

STABLE AND PALATABLE COMPOSITION OF VITAMIN C AND ZINC
LOZENGE TABLETS

5 BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to palatable lozenge tablets containing vitamin C and zinc, wherein the vitamin C is present at high concentration and is stable against oxidation and formation of carbon dioxide.

10 *2. Background of the Invention*

Zinc is one of the most important mineral nutrients. One third of the global population is believed to be zinc deficient. Zinc deficiency is associated with impaired immune function.

15 Vitamin C is the most widely used vitamin for immunity. Vitamin C and zinc are combined in a single formulation to complement their immunity benefits. However, combining Vitamin C and zinc is difficult because Vitamin C is particularly susceptible to oxidation, and this oxidation is enhanced by polyvalent metals such as zinc. This oxidation is facilitated by moisture, and leads to
20 spotting, darkening, and carbon dioxide formation.

While spotting/darkening is a known problem with solid dosage formats of vitamin C, an equally important but less appreciated problem is the formation of carbon dioxide which leads to bloating of common unit dose packs such as blister and aluminum foil. In the case of multiple units packed in bottles, the gas
25 pressure eventually destroys the seal of the protective liner, allowing moisture from the environment to enter the bottle, thereby causing more degradation.

- Solid dosage formats of vitamin C and zinc include capsules, coated tablets, effervescent tablets, and lozenges. Due to the high sodium content of effervescent tablets, lozenges are more suitable for pediatric and geriatric patients who have difficulty swallowing. However, vitamin C and zinc lozenges are very difficult to make palatable. Further, since lozenges cannot be coated, they must be very stable since any slight spotting/darkening is readily apparent and unacceptable to consumers. While it is relatively easy to hide spotting/darkening in a swallow tablet by coating the tablet, it is extremely difficult with lozenges since the spotting/darkening is still apparent even with colored tablets.
- Lozenges can refer to molded lozenges, which are hard candies, or to compressed lozenges, which are essentially produced the same way as compressed pharmaceutical tablets. Molded lozenges are more difficult to make and require high manufacturing temperature up to more than 100°C, which can cause significant degradation of the vitamin C. Therefore, this instant invention is limited to compressed lozenges which we will hereafter refer to as lozenge tablets, and includes both orodispersible and chewable tablets.

- The difficulty of combining vitamin C and zinc in a stable tablet is known in the prior art. Singla and Nagrath (Drug Dev. Ind. Pharm. Vol. 14, Issue 10, pages 1471-1479, 1988) showed significant zinc-catalyzed oxidation of vitamin C.
- The authors teach that this degradation due to zinc can be reduced/eliminated by microencapsulation (coacervation-phase separation) of the vitamin C with ethylcellulose, or by embedding the vitamin C in stearic acid or polyethylene glycol matrix by melt granulation. Melt granulation or microencapsulation can lead to dissolution failure, and are generally complicated and expensive manufacturing processes better suited for stabilizing expensive active ingredients.

US 2014/0220151A1 discloses stable formulations of vitamin C with at least one polyvalent metal such as zinc wherein the tablet is substantially free of mobile bound water. Mobile bound water refers to water of hydration and substantially free means less than 0.3% w/w of the composition. US 2014/0220151A1 is used
5 in Centrum Multivitamins and Minerals tablet (Pfizer/Wyeth, NY). Centrum is a coated tablet containing 60 mg of Vitamin C, 15 mg of zinc, other vitamins and polyvalent metals, wherein the Vitamin C is less than 5% of tablet weight. Centrum tablet uses zinc oxide as the source of zinc. Zinc oxide is poorly absorbed, but the main reason for using zinc oxide, as inferred from US
10 2014/0220151A1, is to reduce the mobile bound water. Most zinc salts other than zinc oxide are hygroscopic and are commercially available as their stable hydrates.

The prior art references above show how difficult it is to stabilize vitamin C in the presence of zinc. These references are for swallow tablets that can be coated
15 so palatability is not an issue. In a lozenge tablet, not only must the product be very stable because coating cannot be used to hide spotting/darkening, but the tablet must also be palatable.

US 6,316,008B1 teaches that when vitamin C is combined with zinc in a lozenge, the foul taste of zinc, which can last for more than 24 hours, is normally orders of
20 magnitude stronger than zinc alone. US 6,316,008B1 discloses that palatability can be improved by combining the zinc with a mono-carboxylic amino acid, and wherein the vitamin C is magnesium ascorbate or an ascorbyl ester. The examples of US 6,316,008B1 are molded lozenges wherein the vitamin C and zinc are added to the melted hard candy base at 104°C. US 6,316,008B1 does
25 not disclose how much of the vitamin C is degraded during production, nor the stability of this residual vitamin C with time.

The commercially available vitamin C and zinc lozenge tablets are generally large tablets wherein the tablet weight is from 1.5 to 4 grams. The reason for these huge tablets is to dilute the vitamin C and zinc by adding a large amount of the monosaccharide sweeteners glucose and fructose, and flavors to improve palatability. These large tablets can pose a choking hazard if accidentally swallowed.

The present invention relates to palatable lozenge tablets containing vitamin C and zinc, wherein the vitamin C is present at high concentration and is stable against oxidation and formation of carbon dioxide. The composition of the present invention can contain significantly more mobile bound water than the required limit taught by US 2014/0220151A1 to produce stable tablets.

SUMMARY OF THE INVENTION

We have surprisingly found that stable and palatable lozenge tablets of Vitamin C and zinc where Vitamin C is present at high concentration can be prepared by using a citrate or malate salt of zinc, sodium ascorbate or a mixture of ascorbic acid and sodium ascorbate with about 65% to 100% of the vitamin C coming from sodium ascorbate, and sweeteners; wherein the vitamin C and zinc are not microencapsulated, coated or melt granulated, and wherein the formulation is substantially free of monosaccharide, organic acid, and monocarboxylic amino acid. The composition of the present invention is stable even with very high level of mobile bound water.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a graph showing the degree of spotting/discoloration as a function of the percentage of Vitamin C from sodium ascorbate when the zinc salt is zinc citrate (Example 1) and zinc oxide (Example 2).

FIG. 2 is a graph showing the degree of bloating as a function of the percentage of Vitamin C from sodium ascorbate when the zinc salt is zinc citrate (Example 1) and zinc oxide (Example 2).

DETAILED DESCRIPTION OF THE INVENTION

- 5 The vitamin C is sodium ascorbate or a mixture of ascorbic acid and sodium ascorbate, wherein at least about 65% of the vitamin C is from sodium ascorbate, more preferably at least about 70%, and most preferably at least about 75%. In the present invention, the vitamin C is not microencapsulated, coated or melt granulated.
- 10 The vitamin C is preferably present at a concentration of at least about 10% w/w, more preferably at least about 15% w/w, and most preferably at least about 20% w/w. The amount of vitamin C is preferably about 50-250 mg/tablet, more preferably about 75-200 mg/tablet. The ascorbic acid and sodium ascorbate are preferably already in granular form ready for compression. These directly
- 15 compressible vitamin C and sodium ascorbate are commercially available containing about 1-5% binder and very low moisture typically below 0.15% w/w.

- Zinc compounds useful in this invention are the citrate, malate, citrate malate mixed salts, and combinations thereof. The preferred zinc salt is zinc citrate, preferably the commercially available dihydrate and trihydrate forms. The
- 20 amount of elemental zinc is preferably at least about 3 mg/tablet, more preferably at least about 5 mg/tablet, and most preferably at least about 10 mg/tablet. In the present invention, the zinc is not microencapsulated, coated or melt granulated.

- The composition of the present invention is substantially free of any monosaccharide, organic acid, and mono-carboxylic amino acid.
- 25 Monosaccharides include, but are not limited to, glucose, galactose and fructose.

Organic acids include, but are not limited to, tartaric, citric and malic acid. Mono-carboxylic amino acids include all the amino acids disclosed in US 6,316,008B1. By the term “substantially free” it is understood that the monosaccharide, organic acid, or monocarboxylic amino acid content is non-existent or low that the pharmaceutical compositions of the present invention is still palatable and stable against oxidation and formation of carbon dioxide.

The sweeteners of the present invention include, but are not limited to, sugar disaccharides such as sucrose and lactose; sugar alcohols such as sorbitol, xylitol, mannitol, lactitol, erythritol, maltitol and isomalt. These sweeteners are preferably combined with a high-intensity sweetener such as sucralose, aspartame, acesulfame, and saccharin. The preferred sweeteners are sucrose, lactose, maltitol, and mixtures thereof, combined with sucralose. Sucrose, lactose, and maltitol are preferably used in their commercially available directly compressible grades. The amount of sweetener is preferably at least about 40% w/w, more preferably at least about 50% w/w, and most preferably at least about 60% w/w.

Preferably, the lozenge tablets of the present invention contain only vitamin C and zinc. However, the compositions of the present invention may optionally contain other vitamins and minerals. Vitamins include, but are not limited, to Vitamin E, thiamine (Vitamin B1), riboflavin (Vitamin B2), niacin (Vitamin B3), pyridoxine (Vitamin B6), folic acid, cobalamins (Vitamin B12), Pantothenic acid (Vitamin B5), Biotin, Vitamin A (and Vitamin A precursors), Vitamin D, Vitamin K, other B complex vitamins, B complex related compounds such as Choline and Inositol, and carotenoids such as lutein, lycopene, zeaxanthin, and astaxanthin. Minerals include, but are not limited to, iron, iodine, magnesium, selenium, copper, calcium, manganese, silicon, molybdenum, vanadium, boron, nickel, tin phosphorus, chromium, cobalt, chloride, and potassium. It is within the ability of one ordinarily skilled in the art to determine which vitamins and

minerals can be incorporated into the composition of the present invention without affecting stability and palatability.

The pharmaceutical compositions may also include pharmaceutically acceptable excipients like binders, diluents, disintegrants, glidants, and lubricants. The total
5 amount of these excipients must be kept low to reduce their effect on the palatability of the lozenge. The total amount of these excipients combined is preferably less than about 20% w/w, more preferably less than about 15% w/w, and most preferably less than about 10% w/w.

Binders which may be used include gums like acacia, guar gum, alginic acid,
10 sodium alginate; starch, carbomer, dextrin, gelatin, ethylcellulose, methylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, hydroxyethylcellulose, polyvinylpyrrolidone, copovidone, pregelatinized starch, polymethacrylates, and the like. The binder may be present in an amount ranging from about 1% to about 10% by weight of the composition. The binder may be
15 incorporated into the composition in two ways, for example, the binder may be mixed with the active ingredients and other excipients and the blend may then be processed into granules by addition of a granulating solvent (wet granulation) or the blend of active ingredients, binder and excipients may be dry mixed or roller compacted without a solvent (dry granulation).

20 **Disintegrants** may be selected from starch, crospovidone, croscarmellose sodium, and sodium starch glycolate.

Diluents may be selected from cellulose-derived materials such as powdered cellulose, microcrystalline cellulose, microfine cellulose, and the like; starch, pregelatinized starch, and the like; dextrates, dextrin, inorganic diluents like
25 calcium carbonate, calcium sulphate, dibasic calcium phosphate and its hydrate,

tribasic calcium phosphate and its hydrate, magnesium carbonate, magnesium oxide, or mixture of one or more of such diluent.

Glidants which may be used include talc, colloidal silicon dioxide, magnesium trisilicate, powdered cellulose, starch and tribasic calcium phosphate. The glidant
5 may be present in an amount ranging from 0.5% to 3% w/w of the composition.

Lubricants which may be used include magnesium stearate, calcium stearate, glyceryl monostearate, glyceryl palmitostearate, hydrogenated castor oil, hydrogenated vegetable oil, mineral oil, polyethylene glycol, sodium stearyl fumarate, stearic acid, and zinc stearate. The lubricant may be present in an
10 amount ranging from about 0.25% to about 3% w/w of the composition.

The weight of the lozenge tablet of the present invention is preferably less than about 1,200 mg, more preferably less than about 800 mg, and most preferably less than about 600 mg.

EXAMPLE 1

15 Chewable lozenge tablets with 10 mg elemental zinc from zinc citrate and 105 mg of vitamin C obtained from different combinations of ascorbic acid and sodium ascorbate were prepared according to Table 1, each with a batch size of 5 kg.

20 Ascorbic acid C-97 (Aland, China) is Vitamin C granulated with 3% starch for direct compression. Sodium ascorbate SA-99 (Aland, China) is sodium ascorbate granulated with 1% starch for direct compression. The moisture content of these two vitamin C granules is less than 0.15% w/w. Ludipress® (BASF, Germany) is a directly compressible lactose consisting of 93% lactose monohydrate, 3.5% povidone K30 (binder), and 3.5% crospovidone (disintegrant).

Table 1 (in mg/tablet)

Ingredient	Ex. 1A	Ex. 1B	Ex. 1C	Ex. 1D	Ex. 1E	Ex. 1F	Ex. 1G	Ex. 1H
% Vitamin C from Sodium Ascorbate	0	25%	30%	50%	70%	75%	80%	100%
Ascorbic Acid C-97	108.2	81.2	75.4	54.1	32.5	27.1	21.6	-
Sodium Ascorbate SA-99	-	29.8	35.8	59.6	83.5	89.4	95.4	119.3
Zinc Citrate 3H ₂ O	32.1	32.1	32.1	32.1	32.1	32.1	32.1	32.1
Compressible sugar	156.7	153.9	153.7	151.2	148.9	148.4	147.9	145.6
Ludipress [®]	124	124	124	124	124	124	124	124
Crospovidone	9.0	9.0	9.0	9.0	9.0	9.0	9.0	9.0
Colloidal Silicon Dioxide	2.3	2.3	2.3	2.3	2.3	2.3	2.3	2.3
Sucralose	3.6	3.6	3.6	3.6	3.6	3.6	3.6	3.6
Orange Flavor	9.0	9.0	9.0	9.0	9.0	9.0	9.0	9.0
FDC Yellow #6 Lake (17-19%)	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6
Magnesium Stearate	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5
Tablet weight (mg)	450	450	450	450	450	450	450	450
Mobile bound water (w/w)	1.9%	1.9%	1.9%	1.9%	1.9%	1.9%	1.9%	1.9%

- The process for preparation of the granules for tableting is as follows: 1). premix colorant with crospovidone and pass through a comminuting machine using mesh #30; 2). premix colloidal silicon dioxide with a portion of the compressible sugar (DIPAC[®], Domino Specialty Ingredients, USA) and pass through the comminuting machine; 3). premix sucralose and a portion of the compressible sugar and pass through the comminuting machine; 4). pass the rest of the compressible sugar through the comminuting machine; 5). pass zinc citrate and Ludipress[®] through steel mesh #20; 6). mix ascorbic acid and/or sodium ascorbate, all the comminuted ingredients, sieved ingredients, and orange flavor in a mixer for 30 minutes. 7). sieve the magnesium stearate through a steel mesh #30, add to the sigma mixer, and mix for another 5 minutes. Compress the granules in a tableting machine using an 11 mm circular punch to a hardness of 6-12 kp.

The tablets were packed individually into aluminum flex foil, and stored under accelerated stability at 80°C for 5 days, after which the samples were evaluated for:

- 1). Spotting/Discoloration using a 0 to 10 scale with +10 indicating severe spotting/discoloration compared to unexposed samples.
- 2). Bloating of the aluminum foil using a 0 to 5 scale with +5 indicating severe bloating. Bloating is a measure of the carbon dioxide released due to oxidation of vitamin C.

Figures 1 and 2 show the results of the accelerated stability. Peak instability in the presence of zinc citrate occurs when the vitamin C from sodium ascorbate is about 50%. Improved stability is obtained when at least about 65% of the vitamin C is from sodium ascorbate. This is surprising because prior art teaches that ascorbic acid is more stable than sodium ascorbate (Hiatt et al., J. Agric. Food Chem. 2010, 58, 3532-3540).

15

EXAMPLE 2

Chewable lozenge tablets with 10 mg elemental zinc from zinc oxide and 105 mg of vitamin C obtained from different combinations of ascorbic acid and sodium ascorbate were prepared according to Table 2, each with a batch size of 5 kg. The tablets were prepared essentially as in Example 1.

Table 2 (in mg/tablet)

Ingredient	Ex. 2A	Ex. 2B	Ex. 2C	Ex. 2D	Ex. 2E	Ex. 2F	Ex. 2G	Ex. 2H
% Vitamin C from Sodium Ascorbate	0	25%	30%	50%	70%	75%	80%	100%
Ascorbic Acid C-97	108.2	81.2	75.4	54.1	32.5	27.1	21.6	-
Sodium Ascorbate SA-99	-	29.8	35.8	59.6	83.5	89.4	95.4	119.3
Zinc Oxide	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
Compressible sugar	176.3	173.5	173.3	170.8	168.5	168.0	167.5	165.2
Ludipress®	124	124	124	124	124	124	124	124
Crospovidone	9.0	9.0	9.0	9.0	9.0	9.0	9.0	9.0
Colloidal Silicon Dioxide	2.3	2.3	2.3	2.3	2.3	2.3	2.3	2.3
Sucralose	3.6	3.6	3.6	3.6	3.6	3.6	3.6	3.6
Orange Flavor	9.0	9.0	9.0	9.0	9.0	9.0	9.0	9.0
FDC Yellow #6 Lake (17-19%)	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6
Magnesium Stearate	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5
Tablet weight (mg)	450	450	450	450	450	450	450	450
Mobile bound water (w/w)	1.3%	1.3%	1.3%	1.3%	1.3%	1.3%	1.3%	1.3%

Figures 1 and 2 show the results of the accelerated stability. Peak instability in the presence of zinc oxide is similar to zinc citrate and occurs when the vitamin C from sodium ascorbate is about 50%. Overall, the formulation is more stable when zinc citrate is used instead of zinc oxide. This is surprising because zinc oxide is insoluble, 300x more insoluble than zinc citrate, and therefore releases less zinc ion to catalyze the oxidation of vitamin C.

EXAMPLE 3

Chewable lozenge tablets with 105 mg of vitamin C (80% from sodium ascorbate) and 10 mg of elemental zinc from different zinc salts were prepared according to Table 3. The tablets were prepared essentially as in Example 1.

Table 3 (in mg/tablet)

Ingredient	Ex. 3A	Ex. 3B	Ex. 3C	Ex. 3D	Ex. 3E
Ascorbic Acid C-97	21.6	21.6	21.6	21.6	21.6
Sodium Ascorbate SA-99	95.4	95.4	95.4	95.4	95.4
Zinc Sulfate H ₂ O	27.5	-	-	-	-
Zinc Acetate 2H ₂ O	-	33.5	-	-	-
Zinc Ascorbate H ₂ O	-	-	66.2	-	-
Zinc Citrate 3H ₂ O	-	-	-	32.1	-
Zinc Oxide	-	-	-	-	12.5
Compressible sugar	152.5	146.5	113.8	147.9	167.5
Ludipress [®]	124	124	124	124	124
Crospovidone	9.0	9.0	9.0	9.0	9.0
Colloidal Silicon Dioxide	2.3	2.3	2.3	2.3	2.3
Sucralose	3.6	3.6	3.6	3.6	3.6
Orange Flavor	9.0	9.0	9.0	9.0	9.0
FDC Yellow #6 Lake (17-19%)	0.6	0.6	0.6	0.6	0.6
Magnesium Stearate	4.5	4.5	4.5	4.5	4.5
Tablet weight (mg)	450	450	450	450	450

The taste profiles of the above tablets were compared. Zinc sulfate, zinc acetate, and zinc ascorbate, all soluble zinc salts, are extremely bad tasting that for all practical purposes, they cannot be used in their naked forms to produce palatable
5 lozenge tablets of the present invention. Taste descriptions include burnt plastic, drying, astringent, fishy, foul, and lingering metallic taste lasting for hours.

Only zinc citrate and zinc oxide provide palatable tablets, and their taste profiles are further scrutinized in Experiment 4.

EXAMPLE 4

- 10 Chewable lozenge tablets with 105 mg of vitamin C (100% from sodium ascorbate) and 5-10 mg of elemental zinc from different zinc salts were prepared according to Table 4. The tablets were prepared essentially as in Example 1.

Table 4 (in mg/tablet)

Ingredient	Ex. 4A	Ex. 4B	Ex 4C	Ex. 4D	Ex. 4E
Sodium Ascorbate SA-99	119.3	119.3	119.3	119.3	119.3
Zinc Citrate 3H ₂ O	-	16.1	32.1	-	-
Zinc Oxide	-	-	-	12.5	-
Zinc Gluconate 3H ₂ O	-	-	-	-	79
Elemental Zinc (mg)	0	5	10	10	10
Compressible sugar	177.7	161.6	145.6	165.2	98.7
Ludipress [®]	124	124	124	124	124
Crospovidone	9.0	9.0	9.0	9.0	9.0
Colloidal Silicon Dioxide	2.3	2.3	2.3	2.3	2.3
Sucralose	3.6	3.6	3.6	3.6	3.6
Orange Flavor	9.0	9.0	9.0	9.0	9.0
FDC Yellow #6 Lake (17-19%)	0.6	0.6	0.6	0.6	0.6
Magnesium Stearate	4.5	4.5	4.5	4.5	4.5
Tablet weight (mg)	450	450	450	450	450

Since the optimum stability in the presence of zinc according to Experiment 1 is achieved when at least about 65% of the vitamin C is from sodium ascorbate, there is an associated taste issue that needs to be addressed related to the saltiness of sodium ascorbate.

Example 4E contains 10 mg of elemental zinc from zinc gluconate. Zinc gluconate is described in the prior art to have mild, faint taste. However, in the presence of sodium ascorbate, the astringent taste of zinc is very prominent. This is consistent with US 6,316,008B1 which teaches that zinc gluconate cannot be combined with ascorbic acid or sodium ascorbate due to poor taste. In US 6,316,008B1, a palatable hard candy is obtained when zinc gluconate is combined with a mono-carboxylic amino acid, such as glycine, and Vitamin C is selected from magnesium ascorbate and ascorbyl esters. Taste comparison of Example 4E with Example 4A showed similar saltiness, indicating that zinc gluconate does not reduce the saltiness of sodium ascorbate.

Example 4D contains 10 mg elemental zinc from zinc oxide. Because zinc oxide is insoluble, the zinc taste is not apparent, consistent with the neutral taste of zinc oxide described in the prior art. Taste comparison of Example 4D with Example 4A showed similar saltiness, indicating that zinc oxide does not reduce the
5 saltiness of sodium ascorbate.

However, when zinc citrate is added to sodium ascorbate, we have surprisingly found that 1). Zinc citrate is able to reduce/eliminate the saltiness of sodium ascorbate; 2). the metallic taste of zinc is reduced/eliminated. In particular, Example 4B is less salty than Example 4A, and Example 4C, with higher level of
10 zinc citrate, is not salty and the zinc taste is not perceptible. This is contrary to the teaching of US 6,316,008B1 which teaches that zinc salt, including zinc citrate, cannot be combined with sodium ascorbate due to poor taste.

Without wishing to be bound by theory, we believe that the reduction in the saltiness of the sodium ascorbate is due to the very small amount of citrate ion
15 that is liberated from the limited dissolution of the slightly soluble zinc citrate. Therefore, included in the scope of the present invention are the slightly soluble citrate, malate, and citrate malate mixed salts of zinc.

EXAMPLE 5

Prior art has tried to address the saltiness of chewable vitamin C tablet containing
20 sodium ascorbate by the addition of organic acids, such as citric and malic acid. Example 5 shows that the addition of organic acid to the compositions of the present invention causes severe oxidation of vitamin C.

Chewable lozenge tablets with 100 mg of vitamin C (100% from sodium ascorbate) and 5 mg of elemental zinc from zinc citrate were prepared according
25 to Table 5. The tablets were prepared essentially as in Example 1.

Table 5 (in mg/tablet)

Ingredient	Ex. 5A	Ex. 5B	Ex 5C	Ex. 5D	Ex. 5E	Ex. 5F
Sodium Ascorbate SA-99	113.6	113.6	113.6	113.6	113.6	113.6
Zinc Citrate 3H ₂ O	16.1	16.1	16.1	16.1	16.1	16.1
Compressible sugar	167.3	144.8	144.8	-	-	-
Ludipress [®]	124	124	124	-	-	-
Maltitol (Sweet Pearl [®])	-	-	-	289	266.5	266.5
Citric Acid	-	22.5	-	-	22.5	-
Malic Acid	-	-	22.5	-	-	22.5
Crospovidone	9.0	9.0	9.0	9.0	9.0	9.0
Colloidal Silicon Dioxide	2.3	2.3	2.3	2.3	2.3	2.3
Sucralose	3.6	3.6	3.6	3.6	3.6	3.6
Orange Flavor	9.0	9.0	9.0	9.0	9.0	9.0
FDC Yellow #6 Lake (17-19%)	0.6	0.6	0.6	0.6	0.6	0.6
Magnesium Stearate	4.5	4.5	4.5	6.8	6.8	6.8
Tablet weight (mg)	450	450	450	450	450	450
Spotting/Discoloration (80°C x 3 days)	+1	+10	+9	+2	+10	+10

Examples 5A, 5B, and 5C shows that the addition of an organic acid significantly enhances spotting/discoloration of the tablet. Sugar-free formulation Examples 5D, 5E, and 5F show similar results. The use of organic acid to improve the palatability of prior art formulations is not required in the compositions of the present invention because the taste is already good in the absence of organic acid. In fact, the addition of organic acid in the compositions of the present invention causes significant vitamin C oxidation. Therefore, the compositions of the present invention are substantially free of organic acid. It is surprising that palatable and stable vitamin C and zinc lozenge tablets can be formulated according to the present invention without the organic acids widely used in prior art commercially available products.

EXAMPLE 6

Prior art has tried to address the palatability of chewable vitamin C tablet containing zinc by the addition of large amount of the monosaccharides glucose

and fructose to dilute the zinc, and to overwhelm the zinc taste with extreme sweetness. This approach results in large tablets that pose choking risk. Example 6 shows that the addition of monosaccharide to the compositions of the present invention causes severe oxidation of vitamin C.

- 5 Chewable lozenge tablets with 105 mg of vitamin C (80% from sodium ascorbate) and 10 mg of elemental zinc from zinc citrate were prepared according to Table 6. The tablets were prepared essentially as in Example 1.

Table 6 (in mg/tablet)

Ingredient	Ex. 6A	Ex. 6B	Ex 6C
Ascorbic Acid C-97	21.6	21.6	21.6
Sodium Ascorbate SA-99	95.4	95.4	95.4
Zinc Citrate 3H ₂ O	32.1	32.1	32.1
Compressible sugar	147.9	-	-
Ludipress [®]	124	124	124
Glucose	-	147.9	-
Fructose	-	-	147.9
Crospovidone	9.0	9.0	9.0
Colloidal Silicon Dioxide	2.3	2.3	2.3
Sucralose	3.6	3.6	3.6
Orange Flavor	9.0	9.0	9.0
FDC Yellow #6 Lake (17-19%)	0.6	0.6	0.6
Magnesium Stearate	4.5	4.5	4.5
Tablet weight (mg)	450	450	450
Spotting/Discoloration (80°C x 3 days)	+2	+6	+10

- 10 According to prior art, the use of monosaccharides causes significant oxidation of vitamin C. Therefore, the compositions of the present invention are substantially free of monosaccharides. It is surprising that palatable and stable vitamin C and zinc lozenge tablets can be formulated according to the present invention without the monosaccharides widely used in prior art commercially available products.

EXAMPLE 7

Calcium ascorbate has been used in the prior art as a source of vitamin C. In the compositions of the present invention, calcium ascorbate cannot be used to replace sodium ascorbate.

- 5 Chewable lozenge tablets with 105 mg of vitamin C and 5 mg of elemental zinc from zinc citrate were prepared according to Table 7. The tablets were prepared essentially as in Example 1.

Table 7 (in mg/tablet)

Ingredient	Ex. 7A	Ex. 7B	Ex 7C
Vitamin C from sodium or calcium ascorbate	80%	80%	100%
Ascorbic Acid C-97	21.6	21.6	-
Sodium Ascorbate SA-99	95.4	-	-
Calcium Ascorbate C-97	-	91.4	114.2
Zinc Citrate 3H ₂ O	16.1	16.1	16.1
Compressible sugar	163.9	167.9	166.7
Ludipress [®]	124	124	124
Crospovidone	9.0	9.0	9.0
Colloidal Silicon Dioxide	2.3	2.3	2.3
Sucralose	3.6	3.6	3.6
Orange Flavor	9.0	9.0	9.0
FDC Yellow #6 Lake (17-19%)	0.6	0.6	0.6
Magnesium Stearate	4.5	4.5	4.5
Tablet weight (mg)	450	450	450

- Example 7A of the present invention contains 80% of vitamin C from sodium ascorbate. Example 7B contains 80% of the vitamin C from calcium ascorbate. Example 7A is good tasting, while Example 7B is slightly bitter, with perceivable astringent taste of zinc. Example 7C contains 100% of vitamin C from calcium ascorbate and possesses the same taste profile as Example 7B.

EXAMPLE 8

Chewable lozenge tablets according to the embodiments of the present invention containing 105 mg of vitamin C and 5-10 mg of elemental zinc from zinc citrate were prepared. The 600 mg version was tabletted using an 11.5 mm flat faced
 5 beveled edge round punch to a hardness of 8-14 kp.

Table 8 (in mg/tablet)

Ingredient	Ex. 8A	Ex. 8B	Ex 8C
Vitamin C from sodium ascorbate	80%	80%	80%
Ascorbic Acid C-97	21.6	21.6	21.6
Sodium Ascorbate SA-99	95.4	95.4	95.4
Zinc Citrate 3H ₂ O	16.1	32.1	32.1
Elemental Zinc (mg)	5	10	10
Compressible sugar	163.9	147.8	248.4
Ludipress [®]	124	124	165
Crospovidone	9.0	9.0	12.0
Colloidal Silicon Dioxide	2.3	2.3	3.1
Sucralose	3.6	3.6	3.6
Orange Flavor	9.0	9.0	12.0
FDC Yellow #6 Lake (17-19%)	0.6	0.6	0.8
Magnesium Stearate	4.5	4.5	6.0
Tablet weight (mg)	450	450	600
Mobile bound water (w/w)	1.6%	1.9%	1.7%
Spotting/Discoloration (80°C x 3 days)	+1	+1	+2
Bloating (80°C x 3 days)	+0.5	+0.5	+0.5

The three formulations above all have acceptable taste: not salty, and no astringent zinc taste.

The samples were individually packed in aluminum flex foil, and stored at
 10 25°C/65% RH for 24 months, and 40°C/75% RH for 6 months. Under these storage conditions, the samples did not show any spotting/discoloration, the packaging did not bloat, and the taste profile was similar to time zero samples. Further, the assays of vitamin C did not change confirming that significant

- oxidation did not occur. The amount of mobile bound water in the tablet from the zinc salt and lactose is 1.6-1.9% w/w. This is surprising, given the disclosure of US 2014/0220151A1 which teaches that the mobile bound water should be less than 0.3% to stabilize Vitamin C in the presence of polyvalent metals. Note
- 5 that the compositions in US 2014/0220151A1 contain less than 10% w/w of Vitamin C, while the above embodiments of the present invention contain 17.5-23.3% of Vitamin C, which is more difficult to stabilize because of the high level of Vitamin C.

EXAMPLE 9

- 10 Chewable sugar-free lozenge tablets according to the embodiments of the present invention containing 105 mg of vitamin C (100% from sodium ascorbate) and 5-10 mg of elemental zinc from zinc citrate were prepared.

Table 9 (in mg/tablet)

Ingredient	Ex. 9A	Ex. 9B	Ex 9C
Sodium Ascorbate SA-99	119.3	119.3	119.3
Zinc Citrate 3H ₂ O	16.1	32.1	32.1
Elemental Zinc (mg)	5	10	10
Maltitol (Sweet Pearl [®] 300DC)	285.9	269.4	409.6
Crospovidone	9.0	9.0	12.0
Colloidal Silicon Dioxide	2.3	2.3	3.1
Sucralose	1.0	1.5	2.0
Orange Flavor	9.0	9.0	12.0
FDC Yellow #6 Lake (17-19%)	0.6	0.6	0.8
Magnesium Stearate	6.8	6.8	9.1
Tablet weight (mg)	450	450	600
Mobile bound water (w/w)	0.31%	0.61%	0.46%
Spotting/Discoloration (80°C x 3 days)	+1	+1	+1
Bloating (80°C x 3 days)	0	0	+0.5

The three formulations above all have acceptable taste: not salty, and no astringent zinc taste.

The samples were individually packed in aluminum flex foil, and stored at 25°C/65% RH for 24 months, and 40°C/75% RH for 6 months. Under these storage conditions, the samples did not show any spotting/discoloration, the packaging did not bloat, and the taste profile was similar to time zero samples. Further, the assays of vitamin C did not change confirming that significant oxidation did not occur. The amount of mobile bound water in the tablet from the zinc salt is 0.31-0.61% w/w. This is surprising, given the disclosure of US 2014/0220151A1 which teaches that the mobile bound water should be less than 0.3% to stabilize Vitamin C in the presence of polyvalent metals. Note that the compositions in US 2014/0220151A1 contain less than 10% w/w of Vitamin C, while the above embodiments of the present invention contain 17.5-23.3% of Vitamin C, which is more difficult to stabilize because of the high level of Vitamin C.

EXAMPLE 10

Chewable sugar-free lozenge tablets according to the embodiments of the present invention containing 105 mg of vitamin C and 5-10 mg of elemental zinc from zinc citrate were prepared.

Table 10 (in mg/tablet)

Ingredient	Ex. 10A	Ex. 10B	Ex 10C
Vitamin C from sodium ascorbate	80%	100%	70%
Ascorbic Acid C-97	21.6	-	31.7
Sodium Ascorbate SA-99	95.4	119.3	83.5
Zinc Citrate 3H ₂ O	16.1	32.1	32.1
Elemental Zinc (mg)	5	10	10
Sorbitol (Neosorb [®])	287.4	269.1	413.3
Crospovidone	9.0	9.0	12.0
Colloidal Silicon Dioxide	2.3	2.3	3.1
Sucralose	1.8	1.8	2.4
Orange Flavor	9.0	9.0	12.0
FDC Yellow #6 Lake (17-19%)	0.6	0.6	0.8
Magnesium Stearate	6.8	6.8	9.1
Tablet weight (mg)	450	450	600
Mobile bound water (w/w)	0.61%	0.61%	0.46%
Spotting/Discoloration (80°C x 3 days)	+1	+1	+1
Bloating (80°C x 3 days)	+0.5	+0.5	+0.5

The three formulations above all have acceptable taste: not salty, and no astringent zinc taste.

The samples were individually packed in aluminum flex foil, and stored at
5 25°C/65% RH for 24 months, and 40°C/75% RH for 6 months. Under these storage conditions, the samples did not show any spotting/discoloration, the packaging did not bloat, and the taste profile was similar to time zero samples. Further, the assays of vitamin C did not change confirming that significant oxidation did not occur. The amount of mobile bound water in the tablet from
10 the zinc salt is 0.46-0.61% w/w. This is surprising, given the disclosure of US 2014/0220151A1 which teaches that the mobile bound water should be less than 0.3% to stabilize Vitamin C in the presence of polyvalent metals. Note that the

compositions in US 2014/0220151A1 contain less than 10% w/w of Vitamin C, while the above embodiments of the present invention contain 17.5-23.3% of Vitamin C, which is more difficult to stabilize because of the high level of Vitamin C.

5

COMPARATIVE EXAMPLES 1-10

The following representative commercial Vitamin C and zinc lozenge tablets (Table 11) were purchased online from Amazon US/UK. These lozenge tablets are mostly large, unstable, and mostly unpalatable. These tablets were repacked in aluminum flex foil and stored at 80°C for 3 days to assess stability. From our
10 experience, a product that has a spotting/discoloration score of not more than +2, and a bloating score of not more than +1, will be stable for two years at 25°C/65% RH and six months at 40°C/75% RH, with good physical appearance, chemical stability, zero or very negligible carbon dioxide formation, and excellent packaging integrity.

15 Comparative Example 1: Nature's Way (Nature's Way Products, Inc. USA). The tablet is big (> 1,200 mg), the vitamin C concentration is low, taste is bad, and stability is extremely poor (+10 spotting/discoloration, +5 bloating). Poor stability and taste are due to the use of 100% ascorbic acid, zinc gluconate, and fructose.

20 Comparative Example 2: Wellness Source Naturals (Source Naturals, Inc. USA). The tablet is big (> 2,200 mg), vitamin C concentration is very low, taste is bad, and stability is extremely poor (+10 spotting/discoloration, +5 bloating). Poor stability and taste are due to use of zinc ascorbate, zinc gluconate, and fructose.

Comparative Example 3: Puritan's Pride (Puritan's Pride, USA). Vitamin C
25 concentration is low, taste is borderline, and stability is poor (+7

spotting/discoloration, +3 bloating). Poor stability and taste are due to use of 100% ascorbic acid and zinc gluconate.

Comparative Example 4: Rugby (Rugby laboratories, USA). Tablet is big (>1,200 mg), Vitamin C concentration is very low, taste is borderline, and stability is extremely poor (+10 spotting/discoloration, +4 bloating). Poor stability is due to use of 100% ascorbic acid, fructose, citric acid, and malic acid.

Comparative Example 5: Now (Now Foods, Inc. USA). Tablet is big (> 2,800 mg), Vitamin C concentration is low, taste is bad, and stability is poor (+10 spotting/discoloration, +3 bloating). This formulation contains a combination of ascorbic acid and sodium ascorbate but the percentage of vitamin C from sodium ascorbate cannot be ascertained because the sodium level is not disclosed. However, this formulation is outside the scope of the present invention because of the very low vitamin C concentration, and in addition, the poor stability and taste are due to use of zinc gluconate, and fructose.

Comparative Example 6: Country Life (Country Life LLC, USA). Tablet is big (> 1,200 mg), Vitamin C concentration is very low, taste is bad, and stability is extremely poor (+10 spotting/discoloration, +4 bloating). The poor stability and taste are due to the use of non-optimal level of sodium ascorbate (38% of vitamin C is from sodium ascorbate), zinc gluconate, fructose, glucose, and citric acid.

Comparative Example 7: Bluebonnet Nutrition (Bluebonnet Nutrition Corporation, USA). Tablet is big (> 1,200 mg), Vitamin C concentration is very low, taste is borderline, and stability is poor (+7 spotting/discoloration, +3 bloating). Poor stability and taste are due to the use of non-optimal level of sodium ascorbate (54% of vitamin C is from sodium ascorbate), zinc gluconate, and glucose.

Comparative Example 8: Emergen-C (Pfizer, USA). Tablet is very big (2,870 mg), taste is borderline, but stability is extremely poor (+10 spotting/discoloration, +5 bloating). Poor stability and borderline taste are due to the use of non-optimal level of sodium ascorbate (54% of vitamin C is from sodium ascorbate), zinc oxide, and glucose.

Comparative Example 9: Bioglan Vitamelts (PharmaCare Europe Ltd, UK). Stability is poor (+6 spotting/discoloration, +2 bloating) due to the use of non-optimal level of sodium ascorbate (30% of vitamin C is from sodium ascorbate), and honey (contains glucose and fructose).

Comparative Example 10: Redoxon Kids (Bayer, Switzerland). Extremely poor stability (+10 spotting/discoloration, +5 bloating) due to the use of 100% ascorbic acid.

In summary, formulations based on prior art are mostly bad tasting, mostly containing very low level of vitamin C, mostly very large tablet, but more importantly, almost all are unstable.

Table 11

Brand name	Vitamin C	Zinc (salt)	Other ingredients	Tablet weight
1. Nature's Way < 8% w/w vitamin C	100 mg (ascorbic acid)	23 mg (citrate, gluconate)	sorbitol, fructose, mannitol, wildberry, sodium bicarbonate, magnesium stearate, flavor	> 1200 mg
2. Wellness Source Naturals < 1.4% w/w vitamin C	30 mg (zinc ascorbate)	23 g (gluconate)	fructose, flavor, stearic acid, flavor, magnesium stearate	> 2200 mg
3. Puritan's Pride 8% w/w vitamin C	60 mg (ascorbic acid)	15 mg (oxide, gluconate)	cellulose, crospovidone, stearic acid, mannitol, flavors, silicon dioxide, color, magnesium stearate	750 mg
4. Rugby < 2.5% w/w vitamin C	30 mg (ascorbic acid)	15 mg (citrate, aspartate, oxide)	Sucrose, fructose, mono/diglycerides, cellulose, soybean oil, maltodextrin, starch, flavor, citric acid, malic acid, magnesium stearate, silicon dioxide, hydroxypropyl methyl cellulose, curcumin	> 1200 mg
5. Now (contains also 100 mg elderberry) < 6% w/w ascorbic acid	150 mg (ascorbic, sodium ascorbate)	12 mg (gluconate)	fructose, sorbitol, magnesium stearate, silicon dioxide, cellulose, flavor	> 2800 mg
6. Country Life < 8.3% w/w vitamin C	100 mg (62% as ascorbic acid, 38% as sodium ascorbate)	23 mg (gluconate, citrate)	fructose, glucose, sorbitol, stearic acid, honey, silicon dioxide, cellulose, magnesium stearate, lemon, citric acid	> 1200 mg

Table 11 continued

Brand name	Vitamin C	Zinc (salt)	Other ingredients	Tablet weight
7. Bluebonnet Nutrition < 8.3% w/w vitamin C	100 mg (46% as ascorbic acid, 54% as sodium ascorbate)	15 mg (citrate, gluconate)	flavor, earthsweet juice (glucose, sucrose), stearic acid, magnesium stearate	> 1200 mg
8. Emergen-C (contains also vitamin E, B6, biotin) 17.4% w/w vitamin C	500 mg (46% as ascorbic acid, 54% as sodium ascorbate)	2.5 mg (oxide)	sugar, maltodextrin, glucose, stearic acid, ascorbyl palmitate. Beta carotene, calcium phosphate dibasic, gelatin, hydrogenated soy oil, magnesium stearate, flavors, color, silicon dioxide	2870 mg
9. Bioglan Vitamelts 18.6% w/w vitamin C	80 mg (70% as ascorbic acid, 30% as sodium ascorbate)	10 mg (oxide)	mannitol, starch, polyvinylpyrrolidone, honey powder, flavor, stearic acid, silicon dioxide, sucralose, color	430 mg
10. Redoxon Kids 31% w/w	250 mg (ascorbic acid)	5 mg (citrate)	sorbitol, mannitol, talc, flavor, magnesium stearate, aspartame, color	800 mg

We claim:

1. A stable palatable lozenge tablet comprising:
 - i.) at least about 10% w/w Vitamin C;
 - ii.) a zinc salt selected from citrate, malate, citrate malate mixed salts, or combinations thereof;
 - iii.) at least one sweetener; and
 - iv.) optionally other pharmaceutically acceptable excipients, and is substantially free of monosaccharide, organic acid, and mono-carboxylic amino acid.
- Wherein:
 - i.) the vitamin C is sodium ascorbate or a mixture of ascorbic acid and sodium ascorbate;
 - ii.) the vitamin C from the sodium ascorbate is about 65% to 100% of the total vitamin C; and
 - iii.) the vitamin C and zinc are not microencapsulated, coated, or melt granulated.
2. The tablet according to claim 1, wherein the Vitamin C is at least about 15% w/w.
3. The tablet according to claim 2, wherein the Vitamin C is at least about 20% w/w.
4. The tablet according to claim 1, wherein the vitamin C from the sodium ascorbate is about 75% to 100% of the total vitamin C.
5. The tablet according to claim 1, wherein the vitamin C is about 50-250 mg per tablet.

6. The tablet according to claim 5, wherein the vitamin C is about 75-200 mg per tablet.
7. The tablet according to claim 1, wherein the zinc is at least about 3 mg per tablet.
- 5 8. The tablet according to claim 7, wherein the zinc is at least about 5 mg per tablet.
9. The tablet according to claim 1, wherein the sweetener is greater than about 40% w/w.
- 10 10. The tablet according to claim 9, wherein the sweetener is greater than about 50% w/w.
11. The tablet according to claim 10, wherein the sweetener is greater than about 60% w/w.
12. The tablet according to claim 1, wherein the sweetener is a sugar disaccharide, sugar alcohol or mixtures thereof.
- 15 13. The tablet according to claim 12, wherein the sugar disaccharide is selected from sucrose and lactose, and the sugar alcohol is maltitol.
14. The tablet according to claim 1, which further contains a high-intensity sweetener.
- 20 15. The tablet according to claim 14, wherein the high intensity sweetener is sucralose.
16. The tablet according to claim 1, wherein the tablet weight is less than about 1,200 mg.

17. The tablet according to claim 16, wherein the tablet weight is less than about 800 mg.
18. The tablet according to claim 17, wherein the tablet weight is less than about 600 mg.
- 5 19. The tablet according to claim 1, wherein the composition is not substantially free of mobile bound water.
20. The tablet according to claim 19, wherein the composition contains about 0.3-3% w/w mobile bound water.
21. The tablet according to claim 20, wherein the composition contains about
10 0.3-2% w/w mobile bound water.
22. A stable palatable lozenge tablet comprising:
- i.) 20-25% w/w Vitamin C;
- ii.) 3-10 mg of zinc from zinc citrate;
- iii.) greater than about 55% w/w of sucrose, lactose, maltitol, or mixtures
15 thereof;
- iv.) optionally other pharmaceutically acceptable excipients, and is substantially free of monosaccharide, organic acid, and mono-carboxylic amino acid.
- Wherein:
- 20 i.) the vitamin C is sodium ascorbate or a mixture of ascorbic acid and sodium ascorbate;
- ii.) the vitamin C from the sodium ascorbate is about 75% to 100% of the total vitamin C;
- iii.) the vitamin C and zinc are not microencapsulated, coated, or melt
25 granulated;

- iv.) the mobile bound water is about 0-2% w/w; and
- v.) the tablet weight is less than about 600 mg.

- 23. The tablet according to Claim 22 wherein the mobile bound water is about 0.3-2% w/w.
- 5 24. The tablet according to Claim 22 which further contains a high-intensity sweetener.
- 25. The tablet according to Claim 24 wherein the high-intensity sweetener is sucralose.