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(54) Title: COMPOSITION

(57) Abstract: Toothpaste composition and method for making such, the toothpaste comprising water, a zinc salt, a chelating agent for the zinc, the chelating agent having a log Ks1 as herein defined of from 3.0 to 7.0, and calcium carbonate as abrasive.



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COMPOSITION

The present invention relates to a toothpaste composition comprising bioactive zinc salts in a chalk formulation. The invention also relates to a method for making said composition.

EP-A1-0 740 932 (Unilever) discloses a visually-clear gel type dentifrice comprising a zinc salt which is more water soluble than zinc citrate, an amino acid which can bind zinc and a low refractive index type abrasive silica.

US 5 470 561 (Klugkist) discloses an anti-plaque mouthwash comprising a zinc salt and triclosan. The composition may also comprise glycine and has a pH of between 4 and 8, preferably between 5 and 7, the preferred pH being 6.

GBA-2 052 978 (Unilever) discloses a toothpaste comprising zinc salts with glycine and a pH of from 4.5 to 8.0.

US 5 632 972 (Williams) discloses a method for minimising damage to gingival and periodontal tissue by delivering a first component comprising zinc and a second component comprising a bicarbonate.

The invention provides a toothpaste composition comprising a first phase and a second phase stored in contact with one another, the first phase comprising water and a zinc salt, the second phase comprising calcium carbonate as abrasive and a chelating agent for the zinc salt, the chelating agent having a log K_{s1} as herein defined of from 3.0 to 7.0.

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The zinc salt is present at from 0.01 to 5% by weight of the toothpaste composition, preferably from 0.5 to 3.0% by weight of the composition. Where the zinc salt is sparingly soluble, for example zinc citrate, the log K_{s1} of the chelating ligand with the zinc ion is equal to or greater than the log K_{s1} of the acid anion and the zinc ion of the sparingly soluble zinc salt. However, water soluble zinc salts are preferred. Suitable zinc salts include zinc chloride, zinc sulphate and zinc fluoride. The preferred zinc salt is zinc sulphate which, in this type of formulation, provides an optimal balance between making enough zinc ions bioavailable, and capable of interacting with bacteria, without forming a deleterious amount of water-insoluble zinc hydroxide.

It is preferred that the chelating agent for the zinc salt has a log K_{s1} of from 4.0 to 6.0. The log K_{s1} is the logarithm of the primary Stability Constant which is the binding affinity for a particular ligand with a particular metal ion, in the present invention zinc. For example, when the chelating agent is glycine, the primary Stability Constant is the binding affinity for one glycine ligand with the free zinc ion and is defined by the following: $K_{s1} = [ML]/[M].[L]$, where $[ML]$ is the concentration of the metal-ligand complex, $[M]$ is the concentration of the free metal ion and $[L]$ is the concentration of the free ligand. Since $[L]$ is a function of the solution pH, due to the required initial deprotonation of the ligand, as a reference point, the log K_{s1} values described were recorded at pH 7.4.

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The chelating agent is present at from 0.001 to 6% by weight of the composition, preferably at from 0.5 to 4.0% by weight of the composition. Preferred chelating agents include alkali metal salts of citric acid, alanine, glycine and
5 serine. The most preferred is glycine, which provides an optimal balance between being able to protect the zinc salt from hydrolysis (leading to formation of insoluble zinc hydroxide) in the chalk system and keeping it soluble and bioavailable.

10

The abrasive system employed in the present invention is calcium carbonate based. This does not prevent the use of non-calcium carbonate abrasives in addition, such as silicas, tungsten carbide and silicon carbide.

15

The abrasive system is present at from 10 to 70% by weight of the second phase of the composition. In a preferred embodiment this comprises calcium carbonate at from 10 to 70% by weight of the second phase, more preferably from 20%
20 and most preferably from 45 to 60% by weight of the second phase calcium carbonate.

Preferred calcium carbonates include fine ground natural chalk since it has a surprising stability with regard to its
25 interactivity with zinc salts. The term fine ground natural chalk (FGNC) is a known term in the art and suitable examples of such are disclosed in US 2003/0072721 A1 (Riley) the contents of which with regards to the definition, types and grades of FGNC are incorporated herein by reference.
30 Nevertheless, by FGNC is meant chalk which is obtained by milling limestone or marble deposits. Preferably, the FGNC

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comprises particulate matter of weight-based median particle size ranging from 1 to 15 μm and BET surface area ranging from 0.5 to 3 m^2/g .

5 The composition according to the invention also preferably comprises a fluoride ion source such as an alkali metal salt of monofluorophosphate, preferably sodium monofluorophosphate. Such fluoride ion source will be present at such an amount to provide free fluoride ion at
10 from 100 to 2000 ppm, preferably from 900 to 1500 ppm.

The oral composition according to the invention comprise further ingredients which are common in the art, such as:

15 antimicrobial agents, e.g. chlorhexidine, sanguinarine extract, metronidazole, quaternary ammonium compounds, such as cetylpyridinium chloride; bis-guanides, such as chlorhexidine digluconate, hexetidine, octenidine, alexidine; and halogenated bisphenolic compounds, such as
20 2,2' methylenebis-(4-chloro-6-bromophenol);

anti-inflammatory agents such as ibuprofen, flurbiprofen, aspirin, indomethacin etc.;

25 anti-caries agents such as sodium- and stannous fluoride, aminefluorides, sodium monofluorophosphate, sodium trimeta phosphate and casein;

plaque buffers such as urea, calcium lactate, calcium
30 glycerophosphate and strontium polyacrylates;

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vitamins such as Vitamins A, C and E;

plant extracts;

5 desensitising agents, e.g. potassium citrate, potassium chloride, potassium tartrate, potassium bicarbonate, potassium oxalate, potassium nitrate and strontium salts;

anti-calculus agents, e.g. alkali-metal pyrophosphates,
10 hypophosphite-containing polymers, organic phosphonates and phosphocitrates etc.;

biomolecules, e.g. bacteriocins, antibodies, enzymes, etc.;

15 flavours, e.g. peppermint and spearmint oils;

proteinaceous materials such as collagen;

preservatives;

20

opacifying agents;

colouring agents;

25 pH-adjusting agents;

sweetening agents;

pharmaceutically acceptable carriers, e.g. starch, sucrose,
30 water or water/alcohol systems etc.;

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surfactants, such as anionic, nonionic, cationic and zwitterionic or amphoteric surfactants;

particulate abrasive materials such as silicas, aluminas,
5 calcium carbonates, dicalciumphosphates, calcium pyrophosphates, hydroxyapatites, trimetaphosphates, insoluble hexametaphosphates and so on, including agglomerated particulate abrasive materials, usually in amounts between 3 and 60% by weight of the oral care
10 composition. Preferred abrasives are chalk and silica, more preferably fine ground natural chalk.

Humectants such as glycerol, sorbitol, propyleneglycol, xylitol, lactitol etc.;

15 binders and thickeners such as sodium carboxymethyl-cellulose, hydroxyethyl cellulose (Natrosol®), xanthan gum, gum arabic etc. as well as synthetic polymers such as polyacrylates and carboxyvinyl polymers such as Carbopol®;

20 polymeric compounds which can enhance the delivery of active ingredients such as antimicrobial agents can also be included;

25 buffers and salts to buffer the pH and ionic strength of the oral care composition; and

other optional ingredients that may be included are e.g. bleaching agents such as peroxy compounds e.g. potassium
30 peroxydiphosphate, effervescing systems such as sodium

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bicarbonate/citric acid systems, colour change systems, and so on.

Liposomes may also be used to improve delivery or stability
5 of active ingredients.

In a second aspect of the invention there is provided a method of making an oral composition according to the first aspect the method comprising the steps of forming a zinc-
10 chelate solution and buffering to a pH which is equal to or higher than that of the calcium carbonate in an aqueous suspension before mixing with the suspended calcium carbonate. Further materials such as flavours may be added to the final mix.

15

Except in the operating and comparative examples, or where otherwise explicitly indicated, all numbers in this description indicating amounts of material ought to be understood as modified by the word 'about'.

20

The term 'comprising' is meant not to be limiting to any subsequently stated elements but rather to encompass non-specified elements of major or minor functional importance. In other words the listed steps, elements or options need
25 not be exhaustive. Whenever the words 'including' or 'having' are used, these terms are meant to be equivalent to 'comprising' as defined above.

Embodiments according to the invention shall now be
30 discussed with reference to the following non-limiting examples.

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EXAMPLE 1

The following example formulation is an embodiment according to the invention.

5

Ingredient	% w/w gel	% w/w chalk paste
sorbitol	66	45
abrasive silica	8	0
fine ground natural chalk	0	40
thickening silica	8	4.75
polyethylene glycol	2	0
sodium carboxymethyl cellulose	0.65	0.45
trisodium orthophosphate	0.65	0.45
saccharine	0.25	0.25
sodium lauryl sulphate	2.5	2.5
titanium dioxide	0	0.5
sodium monofluorophosphate	0.76	0.76
zinc sulphate	2	0
glycine	0	2.5
sodium hydroxide	0	0.4
water	to 100	to 100
total	100	100

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CLAIMS

1. Toothpaste composition comprising a first phase and a second phase stored in contact with one another, the
5 first phase comprising water and a zinc salt, the second phase comprising calcium carbonate as abrasive and a chelating agent for the zinc salt, the chelating agent having a log K_{s1} as herein defined of from 3.0 to 7.0.
10
2. Toothpaste composition according to claim 1, wherein the second phase has a pH of from 8.0 to 10.0
3. Toothpaste composition according to any preceding
15 claim, wherein the calcium carbonate is fine ground natural chalk.
4. Toothpaste composition according to any preceding claim, wherein the composition comprises a fluoride ion
20 source.
5. Toothpaste composition according to any preceding claim, wherein the zinc salt is a water soluble zinc salt.
25
6. Toothpaste composition according to any preceding claim, wherein the zinc salt is zinc sulphate.
7. Toothpaste composition according to any preceding
30 claim, wherein the chelating agent is glycine.

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8. Toothpaste composition according to any preceding claim, wherein the chelating agent is serine.
9. Toothpaste composition according to any preceding
5 claim, wherein the chelating agent is alanine.
10. Toothpaste composition according to any preceding claim, wherein the chelating agent is an alkali metal salt of citric acid.
10
11. Toothpaste according to any preceding claim comprising an agent selected from the group consisting of anti-caries agents, anti-tartar agents, anti-malodour agents, whitening teeth agents, anti-gingivitis agents
15 and mixtures thereof.
12. Toothpaste according to any preceding claim, wherein the first and second phases are coaxially arranged in and dispensed from a toothpaste tube, the first phase
20 substantially surrounding the second phase.

INTERNATIONAL SEARCH REPORT

International Application No

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A. CLASSIFICATION OF SUBJECT MATTER

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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

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

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

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 015 547 A (YAM ET AL) 18 January 2000 (2000-01-18) column 2, line 11 - line 42 column 3, line 12 - line 16 column 7, line 38 - line 48 column 10, line 42 - column 11, line 39 claims 1-8,13,18,19	1-12
A	EP 0 740 932 A (UNILEVER N.V; UNILEVER PLC) 6 November 1996 (1996-11-06) page 3, line 29 - line 30 claims	1-12
A	US 5 616 313 A (WILLIAMS ET AL) 1 April 1997 (1997-04-01) column 7; table 1	1-12
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 948 390 A (NELSON ET AL) 7 September 1999 (1999-09-07) column 6; example 3 claims 1,5,9	1
A	EP 1 072 253 A (SUNSTAR KABUSHIKI KAISHA) 31 January 2001 (2001-01-31) page 16; example 32	1-12
A	US 2 772 203 A (SALZMANN GERHARD MARTIN) 27 November 1956 (1956-11-27) column 5; example 4 claims 1,3-5	1-12
A	US 1 639 699 A (HOPKINS NEVIL MONROE) 23 August 1927 (1927-08-23) claims; figures	12
A	GB 1 271 944 A (BEECHAM GROUP LIMITED) 26 April 1972 (1972-04-26) examples	12

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP2005/007529

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 6015547	A	18-01-2000	AU 1274799 A CA 2305750 A1 EP 1035847 A1 WO 9921547 A1 US 5855873 A	17-05-1999 06-05-1999 20-09-2000 06-05-1999 05-01-1999
EP 0740932	A	06-11-1996	EP 1203575 A2	08-05-2002
US 5616313	A	01-04-1997	US 5632972 A	27-05-1997
US 5948390	A	07-09-1999	NONE	
EP 1072253	A	31-01-2001	CA 2329622 A1 ID 26720 A WO 9955296 A1 JP 2000247852 A US 6471946 B1	04-11-1999 01-02-2001 04-11-1999 12-09-2000 29-10-2002
US 2772203	A	27-11-1956	NONE	
US 1639699	A	23-08-1927	NONE	
GB 1271944	A	26-04-1972	AT 331417 B BE 736316 A CH 532933 A DE 1937001 A1 DK 122159 B FI 50764 B FR 2013525 A5 IE 33189 B1 JP 55044044 B NL 6910667 A NO 140917 B	25-08-1976 31-12-1969 31-01-1973 29-01-1970 31-01-1972 31-03-1976 03-04-1970 17-04-1974 10-11-1980 27-01-1970 03-09-1979