

(12) STANDARD PATENT
(19) AUSTRALIAN PATENT OFFICE

(11) Application No. **AU 2020234299 C1**

(54) Title
Compositions and methods for promoting mineralization

(51) International Patent Classification(s)
A61K 6/838 (2020.01) **A61K 33/06** (2006.01)
A61K 8/21 (2006.01) **A61K 33/16** (2006.01)
A61K 8/24 (2006.01) **A61K 33/42** (2006.01)
A61K 9/08 (2006.01) **A61Q 11/00** (2006.01)

(21) Application No: **2020234299** (22) Date of Filing: **2020.03.13**

(87) WIPO No: **WO20/181334**

(30) Priority Data

(31) Number	(32) Date	(33) Country
2019900834	2019.03.13	AU
2019903859	2019.10.14	AU

(43) Publication Date: **2020.09.17**

(44) Accepted Journal Date: **2024.05.30**

(44) Amended Journal Date: **2024.10.10**

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(56) Related Art
WO 98/40406 A1
WO 03/059303 A2
EP 1525878 B1
WO 2015/010166 A1

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property

Organization

International Bureau

(43) International Publication Date

17 September 2020 (17.09.2020)



(10) International Publication Number

WO 2020/181334 A1

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A61Q 11/00 (2006.01) A61K 33/42 (2006.01)

A61K 8/24 (2006.01) A61K 9/08 (2006.01)

EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

(21) International Application Number:

PCT/AU2020/050236

Declarations under Rule 4.17:

— of inventorship (Rule 4.17(iv))

(22) International Filing Date:

13 March 2020 (13.03.2020)

Published:

— with international search report (Art. 21(3))

— with sequence listing part of description (Rule 5.2(a))

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

2019900834 13 March 2019 (13.03.2019) AU

2019903859 14 October 2019 (14.10.2019) AU

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(81) Designated States (unless otherwise indicated, for every

kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every

kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK,

(54) Title: COMPOSITIONS AND METHODS FOR PROMOTING MINERALIZATION

(57) Abstract: The present invention relates to compositions for uses including mineralizing a dental surface, in particular tooth enamel. Methods of mineralizing hypomineralized lesions (including subsurface lesions) in the tooth enamel caused by various means including dental caries, dental corrosion and fluorosis are also provided. In one aspect, the present invention provides a method of mineralizing a dental surface or sub-surface comprising contacting the dental surface or subsurface with stabilized amorphous calcium phosphate (ACP) and/or amorphous calcium fluoride phosphate (ACFP), and simultaneously or subsequently, heating the dental surface or sub-surface to which the stabilized ACP and/or ACFP has been, or is being, applied to a temperature greater than 37°C. In another aspect, the present invention provides a method of mineralizing a dental surface or sub-surface comprising contacting the dental surface or subsurface with a liquid composition comprising greater than 20% w/v stabilized amorphous calcium phosphate (ACP) and/or amorphous calcium fluoride phosphate (ACFP).



WO 2020/181334 A1

Compositions and methods for promoting mineralization

Cross-reference to earlier application(s)

This application claims priority to Australian provisional applications 2019900834 and 2019903859, the entire contents of each are herein incorporated by reference in
5 their entirety.

Field of the invention

The present invention relates to compositions for uses including mineralizing a dental surface, in particular tooth enamel. Methods of mineralizing hypomineralized lesions (including subsurface lesions) in the tooth enamel caused by various means
10 including dental caries, dental erosion and fluorosis are also provided.

Background of the invention

Common causes of hypomineralized lesions are caries and fluorosis.

Dental caries result from the demineralization of hard tissue of the teeth usually because of fermentation of dietary sugar by dental plaque odontopathogenic bacteria.
15 Further, restored tooth surfaces can be susceptible to further dental caries around the margins of the restoration. Dental erosion or corrosion is the loss of tooth mineral by dietary or regurgitated acids. Dental hypersensitivity is due to exposed dentinal tubules through loss of the protective mineralized layer, cementum. Dental calculus is the unwanted accretion of calcium phosphate minerals on the tooth surface. All these
20 conditions, dental caries, dental erosion, dental hypersensitivity and dental calculus are therefore related to imbalances in the level of calcium phosphates.

Enamel fluorosis (mottling) has been recognized for nearly a century, however, the aetiological role of fluoride was not identified until 1942. The characteristic appearance of fluorosis may be differentiated from other enamel disturbances. The
25 clinical features of fluorotic lesions of enamel (FLE) represent a continuum ranging from fine opaque lines following the perikymata, to chalky, white enamel. The presence of a comparatively highly mineralized enamel outer surface and a hypomineralized subsurface in the fluorotic lesion stimulates the incipient enamel "white spot" carious lesion. With increasing severity, both the depth of enamel involved in the lesion and the

degree of hypomineralization increases. The development of fluorosis is highly dependent on the dose, duration and timing of fluoride exposure and is believed to be related to elevated serum fluoride concentrations. Chalky “white spot” lesions may also form on developing teeth in children such as after treatment with antibiotics or fever.

5 Such lesions indicate areas of hypomineralization (i.e. too little mineralization) of the tooth enamel.

Depending on lesion severity, fluorosis has been managed clinically by restorative replacement or micro-abrasion of the outer enamel. These treatments are unsatisfactory because they involve restorations or removal of tooth tissue. What is
10 desired is a treatment that will mineralize the hypomineralized enamel to produce a natural appearance and structure.

Specific complexes of casein phosphopeptides and amorphous calcium phosphate (“CPP-ACP”, available commercially as Recaldent™) have been shown to remineralize enamel subsurface lesions *in vitro* and *in situ*.

15 WO 98/40406 in the name of The University of Melbourne (the contents of which are herein incorporated fully by reference) describes casein phosphopeptide-amorphous calcium phosphate complexes (CPP-ACP) and CPP-stabilized amorphous calcium fluoride phosphate complexes (CPP-ACFP), which have been produced at alkaline pH. Such complexes have been shown to prevent enamel demineralization and
20 promote remineralization of enamel subsurface lesions in animal and human *in situ* caries models. Improved casein phosphopeptide-amorphous calcium phosphate complexes (CPP-ACP) and CPP-stabilized amorphous calcium fluoride phosphate complexes (CPP-ACFP) have also been described in WO2006/056013 and WO2006/135982, including preferred complexes formed at a pH of 5 to 6.5.

25 The CPP which are active in forming the complexes do so whether or not they are part of a full-length casein protein. Examples of active (CPP) that can be isolated after tryptic digestion of full length casein have been specified in US Patent No. 5,015,628 and include peptides Bos α_{s1} -casein X-5P (f59-79), Bos β -casein X-4P (f1-25), Bos α_{s2} -casein X-4P (f46-70) and Bos α_{s2} -casein X-4P (f1-21).

While CPP-ACP and CPP-ACFP complexes are efficacious in remineralisation of hypomineralised enamel, the current methods of manufacture limit the amount of CPP-ACP or CPP-ACFP that can be used in liquid form due to the propensity of the complexes to cross-link to form a gel. The formation of a gel lowers the activity
5 (bioavailability) of the ions required for enamel subsurface lesion remineralisation. This is a significant limitation clinically as remineralisation is a slow process and can take several months at CPP-ACP or CPP-ACFP concentrations of 10% to effect noticeable remineralisation.

There is a need to provide improved or alternative treatments for
10 hypomineralized lesions.

Reference to any prior art in the specification is not an acknowledgment or suggestion that this prior art forms part of the common general knowledge in any jurisdiction or that this prior art could reasonably be expected to be understood, regarded as relevant, and/or combined with other pieces of prior art by a skilled person
15 in the art.

Summary of the invention

In one aspect, the present invention provides a method of mineralizing a dental surface or sub-surface comprising

contacting the dental surface or subsurface with stabilized amorphous calcium
20 phosphate (ACP) and/or amorphous calcium fluoride phosphate (ACFP), and simultaneously or subsequently,

heating the dental surface or subsurface to which the stabilized ACP and/or ACFP has been, or is being, applied to a temperature greater than 37°C.

In another aspect, the present invention provides a method of mineralizing a
25 dental surface or sub-surface comprising

contacting the dental surface or subsurface with a liquid composition comprising greater than 20% w/v stabilized amorphous calcium phosphate (ACP) and/or amorphous calcium fluoride phosphate (ACFP).

In another aspect, the present invention provides a method of mineralizing a dental surface or sub-surface comprising

contacting the dental surface or subsurface with a liquid composition comprising greater than 20% w/v stabilized amorphous calcium phosphate (ACP) and/or
5 amorphous calcium fluoride phosphate (ACFP), and simultaneously or subsequently,

heating the dental surface or subsurface to which the liquid composition comprising greater than 20% w/v stabilized ACP and/or ACFP has been, or is being, applied to a temperature greater than 37°C.

In a further aspect of the present invention there is provided a method for
10 remineralizing a dental lesion, the method comprising:

contacting the hypomineralised dental surface or subsurface with a liquid composition comprising at least 40% w/w of phosphopeptide (PP)-stabilized amorphous calcium phosphate (ACP) and/or amorphous calcium fluoride phosphate (ACFP) at a pH of greater than or equal to pH 5 but less than or equal to pH 9,

15 thereby remineralizing the dental lesion. Preferably, the liquid composition has a pH of greater than or equal to pH 6 but less than or equal to pH 8, for example greater than or equal to pH 7 but less than or equal to pH 8.

In any aspect of the invention, the method comprises heating the dental surface or subsurface to which the stabilized ACP and/or ACFP (for example, in a liquid
20 composition) has been, or is being, applied to a temperature greater than or equal to 40°C, greater than or equal to 45°C, greater than or equal to 50°C, greater than or equal to 55°C, greater than or equal to 60°C or greater than or equal to 65°C.

In any aspect of the invention, the method comprises heating the dental surface or subsurface to which the stabilized ACP and/or ACFP (for example, in a liquid
25 composition) has been, or is being, applied to a temperature greater than 37°C but equal to or less than 65°C, greater than 40°C but equal to or less than 65°C, greater than 45°C but equal to or less than 65°C, greater than 50°C but equal to or less than 65°C, greater than 55°C but equal to or less than 65°C, greater than 60°C but equal to or less than 65°C.

In any aspect of the present invention, the liquid composition comprising greater than 20% w/v stabilized amorphous calcium phosphate (ACP) and/or amorphous calcium fluoride phosphate (ACFP) comprises greater than or equal to 25% w/v, greater than or equal to 30% w/v, greater than or equal to 35% w/v, greater than or equal to 40% w/v, greater than or equal to 45% w/v, greater than or equal to 50% w/v, greater than or equal to 55% w/v, greater than or equal to 60% w/v, greater than or equal to 65% w/v stabilized ACP and/or ACFP, greater than or equal to 70% w/v stabilized ACP and/or ACFP, or greater than or equal to 75% w/v stabilized ACP and/or ACFP.

In any aspect of the present invention, the liquid composition comprising greater than 20% w/v stabilized amorphous calcium phosphate (ACP) and/or amorphous calcium fluoride phosphate (ACFP) comprises greater than 20% w/v stabilized ACP and/or ACFP but less than 80% w/v stabilized ACP and/or ACFP, greater than 25% w/v stabilized ACP and/or ACFP but less than 80% w/v stabilized ACP and/or ACFP, greater than 30% w/v stabilized ACP and/or ACFP but less than 80% w/v stabilized ACP and/or ACFP, greater than 35% w/v stabilized ACP and/or ACFP but less than 80% w/v stabilized ACP and/or ACFP, greater than 40% w/v stabilized ACP and/or ACFP but less than 80% w/v stabilized ACP and/or ACFP, greater than 45% w/v stabilized ACP and/or ACFP but less than 80% w/v stabilized ACP and/or ACFP, greater than 50% w/v stabilized ACP and/or ACFP but less than 80% w/v stabilized ACP and/or ACFP, greater than 55% w/v stabilized ACP and/or ACFP but less than 80% w/v stabilized ACP and/or ACFP, greater than 60% w/v stabilized ACP and/or ACFP but less than 80% w/v stabilized ACP and/or ACFP, greater than 65% w/v stabilized ACP and/or ACFP but less than 80% w/v stabilized ACP and/or ACFP, greater than 70% w/v stabilized ACP and/or ACFP but less than 80% w/v stabilized ACP and/or ACFP, or greater than 75% w/v stabilized ACP and/or ACFP but less than 80% w/v stabilized ACP and/or ACFP.

In any aspect of the present invention, the liquid composition comprises greater than 40% w/w phosphopeptide (PP)-stabilized ACP and/or ACFP, greater than 45% w/w, greater than 50% w/w stabilized ACP and/or ACFP, greater than 55% w/w stabilized ACP and/or ACFP, greater than 60% w/w stabilized ACP and/or ACFP, greater than about 65% w/w stabilized ACP and/or ACFP, greater than about 70% w/w

stabilized ACP and/or ACFP, or greater than about 75% w/w stabilized ACP and/or ACFP.

In any aspect of the present invention, the liquid composition comprises greater than 40% w/w phosphopeptide (PP)-stabilized ACP and/or ACFP, greater than 40% w/w stabilized ACP and/or ACFP but less than 80% w/w stabilized ACP and/or ACFP, greater than 45% w/w stabilized ACP and/or ACFP but less than 80% w/w stabilized ACP and/or ACFP, greater than 50% w/w stabilized ACP and/or ACFP but less than 80% w/w stabilized ACP and/or ACFP, greater than 55% w/w stabilized ACP and/or ACFP but less than 80% w/w stabilized ACP and/or ACFP, greater than 60% w/w stabilized ACP and/or ACFP but less than 80% w/w stabilized ACP and/or ACFP, greater than 65% w/w stabilized ACP and/or ACFP but less than 80% w/w stabilized ACP and/or ACFP, greater than 70% w/w stabilized ACP and/or ACFP but less than 80% w/w stabilized ACP and/or ACFP, or greater than 75% w/w stabilized ACP and/or ACFP but less than 80% w/w stabilized ACP and/or ACFP.

In any aspect, the liquid composition is degassed. Degassing may be by any method that forms a negative pressure above the liquid composition. Exemplary methods involve a vacuum pump or system, for example a venturi vacuum water system.

In any aspect of the present invention, the stabilized amorphous calcium phosphate (ACP) and/or amorphous calcium fluoride phosphate (ACFP) is phosphopeptide stabilized. Preferably, the phosphopeptide (as defined below) is a casein phosphopeptide.

In any aspect, the calcium ion content of the stabilised ACP or ACFP complex is greater than about 30 moles per mole of PP. Preferably, the calcium ion content is in the range of about 30 to 100 moles of calcium per mole of PP. More preferably, the calcium ion content is in the range of about 30 to about 50 moles of calcium per mole of PP.

In a preferred embodiment of each aspect of the invention, the phosphopeptide stabilized ACP or ACFP complex in the composition has tightly bound and loosely bound calcium, wherein the bound calcium in the complex is less than the tightly bound

calcium in an ACP or ACFP complex formed at a pH of 7.0. Optionally, the ACP or ACFP is predominantly in a basic form.

In any aspect, the stabilised ACP complex is a stannous-associated phosphopeptide (PP) ACP complex, and the stabilised ACFP complex is a stannous-associated phosphopeptide (PP) stabilized amorphous calcium fluoride phosphate (ACFP) complex.

In any aspect, the ACP and/or ACFP complex is in the form of a casein phosphopeptide stabilized ACP and/or ACFP complex.

Preferably, the phase of the ACP is primarily (i.e. >50%) a basic phase, wherein the ACP comprises predominantly the species Ca^{2+} , PO_4^{3-} and OH^- . The basic phase of ACP may have the general formula $[\text{Ca}_3(\text{PO}_4)_2]_x[\text{Ca}_2(\text{PO}_4)(\text{OH})]$ where $x \geq 1$. Preferably $x = 1-5$. More preferably, $x = 1$, i.e. the two components of the formula are present in equal proportions. Accordingly, in one embodiment, the basic phase of ACP has the formula $\text{Ca}_3(\text{PO}_4)_2\text{Ca}_2(\text{PO}_4)(\text{OH})$.

Preferably, the phase of the ACFP is a primarily (i.e. >50%) basic phase, wherein the ACFP comprises predominantly the species Ca^{2+} , PO_4^{3-} and F^- . The basic phase of ACFP may have the general formula $[\text{Ca}_3(\text{PO}_4)_2]_x[\text{Ca}_2(\text{PO}_4)\text{F}]_y$ where $x \geq 1$ when $y = 1$ or where $y \geq 1$ when $x = 1$. Preferably, $y = 1$ and $x = 1-3$. More preferably, $y = 1$ and $x = 1$, i.e. the two components of the formula are present in equal proportions. Accordingly, in one embodiment, the basic phase of ACFP has the formula $\text{Ca}_3(\text{PO}_4)_2\text{Ca}_2(\text{PO}_4)\text{F}$.

In one embodiment, the ACP complex consists essentially of phosphopeptides, calcium, phosphate and hydroxide ions and water. Preferably, the complex further includes stannous ions.

In one embodiment, the ACFP complex consists essentially of phosphopeptides, calcium, phosphate, fluoride and hydroxide ions and water. Preferably, the complex further includes stannous ions.

In one aspect, the present invention provides a method of treating fluorosis comprising

contacting a fluorotic lesion, preferably in dental enamel, with stabilized ACP and/or ACFP, and simultaneously or subsequently,

heating the fluorotic lesion to which the stabilized ACP and/or ACFP has been, or is being, applied to a temperature greater than 37°C.

5 In another aspect, the present invention provides a method of treating fluorosis comprising

contacting a fluorotic lesion, preferably in dental enamel, with a liquid composition comprising greater than 20% w/v stabilized ACP and/or ACFP.

10 In another aspect, the present invention provides a method of treating fluorosis comprising

contacting a fluorotic lesion, preferably in dental enamel, with a liquid composition comprising greater than 20% w/v stabilized ACP and/or ACFP, and simultaneously or subsequently,

15 heating the fluorotic lesion to which the liquid composition comprising greater than 20% w/v stabilized ACP and/or ACFP has been, or is being, applied to a temperature greater than 37°C.

In one aspect, the present invention provides a method of treating dental caries comprising

20 contacting a caries lesion with stabilized ACP and/or ACFP, and simultaneously or subsequently,

heating the caries lesion to which the stabilized ACP and/or ACFP has been, or is being, applied to a temperature greater than 37°C.

In another aspect, the present invention provides a method of treating dental caries comprising

25 contacting a caries lesion with a liquid composition comprising greater than 20% w/v stabilized ACP and/or ACFP.

In another aspect, the present invention provides a method of treating dental caries comprising

contacting a caries lesion with a liquid composition comprising greater than 20% w/v stabilized ACP and/or ACFP, and simultaneously or subsequently,

5 heating the caries lesion to which the liquid composition comprising greater than 20% w/v stabilized ACP and/or ACFP has been, or is being, applied to a temperature greater than 37°C.

In any aspect of the present invention, a method, use or composition of the invention may be used for treating dental erosion. In this aspect, a lesion in tooth
10 enamel caused by erosion is contacted with stabilized ACP and/or ACFP or liquid composition comprising greater than 20% w/v stabilized ACP and/or ACFP.

In any aspect of the present invention, a method, use or composition of the invention may be used for reducing white spot lesions. In this aspect, a white spot lesion, preferably on tooth enamel, is contacted with stabilized ACP and/or ACFP or
15 liquid composition comprising greater than 20% w/v stabilized ACP and/or ACFP.

In any aspect of the present invention, a method, use or composition of the invention may be used for remineralizing a lesion in tooth enamel or dentine. In this aspect, the lesion, preferably on tooth enamel, is contacted with stabilized ACP and/or ACFP or liquid composition comprising greater than 20% w/v stabilized ACP and/or
20 ACFP.

In any aspect of the present invention, the liquid composition comprises equal to, or greater than, about 40% w/v stabilized ACP.

In any aspect of the present invention, the liquid composition comprises equal to, or greater than, about 50% w/v stabilized ACFP.

25 In any aspect of the present invention, the dental surface or subsurface, or lesion (e.g. fluorotic, caries, white spot or caused by erosion), may be heated to a temperature equal to or greater than about 45°C. Preferably, the temperature does not exceed 65°C.

In any aspect of the invention, the pH of the liquid composition is less than or equal to 6. Preferably, the pH is equal to or less than 5.5. Alternatively, the pH of the liquid composition is greater than or equal to pH 5 but less than or equal to pH 9, preferably, greater than or equal to pH 6 but less than or equal to pH 8, most preferably
5 greater than or equal to pH 7 but less than or equal to pH 8.

In one embodiment, when the %w/v of stabilized ACP and/or ACFP is greater than 20%w/v but less than 40%w/v the pH of the liquid composition is between about 5 to about 8, preferably about 5 to about 7, preferably between 5 and 7. In another embodiment, when the %w/v of stabilized ACP and/or ACFP is greater than 40%w/v the
10 pH of the liquid composition is less than or equal to 6. Preferably, the pH is equal to or less than 5.5.

In any aspect of the invention described herein, stabilized ACP or ACFP, liquid composition comprising stabilized ACP or ACFP, and/or heat is applied to the mouth, tooth or lesion by a dental health care professional.

15 In any aspect of the present invention, the dental surface or subsurface, or lesion (e.g. fluorotic, caries, white spot or caused by erosion), may be heated for about 1 to 60 minutes, or for about 1 to 30 minutes.

Preferably the stabilized ACP and/or ACFP or liquid composition comprising stabilized ACP and/or ACFP are contacted with the dental surface for a period of about
20 1 minute to 2 hours, or 5 minutes to 60 minutes or about 10 minutes.

In any aspect, the dental surface or subsurface, or lesion, is in need of such treatment. Therefore the invention includes in addition to the steps of any method described herein a step of identifying a subject suffering fluorosis, dental caries, dentinal hypersensitivity or dental calculus, a white spot lesion; a fluorotic lesion; a caries lesion;
25 or a lesion caused by tooth erosion.

In another aspect, the present invention provides a liquid composition comprising greater than 20% w/v stabilized ACP and/or ACFP. Preferably, the liquid composition comprising greater than 20% w/v stabilized ACP and/or ACFP comprises greater than or equal to 25% w/v, greater than or equal to 30% w/v, greater than or equal to 35%
30 w/v, greater than or equal to 40% w/v, greater than or equal to 45% w/v, greater than or

equal to 50% w/v stabilized ACP and/or ACFP, greater than or equal to 55% w/v stabilized ACP and/or ACFP, greater than or equal to 60% w/v stabilized ACP and/or ACFP, greater than or equal to 65% w/v stabilized ACP and/or ACFP, greater than or equal to 70% w/v stabilized ACP and/or ACFP, or greater than or equal to 75% w/v stabilized ACP and/or ACFP.

In this aspect of the present invention, the liquid composition may comprise greater than 20% w/v stabilized ACP and/or ACFP but less than 80% w/v stabilized ACP and/or ACFP, greater than 25% w/v stabilized ACP and/or ACFP but less than 80% w/v stabilized ACP and/or ACFP, greater than 30% w/v stabilized ACP and/or ACFP but less than 80% w/v stabilized ACP and/or ACFP, greater than 35% w/v stabilized ACP and/or ACFP but less than 80% w/v stabilized ACP and/or ACFP, greater than 40% w/v stabilized ACP and/or ACFP but less than 80% w/v stabilized ACP and/or ACFP, greater than 45% w/v stabilized ACP and/or ACFP but less than 80% w/v stabilized ACP and/or ACFP, greater than 50% w/v stabilized ACP and/or ACFP but less than 80% w/v stabilized ACP and/or ACFP, greater than 55% w/v stabilized ACP and/or ACFP but less than 80% w/v stabilized ACP and/or ACFP, greater than 60% w/v stabilized ACP and/or ACFP but less than 80% w/v stabilized ACP and/or ACFP, greater than 65% w/v stabilized ACP and/or ACFP but less than 80% w/v stabilized ACP and/or ACFP, greater than 70% w/v stabilized ACP and/or ACFP but less than 80% w/v stabilized ACP and/or ACFP, or greater than 75% w/v stabilized ACP and/or ACFP but less than 80% w/v stabilized ACP and/or ACFP.

In this aspect, the liquid composition comprises greater than 40% w/w phosphopeptide (PP)-stabilized ACP and/or ACFP, greater than 45% w/w, greater than 50% w/w stabilized ACP and/or ACFP, greater than 55% w/w stabilized ACP and/or ACFP, greater than 60% w/w stabilized ACP and/or ACFP, greater than about 65% w/w stabilized ACP and/or ACFP, greater than about 70% w/w stabilized ACP and/or ACFP, or greater than about 75% w/w stabilized ACP and/or ACFP.

In this aspect, the liquid composition comprises greater than 40% w/w phosphopeptide (PP)-stabilized ACP and/or ACFP, greater than 40% w/w stabilized ACP and/or ACFP but less than 80% w/w stabilized ACP and/or ACFP, greater than 45% w/w stabilized ACP and/or ACFP but less than 80% w/w stabilized ACP and/or

ACFP, greater than 50% w/w stabilized ACP and/or ACFP but less than 80% w/w stabilized ACP and/or ACFP, greater than 55% w/w stabilized ACP and/or ACFP but less than 80% w/w stabilized ACP and/or ACFP, greater than 60% w/w stabilized ACP and/or ACFP but less than 80% w/w stabilized ACP and/or ACFP, greater than 65% w/w stabilized ACP and/or ACFP but less than 80% w/w stabilized ACP and/or ACFP, greater than 70% w/w stabilized ACP and/or ACFP but less than 80% w/w stabilized ACP and/or ACFP, or greater than 75% w/w stabilized ACP and/or ACFP but less than 80% w/w stabilized ACP and/or ACFP.

In any aspect as described herein, the liquid composition may further comprise fluoride ions, preferably free fluoride ions. The fluoride ions may be present in the liquid composition at a concentration in the range of about 200 ppm to 50,000 ppm. In a preferred embodiment, the fluoride ions are at a concentration in the range of about 2,600 ppm to about 10,000 ppm. In a further preferred embodiment, the fluoride ions in the liquid composition are at a concentration of about 8,200 ppm, or about 6,500 ppm.

The fluoride ions may be present in the liquid composition at any ppm described herein, particularly the Examples. In any embodiment, the fluoride ions are at a concentration of about 2,600 ppm, 3,900 ppm, 5,200 ppm, 6,500 ppm or 7,800 ppm. Typically, the fluoride ions are at a concentration of about 2600ppm for 20% w/v stabilized-ACP or ACFP, about 3,260 ppm for 25% w/v stabilized-ACP or ACFP, about 3,900 ppm for 30% w/v stabilized-ACP or ACFP, about 4,890 ppm for 38% stabilized-ACP or ACFP, 5,200 ppm for 40% w/v stabilized-ACP or ACFP, 6,500 ppm for 50% w/v stabilized-ACP or ACFP, about 8,200 ppm for 63% stabilized-ACP or ACFP and about 9,900 ppm for 75% stabilized-ACP or ACFP. In another embodiment, the fluoride ions are at a concentration of about 5,200 ppm for 40%w/w CPP-ACP or about 7,800 ppm for 60% w/w CPP-ACP. Preferably, the stabilized-ACP and/or ACFP is phosphopeptide stabilized. Preferably, the phosphopeptide is a casein phosphopeptide.

Any composition described herein can be used in any one of the methods described herein. The composition is a physiologically acceptable composition as described herein.

In another aspect, the present invention provides a liquid composition comprising greater than 20% w/v stabilized ACP and/or ACFP for use in:

- mineralizing a dental surface or subsurface, or any lesion as described herein; or
- treating or preventing one or more of each of dental caries, tooth decay, dental erosion, white spot lesions and fluorosis.

5 In a further aspect there is provided the use of a liquid composition comprising greater than 20% w/v stabilized ACP and/or ACFP in the manufacture of a composition or medicament for the mineralizing a dental surface or subsurface, or treatment and/or prevention of one or more of dental caries, tooth decay, dental erosion and fluorosis.

10 In a further aspect, there is provided a use of a phosphopeptide (PP)-stabilized amorphous calcium phosphate (ACP) and/or amorphous calcium fluoride phosphate (ACFP) in the manufacture of a product comprising or consisting of a liquid composition for remineralizing a dental surface or subsurface,

the liquid composition comprising at least 40% w/w of said phosphopeptide (PP)-stabilized amorphous calcium phosphate (ACP) and/or amorphous calcium fluoride phosphate (ACFP) at a pH of greater than or equal to pH 5 but less than or equal to pH 9, In one embodiment, the product is a cosmetic product.

The invention also relates to a kit for the treatment or prevention of one or more of dental caries, fluorosis and dental erosion, or mineralizing a dental surface or subsurface or lesion as described herein comprising (a) a liquid composition comprising greater than 20% w/v stabilized ACP and/or ACFP, and (b) a heat source. Desirably, the kit further includes instructions for their use in any method or use described herein. The instructions may describe the use of the kit to treat or prevent one or more of each of dental caries, tooth decay, dental erosion and fluorosis. In one embodiment, the liquid composition is present in suitable amounts for treatment of a patient. Preferably, the stabilized ACP and/or ACFP is phosphopeptide (PP)-stabilized. Preferably, the phosphopeptide (as defined below) is a casein phosphopeptide. Preferably, the ACP or ACFP is in the form of a casein phosphopeptide stabilized ACP or ACFP complex.

The composition or kit of the invention may further include a source of fluoride ions. The fluoride ions may be from any suitable source. A source of fluoride ions may include free fluoride ions or fluoride salts. Examples of sources of fluoride ions include,

but are not limited to the following: sodium fluoride, sodium monofluorophosphate, stannous fluoride, sodium silicofluoride, silver fluoride, amine fluoride or any metal ion fluoride salt. A source of fluoride ions may be a hypofluorite. These sources of fluoride ions may be provided in solution (typically an aqueous solution), or a suspension.

5 In another aspect, the present invention provides a method or process for preparing a liquid composition comprising greater than 20% w/v stabilized ACP and/or ACFP, the method or process comprising or consisting of:

 mixing a solvent and a powder comprising or consisting of stabilized-ACP and/or ACFP, and

10 maintaining the pH below 7. Preferably, the pH is maintained at, or below, 6, preferably the pH is maintained at, or below, 5.5.

 In another aspect, the present invention provides a method or process for preparing a liquid composition comprising greater than 20% w/v stabilized ACP and/or ACFP, the method or process comprising or consisting of:

15 mixing a solvent and a powder comprising or consisting of stabilized ACP and/or ACFP, and

 lowering the pH below 7. Preferably, the pH is lowered to, or below, 6, preferably 5.5. Typically, the pH is maintained below, 7, more preferably the pH is maintained at, or below, 6, even more preferably 5.5.

20 In another aspect, the present invention provides a method or process for preparing a liquid composition comprising greater than 20% w/v stabilized ACP and/or ACFP, the method or process comprising or consisting of:

 mixing a fluoride containing solution and a powder comprising or consisting of stabilized ACP and/or ACFP, and

25 adjusting the pH to between 6.5 and 8. Preferably, the pH is adjusted to about pH 7.8. Preferably, the pH is adjusted with HCl.

In this aspect, the method further comprises the step of mixing the solution for at least about 10 minutes, at least about 20 minutes, or at least about 30 minutes after the pH is adjusted.

5 In this aspect, the method further comprises the step of degassing the liquid composition.

In any aspect, the step of mixing a solvent and a powder comprising or consisting of PP stabilized ACP and/or ACFP, comprises adding the solvent to the powder. Alternatively, the step comprises adding the powder to the solvent.

10 In any method or process for preparing a liquid composition as described herein, the method or process further comprises the step of degassing the liquid composition. Degassing may be by any method that forms a negative pressure above the liquid composition, including methods described herein.

15 In any method or process for preparing a liquid composition as described herein, the method or process further comprises a step of mixing the liquid composition with a solution comprising fluoride ions.

In another aspect, the present invention provides a method or process for preparing a liquid composition comprising greater than 20% w/v stabilized ACP and/or ACFP, the method or process comprising or consisting of the steps as described in Example 2 or 4 herein.

20 In any aspect, the present invention provides a method or process that further comprises the following steps to prepare a powder comprising or consisting of stabilized-ACP and/or ACFP:

25 admixing one or more solutions comprising phosphopeptides, calcium ions, phosphate ions, hydroxide ions and optionally fluoride ions, while maintaining the pH at about 7.0 or above, preferably about 9, to form a solution comprising stabilized-ACP and/or ACFP, and

drying the solution comprising stabilized-ACP and/or ACFP,

thereby forming a powder comprising or consisting of stabilized-ACP and/or ACFP. Preferably drying is spray drying or freeze drying.

In one embodiment, the method or process further comprises the steps;

5 filtering the solution comprising stabilized-ACP and/or ACFP, prior to drying, to form a retentate, wherein the retentate is subsequently dried to form powder comprising or consisting of stabilized-ACP and/or ACFP.

In another aspect, the present invention provides a method or process for preparing a liquid composition comprising at least 40% w/w PP stabilized ACP and/or ACFP, the method or process comprising or consisting of:

10 mixing a solvent and a powder comprising or consisting of PP stabilized ACP and/or ACFP, and

lowering the pH below 9, preferably 8. Preferably the solvent comprises fluoride.

In this aspect, the method further comprises a step of stirring the liquid composition after the pH is lowered. Preferably, the stirring occurs for at least 5, 10, 15,
15 20, 25 or 30 minutes.

In this aspect, the liquid composition is degassed to remove trapped air bubbles, preferably by placing the solution under vacuum, most preferably for 24 hours.

In another aspect, the present invention provides a method or process for preparing a liquid composition comprising at least 40% w/w, preferably 60%w/w, PP
20 stabilized ACP and/or ACFP, the method or process comprising or consisting of the steps as described in Example 4 herein.

In any method or process for preparing a liquid composition comprising greater than 20% w/v or greater than 40%w/w stabilized ACP and/or ACFP, the solvent is water.

25 In any method or process for preparing a liquid composition comprising greater than 20% w/v stabilized ACP and/or ACFP, the pH is lowered or maintained using 1-10M HCl, or 11M HCl.

In any aspect, the method or process for preparing a liquid composition comprising greater than 20% w/v stabilized ACP and/or ACFP, may be for preparing a liquid composition comprising equal to or greater than 25% w/v, 30% w/v, 35% w/v, 40% w/v, 45% w/v, 50% w/v, 55% w/v, 60% w/v, 65% w/v, 70% w/v, 75% w/v or 80% w/v stabilized ACP and/or ACFP.

In any method or process for preparing a liquid composition comprising greater than 20% w/v stabilized ACP and/or ACFP, the stabilized ACP or ACFP is CPP-ACP or CPP-ACFP as described herein.

In any method or process for preparing a liquid composition comprising greater than 20% w/v stabilized ACP and/or ACFP, the liquid composition is for use in any method of dental treatment, preferably those described herein (e.g. mineralizing a dental surface or sub-surface).

In another aspect, the present invention provides a liquid composition comprising greater than 20% w/v stabilized ACP and/or ACFP prepared by a method or process described herein.

Further aspects of the present invention and further embodiments of the aspects described in the preceding paragraphs will become apparent from the following description, given by way of example and with reference to the accompanying drawings.

Brief description of the drawings

Figure 1: Effect of Temperature on Remineralisation of Enamel Subsurface Lesions *in vitro*.

Figure 2: Remineralisation by high concentrations of CPP-ACP in the presence of fluoride.

Figure 3: Remineralisation by high concentrations of CPP-ACP.

Detailed description of the embodiments

It will be understood that the invention disclosed and defined in this specification extends to all alternative combinations of two or more of the individual features

mentioned or evident from the text or drawings. All of these different combinations constitute various alternative aspects of the invention.

Further aspects of the present invention and further embodiments of the aspects described in the preceding paragraphs will become apparent from the following
5 description, given by way of example and with reference to the accompanying drawings.

Reference will now be made in detail to certain embodiments of the invention. While the invention will be described in conjunction with the embodiments, it will be understood that the intention is not to limit the invention to those embodiments. On the contrary, the invention is intended to cover all alternatives, modifications, and
10 equivalents, which may be included within the scope of the present invention as defined by the claims.

One skilled in the art will recognize many methods and materials similar or equivalent to those described herein, which could be used in the practice of the present invention. The present invention is in no way limited to the methods and materials
15 described.

All of the patents and publications referred to herein are incorporated by reference in their entirety.

For purposes of interpreting this specification, terms used in the singular will also include the plural and vice versa.

20 As used herein, except where the context requires otherwise, the term "comprise" and variations of the term, such as "comprising", "comprises" and "comprised", are not intended to exclude further additives, components, integers or steps. As used herein, except where the context requires otherwise, "comprise" and "include" can be used interchangeably.

25 An aspect of an invention described herein is based on the surprising finding that it is possible to achieve a composition of a high concentration of stabilized ACP and/or ACFP and the composition still maintain a liquid state (i.e. does not form a gel). Prior to the present invention it was thought that high concentrations of phosphopeptide-stabilized ACP and/or ACFP would result in the composition forming a gel or paste, and
30 all liquid compositions described to date had relatively low concentrations of phosphopeptide-stabilized ACP and/or ACFP. The unexpected property of a high

concentration composition of phosphopeptide-stabilized ACP and/or ACFP maintaining a liquid state prior to application to a dental surface or subsurface allows more rapid penetrance into a hypomineralized site. Without being bound by any theory or mode of action, it is believed that a higher concentration of stabilized ACP and/or ACFP can be achieved in the lesion which results in more rapid remineralization and to a greater extent. This provides the advantage that the high concentration liquid composition can be applied by a dental professional directly onto a lesion allowing more extensive remineralization to occur compared to in-home application of low concentration compositions, such as pastes or mousses.

Further, a separate aspect of an invention described herein is based on the surprising finding that heating the dental surface or subsurface at the same time as, or subsequent to, the application of stabilized ACP and/or ACFP increases the extent of mineralization, even up to relatively high temperatures.

Finally, a combination of both high concentration liquid compositions with heating of the dental surface to which the stabilized ACP and/or ACFP has been or is being applied, provides for extensive and rapid remineralization.

Any heat source may be used in a method or use of the invention to heat the dental surface or subsurface. Heat sources that emit light or radiation and are suitable for use in dental applications are known in the art. Specific examples include dental curing lights, for example a 10W high-power blue light LED such as X-Cure by Guilin Woodpecker Medical Instrument Co. Ltd.

As used herein % w/v may be taken to be equivalent to g/100ml.

As used herein, “stabilized-ACP or ACFP” and “stabilized-ACP or ACFP complex” are used interchangeably.

A stabilized-ACP or ACFP complex as described in the current specification may be the “closed” complexes are shown in Figure 2 of Cross *et al.*, 2007.

A stabilized-ACP or ACFP as referred to herein include a stabilized-ACP or ACFP as described in WO2006/056013 (PCT/AU2005/001781) the contents of which are incorporated by reference.

In a preferred embodiment, the phosphopeptide stabilised amorphous calcium phosphate (ACP) or amorphous calcium fluoride phosphate (ACFP) complex has tightly bound and loosely bound calcium, wherein the bound calcium in the complex is less than the tightly bound calcium in an ACP or ACFP complex formed at a pH of 7.0.

5 Optionally, the ACP or ACFP is predominantly in a basic form.

A stabilized-ACP or ACFP complex as referred to herein include a stabilized-ACP or ACFP complex formed at a pH of below 7.0. Preferably the complex is formed at a pH in the range of about 5.0 up to but below 7.0. More preferably the complex is formed at a pH range of about 5.0 to about 6.0. In a preferred embodiment, the complex is
10 formed at a pH of about 5.5. Preferably, the ACP or ACFP in the complex is predominantly in a basic form.

A stabilized-ACP may be produced by a method comprising the steps of:

- (i) obtaining a solution comprising at least one phosphopeptide and;
- (ii) admixing solutions comprising calcium ions, phosphate ions and hydroxide
15 ions, while maintaining the pH at about 5.5 to 9.

In one embodiment, the pH is maintained at about 7.0 or below.

A stabilised ACFP may be produced by a method comprising the steps of:

- (i) obtaining a solution comprising at least one phosphopeptide and;
- (ii) admixing solutions comprising calcium ions, phosphate ions, hydroxide
20 ions and fluoride ions, while maintaining the pH at about 5.5 to 9.

In one embodiment, the pH is maintained at about 7.0 or below.

A phosphopeptide stabilised amorphous calcium phosphate (ACP) or amorphous calcium fluoride phosphate (ACFP) complex may also include wherein the ACP in the complex has tightly bound and loosely calcium, wherein the tightly bound calcium in the
25 complex is less than the tightly bound calcium in an ACP or ACFP complex formed at a pH of 7.0 and the ACP or ACFP is predominantly in a basic form, obtainable or obtained by a method comprising:

- a) admixing a first solution comprising calcium ions, a second solution comprising phosphate ions, and optionally a third solution comprising fluoride ions, to a solution comprising phosphopeptides and a solvent with a pH of from about 5 up to but below 7; and
- 5 b) maintaining the pH of the solution at about 5.0 up to but below 7.0 during the admixing by adding hydroxide ions.

“Tightly” and “loosely” bound calcium and phosphate in ACP or ACFP can be determined using analytical ultrafiltration. Briefly, the solution of phosphopeptide, calcium, phosphate and optionally fluoride admixed while maintaining the pH at about 10 7.0 or below can be first filtered through a 0.1 micron filter to remove free calcium and phosphate that is not associated with the complexes. This free calcium and phosphate is present in the filtrate and discarded. Any free calcium or phosphate that is not associated in any way with the complexes would not be bioavailable, i.e. delivered by the phosphopeptide to the tooth. The retentate from the 0.1 micron filtration can be 15 further analyzed by centrifugation through a 3000 mw cut-off filter at 1,000 g for 15 min. The resulting filtrate contains calcium and phosphate that is loosely bound or associated with the complexes. At this centrifugal force calcium and phosphate that is not tightly bound to the complexes are released and move to into the filtrate. The Ca and Pi that is tightly bound in the complexes is retained in the retentate. The amount of tightly bound 20 Ca and Pi in the retentate can then be determined by subtracting the amount of Ca and Pi in the filtrate from the total amount of Ca and Pi in the retentate of the 0.1 micron filtration.

A stabilized-ACP or ACFP complex as referred to herein include a stabilized-ACP or ACFP complex as described in WO2006/135982 (PCT/AU2006/000885) the contents 25 of which are incorporated by reference.

A “superloaded” phosphopeptide or phosphoprotein (PP) stabilized-amorphous calcium phosphate (ACP) or amorphous calcium fluoride phosphate (ACFP) complex. The complex may be formed at any pH (e.g. 3-10). Preferably the phosphopeptide includes the sequence -A-B-C-, where A is a phosphoamino acid, preferably 30 phosphoserine, B is any amino acid including a phosphoamino acid and C is glutamic acid, aspartic acid or a phosphoamino acid. The phosphoamino acid may be

phosphoserine. The PP is superloaded with calcium and phosphate ions. The calcium ions may be in the range 30-1000 mole Ca per mole of PP, or in the range of 30-100 or 30-50 mole Ca per mole of PP. In another embodiment, the mole Ca per mole of PP is at least 25, 30, 35, 40, 45 or 50.

5 The phosphopeptide or phosphoprotein (PP) stabilized amorphous calcium phosphate or amorphous calcium fluoride phosphate complex may have a calcium ion content greater than about 30 moles of calcium per mole of PP. In a preferred embodiment, the calcium ion content is in the range of about 30 to 100 moles of calcium per mole of PP. More preferably, the calcium ion content is in the range of about 30 to
10 about 50 moles of calcium per mole of PP.

The phosphopeptide or phosphoprotein (PP) stabilized-amorphous calcium phosphate (ACP) or amorphous calcium fluoride phosphate (ACFP) complex may be produced by a method comprising the steps of:

- (i) obtaining solutions comprising calcium, inorganic phosphate and fluoride
15 (optional); and
- (ii) admixing (i) with a solution comprising PP-ACP.

In a preferred embodiment, the PP is casein phosphopeptide (CPP).

The PP stabilized ACP and/or ACFP complex may further include at least an equal amount by weight of calcium phosphate. Preferably the calcium phosphate is
20 CaHPO_4 . Preferably, the calcium phosphate (e.g. CaHPO_4) is dry blended with the PP stabilized ACP and/or ACFP complex. In a preferred embodiment, the PP-ACP and/or PP-ACFP complex: calcium phosphate ratio is about 1:1-50, more preferably about 1: 1-25, more preferably about 1:5-15. In one embodiment, the PP-ACP and/or PP-ACFP complex: calcium phosphate ratio is about 1:10.

25 The oral care formulation that includes a phosphopeptide or phosphoprotein (PP) stabilized amorphous calcium phosphate (ACP) and/or amorphous calcium fluoride phosphate (ACFP) complex having a calcium ion content greater than about 30 moles of calcium per mole of PP when used in the oral cavity may be produced by a method including the steps of:

- (i) obtaining a powder including a PP-ACP and/or PP-ACFP complex;
- (ii) dry blending with an effective amount of calcium phosphate; and
- (iii) formulating the dry blended PP-ACP and/or PP-ACFP and calcium phosphate mixture into an oral care formulation.

5 Preferably, the form of calcium phosphate for dry blending is any soluble calcium phosphate including, but not limited to, CaHPO_4 , Ca_2HPO_4 and calcium lactate.

A composition as described herein may further include free fluoride ions. The fluoride ions may be from any suitable source. A source of fluoride ions may include free fluoride ions or fluoride salts. Examples of sources of fluoride ions include, but are
10 not limited to the following: sodium fluoride, sodium monofluorophosphate, stannous fluoride, sodium silicofluoride and amine fluoride. These may be provided in solution (typically an aqueous solution), or a suspension.

The fluoride ions are preferably present in the composition in an amount greater than 1ppm. More preferably, the amount is more than 3 ppm. In another embodiment,
15 it is preferably more than 10 ppm. In typical embodiments described below, the amount may be several hundred or thousand ppm. Typically, the free fluoride ions are in the range of 1000 ppm to 50,000 ppm F. The ppm F may be any amount or concentration described herein. The fluoride content is typically measured as a ppm in oral compositions in the manner commonly used in the art. Where the fluoride is provided
20 from a source with the stabilized ACP, the ppm refers to the concentration of the fluoride in that source, typically a solution or suspension of bioavailable fluoride.

A stannous-associated ACP or ACFP complex as referred to herein include any described in PCT/AU2014/050447, the entire contents of which are incorporated by reference in its entirety.

25 A composition as described herein for use in a method of use of the invention may include a stannous-associated ACP or ACFP complex. The composition may include 2% CPP-ACP and 290 ppm fluoride with 220 ppm fluoride as stannous fluoride and 70 ppm as sodium fluoride.

“Phosphopeptide” in the context of the description of this invention means an amino acid sequence in which at least one amino acid is phosphorylated. Preferably, the phosphopeptide includes one or more of the amino acid sequence -A-B-C-, where A is a phosphoamino residue, B is any amino acyl residue including a phosphoamino residue and C is selected from a glutamyl, aspartyl or phosphoamino residue. Any of the phosphoamino residues may independently be a phosphoserine residue. B is desirably a residue the side-chain of which is neither relatively large nor hydrophobic. It may be Gly, Ala, Val, Met, Leu, Ile, Ser, Thr, Cys, Asp, Glu, Asn, Gln or Lys.

In another embodiment, at least two of the phosphoamino acids in the sequence are preferably contiguous. Preferably the phosphopeptide includes the sequence A-B-C-D-E, where A, B, C, D and E are independently phosphoserine, phosphothreonine, phosphotyrosine, phosphohistidine, glutamic acid or aspartic acid, and at least two, preferably three, of the A, B, C, D and E are a phosphoamino acid. In a preferred embodiment, the phosphoamino acid residues are phosphoserine, most preferably three contiguous phosphoserine residues. It is also preferred that D and E are independently glutamic or aspartic acid.

In one embodiment, the ACP or ACFP is stabilized by a casein phosphopeptide (CPP), which is in the form of intact casein or fragment of the casein, and the complex formed preferably has the formula $[\text{CPP}(\text{ACP})_8]_n$ or $[(\text{CPP})(\text{ACFP})_8]_n$ where n is equal to or greater than 1, for example 6. The complex formed may be a colloidal complex, where the core particles aggregate to form large (e.g. 100 nm) colloidal particles suspended in water. Thus, the PP can be a casein protein or a phosphopeptide.

The PP may be from any source; it may be present in the context of a larger polypeptide, including a full length casein polypeptide, or it may be isolated by tryptic or other enzymatic or chemical digestion of casein, or other phosphoamino acid rich proteins such as phosphitin, or by chemical or recombinant synthesis, provided that it comprises the sequence -A-B-C- or A-B-C-D-E as described above. The sequence flanking this core sequence may be any sequence. However, those flanking sequences in $\alpha_{s1}(59-79)$, $\beta(1-25)$, $\alpha_{s2}(46-70)$ and $\alpha_{s2}(1-21)$ are preferred. The flanking sequences may optionally be modified by deletion, addition or conservative substitution of one or

more residues. The amino acid composition and sequence of the flanking region are not critical.

Examples of conservative substitutions are shown in Table A below.

TABLE A

Original Residue	Exemplary Conservative Substitution	Preferred Conservative Substitution
Ala	Val, Leu, Ile	Val
Asn	Gln Lys His Phe	Gln
Gln	Asn	Asn
Gly	Pro	Pro
Ile	Leu, Val, Met, Ala, Phe	Leu
Leu	Ile, Val, Met, Ala, Phe	Ile
Lys	Arg, Gln, Asn	Arg
Phe	Leu, Val, Ile, Ala	Leu
Pro	Gly	Gly
Ser	Thr	Thr
Val	Ile, Leu, Met, Phe, Ala	Leu
Asp	Glu	Glu
Thr	Ser	Ser
Trp	Tyr	Tyr
Tyr	Trp Phe Thr Ser	Phe

The flanking sequences may also include non-naturally occurring amino acid residues. Commonly encountered amino acids which are not encoded by the genetic code, include:

- 2-amino adipic acid (Aad) for Glu and Asp;
- 5 2-aminopimelic acid (Apm) for Glu and Asp;
- 2-aminobutyric (Abu) acid for Met, Leu, and other aliphatic amino acids;
- 2-aminoheptanoic acid (Ahe) for Met, Leu and other aliphatic amino acids;
- 2-aminoisobutyric acid (Aib) for Gly;
- cyclohexylalanine (Cha) for Val, and Leu and Ile;
- 10 homoarginine (Har) for Arg and Lys;
- 2, 3-diaminopropionic acid (Dpr) for Lys, Arg and His;
- N-ethylglycine (EtGly) for Gly, Pro, and Ala;
- N-ethylasparagine (EtAsn) for Asn, and Gln;
- Hydroxylysine (Hyl) for Lys;
- 15 allohydroxylysine (AHyl) for Lys;
- 3-(and 4) hydroxyproline (3Hyp, 4Hyp) for Pro, Ser, and Thr;
- alloisoleucine (Alle) for Ile, Leu, and Val;
- p-amidinophenylalanine for Ala;
- N-methylglycine (MeGly, sarcosine) for Gly, Pro, Ala.
- 20 N-methylisoleucine (Melle) for Ile;
- Norvaline (Nva) for Met and other aliphatic amino acids;
- Norleucine (Nle) for Met and other aliphatic amino acids;

Ornithine (Orn) for Lys, Arg and His;

Citrulline (Cit) and methionine sulfoxide (MSO) for Thr, Asn and Gln;

N-methylphenylalanine (MePhe), trimethylphenylalanine, halo (F, Cl, Br and I) phenylalanine, triflourylphenylalanine, for Phe.

- 5 In one embodiment, the PP is one or more phosphopeptides selected from the group consisting of $\alpha_{s1}(59-79)$ [1], $\beta(1-25)$ [2], $\alpha_{s2}(46-70)$ [3] and $\alpha_{s2}(1-21)$ [4]:

[1] Gln⁵⁹-Met-Glu-Ala-Glu-Ser(P)-Ile-Ser(P)-Ser(P)-Ser(P)-Glu-Glu-Ile-Val-Pro-Asn-Ser(P)-Val-Glu-Gln-Lys⁷⁹ (SEQ ID NO: 1) $\alpha_{s1}(59-79)$

[2] Arg¹-Glu-Leu-Glu-Glu-Leu-Asn-Val-Pro-Gly-Glu-Ile-Val-Glu-Ser(P)-Leu-Ser(P)-Ser(P)-Ser(P)-Glu-Glu-Ser-Ile-Thr-Arg²⁵ (SEQ ID NO: 2) $\beta(1-25)$

10

[3] Asn⁴⁶-Ala-Asn-Glu-Glu-Glu-Tyr-Ser-Ile-Gly-Ser(P)-Ser(P)-Ser(P)-Glu-Glu-Ser(P)-Ala-Glu-Val-Ala-Thr-Glu-Glu-Val-Lys⁷⁰ (SEQ ID NO: 3) $\alpha_{s2}(46-70)$

[4] Lys¹-Asn-Thr-Met-Glu-His-Val-Ser(P)-Ser(P)-Ser(P)-Glu-Glu-Ser-Ile-Ile-Ser(P)-Gln-Glu-Thr-Tyr-Lys²¹ (SEQ ID NO: 4) $\alpha_{s2}(1-21)$.

- 15 In certain preferred forms of the invention a liquid composition may a mouthwash, rinse or spray. In such a preparation the vehicle is typically a water-alcohol mixture desirably including a humectant as described below. Generally, the weight ratio of water to alcohol is in the range of from about 1:1 to about 20:1. The total amount of water-alcohol mixture in this type of preparation is typically in the range of from about 70 to
- 20 about 99.9% by weight of the preparation. The alcohol is typically ethanol or isopropanol. Ethanol is preferred.

It will be understood that, as is conventional, the oral preparations will usually be sold or otherwise distributed in suitable labelled packages. Thus, a jar of mouth rinse will have a label describing it, in substance, as a mouth rinse or mouthwash and having

25 directions for its use.

Organic surface-active agents may be used in the compositions of the present invention to achieve increased prophylactic action, assist in achieving thorough and

complete dispersion of the active agent throughout the oral cavity, and render the instant compositions more cosmetically acceptable. The organic surface-active material is preferably anionic, non-ionic or ampholytic in nature and preferably does not interact with the active agent. It is preferred to employ as the surface-active agent a deter-
5 sive material which imparts to the composition deter- sive and foaming properties. Suitable examples of anionic surfactants are water-soluble salts of higher fatty acid monoglyceride monosulfates, such as the sodium salt of the monosulfated monoglyceride of hydrogenated coconut oil fatty acids, higher alkyl sulfates such as sodium lauryl sulfate, alkyl aryl sulfonates such as sodium dodecyl benzene sulfonate,
10 higher alkylsulfo-acetates, higher fatty acid esters of 1,2-dihydroxy propane sulfonate, and the substantially saturated higher aliphatic acyl amides of lower aliphatic amino carboxylic acid compounds, such as those having 12 to 16 carbons in the fatty acid, alkyl or acyl radicals, and the like. Examples of the last mentioned amides are N-lauroyl sarcosine, and the sodium, potassium, and ethanolamine salts of N-lauroyl, N-myristoyl,
15 or N-palmitoyl sarcosine which should be substantially free from soap or similar higher fatty acid material. The use of these sarconite compounds in the oral compositions of the present invention is particularly advantageous since these materials exhibit a prolonged marked effect in the inhibition of acid formation in the oral cavity due to carbohydrates breakdown in addition to exerting some reduction in the solubility of tooth
20 enamel in acid solutions. Examples of water-soluble non-ionic surfactants suitable for use are condensation products of ethylene oxide with various reactive hydrogen-containing compounds reactive therewith having long hydrophobic chains (e.g. aliphatic chains of about 12 to 20 carbon atoms), which condensation products ("ethoxamers") contain hydrophilic polyoxyethylene moieties, such as condensation products of poly
25 (ethylene oxide) with fatty acids, fatty alcohols, fatty amides, polyhydric alcohols (e.g. sorbitan monostearate) and polypropyleneoxide (e.g. Pluronic materials).

The surface active agent is typically present in amount of about 0.1-5% by weight. It is noteworthy, that the surface active agent may assist in the dissolving of the active agent of the invention and thereby diminish the amount of solubilizing humectant
30 needed.

Various other materials may be incorporated in the oral preparations of this invention such as whitening agents, preservatives, silicones, chlorophyll compounds

and/or ammoniated material such as urea, diammonium phosphate, and mixtures thereof. These adjuvants, where present, are incorporated in the preparations in amounts which do not substantially adversely affect the properties and characteristics desired.

5 Any suitable flavouring or sweetening material may also be employed. Examples of suitable flavouring constituents are flavouring oils, e.g. oil of spearmint, peppermint, wintergreen, sassafras, clove, sage, eucalyptus, marjoram, cinnamon, lemon, and orange, and methyl salicylate. Suitable sweetening agents include sucrose, lactose, maltose, sorbitol, xylitol, sodium cyclamate, perillartine, AMP (aspartyl phenyl
10 alanine, methyl ester), saccharine, and the like. Suitably, flavour and sweetening agents may each or together comprise from about 0.1% to 5% more of the preparation.

In another embodiment, the compositions of the invention as described herein do not include a phosphate buffer and/or a calcium chelator. For example, any dentifrice described herein may not include a phosphate buffer and/or a calcium chelator.

15 In an embodiment of the present invention there is provided a composition, wherein the composition does not include a phosphate buffer and/or calcium chelator.

In another embodiment, the compositions of the invention as described herein do not include a viscosity regulator, or a viscosity regulator at 0.5 to 50%.

In another embodiment, the compositions of the invention as described herein do
20 not include sodium carboxymethylcellulose, or 0.01 to 10% sodium carboxymethylcellulose having the esterification degree of 0.7 to 1.0.

In one embodiment, the active components of the composition consist essentially of the stabilized ACP or ACFP complexes.

It will be clearly understood that, although this specification refers specifically to
25 applications in humans, the invention is also useful for veterinary purposes. Thus in all aspects the invention is useful for domestic animals such as cattle, sheep, horses and poultry; for companion animals such as cats and dogs; and for zoo animals.

The invention also provides a kit comprising stabilized amorphous calcium phosphate (ACP) and/or stabilized amorphous calcium fluoride phosphate (ACFP) said kit being adapted for use in the above described methods.

5 The invention also provides a kit comprising a liquid composition as described herein.

In any aspect, the kit may further comprise a label or package insert with instructions for use in any method described herein.

The kit may include:

- 10 - a container holding a composition comprising stabilized amorphous calcium phosphate (ACP) and/or stabilized amorphous calcium fluoride phosphate (ACFP);
- a label or package insert with instructions for use.

In certain embodiments the kit may contain one or more further active principles or ingredients for treatment or prevention of a disease or condition as described herein.

15 The kit may comprise a container and a label or package insert on or associated with the container. Suitable containers include, for example, bottles, vials, syringes, blister pack, etc. The containers may be formed from a variety of materials such as glass or plastic. The container holds a therapeutic composition which is effective for treating the condition and may have a sterile access port (for example the container may be an intravenous solution bag or a vial having a stopper pierceable by a
20 hypodermic injection needle). The label or package insert indicates that the therapeutic composition is used for treating the condition of choice. In one embodiment, the label or package insert includes instructions for use and indicates that the therapeutic composition can be used for treatment of the given condition.

25 The kit may comprise (a) a liquid composition as described herein; and (b) a second container with a second active principle or ingredient contained therein. The kit in this embodiment of the invention may further comprise a package insert indicating that the composition and other active principle can be used to treat a condition as described herein. Alternatively, or additionally, the kit may further comprise a second (or

third) container comprising a pharmaceutically-acceptable buffer, such as bacteriostatic water for injection (BWFI), phosphate-buffered saline, Ringer's solution and dextrose solution. It may further include other materials desirable from a commercial and user standpoint, including other buffers, diluents, filters, needles, and syringes.

5 It will be understood that the invention disclosed and defined in this specification extends to all alternative combinations of two or more of the individual features mentioned or evident from the text or drawings. All of these different combinations constitute various alternative aspects of the invention.

The invention will now be further described with reference to the following non-
10 limiting examples.

Examples

Example 1

Effect of Temperature on Remineralisation of Enamel Subsurface Lesions. The aim of these experiments was to determine the effect of temperature on remineralisation
15 of enamel subsurface lesions using an *in vitro* model.

Solutions were prepared using CPP-ACP, and optionally NaF, to produce 1.0% w/v CPP-ACP pH 5.5 or 1.0% w/v CPP-ACFP pH 5.5.

Five different temperatures tested: (i) 25°C, (ii) 35°C, (iii) 45°C, (iv) 55°C and (v) 65°C.

20 Human tooth enamel demineralized subsurface lesions were prepared in third molar enamel blocks using the method of Reynolds (J. Dent. Res. 1997, 76(9):1587-95).

Half the blocks were kept as control and the other half blocks were remineralized by suspending them individually in the 1.0% CPP-ACP + 725ppm F for 14 days at five
25 different temperatures (25, 35, 45, 55, and 65 °C).

After remineralization the enamel blocks were embedded, sectioned and subjected to transverse microradiography and densitometric image analysis as

previously described by Reynolds (1997, *J Dent Res, supra*) to determine percent mineral content gain (%Remineralization). Figure 1 shows the direct correlation between increasing temperature and increasing amount of remineralization.

Table 1: Results of the Effect of Temperature on Remineralisation of Enamel

5 Subsurface Lesions

	LDd	LDd-LDr	Δ Zd	Δ Zd- Δ Zr	%R
25 °C	110.62 ± 10.11	10.16 ± 3.29	3138.78 ± 568.20	856.66 ± 160.90 ^{abc}	27.30 ± 1.36 ^{abcd}
35 °C	107.28 ± 6.38	11.85 ± 4.43	2703.38 ± 610.76	844.06 ± 194.21 ^{de}	31.30 ± 1.14 ^{aefg}
45 °C	102.79 ± 7.62	18.10 ± 2.63	2462.15 ± 139.28	872.76 ± 57.50 ^{a#f}	35.44 ^b ± 0.94 ^{beh}
55 °C	108.76 ± 5.36	17.24 ± 10.81	3853.07 ± 429.12	1528.36 ± 166.34 ^{bd#}	39.67 ^d ± 1.01 ^{cf}
65 °C	107.89 ± 9.70	21.03 ± 6.34	3625.38 ± 989.41	1514.64 ± 394.85 ^{cef}	41.73 ± 3.52 ^{dgh}
treatment effect	> 0.05	> 0.05	> 0.05	< 0.0001	< 0.0001

LDd ANOVA using untransformed data

LDd-LDr ANOVA using untransformed data - (LDd removed from model as its effect was insignificant in the model ($p > 0.05$))

Zd Kruskal-Wallis test with pairwise comparisons using a Bonferroni correction

- 10 Zd-Zr ANCOVA using square root-transformed data with *post hoc* pairwise comparisons using a Sidak adjustment. Zd as a covariate retained in model as it had a highly significant effect ($p < 0.0001$). ^f $p < 0.01$; ^{ad} < 0.001 ; ^{bce} < 0.0001 ; [#] $p = 0.051$ (bordering on significance). Note: 25 °C vs 35 °C $p = 0.071$; 35 °C vs 45 °C $p = 0.085$ (approaching significance)

%R ANOVA using log-transformed data with *post hoc* Sidak multiple comparison tests. Z_d as a covariate removed from model as it had an insignificant effect ($p > 0.05$). $a^e < 0.05$; $^h < 0.01$; $bcd^fg < 0.0001$; Note: 45 °C vs 55 °C $p = 0.065$ (approaching significance)

5 Note ANOVA gives same result as ANCOVA when covariate is removed.

Example 2

A method for producing high concentration liquid compositions comprising CPP-ACP or CPP-ACP with free fluoride is described below.

Stock solutions of 3.25M CaCl₂ and 1.25 M NaH₂PO₄ (pH 5.5) were added in
 10 approximately thirty aliquots to a 10 - 15 % w/v tryptic digest of casein until just before precipitation or gelation (usually producing a final concentration of approximately 78 mM to 124 Ca²⁺ and 48 to 76 mM inorganic phosphate). The solutions were added slowly (that is, less than approximately 1% volume addition per minute) with adequate mixing. An aliquot of the phosphate solution was added first, followed by an aliquot of the
 15 calcium solution. The bulk solution pH was maintained at 9.0 using 1 to 10 M NaOH with thorough mixing. The sodium hydroxide solution was added automatically by a pH stat with the addition of the hydroxide ions usually being after each addition of the calcium ions. After completion of the addition of the calcium ions, phosphate ions and hydroxide ions the solution was filtered through a 0.1 micron filter to concentrate 1-2
 20 fold. The retentate was then washed with 1-2 volumes of water to remove salts and inactive (and bitter tasting) peptides. The CPP-ACP solutions prepared were then spray dried or freeze dried to produce a white powder. This dried powder was then added to water to form 20% to 75% w/v CPP-ACP solutions at pH 5.5 by addition of 1 – 10 M HCl, or with added NaF to produce 3260ppm F for 25% w/v, 4890ppm F for 38%,
 25 6520ppm F for 50%w/v, 8151ppm F for 63% CPP-ACP and 9,880 ppm F for 75% CPP-ACP at pH 5.5.

The 75% w/v solution was prepared by adding 75 g CPP-ACP powder to 20 ml water with a small amount of powder each addition (0.5 g/min) while maintaining the pH at 5.5 by the addition of 10 M HCl. The solution was thoroughly mixed after each
 30 addition to ensure dispersion. A concentrated NaF (0.95 M) solution was added

together with 10 M HCl to ensure that 52 mmol of F was finally added. The CPP-ACP powder, NaF and HCl were added over 2-3 hours with water to a final volume of 100 ml. This produced a very viscous solution of 75 %w/v CPP-ACP, 9,880 ppm F at pH 5.5.

Example 3

- 5 Remineralisation by CPP-ACFP and CPP-ACP *in vitro* at high concentrations. The aim of these experiments was to compare remineralisation by CPP-ACP + fluoride (F) and CPP-ACP at high concentrations (e.g. 20% w/v, 25% w/v, 30% w/v, 38% w/v, 40% w/v, 50% w/v and 63% w/v).

10 Human tooth enamel demineralized subsurface lesions were prepared in third molar enamel blocks. Half the blocks were kept as control and the other half blocks were treated as below:

Each enamel sample was pre-treated with 1M NaOH (5ml) for 5 min at 45 °C then wash with water for 10 sec/pat dry;

15 Remineralized by suspending them individually in one of the following remineralization solutions:

- CPP-ACP + F liquid compositions at 25% w/v, 38% w/v, 50% w/v, and 63% w/v CPP-ACP; or
- CPP-ACP only (no fluoride) liquid compositions at 20% w/v, 30% w/v, 40% w/v, and 50% w/v CPP-ACP,

20 for 4 hours at 45 °C.

Fluoride content for CPP-ACP + F liquid compositions is as shown in Table 2, specifically 3,260 ppm F for 25% w/v, 4,890 ppm F for 38% w/v, 6,520 ppm F for 50% w/v and 8,151 ppm F for 63% w/v CPP-ACP, respectively.

25 Enamel block was removed and paired with its control for embedding, sectioning and transverse microradiography and densitometric image analysis to determine percent mineral content gain (%Remineralization).

Table 2: Results of Remineralisation by CPP-ACP + F and CPP-ACP *in vitro* at high concentrations.

Treatment	LDd (μm)	ΔZd (vol. μm)	$\Delta\text{Zd}-\Delta\text{Zr}$ (vol. μm)	%R
25% w/v CPP-ACP + 3260ppmF	114.73 $\pm$ 8.80	3021.30 $\pm$ 578.92	389.30 $\pm$ 71.06	13.05 $\pm$ 2.09
20% w/v CPP-ACP	102.51 $\pm$ 6.30	2826.42 $\pm$ 349.81	234.83 $\pm$ 59.38	8.30 $\pm$ 2.24
38% w/v CPP-ACP + 4890ppmF	102.04 $\pm$ 9.06	2692.09 $\pm$ 448.70	515.01 $\pm$ 121.81	18.92 $\pm$ 2.27
30% w/v CPP-ACP	104.02 $\pm$ 9.48	3041.59 $\pm$ 536.66	438.07 $\pm$ 65.16	14.43 $\pm$ 1.28
50% w/v CPP-ACP + 6520ppmF	112.45 $\pm$ 7.76	3145.51 $\pm$ 534.90	822.27 $\pm$ 181.33	25.81 $\pm$ 1.42
40% w/v CPP-ACP	99.24 $\pm$ 6.87	2794.54 $\pm$ 501.81	458.38 $\pm$ 63.67	16.34 $\pm$ 1.47
63% w/v CPP-ACP + 8151ppmF	118.05 $\pm$ 10.67	3139.87 $\pm$ 218.49	859.84 $\pm$ 115.10	27.21 $\pm$ 2.14
50% w/v CPP-ACP	104.00 $\pm$ 7.79	2691.53 $\pm$ 745.94	375.62 $\pm$ 129.73	13.98 $\pm$ 3.72

The levels of enamel subsurface remineralisation in only 4 hours are the highest
 5 level of remineralisation reported in such a short exposure time and has been achieved
 by the novel preparation of the liquid compositions containing high concentration CPP-
 ACP(F) and the novel use of temperature to facilitate remineralisation.

Example 4

A method for producing high concentration liquid compositions comprising CPP-
 10 ACP or CPP-ACP with free fluoride is described below.

30 g of CPP-ACP powder (commercial Recaldent) was added to 19.5 g of a

20,000 ppm F (NaF) solution to which 0.5 g of an 11 M HCl solution was added to give the final weight 50 g (hence this final solution is a 60% w/w CPP-ACP with 7,800 ppm F at pH 7.8 or 75% w/v CPP-ACP containing 10,000 mg/L F at pH 7.8). With thorough stirring (around 30 min) a homogeneous very viscous but stable solution was prepared
5 with a pH of 7.8. This solution was then degassed to remove trapped air bubbles by placing the solution under vacuum for 24 hours.

The viscous, stable and safe (neutral pH) solution is easy to apply in the dental surgery and is more concentrated so produces a better effect over a longer period of time. The composition is still in liquid form so can be applied to the dental surface with a
10 microbrush.

CLAIMS

1. A method of mineralizing a dental surface or sub-surface comprising
contacting the dental surface or subsurface with stabilized amorphous calcium
phosphate (ACP) and/or amorphous calcium fluoride phosphate (ACFP), and
5 simultaneously,
heating the dental surface or subsurface to which the stabilized ACP and/or ACFP
has been, or is being, applied to a temperature of greater than 37°C.
2. Use of stabilized amorphous calcium phosphate (ACP) and/or amorphous
calcium fluoride phosphate (ACFP) in the manufacture of a composition or medicament
10 for mineralizing a dental surface or sub-surface,
wherein the dental surface or subsurface to which the stabilized ACP and/or ACFP
has been, or is being, applied is simultaneously heated to a temperature of greater than
37°C.
3. The method or use according to claim 1 or 2, wherein the stabilized
15 ACP/ACFP is provided in a liquid composition comprising equal to, or greater than, 20%
w/v stabilized-ACP and/or ACFP, or equal to, or greater than, 25% w/v stabilized-ACP
and/or ACFP.
4. A method of mineralizing a dental surface or sub-surface comprising
contacting the dental surface or subsurface with a liquid composition comprising
20 equal to, or greater than, 30% w/v stabilized amorphous calcium phosphate (ACP) and/or
amorphous calcium fluoride phosphate (ACFP).
5. Use of stabilized amorphous calcium phosphate (ACP) and/or amorphous
calcium fluoride phosphate (ACFP) in the manufacture of a composition or medicament
for mineralizing a dental surface or sub-surface,
25 wherein the stabilized ACP and/or ACFP is provided in a liquid composition
comprising equal to, or greater than, 30% w/v stabilized amorphous calcium phosphate
(ACP) and/or amorphous calcium fluoride phosphate (ACFP).

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6. The method or use according to claim 4 or 5, wherein the dental surface or sub-surface to which the stabilized ACP and/or ACFP has been, or is being, applied is simultaneously or subsequently heated to a temperature greater than 37°C.

5 7. The method or use according to any one of claims 1 to 3 and 6, wherein the dental surface or subsurface to which the stabilized ACP and/or ACFP has been, or is being, applied is heated to a temperature of greater than or equal to 40°C, greater than or equal to 45°C, greater than or equal to 50°C, greater than or equal to 55°C, greater than or equal to 60°C, greater than or equal to 65°C.

10 8. The method or use according to any one of claims 1 to 3 and 6 to 7, wherein the dental surface or subsurface is heated to a temperature that does not exceed 65°C.

9. The method or use according to any one of claims 1 to 3 and 6 to 8, wherein the dental surface or subsurface is heated for about 1 to 60 minutes, or for about 1 to 30 minutes.

15 10. The method or use according to any one of claims 3 to 9, wherein the liquid composition comprises equal to, or greater than, 35% w/v stabilized-ACP and/or ACFP; equal to, or greater than 40% w/v stabilized-ACP and/or ACFP; equal to, or greater than 45% w/v stabilized-ACP and/or ACFP; equal to, or greater than 50% w/v stabilized-ACP and/or ACFP; equal to, or greater than 55% w/v stabilized-ACP and/or ACFP; equal to, or greater than 60% w/v stabilized-ACP and/or ACFP; or equal to, or greater than 65% w/v stabilized-ACP and/or ACFP.

25 11. The method or use according to any one of claims 3 to 9, wherein the liquid composition comprises equal to, or greater than, 40% w/w stabilized-ACP and/or ACFP; equal to, or greater than, 45% w/w stabilized-ACP and/or ACFP; equal to, or greater than, 50% w/w stabilized-ACP and/or ACFP; equal to, or greater than, 55% w/w stabilized-ACP and/or ACFP; equal to, or greater than, 60% w/w stabilized-ACP and/or ACFP; or equal to, or greater than, 65% w/w stabilized-ACP and/or ACFP.

12. The method or use according to any one of claims 1 to 11, wherein the stabilized ACP and/or ACFP is phosphopeptide stabilized.

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13. The method or use according to claim 12, wherein the phosphopeptide is a casein phosphopeptide.

14. The method or use according to any one of claims 1 to 13, wherein the dental surface or subsurface is a fluorotic lesion, a white spot lesion, a caries lesion or a lesion caused by erosion.

15. A liquid composition comprising equal to, or greater than, 30% w/v stabilized amorphous calcium phosphate (ACP) and/or amorphous calcium fluoride phosphate (ACFP).

16. A liquid composition according to claim 15, wherein the composition comprises equal to, or greater than, 35% w/v stabilized ACP and/or ACFP; equal to, or greater than 40% w/v stabilized-ACP and/or ACFP; equal to, or greater than 45% w/v stabilized-ACP and/or ACFP; equal to, or greater than 50% w/v stabilized-ACP and/or ACFP; equal to, or greater than 55% w/v stabilized-ACP and/or ACFP; equal to, or greater than 60% w/v stabilized-ACP and/or ACFP; equal to, or greater than 65% w/v stabilized-ACP and/or ACFP; equal to, or greater than 70% w/v stabilized-ACP and/or ACFP; or equal to, or greater than 75% w/v stabilized-ACP and/or ACFP.

17. The liquid composition according to claim 15, wherein the liquid composition comprises equal to, or greater than, 40% w/w stabilized-ACP and/or ACFP; equal to, or greater than, 45% w/w stabilized-ACP and/or ACFP; equal to, or greater than, 50% w/w stabilized-ACP and/or ACFP; equal to, or greater than, 55% w/w stabilized-ACP and/or ACFP; equal to, or greater than, 60% w/w stabilized-ACP and/or ACFP; or equal to, or greater than, 65% w/w stabilized-ACP and/or ACFP.

18. The liquid composition according to any one of claims 15 to 17, wherein the composition further comprises fluoride.

19. The liquid composition according to any one of claims 15 to 18, wherein the stabilized ACP and/or ACFP is phosphopeptide stabilized.

20. The method or use according to claim 19, wherein the phosphopeptide is a casein phosphopeptide.

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21. A kit for the treatment or prevention of one or more of dental caries, fluorosis and dental erosion, or mineralizing a dental surface or subsurface or lesion as described herein comprising a liquid composition comprising:

- 5 - equal to, or greater than, 30% w/v stabilized amorphous calcium phosphate (ACP) and/or amorphous calcium fluoride phosphate (ACFP); and
- a label or package insert with instructions for use.

22. The kit according to claim 21, the kit further comprising a heat source.

23. A method or process for preparing a liquid composition comprising equal to, or greater than, 30% w/v stabilized ACP and/or ACFP, the method or process comprising
10 or consisting of:

 mixing a solvent and a powder comprising or consisting of stabilized-ACP and/or ACFP, and

 maintaining the pH below 9, preferably below 8 or 7.

24. A method or process for preparing a liquid composition comprising equal to,
15 or greater than, 30% w/v stabilized ACP and/or ACFP, the method or process comprising or consisting of:

 mixing a solvent and a powder comprising or consisting of stabilized ACP and/or ACFP, and

 lowering the pH below 9, preferably, the pH is lowered to, or below, 7 or 6,
20 preferably 5.5.

25. The method or process according to claim 23 or 24, wherein:

 - the pH is maintained at, or below, 6, preferably the pH is maintained at, or below, 5.5; and/or

 - the pH is lowered or maintained using 1-10M HCl, or 11M HCl.

25 26. The method or process according to any one of claims 23 to 25, wherein the solvent is water.

27. The method or process according to any one of claims 23 to 26, wherein the powder:

- is mixed with the solvent at a rate of about 2.5%w/v / min; or
- is slowly mixed with the solvent over about 2-3 hours.

5 28. The method or process according to any one of claims 23 to 27, further comprising the step of stirring the liquid composition after the pH is lowered.

29. The method or process according to claim 28, wherein the stirring occurs for at least 5, 10, 15, 20, 25 or 30 minutes.

10 30. The method or process according to any one of claims 23 to 29, further comprising degassing the liquid composition.

31. The method or process according to claim any one of claims 23 to 30, wherein the powder comprising or consisting of stabilized-ACP and/or ACFP is prepared by:

15 admixing one or more solutions comprising phosphopeptides, calcium ions, phosphate ions, hydroxide ions and optionally fluoride ions, while maintaining the pH at about 7.0 or above, preferably about 9, to form a solution comprising stabilized-ACP and/or ACFP;

filtering the solution comprising phosphopeptide-stabilized ACP and/or ACFP to form a retentate; and

20 drying said retentate to obtain the powder consisting of phosphopeptide-stabilized ACP and/or ACFP.

32. The method or process according to claim 31, wherein the solutions are added slowly at a rate of less than about 1% volume addition per minute with adequate mixing.

FIGURES

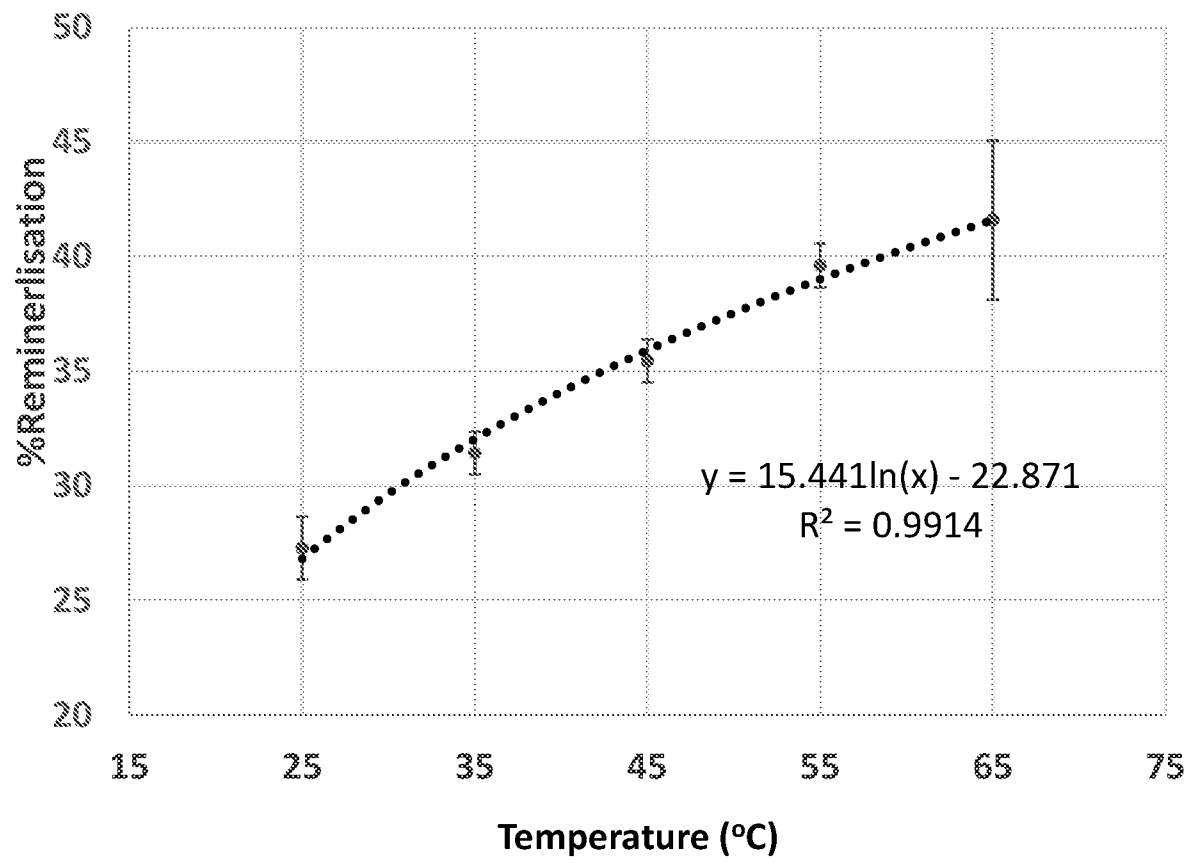
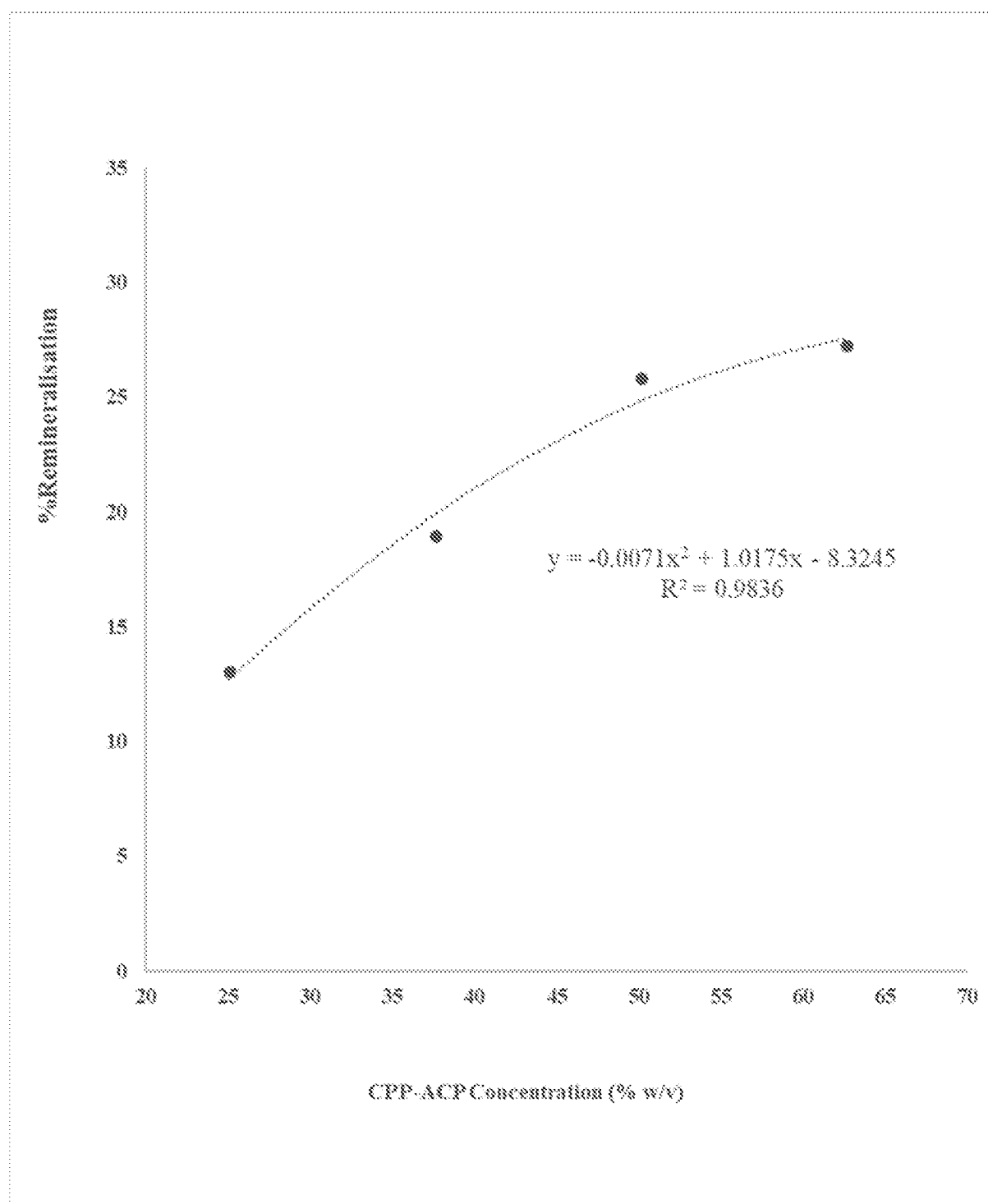


Figure 1

**Figure 2**

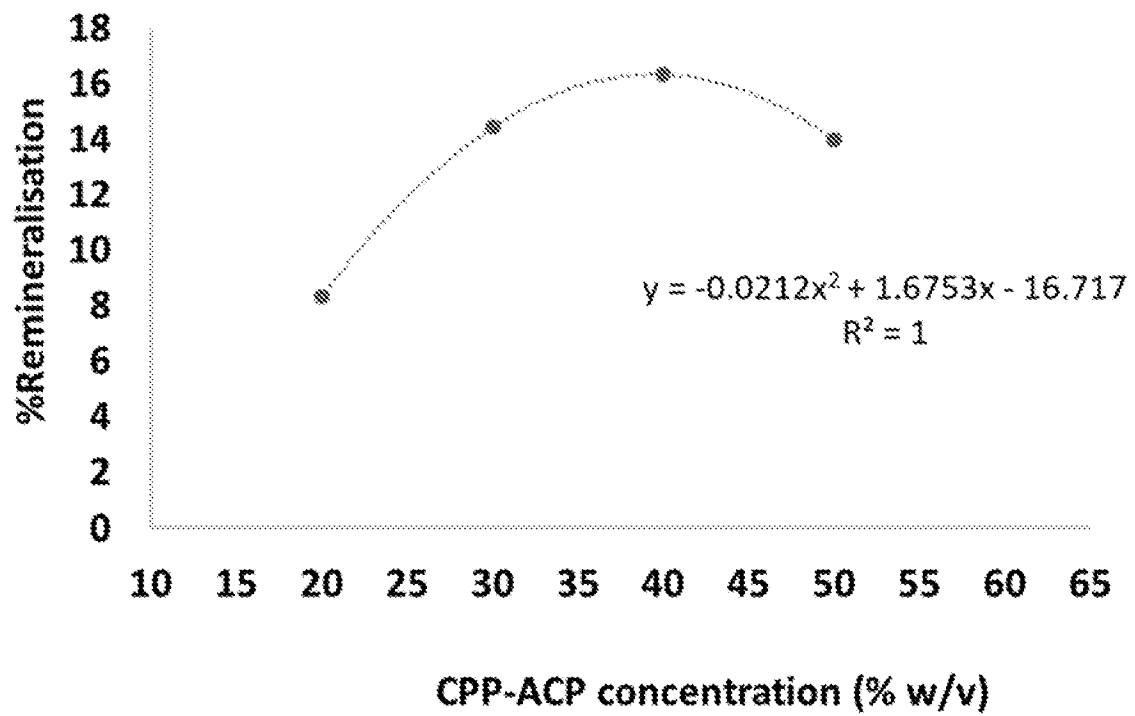


Figure 3

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