed in an amber glass pharmaceutical bottle, remained fully flavor-masked for over a one-year period.
- Surprisingly and unexpectedly, zinc acetate compressed tablets, in a base of crystalline fructose and agglomerated sucrose (Mendell's Sugartab®) in various ratios, which also contained 14-mg saccharin, and flavors, retained a pleasant sweet taste, and had no objectionable aftertaste after a two-year storage period. Zinc acetate does not become bitter upon aging in the presence of fructose or sucrose or other sugars.
- Surprisingly and unexpectedly, zinc acetate compressed tablets in a base of crystalline fructose and agglomerated sucrose (Mendell's Sugartab®) in a 10 to 1

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ratio with a peppermint flavor added had after a two year storage period in an amber glass pharmaceutical bottle the original delightful peppermint flavor and sweet taste and pleasant aftertaste of the original composition.

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• Surprisingly and unexpectedly, compressed tablets containing zinc acetate in a tablet base of pure fructose agglomerated with polyethylene glycol 8000 (PEG-8000) which also contained 14-mg saccharin and which had
10 peppermint flavor added had, after a two year storage period in an amber glass pharmaceutical bottle, the original delightful peppermint flavor and sweet taste and pleasant aftertaste of the original unaged composition.

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• Surprisingly and unexpectedly, zinc acetate compressed tablets in a base of crystalline fructose and agglomerated sucrose or other sugars in varying ratios with peppermint, wintergreen or other flavors added had retained, after a one year storage period in unsealed
20 containers, the original sweet taste and pleasant aftertaste of the original unaged composition, although some examples had accumulated moisture due to the hygroscopic nature of fructose and some examples had lost flavor due to evaporation.

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• Surprisingly and unexpectedly, pleasant tasting zinc acetate hard and soft candy lozenges, chewing gums, toothpastes, mouth rinses, gargles, syrups, powders, tablets, sprays and so forth were also pleasantly
30 flavored without objectionable aftertaste with addition of zinc acetate to existing products, with addition of saccharin to increase sweetness being occasionally necessary. Zinc acetate does not become bitter upon aging in conjunction with many ingredients.

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• When the pharmaceutically acceptable carrier was

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sweet or was a sugar, the taste of the composition was best. Although sweetness appears to flavor-mask zinc acetate taste, there is no apparent explanation for the lack of bitterness or objectionable aftertaste associated with other zinc compounds such as zinc gluconate. Small amounts of saccharin were beneficial in improving sweetness when marginally sweet pharmaceutically acceptable carriers such as dextrose, lactose or maltose were used. However, excessive amounts of saccharin (over 50mg) often resulted in a bitter taste.

A generalized characterization of said findings suggests that compositions containing zinc acetate without anethole and without added amino acids are a highly significant improvement over compositions containing either amino acids and zinc gluconate, or anethole and zinc gluconate. Changes in color upon addition of glycine to lozenges containing dextrose upon thermal stressing may indicate that the ingredients are degraded by a Browning Reaction. Loss of flavors by evaporation are expected, but when evaporation of anethole occurs, the flavor masking effect is also lost. Such changes may inhibit commercial utility and preclude wide spread marketability of said zinc compositions as treatment for common colds unless a satisfactory solution is developed. Instant invention does not taste like anethole, anise or licorice, which is a significant improvement to many persons; and is flavor stable upon aging.

30

The surprising and unexpected observation that zinc acetate may be prepared with sucrose, fructose, and other sugars with or without other ingredients without loss of flavor, sweetness or degradation from thermal and storage stresses and without added flavor-masks (amino acids or anethole) is a significant original, surprising and

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unexpected finding new to the art. The surprising and unexpected showing that flavor enhancements to zinc acetate oral compositions occur with increases in sweetness of the pharmaceutically acceptable carrier or
5 added super sweeteners such as saccharin is significant, surprising and unexpected.

Other Findings

10 U.S. Patent 4,684,528 discloses a slow-release candy compositions, comprising a hard candy base (hard boiled sucrose and corn syrup), zinc gluconate, zinc acetate or other zinc compounds, and an amino acid having a molar
15 ratio of said amino acid to zinc of about 2 to 20, and various other oral compositions containing zinc compounds and certain amino acids. Such compositions can be flavor masked by glycine and certain other amino acids.

Importantly, said amino-acid flavor-mask patent
20 teaches that a zinc acetate formulation of hard candy without glycine has a sharp, undesirable taste and an unpleasant aftertaste, which is directly contrary to the findings of the present inventor.

25 The Current Need

There is an important, current need to develop improved, pleasant-tasting zinc ion releasing compositions that are thermally, chemically and flavor
30 stable; and that do not contain undesirable flavor-masks such as amino acids or anethole. Lozenges and other means having a pleasant taste that introduce zinc ions into oral and oral pharyngeal mucous membranes are needed primarily for treatment of common colds, common cold
35 symptoms and nutritional supplementation. Common cold symptoms include nasal drainage, nasal congestion,

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headache, fever, myalgia, sneezing, sore throat, cough, hoarseness and sinusitis. In as much as serious mistakes taken from the prior art of taste management of zinc ions have been made, particularly in the invention of

5 thermally, chemically and flavor stable zinc lozenges for treating common colds; it is apparent that errors of the prior art must receive attention. A new improved way of eliminating objectionable taste and aftertaste of ionizable zinc compositions is needed using stable

10 lozenge ingredients without added flavor-masks.

Accordingly, it is a primary objective of this invention to disclose and claim an improved oral zinc composition that is thermally, chemically, and flavor

15 stable. Said composition shall be devoid of the objectionable flavor and aftertaste commonly associated with oral zinc compositions. Said compositions shall be intended to release zinc ions into oral and oral pharyngeal mucous membranes. Said compositions are

20 primarily intended to be used to shorten duration of common colds or their symptoms, for human nutritional support or for closely related purposes. Said compositions shall contain zinc acetate, an extremely ionizable zinc compound, which has been discovered by the

25 inventor to not have an objectionable taste or aftertaste when properly formulated. These primary objectives and other objectives of this invention will be found apparent from the following general description and detailed examples.

30

Compositions Containing Zinc Acetate Generally

The inventor discloses and claims pleasant tasting compositions specifically containing zinc acetate and

35 pharmaceutically acceptable carriers for use primarily in human common cold treatment and for nutritional support.

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Said compositions are primarily intended to be dissolved in the mouth, masticated or otherwise used in the mouth primarily for release of zinc ion into the tissues of the oral cavity and oral pharyngeal tissues of a human. Said compositions are to be slowly and uniformly released by aqueous dissolution of solid ingredients within said composition, as said compositions are held or retained in the mouth. Saliva, generated by person dissolving said composition, is the source of said aqueous solvent for solid compositions. Liquid compositions may contain zinc acetate in aqueous or other solvents. Ideal oral cavity retention time periods are 15 to 30 minutes per each application or use of composition. Soft candy and chewing gums are to release zinc acetate slowly over a sustained period of time.

Said zinc acetate containing compositions are stable, meaning that negligible degradation in flavor, appearance or chemistry occurs under extended multi-year storage in normal and near normal temperature conditions while sealed in air-tight, opaque containers. Said zinc acetate compositions are pleasant tasting and have a pleasant aftertaste, generally defined by the added flavors, the pharmaceutically acceptable carrier when said carrier is also a sweetener, or by added super sweeteners such as saccharin. Said composition is an improvement upon a slow-release candy composition comprising a hard candy base, zinc acetate and an amino acid as said sweet composition of the present invention excludes amino acids having a molar ratio of said amino acid to zinc of about 2 to 20; and whereby said composition is an improvement upon a medicinal composition for release of zinc ions consisting essentially of a suitable pharmaceutical carrier, zinc acetate and anethole.

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As discovered from said thermal and aging stability studies, compositions are without an objectionable taste or aftertaste even without an added flavor-mask. Compositions are chemically, thermally and flavor stable with no increase in bitterness under high summer-time temperature conditions over multi-year periods of time. This invention primarily discloses and claims the discovery of pleasant tasting and aftertaste-free compositions of zinc acetate dispersed in a consumable pharmaceutically acceptable carrier. By necessity to clearly and more fully describes said compositions, said inventive compositions include:

Zinc acetate in any pharmaceutically acceptable carrier such as fructose, Mendell's Sugartab®, Sweetrex® or Emdex®, sucrose, dextrose, maltose, lactose, sweetened water and the like, singularly or in combination, with following pharmaceutical necessities included singularly or in combination, as desired:

- tablet binders for compressed tablets, lozenges and troches, such as polyethylene glycol-6000 or 8000,
- flavor oils such as peppermint, methyl salicylate, menthol and eucalyptol excluding anethole,
- flavor oil stabilizers, such as spray driers and cyclodextrins,
- coloring agents and dyes,
- glidants, such as silica gel,
- tablet lubricants, such as magnesium stearate,
- other necessities excluding amino acids as disclosed in U.S. Patent 4,684,528;

and with the following medicinal additives included as desired or necessary:

- antiviral agents, such as antirhinoviral agents,

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- anesthetics, such as lidocaine,
- antimycoplasmal agents,
- antibiotics,
- nasal decongestants,
- 5 • antihistamines,
- antinausea agents,
- analgesics,
- cough relievers,
- dental desensitizers,
- 10 • saliva inhibitors,
- vitamins, such as ascorbic acid,
- minerals, other than zinc, and
- other medicinal agents and nutritional supplements
either directly incorporated within compositions or
15 chemically isolated through techniques including
microencapsulated and inclusion within
cyclodextrins. Microencapsulation with insoluble
porous membranes providing a time release capability
for ingredients that might interfere with release of
20 zinc ions or adversely affect taste of composition
is anticipated and recommended.

Such compositions include solid forms such as
tablets, troches, lozenges and powders; chewable forms
25 such as chewing gums and soft candies; and liquid forms
such as syrups, mouth washes and sprays. When said
compositions are applied to oral and oral pharyngeal
membranes of a human, they are palatable and without
undesirable taste or unpleasant aftertaste, yet they
30 allow oral and oral pharyngeal absorption of zinc ions.
When compositions are to be used to treat common colds,
said pharmaceutical necessities and medicinal additives
shall not be present in sufficient quantities to impair
the beneficial action of zinc⁺² on the duration of common
35 colds or they shall be sealed through microencapsulation
or other methods having a similar result.

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Zinc Acetate as Source of Zinc Ions

Although zinc gluconate is the best known source of zinc ions in lozenges for treating common colds, zinc acetate merits special attention. Zinc lozenges for treating common colds contain between 0.2 and 500 mg zinc (0.7 to 1679 mg zinc acetate) and more often contain about 2 to 50 mg of zinc (7 to 168 mg zinc acetate) and most often contain about 23 mg zinc. Zinc acetate offers improved, unexpected characteristics that require close attention. That zinc acetate would be acceptable in zinc lozenges is completely unexpected as undiluted zinc acetate has an extremely strong, vile taste completely offensive by any standard and much worse than the taste of undiluted zinc gluconate. It has chemical properties that are preferable over zinc gluconate for use in zinc lozenges. Zinc acetate dihydrate is 29.78% zinc compared with 13.14% zinc for zinc gluconate. Only 77.23 mg zinc acetate is needed to provide 23 mg zinc whereas 175 mg of zinc gluconate is needed. Over 400 grams zinc acetate will dissolve in a liter of water compared to zinc gluconate at 100 grams/liter. The first stability constant of acetic acid ($\log K_1$ --1.03) is lower than that of gluconic acid ($\log K_1$ --1.64) for zinc. The ready availability of zinc ions from zinc acetate is well known. Zinc acetate was used *in vitro* by Bruce D. Korant (1974) to inhibit replication of rhinoviruses *in vitro*. Zinc ion, from zinc acetate or zinc chloride, is as antirhinoviral and as protective of monolayer cells *in vitro* as interferon.

Surprising and Unexpected Taste Characteristics

Most importantly, surprisingly, totally unexpectedly, and patently unique: zinc acetate diluted with any pharmaceutically acceptable carrier, such as

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sweetened water, fructose, sucrose, dextrose, starch, lactose, other sugars or other dilutants, has neither a long lasting aftertaste nor an offensive aftertaste like that present with zinc gluconate when said composition is retained in the oral cavity of a human for sustained periods of time. Zinc acetate may be sufficiently diluted, yet sufficiently concentrated to be of utility against common colds. Said compositions have a pleasant taste and pleasant aftertaste, however taste is improved with increasing sweetness, but to a limit. All zinc ion compositions for use in shortening common colds are required to be slowly and uniformly released in a sustained manner into the oral cavity as said compositions are being orally consumed or masticated. Said compositions must be stable and have a pleasant taste and aftertaste during composition dissolution. Sustained application of zinc ions to the interior of the mouth including the tongue, oral cavity, throat and oral pharyngeal surfaces from a palatable composition is necessary in order to be effective in reducing the duration of common colds. The inventor also discovered that the objectionable taste of zinc acetate is eliminated with addition of consumable, pharmaceutically acceptable carriers such as fructose, sucrose, dextrose and other sugars and sweeteners; with or without added super sweeteners like saccharin and various flavors; all of which is directly contrary to teachings of U.S. Patent 4,684,528.

30 Fructose, Sucrose and Dextrose as Pharmaceutical Carriers

Fructose is the sweetest of the natural sugars. It is a component of sucrose, a disaccharide, and is an isomer of dextrose, all of which are sugars. Neither fructose, sucrose nor dextrose are believed to chelate zinc in a way that would detract from its utility in

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treating common colds.

It is surprising and unexpected that fructose does not visibly react, change color or form bitter compounds with zinc acetate at higher ambient temperatures as this monosaccharide is a polyhydroxy ketone and is usually considered highly reactive. On the other hand, dextrose, a polyhydroxy aldehyde is normally considered to be an inert monosaccharide. Dextrose reacts with zinc gluconate over time to form bitter complexes, but not with zinc acetate. Since both acetic acid and gluconic acid are closely related monocarboxylic acids, it is strange and unforeseen that they would react so differently. Sucrose and dextrose, but not fructose, react with primary amino acids such as glycine in presence of zinc becoming brown and unattractive at high summer temperatures over time. Various sweet tasting commercial tablet bases having a modified sugar base produced bitter zinc gluconate lozenges after aging for a few weeks, particularly when exposed to high summer temperatures. However, Mendell's Sugartab® and other sugars do not become bitter when used in zinc acetate lozenges, regardless of time or temperature.

Favored compositions of fructose or sucrose with zinc acetate

It can now be revealed that preference is given to compositions of zinc acetate (Heico Chemical zinc acetate dihydrate is USP grade) in a fructose based carrier over other sugars, and to zinc acetate over zinc gluconate. Favored formulation is zinc acetate in lozenges having a carrier of fructose mixed with agglomerated sucrose or agglomerated dextrose. Hard, slow dissolving tablets with crystalline fructose (A. E. Staley's Krystar-300) as a carrier could be bound by Sugartab® at about the same

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weight of crystalline fructose without tablet capping if sufficient pressure is applied. Tablets with crystalline fructose (A. E. Staley's Krystar-300) as a carrier could be bound by Emdex® at about one-half the weight of crystalline fructose without tablet capping. Generally lozenges are made in a 4 to 6 gram size to allow a suitable dissolution rate for lozenges. Dissolution time should be about 12 to 15 minutes in water bath testers at 37 C. degrees or about 30 minutes when dissolved in the mouth as a lozenge. There may be considerable variability (fifteen minutes to one hour and fifteen minutes) in dissolution time, depending on the amount of saliva produced in response to the lozenges. Greatest efficacy occurs when saliva generation is lowest; thus raising zinc molar concentration in the oral cavity, suggesting utility for incorporating saliva inhibitors into compositions. Smaller and larger lozenges from 0.1 up to 15 grams were made and are anticipated by this invention. Other binders, such as polyethylene-glycol 8000 in minor amounts, may be added to increase tablet hardness, but addition may cause a slight loss of sweetness, and loss of zinc ions.

Compressed Tablet Compositions

Lozenges, tablets and troches in this invention are essentially the same, but may differ in shape, size and manufacturing technique. Since fructose is sweeter than sucrose, and other sugars, it is preferred for use in direct compression of lozenges containing zinc acetate. Fructose may be processed for direct compression of tablets, troches and lozenges by incorporation of a tablet binder such as PEG-8000, perhaps using fluid bed agglomeration techniques wherein PEG has been diluted with water. To make directly compressible lozenges, add zinc acetate to PEG-8000 processed fructose; or add zinc

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acetate to crystalline fructose and commercially available, sweet, direct compression products such as Mendell's Sugartab®, Sweetrex®, or Emdex®. Add saccharin if desired, flavors as desired, glidants such as silica gel as needed, and lubricants such as magnesium stearate (about 0.5 to 1.0 %) as needed. Mixture should be kept dry, preferably less than 0.5 % water. Ingredients are mixed and directly compressed into lozenges, tablets or troches using conventional pharmaceutical mixing and tableting equipment. Store in air tight containers in a cool dark place. If heated to high summer-time room temperatures, compositions, when properly prepared and sealed, are pleasantly flavored, do not turn brown over time and do not have a bitter aftertaste. If properly formulated, no flavors are needed for compositions to have sweet pleasant tastes and no offensive aftertaste.

Although added ingredients are not believed necessary to present a pleasantly flavored composition having essentially no zinc aftertaste, addition of super sweeteners, such as saccharin is anticipated to improve the flavor of the basic composition and added pharmaceutical necessities and medicinal additives.

25 Liquid Compositions

Zinc acetate with a pleasant tasting, sweet, pharmaceutically acceptable carrier may be prepared in any liquid form such as syrups, mouth washes or sprays with water or other liquids for repeated delivery of concentrated ionizable zinc to oral and oral pharyngeal mucous membranes over a sustained period of time so as to permit a prolonged contact by ionizable zinc upon mouth and throat tissues.

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Soft Compositions

Zinc acetate in chewable compositions such as soft candy, gum drop, liquid filled candies, chewing gum base
5 and dental supplies, such as toothpastes and mouth washes, may be prepared by adding zinc acetate, and perhaps sweeteners including fructose, sucrose and saccharin as needed.

10 Super Sweeteners

Various super sweeteners including saccharin, aspartame, cyclamates, acesulfame K, neohesperidin dihydrochalcone and other super sweeteners may be added
15 to the carrier in amounts sufficiently low so as not to chemically react with a significant amount of zinc. Preference is given to sodium saccharin, about 1 to 14 mg per 23 mg zinc, as additive super sweetener. Above 50 mg saccharin, compositions may have a bitter saccharin taste
20 and aftertaste.

Flavors

Many flavorings can be added to impart their own
25 flavor including but not restricted to peppermint, peppermint-menthol, eucalyptol, wintergreen, licorice, clove, cinnamon, spearmint, cherry, lemon, orange, lime, menthol and various combinations. Preference is given to peppermint (Bell #113.042) flavor plated onto silica gel
30 for trueness of flavor and proven multi-year stability.

Stabilized Flavors

Some flavor oils may not be stable in long-term
35 storage in zinc acetate lozenges, and must be prevented from contacting zinc, evaporating and degrading

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generally. In lozenges and other dry solid compositions, flavors may be stabilized by spray drying with National Starch's N-Lok or other modified starches, or included within cyclodextrins, and/or coated with PEG 6000 or 8000. Inclusion of flavor oils within cyclodextrins results in essentially complete long-term thermal, oxidative and photo-decomposition stability. Of particular interest, inclusion results in protection against flavor oil degradation and oxidization otherwise accelerated by heat, light and metal salts. Spray dry flavors must not include acacia, a powerful zinc chelator. Zinc acetate may be coated with PEG 6000, 8000 or higher molecular weight PEG or included within cyclodextrins to prevent contact of zinc with flavors. However, peppermint oil (Bell #113.042) plated onto silica gel (Siloid 244FP) is stable with no loss of flavor or aroma for at least two years in directly compressed zinc acetate lozenges in sealed amber glass bottles, and presumably any air-tight, opaque container. Of peculiar interest, anethole reacts with zinc acetate, but not with zinc gluconate, over time to produce bitter flavors, whether it is plated upon silica gel or incorporated within cyclodextrins.

Pharmaceutically Acceptable Carriers

Without regard to desirability of ingredients or intended use of compositions, a more complete list of sweet, consumable, pharmaceutically acceptable carriers includes but is not limited to: (a) carbohydrates including fructose, sucrose, sugar, dextrose, starch, lactose, maltose, maltodextrins, corn syrup solids, honey solids, commercial tablet compositions including Emdex®, Mor-Rex®, Royal-T®, Di-Pac®, Sugar-Tab®, Sweet-Rex®, New-Tab®, (b) sugar alcohols including mannitol, sorbitol, xylitol, and (c) various relatively insoluble

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excipients including dicalcium phosphate, calcium sulfate, calcium carbonate, microcrystalline cellulose and other ingredients. Pharmaceutically acceptable carriers for compositions to be used for treating common
5 colds by release of zinc ions in the oral cavity generally include the above, but exclude the sugar-alcohols.

Undesirable Ingredients for Treating Common Colds

10

Zinc acetate compositions for treating common colds must exclude positively-charged zinc ion-depleting ingredients and other incompatibles. Acacia, mannitol, sorbitol, super sweeteners, citric acid, tartaric acid
15 and other food acids, lake colors, alkalies and their carbonates, oxalates, phosphates, sulfides, lime water, and vegetable decoctions are considered incompatible with zinc acetate; and may cause compositions to be flavor unstable or cause a loss of efficacy against common colds
20 or both. Zinc ion depleting chelators must not be added in chemically significant amounts even if they are physically isolated from zinc acetate within compositions.

25 Mannitol and sorbitol are common tablet bases that destroy beneficial properties of zinc lozenges in shortening common colds; which must not be used in amounts that chelate significant amounts of zinc ions.

30 Examples of Invented Compositions

The following examples will serve to further illustrate, but not to limit, the present invention.

35 Favored zinc acetate lozenges can be prepared by direct compression of ingredients. To make a 5-gram

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fructose and sucrose based, directly compressed tablet containing 23 mg zinc, mix 77.2 mg zinc acetate dihydrate, 17 mg peppermint oil plated onto 17 mg silica gel (Siloid 244FP), 25 to 50 mg magnesium stearate (lubricant), about 2400 mg Sugartab® and sufficient crystalline fructose to make a five-gram lozenge. Compress with tablet press using sufficient pressure to obtain desired dissolution rate. About 6.5 tons of pressure on a properly prepared 3/4-inch diameter 5-gram lozenge results in a 12 to 15 minute dissolution rate in water bath testers. Such composition is thermally, chemically and flavor stable having a pleasant taste and aftertaste. Instant composition is preferred as it is sweet and does not contain saccharin or PEG-8000.

15

To make a 5-gram sucrose based directly compressible tablet containing 23 mg zinc, mix 77.2 mg zinc acetate dihydrate, saccharin (up to 50 mg if desired), 17 mg peppermint oil plated onto 17 mg silica gel (Siloid 244FP), 25 to 50 mg magnesium stearate and sufficient sucrose (Sugartab®) to make a five gram lozenge. Compress into tablet. Such composition is thermally, chemically and flavor stable having a pleasant taste and aftertaste.

25

To make a 5-gram dextrose, fructose, maltose, and isomaltose based directly compressible tablet containing 23 mg zinc, mix 77.2 mg zinc acetate dihydrate, saccharin (1 to 50 mg if desired), 17 mg peppermint oil plated onto 17 mg silica gel, 25 to 50 mg magnesium stearate and sufficient Sweetrex® to make a five-gram lozenge. Compress into tablet. Such composition is thermally, chemically and flavor stable having a pleasant taste and aftertaste.

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To make a 5-gram fructose and dextrose based

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directly compressible tablet containing 23 mg zinc, mix 77.2 mg zinc acetate dihydrate, saccharin (up to 50 mg if desired), 1 to 30 mg peppermint oil plated onto silica gel, 50 mg magnesium stearate and 2.0 to 3.5 grams
5 crystalline fructose and sufficient dextrose (Emdex®) to make a five-gram lozenge. Compress into tablet. Such composition is thermally, chemically and flavor stable having a pleasant taste and aftertaste.

10 To make a 2.5-gram lactose based lozenge containing 23 mg zinc, mix 77.2 mg zinc acetate dihydrate, saccharin (up to 50 mg if desired), about 200 mg wintergreen oil/beta-cyclodextrin complex or as desired, 75 mg magnesium stearate and sufficient directly compressible
15 non-palpable lactose to make a 2.5 gram lozenge. Compress with tablet press using sufficient pressure to obtain desired dissolution rate. Such composition is thermally, chemically and flavor stable having a pleasant taste and aftertaste.

20 To make a 4-gram hard candy lozenge containing 23 mg zinc, mix 64.53 mg anhydrous zinc acetate, 17 mg peppermint oil plated onto 17 mg silica gel, and mix into a molten hard candy base of sucrose and corn syrup, with
25 or without saccharin as desired. Such composition is thermally, chemically and flavor stable having a pleasant taste and aftertaste.

To make a syrup wherein each 7.5 milliliter dose
30 contains about 23 mg zinc from zinc acetate, add to 3 grams of deionized water, 4.5 grams of fructose or sucrose, 77.2 milligrams zinc acetate, saccharin as desired, and flavors as desired. Vary amount of water and fructose to make other liquids such as mouth washes,
35 gargles, and sprays. Such composition has a pleasant taste and aftertaste.

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To make a chewing gum, add to 4 grams of melted chewing gum base, about 5 grams of fructose, 64.53 mg powdered anhydrous zinc acetate, saccharin as desired and flavors as desired. Shape and let cool. To make a soft candy, substitute soft candy for chewing gum base. Such compositions shall be thermally, chemically and flavor stable having a pleasant taste and aftertaste.

Preferred Zinc Composition

10

The zinc compound for use in flavor-stable zinc compositions having no unpleasant aftertaste for oral absorption is zinc acetate. The preferred method of applying zinc acetate to the oral mucosa is with lozenges having a crystalline fructose and directly compressible sucrose or dextrose base, to maximize sweetness without addition of saccharin. The preferred method to prepare flavor oils is by plating them onto silica gel, as potential for chelating zinc by flavor stabilizers is eliminated. All ingredients to be used in compositions within the present invention are consumable (meaning dissolvable, swallowable, suckable, chewable and so forth), and are believed safe for human consumption.

25

Hard boiled candy lozenges using zinc acetate dihydrate flavor masked with anethole were first made by the inventor. Adding zinc acetate dihydrate to a hot molten candy base caused large amounts of water vapor to boil off hot compositions. Vapors and compositions had a strong, unpleasant vinegar odor and taste without a zinc taste or zinc aftertaste. Use of anhydrous zinc acetate prevented boil off, and prevented the release of vinegar taste or odor. Upon loss of anethole to evaporation, compositions remained flavor-masked to the extent that they had no taste or aftertaste of zinc.

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The first compressed lozenge examples of compositions contained 86.98 mg zinc acetate dihydrate, 3260 mg fructose, 350 mg Mendell Sugartab®, 67 mg sodium saccharin and 24 mg peppermint flavor. Said composition
5 was both excessively sweet and excessively flavored. Sealed compositions showed no loss of sweetness, change in color, degradation of flavor or unpleasant aftertaste over a storage period of well over two years under high summer-time temperature conditions. Other early
10 compositions contained 64.5 mg zinc acetate, 14 mg saccharin, 4434 mg fructose, 500 mg PEG and flavors consisting of 12 mg anethole, 8 mg menthol, and 6 mg eucalyptol plated onto silica gel. Compositions were not sealed from the atmosphere and they lost all of their
15 flavor and anethole flavor mask over the following year, but continued to have a pleasant taste and aftertaste. Sealed zinc acetate and fructose or sucrose lozenges are believed to be chemically, thermally and flavor stable for over five years even when exposed to high room
20 temperatures without development of bitter aftertastes.

A flavor stable lozenge means that there is no increase in bitterness after manufacturer as may be found for zinc gluconate lozenges in sucrose. A flavored
25 lozenge has the taste property of the individual added flavor, which may have considerable variability in stability depending upon the flavor and flavor stabilization method used.

30 Flavor-stable oral zinc compositions are important in that a soluble and ionizable zinc compound, zinc gluconate, has been demonstrated useful in lozenge form to shorten duration of common colds. Zinc acetate is more soluble and more ionizable than zinc gluconate,
35 offering improved performance in treating common colds according to U.S. Patent 4,956,385. Zinc acetate is

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known to be as antirhinoviral and as protective of cells
in vitro as interferon. Zinc ions are strong interferon
inducers. Common colds often require oral zinc treatment
about every two to three hours in order to shorten them
5 by about 7 days. Highly palatable oral zinc compositions
are needed as encouragement for a person in need of such
treatment to continue treatment until symptoms are
eliminated. Above examples serve to demonstrate that
palatable zinc acetate lozenges and other oral
10 compositions without unpleasant aftertaste are possible
using a fructose, sucrose or other sweet diluent with
neither amino acids nor anethole. The examples also
show that compositions can retain their pleasant flavor
for commercially interesting periods of time.

15
As will be apparent from examples, the amount of
zinc ion which will be released can be controlled by the
amount of zinc acetate incorporated in compositions. As
will be readily understood, if compositions with a larger
20 or smaller ratio of fructose or sucrose or other sweet
base to zinc is used, that such is anticipated. Also, as
will be readily understood, other release rates of zinc
and fructose, sucrose or other bases are possible and
anticipated. Any appropriate means of oral
25 administration such as different size lozenges, hard
molded candies, syrups, mouth washes, gargles,
toothpastes, tablets, liquids, chewing gums, powders,
sprays, and aerosols and various similar means may be
used and are anticipated. Any means suitable for
30 delivery of zinc acetate and a consumable, sweet
pharmaceutically acceptable carrier to oral and oral
pharyngeal mucous membranes to permit a pleasant
prolonged contact of zinc in the mouth may be used and is
anticipated. Present invention provides pleasant, new
35 means of releasing zinc in the oral cavity, in various
amounts, and at various rates determined by the

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formulation and composition used in a manner that is a substantial improvement in flavor, thermal and chemical stability over plain or otherwise flavored zinc compounds. As will be apparent to one skilled in the art, variations can be made within the scope of the
5 aforesaid description. Such variations being within the ability of one skilled in the art form a part of the present invention and are embraced by following claims.

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CLAIMS:

1. A composition for release of zinc in the oral cavity of a human comprising zinc acetate in combination with a pharmaceutically acceptable carrier, whereby said composition is flavor stable and has a pleasant taste and aftertaste.
2. The composition of claim 1, further including super sweeteners.
3. A composition for release of zinc in the oral cavity of a human comprising zinc acetate in combination with a sweet pharmaceutically acceptable carrier, whereby said composition is flavor stable and has a pleasant taste and aftertaste.
4. The composition of claim 3, further including super sweeteners.
5. The composition of claim 3 wherein said composition is a hard candy lozenge containing about 0.7 to 1679 mg of zinc acetate dispersed in about 1 to 15 grams of sweet pharmaceutically acceptable carrier.
6. The composition of claim 3 wherein said composition is a compressed tablet containing about 0.7 to 1679 mg of zinc acetate dispersed in about 1 to 15 grams of sweet pharmaceutically acceptable carrier.

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7. The composition of claim 3 wherein said composition is a powder containing about 0.7 to 1679 mg of zinc acetate dispersed in about 1 to 15 grams of sweet pharmaceutically acceptable carrier.

5

8. The composition of claim 3 wherein said composition is a liquid containing about 0.7 to 1679 mg of zinc acetate dispersed in about 1 to 15 grams of sweet pharmaceutically acceptable carrier and water.

10

9. A composition for release of zinc in the oral cavity of a human comprising zinc acetate in combination with a sweet carbohydrate pharmaceutically acceptable carrier, whereby said composition is flavor stable and has a pleasant taste and aftertaste.

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10. The composition of claim 9, further including super sweeteners.

20

11. The composition of claim 9, further including flavors.

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12. The composition of claim 9, further including pharmaceutical necessities.

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13. The composition of claim 9, further including medicinal additives.

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14. The composition of claim 9 wherein said composition

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is a hard candy containing about 7 to 168 mg zinc acetate dispersed in about 1 to 15 grams of sweet carbohydrate pharmaceutical carrier consisting essentially of sucrose and corn syrup.

5

15. The composition of claim 9 wherein said composition is a compressed tablet containing about 7 to 168 mg zinc acetate dispersed in about 1 to 15 grams of sweet carbohydrate pharmaceutical carrier consisting essentially of sucrose.

10

16. The composition of claim 9 wherein said composition is a compressed tablet containing about 7 to 168 mg zinc acetate dispersed in about 1 to 15 grams of sweet carbohydrate pharmaceutical carrier consisting essentially of sucrose and fructose.

15

20

17. The composition of claim 9 wherein said composition is a compressed tablet containing about 7 to 168 mg zinc acetate dispersed in about 1 to 15 grams of sweet carbohydrate pharmaceutical carrier consisting essentially of dextrose and fructose.

25

18. The composition of claim 9 wherein said composition is a compressed tablet containing about 7 to 168 mg zinc acetate and a flavor, dispersed in about 1 to 8 grams of sweet carbohydrate pharmaceutical carrier consisting essentially of sugars.

30

19. The composition of claim 9 wherein said composition is a compressed tablet containing about 7 to 168 mg zinc

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acetate, a super sweetener and a flavor, dispersed in about 1 to 8 grams of sweet carbohydrate pharmaceutical carrier consisting essentially of sugars.

5

20. The composition of claim 9 wherein said composition is a compressed tablet containing about 7 to 168 mg zinc acetate, about 1 to 50 mg saccharin and about 1 to 30 mg flavor dispersed in about 3 to 6 grams of sweet carbohydrate pharmaceutical carrier consisting essentially of sugars.

10

21. The composition of claim 1, 3 or 9, further defined as essentially free of an amino acid flavor mask.

15

22. The composition of claim 1, 3 or 9, further defined as essentially free of an anethole flavor mask.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US91/09487

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ³ According to International Patent Classification (IPC) or to both National Classification and IPC IPC (5): A61K 9/10, 31/315, 33/30 US CL : Please See Attached Sheet.		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁴		
Classification System	Classification Symbols	
U.S.	424/49, 54, 58, 439, 440, 441, 442, 464, 489, 641, 643; 514/466, 494, 643, 849, 888, 931, 934, 974	
Documentation Searched other than Minimum Documentation to the extent that such Documents are included in the Fields Searched ⁵		
III. DOCUMENTS CONSIDERED TO BE RELEVANT ¹⁴		
Category*	Citation of Document, ¹⁶ with indication, where appropriate, of the relevant passages ¹⁷	Relevant to Claim No. ¹⁸
A, P	US, A, 5,059,416 (Cherukuri et al) 22 October 1991, see entire document.	1-22
A	US, A, Re. 33,465 (Eby, III) 27 November 1990, see entire document.	1-22
A	US, A, 4,292,324 (Jonsson et al) 29 September 1981, see entire document.	1-22
A	US, A, 4,503,070 (Eby, III) 05 March 1985, see entire document.	1-22
A	US, A, 4,664,906 (Sipos) 12 May 1987, see entire document.	1-22
A	US, A, 4,684,528 (Godfrey) 04 August 1987, see entire document.	1-22
A	US, A, 4,689,214 (Niles et al) 25 August 1987, see entire document.	1-22
A	US, A, 4,764,375 (Paradissis) 16 August 1988, see entire document.	1-22
A	US, A, 4,766,004 (Moskowitz) 23 August 1988, see entire document.	1-22
* Special categories of cited documents:¹⁶ "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search ²	Date of Mailing of this International Search Report ²	
28 FEBRUARY 1992	13 MAR 1992	
International Searching Authority ¹	Signature of Authorized Officer ²⁰	
ISA/US	Ronald W. Griffin	

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

A	US, A, 4,777,162 (Hijiya et al) 11 October 1988, see entire document.	1-22
A	US, A, 4,794,014 (Siren) 27 December 1988, see entire document.	1-22
A	US, A, 4,814,163 (Barth) 21 March 1989, see entire document.	1-22
A	US, A, 4,814,164 (Barth) 21 March 1989, see entire document.	1-22
A	US, A, 4,956,385 (Eby, III) 11 September 1990, see entire document.	1-22

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE¹

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers , because they relate to subject matter (1) not required to be searched by this Authority, namely:

2. ☐ Claim numbers , because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out (1), specifically:

3. ☐ Claim numbers , because they are dependent claims not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING²

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.
2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:
3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:
4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Search Authority did not invite payment of any additional fee.

Remark on protest

- ☐ The additional search fees were accompanied by applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PREVIOUS SHEETS
(Not for publication)

I. CLASSIFICATION OF SUBJECT MATTER:
US CL :

424/49, 54, 58, 439, 440, 441, 442, 464, 489, 641, 643; 514/466, 494, 643, 849, 888,
931, 934, 974

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category ¹⁶	Citation of Document, ¹⁶ with indication, where appropriate, of the relevant passages ¹⁷	Relevant to Claim No. ¹⁸
A,P	US, A, 4,980,169 (Oppenheimer et al) 25 December 1990, see entire document.	1-22
A,P	US, A, 4,992,259 (Schiraldi et al) 12 February 1991, see entire document.	1-22
A,P	US, A, 5,002,970 (Eby, III) 26 March 1991, see entire document.	1-22
A,P	US, A, 5,059,416 (Cherukuri et al) 22 October 1991, see entire document.	1-22