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(54) Title: PHARYNGEAL OR BUCCAL CAVITY RINSE AND PROCESS OF USE THEREOF

(57) Abstract: A storage stable package is provided that includes a polymeric bottle having a volume filled with an aqueous saline composition acidified with an acid to a pH of 2 to 9 and having a hypertonic saline concentration relative to saliva and blood, or an aqueous hydrogen peroxide composition acidified with an acid to a pH of 2.7 to 5.3 and having a hydrogen peroxide concentration 0.5 to 3 total weight percent, either to achieve a storage stability at 20 degrees Celsius of the composition of at least 10 weeks. The aqueous composition is independent of a synthetic antimicrobial. A cap is provided that is complementary a package opening for selectively sealing the aqueous saline composition within the volume. A process for treating an infection of a pharyngeal or buccal cavity is provided that includes rinsing with one of the aqueous saline composition. The aqueous saline composition is then expectorated.



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PHARYNGEAL OR BUCCAL CAVITY RINSE AND PROCESS OF USE
THEREOF

FIELD OF THE INVENTION

[0001] The present invention in general relates to a pharyngeal or buccal cavity rinse solution that is storage stable, and in particular to an acidified rinse that does not rely on sensitizing antimicrobials to achieve storage stability.

BACKGROUND OF THE INVENTION

[0002] The preparation of a hypertonic salt water solution for immediate use as a gargle and mouthwash is a well-known treatment and preventative for infections of the mouth and throat. Salt water will reduce swollen tissues and draw infection from any abscesses or infections present. Bacteria are single-celled organisms which can multiply rapidly under conditions found in the pharyngeal or buccal cavity. When the reproductive rate of certain strains of bacteria outstrips the immune response, soreness, inflammation, and even fever can result. While some bacteria are actually beneficial to the human body pathogenic bacteria are often directly responsible for many human illnesses, with one of the most common human illnesses being a sore throat.

[0003] Gargling with hypertonic salt water causes osmosis to occur. Osmosis is the process by which solvents, such as water, separated by a semi-permeable membrane, move from a region of lower concentration to higher concentration in order to equilibrate. By introducing hypertonic saline into the pharyngeal or buccal cavity, bacterial dehydration and lysis occurs.

[0004] Inflammation, regardless of the cause, is also reduced as water is drawn from tissues by osmosis. Hypertonic saline solution also helps to draw liquid from the throat. Edemas naturally occur during an infection, and by drawing it out of the tissue, swelling is reduced. This in turn reduces pain.

[0005] The salt may also kill some bacteria, but many strains are now resistant to mild levels of salt. It is a misconception to think that the salt water will directly kill off the bacteria. Gargling or rinsing with hypertonic saline solution simply creates a dehydrated environment that the bacteria find less hospitable and potentially dangerous and has implicated in reducing biofilm formation by *Pseudomonas aeruginosa* and the production of associated virulence factors. Hypertonic saline also appears to increase the levels of two thiols that are protective against oxidative injury namely, glutathione and thiocyanate.

[0006] Unfortunately, diluted hypertonic saline ready for use as a mouthwash or gargle is a growth medium for halophilic organisms that include algae, fungi, and bacteria. Exemplary organism include *Dunaliella*, *Halobacteria*, *Halorhabdus*, and *Eurotiomycetes*. As a result, the production and storage of a hypertonic saline of a concentration suitable as a mouth wash or gargle is problematic. While such solutions can be pasteurized or radiation sterilized for single use applications, such techniques are both expensive and ineffective a multiple use container is contemplated. As an alternative, low molecular weight, synthetic organic molecules have been used as antimicrobials to afford storage stability. Unfortunately, a number of people have sensitivity to such antimicrobials, while still others find the favor profile of antimicrobials unpleasant. Additionally, the usage of such

antimicrobials has raised concerns about downstream effects on the environment and induction of resistance in target microbes.

[0007] Additionally, a certain class of individuals, including those with hypertension cannot safely use a saline rinse. As a result, for such individuals to treat the pharyngeal or buccal cavity for infections, hydrogen peroxide is often used. While 3% hydrogen peroxide in water has stability of greater than one year in a sealed container, opening such a bottle decreases the shelf life. Also, metal ions present in the solution, leached from a container, or introduced through contamination induce catalytic decomposition to water.

[0008] Thus, there exists a need for a mouth wash and gargle solutions that are prepared at ready to use concentrations that have storage stability without resort to small molecule synthetic antimicrobials.

SUMMARY OF THE INVENTION

[0009] A storage stable package is provided that includes a polymeric bottle having a volume filled with an aqueous saline composition acidified with an acid to a pH of 2 to 9 and having a hypertonic saline concentration relative to saliva and blood to achieve a storage stability at 20 degrees Celsius of the composition of at least 10 weeks. The aqueous composition is independent of a synthetic antimicrobial. A cap is provided that is complementary a package opening for selectively sealing the aqueous saline composition within the volume.

[0010] A storage stable package is provided that includes a polymeric bottle having a volume filled with an aqueous hydrogen peroxide composition acidified

with an acid to a pH of 2.7 to 5.3 and having a hydrogen peroxide concentration 0.5 to 3 total weight percent of the aqueous hydrogen peroxide composition to achieve a storage stability at 20 degrees Celsius of the composition of at least 10 weeks. The aqueous composition is independent of a small molecule organic synthetic antimicrobial. A cap is provided that is complementary a package opening for selectively sealing the aqueous saline composition within the volume.

[0011] A process for treating an infection of a pharyngeal or buccal cavity is provided that includes rinsing the pharyngeal or buccal cavity with one of the aqueous saline composition of above for an amount of time sufficient to treat the infection. The aqueous saline composition is then expectorated.

DETAILED DESCRIPTION OF THE INVENTION

[0012] The present invention has utility as a pharyngeal or buccal cavity rinse in the forms of a gargle or mouthwash to treat infections of such regions. Without intending to be bound to a particular theory, an inventive rinse is hypertonic relative to saliva and blood. This hypertonicity is believed to not only desiccate pathogens, but also reduce inflammation through drawing of excess fluid from inflamed tissue. Acidification of the rinse provides storage stability without resort to small organic molecule synthetic antimicrobials.

[0013] It is to be understood that in instances where a range of values are provided that the range is intended to encompass not only the end point values of the range but also intermediate values of the range as explicitly being included within the range and varying by the last significant figure of the range. By way of

example, a recited range of from 1 to 4 is intended to include 1-2, 1-3, 2-4, 3-4, and 1-4.

[0014] As used herein a “small organic molecule synthetic antimicrobial” defines a molecule that has a molecular weight of less than 1000 atomic mass units that is present for this purpose. Specific “small organic molecule synthetic antimicrobials” excluded from inventive compositions include benzalkonium chloride, cetylpyridinium chloride, chlorhexidine gluconate, methylparaben, methyl salicylate, and domiphen bromide.

[0015] A storage stable package is provided includes a polymeric bottle with a cap for selectively enclosing a volume. An aqueous saline composition is provided that has been acidified with an acid to a pH of 2 to 9 and having a hypertonic saline concentration relative to saliva and blood. Alternatively, an aqueous hydrogen peroxide composition is provided that has been acidified with an acid to a pH of 2.7 to 5.3 and having a hydrogen peroxide concentration 0.5 to 3 total weight percent of the aqueous hydrogen peroxide. The saline or peroxide composition is placed in the bottle to achieve a storage stability at 20 degrees Celsius of the composition of at least 10 weeks. The saline or peroxide composition being independent of a synthetic antimicrobial.

[0016] A plastic bottle of an inventive package is formed from a variety of polymers suitable for acid aqueous solution packaging. These polymers illustratively include polyethylene, polypropylene, polyvinyl chloride, polyterephthalates, and block co-polymers containing any of the aforementioned as blocks therein. A cap sized and shaped to engage a plastic bottle opening is likewise

formed of any of the aforementioned polymers. It is appreciated that bottle and cap are each independently formed as transparent, translucent, or opaque articles. In certain inventive embodiments, both the bottle and the cap are opaque.

[0017] An aqueous saline composition according to the present invention is formed by dissolution of sodium chloride in sterile water. In some inventive embodiments, the water has been deionized. The sodium chloride is present from 1.7 to 5.0 total weight percent of the solution. In certain inventive embodiments, the sodium chloride is present from 1.8 to 2.8 total weight percent. In some inventive embodiments, the saline composition pH is between 3.0 and 7.0. In still other, embodiments, the saline composition pH is between 3.6 and 5.4. Generally, an inventive composition is free of phenols and ethanol.

[0018] A hydrogen peroxide composition is provided that includes hydrogen peroxide present in a concentration 0.5 to 3 total weight percent. Such a solution is readily formed through the dilution of more concentrated hydrogen peroxide. Owing to the role spurious metal ions play in catalytic degradation of hydrogen peroxide, the use of deionized water is preferred. In some inventive embodiments, the saline composition pH is between 3.0 and 5.0. In still other, embodiments, the saline composition pH is between 3.6 and 4.4.

[0019] Acids suitable for pH reduction, or acidification, to form an inventive package of mouth wash or gargle include those that are compatible with human mucous membrane contact in diluted form and compatible with other composition and bottle components. Acids operative herein illustratively include hydrochloric,

hydrobromic, lactic, citric, malic, acetic, benzoic, ascorbic, tartaric, oxalic, tannic, butyric, caffeotannic, phosphoric, sulfuric, nitric, or a combination thereof.

[0020] An inventive composition, regardless of whether saline or hydrogen peroxide based, includes various adjuvants. Adjuvants operative herein in terms of function illustratively include antimicrobial, flavorants, desensitizer, a fluoridation agent, or a combination thereof.

[0021] An antimicrobial operative herein illustratively includes sodium benzoate, benzoic acid, methylparaben, ethylparaben, propylparaben, paraben derivatives, or a combination thereof. Typical quantities of an antimicrobial, if present, in the inventive composition range from 0.01 - 3 total weight percent.

[0022] A flavorant operative herein illustratively includes an essential oil, a water soluble plant extract, an alcohol soluble plant extract, or a combination thereof. Exemplary flavorants include cloves, culeb oil, cedarwood oil, eucalyptus oil, lemon oil, menta arvensis extracts (e.g. menthol), mint, wintergreen oil, peppermint oil, mint tea concentrate, sucralose, sodium saccharin, other artificial and natural fruit flavors, and combinations thereof. Typical quantities of an antioxidant, if present, in the inventive composition range from 0.01 - 3 total weight percent.

[0023] A desensitizer operative herein illustratively includes arginine, camphor, potassium nitrate, potassium chloride, potassium citrate, silver nitrate, zinc chloride, gluteraldehyde, strontium chloride hexahydrate, sodium fluoride, stannous fluoride, strontium chloride, potassium oxalate, calcium phosphate, nano-

hydroxyapatite, or a combination thereof. Typical quantities of a desensitizer, if present, in the inventive composition range from 0.1 - 8 total weight percent.

[0024] A fluoridation agent operative herein illustratively includes sodium fluoride, calcium fluoride, hexafluorosilicate, or a combination thereof. Typical quantities of a fluoridation agent, if present, in the inventive composition range from 0.01 – 0.2 total weight percent.

[0025] In some inventive embodiments, fucoidan is present. Fucoidan is a sulfated polysaccharide. As used herein, fucoidan is intended to encompass both F-fucoidan, which is composed predominantly of sulfated esters of fucose, and U-fucoidan, which contains appreciable amounts of glucuronic acid (10 – 30 weight %). Typical quantities of fucoidan, if present, in the inventive composition range from 0.01 – 2.0 total weight percent.

[0026] It has been discovered to improve the function of saline or hydrogen peroxide composition according to the present invention in terms of treating or preventing infections of the pharyngeal or buccal cavities.

[0027] The present invention is further detailed with respect to the following nonlimiting examples. Unless otherwise specified, the percentages detailed herein are total weight percent of the inventive formulation.

Example 1-6

[0028] A series of inventive compositions are developed with a saline solution base as detailed in Tables 1-4:

[0029] **Table 1:** Formulation of saline gargles with fucoidan.

Saline Gargle with Fucoidan	Example 1 % (w/w)	Example 2 % (w/w)
Water	97.49	97.39
NaCl	2.25	2.25
Fucoidan	0.1	0.2
HCl 10%	0.08495	0.08495
Sodium Benzoate	0.05	0.05
Menthol	0.025	0.025
pH	4.01	3.75
Total osmolarity	0.78	0.78

[0030] **Table 2:** Formulation of saline gargle without Fucoidan.

Saline Gargle without Fucoidan	Example 3
Water	97.59
NaCl	2.25
HCl 10%	0.08495
Sodium Benzoate	0.05
Menthol	0.025
pH	3.72
Total osmolarity	0.78

[0031] **Table 3:** Formulation of saline mouthwash with fucoidan.

Saline Mouth Wash with Fucoidan	Example 4 % (w/w)	Example 5 % (w/w)
Water	97.185	97.085
NaCl	1.8	1.8
Sodium Benzoate	0.05	0.05
Fucoidan	0.1	0.2
Arginine	0.8	0.8
Sodium Fluoride	0.04	0.04
Menthol	0.025	0.025
pH	6.05	6.08
Total osmolarity	0.69	0.69

[0032] **Table 4:** Formulation of saline mouthwash without fucoidan.

Saline Mouth Wash without Fucoidan	Example 6 % (w/w)
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Water	97.285
NaCl	1.8
Sodium Benzoate	0.05
Arginine	0.8
Sodium Fluoride	0.04
Menthol	0.025
pH	6.5
Total osmolarity	0.69

Example 7-9

[0033] A series of inventive compositions are developed with a hydrogen peroxide solution base as detailed in Tables 5 and 6:

[0034] **Table 5:** Formulation of hydrogen peroxide gargle with fucoidan.

H₂O₂ Gargle with fucoidan	Example 7 % (w/w)	Example 8 % (w/w)
Hydrogen Peroxide 3 %	50	50
Fucoidan	0.1	0.2
HCl 10%	0.08495	0.08495
Sodium Benzoate	0.05	0.05
Menthol	0.025	0.025
Water	49.74	49.64
pH	3.87	4.29
Total osmolarity	0.45	0.45

[0035] **Table 6:** Formulation of hydrogen peroxide gargle without fucoidan.

H₂O₂ Gargle without fucoidan	Example 9 % (w/w)
Hydrogen Peroxide 3 %	50
Sodium Benzoate	0.05
HCl 10%	0.08495
Menthol	0.025
Water	49.84
pH	4.17
Total osmolarity	0.45

[0036] The antimicrobial properties of the composition of Examples 1,2, and 7-9 are evaluated using ASTM E1052 test method. In an ASTM E1052 test, a suspension of virus is exposed to a test product at a ratio of 1:10 (1 part virus suspension + 9 parts prepared test product). A Control suspension is concurrently processed in the same manner, with cell culture medium employed in place of the test product. Following neutralization, the suspensions are enumerated using standard cell culture (e.g. TCID50) or plaque assay techniques. Log10 and percent reduction values are calculated to determine the effectiveness of the test product suspension relative to the control suspension.

[0037] According to this method MS2 Bacteriophage (MS2), ATCC 15597-B1 is the test virus. Bacterial cells are the hosts for bacteriophages, and *E. coli* 15597 serves this purpose for MS2 bacteriophage.

[0038] In summary the method includes the steps of:

- Stock virus is thawed.
- Test and control substances are dispensed in 9-part equivalent volumes into sterile vessels.
- Test and control substances are each inoculated with 1-part equivalent volumes of the test virus.
- The test suspensions are held for the contact time(s), and then neutralized by ten-fold serial dilutions into the appropriate solution. Gel filtration is employed.
- The control suspension is neutralized in the same manner as the test

suspensions.

- Viral suspensions are quantified to determine the levels of growth
- Infectious virus using standard cell culture (e.g. TCID50) or plaque assay techniques. samples are incubated for the period most suitable for the virus-host cell system (e.g. 7 days).
- After the incubation period, the assay is scored for the presence/absence of test virus and cytotoxic effects. The appropriate calculations are performed (e.g. Spearman-Karber) to determine viral titers and levels of test substance cytotoxicity, where applicable.
- Viral titers are computed for test suspensions relative to the control.

[0039] The test results are summarized in Table 7.

[0040] **Table 7:** bacteriophage inhibition of the Examples 1, 2, and 7-9.

Test Microorganism	Contact Time	Test Substance	Replicate	PFU/ml	Average PFU/ml	Percent Reduction Compared to Control at Time Zero	Log ₁₀ Reduction Compared to Control at Time Zero
MS2 ATCC 15597-	Time Zero	Control	1	8.65E+05	1.20E+06	N/A	
			2	7.70E+05			
			3	1.95E+06			
	30 Seconds	Ex. 1	1	2.59E+05	2.09E+05	82.55%	0.76
			2	1.86E+05			
			3	1.81E+05			
		Ex. 2	1	3.00E+05	2.51E+05	78.97%	0.68
			2	2.22E+05			
			3	2.32E+05			
		Ex. 7	1	1.97E+05	1.90E+05	84.10%	0.80
			2	2.18E+05			
			3	1.56E+05			
		Ex. 8	1	1.02E+05	9.55E+04	92.01%	1.10
			2	8.80E+04			
			3	9.65E+04			
		Ex. 9	1	2.08E+05	2.07E+05	82.68%	0.76
			2	2.06E+05			

3	1.66E+05
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[0041] To further evaluate antimicrobial properties of the inventive compositions, Minimum Inhibitory Concentration Method (MIC) is performed. This is a general microbiological test method that is used to measure the lowest level of an antimicrobial agent that can inhibit microbial proliferation in liquid. The procedure is summarized as follows:

- Test microorganisms are prepared in liquid culture medium for bacteria or on agar for fungi.
- The test substance is prepared by conducting several serial 1:1 dilutions in a 96-well microtiter r in small test tubes, through Mueller-Hinton broth or other appropriate medium.
- All wells or tubes containing diluted test substances are inoculated with test microorganisms, individually, resulting in one additional and final dilution of the product in all test vessels.
- The microtiter plate or test tubes are incubated for 18-24 hours.
- After the incubation period, observations are made.

[0042] The results for various organisms are detailed in Tables 8-13.

[0043] Table 8: 24 hour results for Examples 1-3.

Test Microorganism	Test Substance	24 Hour Result
<i>E. coli</i> ATCC 8739	Solution Ex. 3	-
	Solution Ex. 1	+
	Solution Ex. 2	-
<i>H. influenzae</i> ATCC 8149	Solution Ex. 3	-
	Solution Ex. 1	-
	Solution Ex. 2	-
<i>K. pneumoniae</i> ATCC 29019	Solution Ex. 3	-
	Solution Ex. 1	+
	Solution Ex. 2	-
<i>L. acidophilus</i> ATCC 4356	Solution Ex. 3	+
	Solution Ex. 1	+
	Solution Ex. 2	+
<i>M. catarrhalis</i> ATCC 25238	Solution Ex. 3	-
	Solution Ex. 1	-
	Solution Ex. 2	-

<i>P. aeruginosa</i> ATCC 15442	Solution Ex. 3	+
	Solution Ex. 1	+
	Solution Ex. 2	-
<i>P. mirabilis</i> ATCC 7002	Solution Ex. 3	+
	Solution Ex. 1	+
	Solution Ex. 2	-
<i>S. pneumoniae</i> ATCC 49619	Solution Ex. 3	-
	Solution Ex. 1	+
	Solution Ex. 2	+
<i>S. pyogenes</i> ATCC 19615	Solution Ex. 3	+
	Solution Ex. 1	+
	Solution Ex. 2	+
<i>S. aureus</i> ATCC 33592	Solution Ex. 3	+
	Solution Ex. 1	+
	Solution Ex. 2	-

[0044] Table 9: 24 hour results for Examples 4-6.

Test Microorganism	Test Substance	24 Hour Result
<i>L. acidophilus</i> ATCC 4356	Solution EX. 6	+
	Solution Ex. 4	+
	Solution Ex. 5	+
<i>S. sobrinus</i> ATCC 33478	Solution Ex. 6	+
	Solution Ex. 4	+
	Solution Ex. 5	+
<i>S. sobrinus</i> ATCC 33478	Solution EX. 6	+
	Solution Ex. 4	+
	Solution Ex. 5	+
	Solution EX. 6	-

<i>S. mutans</i> ATCC 25175	Solution Ex. 4	-
	Solution Ex. 5	-

[0045] Table 10: 24 hour results for Examples 7-9.

Test Microorganism	Test Substance	24 Hour Result
<i>H. influenzae</i> ATCC 8149	Solution Ex. 9	-
	Solution Ex. 7	+
	Solution Ex. 8	-
<i>S. pneumoniae</i> ATCC 49619	Solution Ex. 9	-
	Solution Ex. 7	-
	Solution Ex. 8	-
<i>S. pyogenes</i> ATCC 19615	Solution Ex. 9	-
	Solution Ex. 7	-
	Solution Ex. 8	-

[0046] Table 11: MIC and MBC results for Examples 1-3.

Test Microorganism	CFU/ml Results	Test Substance	MIC	MBC	Positive Control	Negative Control
<i>E. coli</i> ATCC 8739	2.05E+05	Solution Ex. 3	No Growth Observed	No MBC Observed	+	-
		Solution Ex. 1	Growth Observed	No MBC Observed	+	-
		Solution Ex. 2	No Growth Observed	No MBC Observed	+	-
<i>H. influenzae</i> ATCC 8149	3.15E+06	Solution Ex. 3	No Growth Observed	No MBC Observed	+	-
		Solution Ex. 1	No Growth Observed	No MBC Observed	+	-
		Solution Ex. 2	No Growth Observed	No MBC Observed	+	-
<i>K. pneumoniae</i> ATCC 29019	3.00E+04	Solution Ex. 3	No Growth Observed	No MBC Observed	+	-
		Solution Ex. 1	Growth Observed	No MBC Observed	+	-
		Solution Ex. 2	No Growth Observed	No MBC Observed	+	-
<i>L. acidophilus</i> ATCC 4356	3.15E+06	Solution Ex. 3	Growth Observed	No MBC Observed	+	-
		Solution Ex. 1	Growth Observed	No MBC Observed	+	-
		Solution Ex. 2	Growth Observed	No MBC Observed	+	-
<i>M. catarrhalis</i> ATCC 25238	4.35E+06	Solution Ex. 3	No Growth Observed	No MBC Observed	+	-
		Solution Ex. 1	No Growth Observed	No MBC Observed	+	-
		Solution Ex. 2	No Growth Observed	No MBC Observed	+	-

Test Microorganism	CFU/ml Results	Test Substance	MIC	MBC	Positive Control	Negative Control
<i>P. aeruginosa</i> ATCC 15442	2.05E+04	Solution Ex. 3	Growth Observed	No MBC Observed	+	-
		Solution Ex. 1	Growth Observed	No MBC Observed	+	-
		Solution Ex. 2	No Growth Observed	No MBC Observed	+	-
<i>P. mirabilis</i> ATCC 7002	7.65E+05	Solution Ex. 3	Growth Observed	No MBC Observed	+	-
		Solution Ex. 1	Growth Observed	No MBC Observed	+	-
		Solution Ex. 2	No Growth Observed	No MBC Observed	+	-
<i>S. pneumoniae</i> ATCC 49619	1.75E+04	Solution Ex. 3	No Growth Observed	MBC	+	-
		Solution Ex. 1	Growth Observed	No MBC Observed	+	-
		Solution Ex. 2	Growth Observed	No MBC Observed	+	-
<i>S. pyogenes</i> ATCC 19615	1.15E+06	Solution Ex. 3	Growth Observed	No MBC Observed	+	-
		Solution Ex. 1	Growth Observed	No MBC Observed	+	-
		Solution Ex. 2	Growth Observed	No MBC Observed	+	-
<i>S. aureus</i> ATCC 33592	2.40E+05	Solution Ex. 3	Growth Observed	No MBC Observed	+	-
		Solution Ex. 1	Growth Observed	No MBC Observed	+	-
		Solution Ex. 2	No Growth Observed	No MBC Observed	+	-

[0047] Table 12: MIC and MBC results for Examples 4-6.

Test Microorganism	CFU/ml Results	Test Substance	MIC	MBC	Positive Control	Negative Control
<i>L. acidophilus</i> ATCC 4356	3.00E+05	Solution Ex. 5	Growth Observed	No MBC Observed	+	-
		Solution Ex. 4	Growth Observed	No MBC Observed	+	-
		Solution Ex. 6	Growth Observed	No MBC Observed	+	-
<i>S. sobrinus</i> ATCC 33478	5.40E+04	Solution Ex. 4	Growth Observed	No MBC Observed	+	-
		Solution Ex. 5	Growth Observed	No MBC Observed	+	-
<i>S. mutans</i> ATCC 25175	8.00E+05	Solution Ex. 6	Growth Observed	No MBC Observed	+	-
		Solution Ex. 4	No Growth Observed	MBC	+	-
		Solution Ex. 5	No Growth Observed	MBC	+	-

[0048] Table 13: MIC and MBC results for Examples 7-9.

Test Microorganism	CFU/ml Results	Test Substance	MIC	MBC	Positive Control	Negative Control
<i>H. influenzae</i> ATCC 8149	3.15E+06	Solution Ex. 9	No Growth Observed	No MBC Observed	+	-
		Solution Ex. 7	Growth Observed	No MBC Observed	+	-
		Solution Ex. 8	No Growth Observed	MBC	+	-
<i>S. pneumoniae</i> ATCC 49619	1.75E+04	Solution Ex. 9	No Growth Observed	MBC	+	-
		Solution Ex. 7	No Growth Observed	MBC	+	-
		Solution Ex. 8	No Growth Observed	MBC	+	-
<i>S. pyogenes</i> ATCC 19615	1.15E+06	Solution Ex. 7	No Growth Observed	MBC	+	-
		Solution Ex. 9	No Growth Observed	MBC	+	-

[0049] Any patents or publications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication was specifically and individually indicated to be incorporated by reference.

[0050] The foregoing description is illustrative of particular embodiments of the invention, but is not meant to be a limitation upon the practice thereof.

CLAIMS

1. A storage stable package comprising:
a polymeric bottle having a volume;
an aqueous saline composition acidified with an acid to a pH of 2 to 9 and having a hypertonic saline concentration relative to saliva and blood to achieve a storage stability at 20 degrees Celsius of the composition of at least 10 weeks, said aqueous composition independent of a synthetic antimicrobial; and
a cap for selectively sealing said aqueous saline composition within the volume.
2. The package of claim 1 wherein said acid is hydrochloric acid.
3. The package of claim 1 wherein said acid is hydrobromic, lactic, citric, malic, acetic, benzoic, ascorbic, tartaric, oxalic, tannic, butyric, caffeotannic, phosphoric, sulfuric, nitric, or a combination thereof.
4. The package of claim 1 wherein said pH is 3.0 to 7.0.
5. The package of claim 1 wherein said pH is 3.6 to 5.4.
6. The package of claim 1 further comprising a flavorant.

7. The package of claim 1 further comprising a desensitizer.
8. The package of claim 1 further comprising a fluoridation agent.
9. The package of claim 1 further comprising focoidan.
10. The package of claim 11 wherein said focoidan is present from 0.1 to 2.0 total weight percent of the said aqueous saline composition.
11. The package of claim 1 wherein the hypertonic saline concentration is between 1.7 and 5.0 total weight percent of the said aqueous saline composition.
12. A storage stable package comprising:
 - a polymeric bottle having a volume;
 - an aqueous hydrogen peroxide composition acidified with an acid to a pH of 2.7 to 5.3 and having a hydrogen peroxide concentration 0.5 to 3 total weight percent of said aqueous hydrogen peroxide composition to achieve a storage stability at 20 degrees Celsius of the composition of at least 10 weeks, said aqueous composition independent of a small molecule organic synthetic antimicrobial; and
 - a cap for selectively sealing said aqueous saline composition within the volume.
13. The package of claim 12 wherein said acid is hydrochloric acid.

14. The package of claim 12 wherein said acid is hydrobromic, lactic, citric, malic, acetic, benzoic, ascorbic, tartaric, oxalic, tannic, butyric, caffeotannic, phosphoric, sulfuric, nitric, or a combination thereof.

15. The package of claim 12 wherein said pH is 3.0 to 5.0.

16. The package of claim 12 wherein said pH is 3.6 to 4.4.

17. The package of claim 12 further comprising a desensitizer.

18. The package of claim 12 further comprising a fluoridation agent.

19. The package of claim 12 further comprising focoidan.

20. The package of claim 21 wherein said focoidan is present from 0.1 to 2.0 total weight percent of the said aqueous saline composition.

21. A process for treating an infection of a pharyngeal or buccal cavity comprising:

rinsing the pharyngeal or buccal cavity with said aqueous saline composition of claim 1 for an amount of time sufficient to treat the infection; and expectorating said aqueous saline composition.

22. The process of claim 23 wherein rinsing is gargling.

23. A process for treating an infection of a pharyngeal or buccal cavity comprising:

rinsing the pharyngeal or buccal cavity with said hydrogen peroxide composition of claim 12 for an amount of time sufficient to treat the infection; and expectorating said hydrogen peroxide composition.

24. The process of claim 25 wherein rinsing is gargling.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2017/041365**A. CLASSIFICATION OF SUBJECT MATTER****A61K 8/58(2006.01)i, A61K 8/73(2006.01)i, A61K 8/22(2006.01)i, A61Q 11/00(2006.01)i**

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K 8/58; B65D 1/04; A61K 33/14; A61K 9/36; A61K 8/73; A61K 33/20; A61K 8/60; A61K 8/20; A61K 9/08; A61K 8/22; A61Q 11/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Korean utility models and applications for utility models
Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

eKOMPASS(KIPO internal) & Keywords: gargle, mouth wash, buccal, pharyngeal, hypertonic saline, hydrogen peroxide, storage stability

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2009-0123570 A1 (WARNER, W. R. et al.) 14 May 2009 See abstract; paragraphs [0023], [0037]; and claims 1, 3.	1-6, 11
Y		7-10
A		12-15, 18-22
Y	WO 2010-054083 A2 (PHARMACARIBE) 14 May 2010 See abstract; paragraphs [0002], [0052]; and claim 1.	7, 19
X	US 5392947 A (GENTILE, J. L.) 28 February 1995 See abstract; columns 4, 6; example; claims 1, 2; and figure 1.	12-15, 18, 20
Y		8, 19, 21, 22
Y	KR 10-2013-0123861 A (DONG-EUI UNIVERSITY INDUSTRY-ACADEMIC COOPERATION FOUNDATION) 13 November 2013 See abstract; and claim 1.	9, 10, 21, 22
E	US 2017-0196783 A1 (GOWANI, J. et al.) 13 July 2017 See claims 1-15, 18-26. [Claims 16 and 17 are missing in this application (PCT Rule 6.1(b)).]	1-15, 18-22

 Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent 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 when the document is taken alone

"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

Date of the actual completion of the international search

02 February 2018 (02.02.2018)

Date of mailing of the international search report

02 February 2018 (02.02.2018)

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INTERNATIONAL SEARCH REPORTInternational application No.
PCT/US2017/041365**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

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

1. Claims Nos.: 23-26
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 23-26 pertain to methods for treatment of the human body by therapy and thus relate to a subject matter which this International Searching Authority is not required, under PCT Article 17(2)(a)(i) and PCT Rule 39.1(iv), to search.
2. Claims Nos.:
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, specifically:
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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.
2. As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of any additional fees.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. 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 claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US2017/041365

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2009-0123570 A1	14/05/2009	None	
WO 2010-054083 A2	14/05/2010	US 2010-0209540 A1 WO 2010-054083 A3	19/08/2010 10/09/2010
US 5392947 A	28/02/1995	None	
KR 10-2013-0123861 A	13/11/2013	KR 10-1450098 B1	14/10/2014
US 2017-0196783 A1	13/07/2017	None	