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(72) Inventor; and

(71) Applicant : **BASIC, Robert** [HR/HR]; Dubravica 30,
10000 Zagreb (HR).(72) Inventors: **SUBOTIC, Boris**; Karela Zahradnika 32,
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(54) Title: DENTAL FORMULATION

(57) Abstract: This invention discloses a dental formulation consisting of of: - calcium alumino silicate having the particles of spherical shape - CAS and - one or more excipients and optional ingredients required to produce a desired final dosage form: oral suspension, toothpaste, dental powder, dental gel and chewing gum. CAS is characterized by: - specific chemical composition: 0.311 - 0.732 wt. % Na₂O, 14.712 - 15.360 wt. % CaO, 27.643 - 28.450 wt. % Al₂O₃, 33.248 - 35.193 wt. % SiO₂ and 20.446 - 23.273 wt. % H₂O; - spherical shape of particles without distinguishing crystal faces and with high surface roughness: RSSA/GSSA = 2.58-2.81 - particles size in the range from 0.4 μm and 5 μm and average particles size in the range from 1.15 μm to 1.848 μm. - external real specific surface area (RSSA) from of 2.375 m²/g to 4.433 m²/g; - external geometrical specific surface area (GSSA) from 0.921 m²/g to 1.593 m²/g. Thanks to these properties of CAS, the formulation of the present invention is efficient desensitizing, mineralizing, and polishing agent for teeth.



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DENTAL FORMULATION

1. FIELD OF INVENTION

This invention discloses the dental formulation suitable for treatment of teeth and mouth cavity. The said dental formulation is suitable, if necessary, for desensitization, stabilization and remineralization of teeth in different etiologies.

2. SUMMARY OF INVENTION

The existing invention solves the technical problem of efficient control of pH, stabilization and remineralization of hard tooth tissues, desensitization of tooth, prevention of the formation of caries and remineralization of tooth lesions, reduction of number of cariogenic and inflammatory bacteria in mouth cavity, stoppage of bleeding in mouth cavity, acceleration of healing of hurts in mouth cavity, prevention of degradation of connective tissues in moth cavity, prevention and treatment of gingivitis and periodontitis, regulation of salivation, prevention of formation of caries and gingivitis during application of mobile and fixed orthodontic devices, improvement of the condition of mouth cavity caused by abidance of diabetes, improvement of the condition of mouth cavity caused by hormonal changes during pregnancy and menopause, stabilization and remineralization of acquired and genetically stipulated hypo-mineralization conditions of tooth enamel, prevention of complications on hard and soft tissues in mouth cavity caused by smoking, prevention of the formation of pathological changes of hard and soft tissues in mouth cavity of children, filling up of natural and acquired morphological defects hard tooth tissue, indirect and direct covering tooth pulp, and apeksification of roots with open apex.

This was achieved by formulation of medium comprising calcium aluminosilicate having the particles of spherical shape – CAS. Its characteristic is considerably accelerated and enhanced releasing of calcium ions which enables a rapid

remineralization of tooth enamel and dentin at optimum pH.

The formulation consists of:

- (i) calcium aluminosilicate having the particles of spherical shape (CAS);
- (ii) one or more excipients and compounds needed for achieving the final desired form of dosage; oral suspension (for washing of mouth), toothpaste, dental gel (adheres to denture) and chewing-gum.

This formulation is particularly efficient for:

- (i) stabilization of hard tooth tissues
- (ii) remineralization of hard tooth tissues
- (iii) desensitization of teeth
- (iv) polishing of teeth
- (v) regulation of pH of mouth cavity
- (vi) regulation of salivation
- (vii) reduction of number of pathological flora of soft and hard tooth tissues
- (viii) prevention of inflammation of soft tissues in mouth cavity as well as treatment of the mentioned inflammatory conditions
- (ix) acceleration of healing of hurts in mouth cavity

3. PRIOR ART

Importance of good oral hygiene declares not only in the control of the formation of caries, periodontal disease and bad odor, but also in interdependent action with other systematic conditions such as diabetes, stroke, heart attack, etc.

The basis for the formation of caries and periodontal diseases is dental plaque which is, accordingly to WHO (1978), defined as a biofilm composed of different kinds of microorganisms in extracellular matrix formed by bacterial metabolic products and components of serum, saliva and blood.

Demineralization, which starts by production of different organic acids (lactic, acetic, propionic, formic) by activity of plaque bacteria, after exposition to fermentable hydrocarbons, is the main process of the development of caries of enamel and dentin.

Demineralization is a progressive process which can be stopped by either decreasing

of acidity or increasing of alkalinity in mouth cavity by:

- (i) application of an orally acceptable neutralizing agent;
- (ii) washing, or
- (iii) mineralization by an appropriate source of calcium (Ca^{2+}) ions; otherwise, caries will be developed.

One of most the most frequent existing strategies for prevention of caries is frequent washing of teeth with fluoride-containing toothpastes. The action of fluoride is based on formation of flour apatite $[\text{Ca}_5(\text{PO}_4)_3\text{F}]$ by reaction of fluoride anions from dentifrice and natural hydroxyapatite from the dental enamel. The solubility of flour-apatite in acidic environment is about ten times lower than the solubility of hydroxyapatite. In this way, fluorides stabilize the dental enamel and dentin by decrease of their solubility in acidic medium as well as by toxic action upon oral microorganisms [J. M. ten Cate, J. D. Featherstone: Mechanistic aspects of the interactions between fluoride and dental enamel, *Crit. Rev. Oral. Biol. Med.* **2** (1991) 283-296].

Numerous patents describe use of fluoride or phosphate for remineralization of teeth, based on the formation of flour apatite. Also, many documents describe the oral formulations based on the mixtures of phosphate and Ca salts.

US Patent 4,080,440 (1976) discloses a method for remineralization of tooth enamel based on metastable water solution of calcium (0.005-5%) and phosphate (0.005-5%) ions with the molar ratio of Ca:P between 0.01-100 and pH 2.5–4. Remineralization occurs by incorporation of calcium and phosphate ions from solution in the demineralized surfaces of teeth.

US Patent 4,083,955 (1976) is related to the remineralization of dental enamel by the washing in two stages. In the first stage, mouth cavity is treated with 0.005–10% aqueous solution of soluble calcium ions or 0.005–10% water solution of soluble phosphate ions. During the treatment (10–30 seconds) calcium ions enter into surface and subsurface parts of tooth enamel. Then the mouth cavity is treated with phosphate ions in the second stage for the same time. During this second treatment, phosphate ions from solution react with the calcium ions previously bounded into enamel,

yielding hydroxyapatite in both cases. The treatment can also be conducted in *vice versa* manner.

US Patent 4,244,931 (1979) discloses the use of calcium hydrogen phosphate dihydrate ($\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$) with sufficient amounts of magnesium phosphate and/or pyrophosphate with improved stability. The formulation on this basis is useful for re-mineralization and polishing of teeth.

US Patent 4,515,772 (1984) discloses an oral compositions for protection of teeth containing 10–70% of metaphosphates, aluminum trioxide, polymerized resins and amorphous silica as abrasives; 50–3500 ppm of fluoride (F^-) ion source, and at least 1.5% alkali metal pyrophosphates (sources of $\text{P}_2\text{O}_7^{4-}$ ions).

US Patent 5,614,175 (1996) discloses non-aqueous compositions for mineralization of lesions, consisting of 0.0–15% of water soluble calcium salts, 0.05–15% of water soluble phosphate salts.

US Patent 5,645,853 (1995) describes a chewing gum composition for mineralization of lesions, containing 0.01–15% of water soluble calcium salts, 0.01–15% of water soluble phosphate salts, and 10–95% of gum base and a layer for encapsulation. During chewing, both calcium and phosphate ions are released from the gum and together with saliva form a mixed solution of calcium and phosphate ions having pH between 4 and 7. Phosphate and calcium ions from saliva deposit on the tooth surface inducing remineralization by crystallization of basic calcium phosphate (hydroxyapatite).

Some of new approaches in mineralization use the properties of amorphous calcium phosphates (ACP) formed from water soluble calcium and phosphate salts. The ACP rapidly transforms into crystalline apatite during application by washing and nursing of teeth with such based formulations [E. D. Eanes in: Z. Amjad (Ed.), *Calcium Phosphates in Biological and Industrial Systems*, Kluwer Academic Pub., Boston, 1998, p.21.; M. S. Tung, US Patent 5,037,639 (1989); M. S. Tung, F. C. Eichmiller: Amorphous calcium phosphates for tooth mineralization, *Compend. Contin. Educ. Dent.* **25** (2004) 9-13].

Amorphous calcium phosphate (ACP) can be stabilized with pyrophosphates ($P_2O_7^{4-}$). Supersaturated solution can be kept stable for a longer time, thus preventing formation of the crystal forms of calcium phosphate [M. S. Park, E. D. Eanes, J. M. Antonucci, D. Skrtic: Mechanical properties of bioactive amorphous calcium phosphate/methacrylate composites, *Dent. Mater.* **14** (1998) 137-141].

A similar strategy of remineralization can be used for treatment of lesions and open pores of dental tubules which, otherwise, would cause hypersensitivity of teeth [US Patent 6,036,944 (1999)].

One of the most known preparations for remineralization of teeth, based on ACP, is sugarless chewing gum (RecaldentTM). This product contains ACP stabilized by casein (a cow milk protein) [J. D. Bader: Casein phosphopeptide-amorphous calcium phosphate shows promise for preventing caries, *Evid. Based Dent.* **11** (2010) 11-12].

NovaMin Technology Inc. and University of Maryland (College of Dentistry, Baltimore, MD, USA) invented a new preparative NovaMin, based on calcium sodium phosphosilicate (bio-glass) and protected by several patents. Originally was made for the treatment of hypersensitivity by the physical occlusion of dentinal tubules, and recent studies has demonstrated a potential of this material to prevent demineralization and/or stimulation of remineralization of tooth surfaces. The mode of action of this material is based on interaction of the mentioned material with aqueous solutions. When introduced to the oral environment, the material releases sodium calcium and phosphate ions which then interact with oral fluids and result in the formation of crystalline hydroxycarbonate apatite (HCA) – a compound which is structurally and chemically similar to natural tooth mineral. [A.K. Burwell, L.J. Litkowski, D.C. Greenspan, Calcium Sodium Phosphosilicate (Novamin): Remineralization Potential, *Adv. Dent Res.* **21** (2009) 35-39.].

Accordingly to the document EP1620064, a preparative containing Ca form of zeolite, source of phosphate ions and matrix proteins is used for stabilization, recalcification and remineralization of tooth enamel and dentin.

Document EP2438010 discloses calcium aluminosilicate with the particles of spherical shape (CAS) and its medical application. The CAS, having the same

properties, as described in the cited document, is used in the invention of a subject.

4. TECHNICAL PROBLEM

Above mentioned methods and corresponding preparations are based on either the water soluble calcium (source of calcium ions) or phosphate (source of phosphate ions) salts or common (and simultaneous) source of both calcium and phosphate ions (ACP, bio-glass). Use of water soluble calcium and phosphate salts as the sources of calcium and phosphate ions, needed for remineralization, cause certain difficulties related to the control of concentrations of calcium and phosphate ions; if the concentrations of the mentioned ions are too low, the required level of remineralization cannot be realized and, on the other hand, too high concentrations of the mentioned ions may cause the crystallization of apathies with defect crystal structure and/or formation of undesired incrustations on teeth surfaces. A special problem is a continuous change (decrease) of concentrations of calcium and phosphate ions during remineralization. Furthermore, water soluble calcium salts can be sources of various anions (chlorides, nitrates, bicarbonates etc.) which might negatively influence the crystallization of hydroxyapatite and stability (solubility) of tooth enamel. Finally, the components (calcium and phosphate salts) of the re-mineralizing agents based on the water soluble salts must be physically separated before use; otherwise, calcium and phosphate ions would react immediately forming different calcium phosphates before application, i.e., during storage.

On the other hand, application of amorphous calcium phosphate (ACP) and bio-glass in the water-containing dentifrices such as tooth paste, oral solutions (mouthwash) dental gels etc. is cause another types of problems; in the presence of water, ACP spontaneously transforms into crystalline, less soluble calcium phosphates and bio-glass spontaneously dissolves producing sodium, calcium phosphate and silicate ions. Mutual reactions of calcium and phosphate ions, formed by dissolution of bio-glass, results in formation of amorphous calcium phosphate (ACP) which subsequently transforms into crystalline calcium phosphates. In this way the

composition of dentifrice continuously changes during storage which is accompanied with decrease of its re-mineralization potential.

Since pH of the mouth cavity is one of the most important factors for the control of stability of mineral parts of tooth (enamel, dentin) and thus, for the control of caries development [M.E. Jensen, *Cariology* **43** (1999) 615.], in many of the mentioned methods and corresponding preparations pH is adjusted by addition of bicarbonates and/or carbamide. Bicarbonates present in dentifrices decrease acidity (increase pH) and thus increase the stability of mineral parts of tooth. On the other hand, the presence of carbonates may cause a negative impact to enamel and dentin. Namely, OH^- ions from hydroxyapatite can be exchanged with carbonate ions from solution (saliva), thus forming carbonate-apatite which solubility in acid environment is considerably higher than solubility of hydroxyapatite under the same conditions. On the other hand, although carbamide is neutral compound, in the presence of acids formed by action of cariogenic bacteria, carbamide hydrolyses to ammonia and carbon dioxide. The formed ammonia neutralizes organic acids and thus decreases the acidity in the mouth cavity. However, comparative studies of commercial chewing gums with and without carbamide have shown that the presence of carbamide has not a marked influence of pH in the mouth cavity. Finally, carbon dioxide formed as the product of carbamide hydrolysis can produce carbonate ions. Again, OH^- ions from hydroxyapatite can be exchanged with such formed carbonate ions, thus forming carbonate-apatite which solubility in acid environment is considerably higher than solubility of hydroxyapatite under the same conditions.

Taking into consideration the mentioned difficulties in the control of pH as well as in the adjusting and control of the concentrations of calcium and phosphate ions in the existing demineralizing preparations, the technical problem of effective mineralization, stabilization and desensitization of teeth is solved in the manner, further disclosed in the text. In spite of the trend in former investigations which undoubtedly show that an optimum preparation for remineralization, recalcification, stabilization and desensitization of teeth needs to contain sources of phosphate (and/or bicarbonate), and/or fluoride and calcium ions, and/or carbamide, surprisingly it has been shown that

remineralization, recalcification, stabilization and desensitization of teeth can be, in an oral preparation, achieved by use of a new kind of calcium aluminosilicate having the particles of spherical shape (CAS), without the presence of the sources of phosphate, bicarbonate, and/or fluoride ions, and/or carbamide. Namely, an average expert in the field knows that pH cannot be regulated only by calcium aluminosilicate. Source of phosphate ions, and/or bicarbonate ions, and/or carbamide is necessary for efficient regulation of pH. Moreover, an average expert in the field knows that phosphate ions are necessary in the oral preparations because of the formation of hydroxyapatite – a compound which comprehends tooth enamel necessary for mineralization, stabilization, remineralization and desensitization of teeth. Just this is one of the most important reasons why the former investigations were focused to the mixtures of the sources of Ca and phosphate ions.

The preparation related to the present invention does not contain phosphate ions as well as bicarbonate ions and carbamide. The preparation maintains an optimal pH at local level, i.e., on the tooth surface; an average pH = 7.6 to 8, even for a long time after treatment. pH on the tooth surface treated with the preparation in accordance to EP1620064 is 7, while pH of the tooth surface treated with the preparation based on the invention of the Maryland University – NovaMin tends to the value of 10 and more because of the presence of sodium in bio glass and because of deactivation of a part of bio glass during storage.

In addition, there are no some indications that efficiency of remineralization, recalcification, stabilization and desensitization of teeth with the preparation related to the present invention is behindhand with the efficiency of remineralization, recalcification, stabilization and desensitization related to the document EP1620064 and to the invention of the Maryland University. Thus, the present invention solves the problem of an alternative way of remineralization, recalcification, stabilization and desensitization of teeth.

Furthermore, if the sources of calcium and phosphate ions are present in the preparation such as toothpaste, the calcium and phosphate ions are partially dissolved in water, i.e., moisture present in the toothpaste, which finally results in the formation

of inactive compounds such as hydroxyapatite. On the other hand, absence of phosphate ions from the present invention solves the problem of partial deactivation of the preparation and thus, results in an enhancement of remineralization, recalcification, stabilization and desensitization abilities of the preparation.

In addition, the present invention uses very small amount of calcium aluminosilicate, e.g., zeolite, relative to the prior art. Calcium aluminosilicate or more specifically, calcium form of zeolite A is, in the preparations related to present invention, contained in the amounts of 1 to 10 weight percentages. In the desired cases, the amount of the above mentioned zeolite is in the range from 2 to 7 % and in the most desired cases of the present invention, these amounts range from 3 to 5 %.

Thus, the present invention solves the technical problem of efficient remineralization, recalcification, stabilization and desensitization of teeth.

This is achieved by formulation of the preparation for nursing of teeth containing calcium aluminosilicate having the particles of spherical shape – CAS. Its characteristic is considerably accelerated and enhanced releasing of calcium ions which enables a rapid re-mineralization of tooth enamel and dentin at optimum pH.

The formulation consists of:

- (i) calcium aluminosilicate having the particles of spherical shape (CAS) and
- (ii) one or more excipients and optional compounds needed for achieving the final desired form of dosage; oral suspension (for washing of mouth), toothpaste, dental gel (adheres to denture) and chewing-gum.
- (iii) This formulation is particularly efficient for:
 - (i) desensitization of teeth;
 - (ii) mineralization of tooth enamel and dentin;
 - (iii) stabilization of tooth enamel and dentin; and
 - (iv) polishing of teeth.

Finally, the preparation related to the present invention exhibits the anti-inflammatory ability, which is confirmed in several individuals, manifested by a considerable reduction of bleeding in periodontosis from which can be concluded that the preparation related to the present invention prevents the destroying of collagen fibers

and supports their regeneration.

5. DETAILED DESCRIPTION OF THE INVENTION

The formulation of this invention consists of:

- (i) calcium aluminosilicate having the particles of spherical shape (CAS) and
- (ii) one or more excipients and compounds needed for achieving the final desired form of dosage; oral suspension (for washing of mouth), toothpaste, dental gel (adheres to denture) and chewing-gum.

Brief description of figures:

Figure 1 SEM image of CAS particles magnified for (a) 10.000× and (b) for 33.000×

Figure 2 Particle size distributions of CAS-P#4. N_D is the number percentage of the particles having the corresponding equivalent spherical diameter D .

Figure 3 Influence of pH on the solubility of hydroxyapatite. C_{Ca} is the concentration of calcium ions in the solution and m_{HA} is the mass of dissolved hydroxyapatite. DE->demineralization; RE->remineralization.

Figure 4 SEM images of dental tubules before (A) and immediately after (B, C) the treatment with the preparation containing CAS.

Figure 5 Average values, S_{av} , of the diminishing of the concentration of calcium ions during demineralization of teeth.

Figure 6: SEM images of the surface of tooth (enamel) before (A) and after (B) of the treatment with the preparation containing CAS.

Figure 7: SEM images of the dental tubules after the treatment with the preparation containing CAS for 6 h (A), 12 h (B), 18 h (C) and 24 h (D).

The synthesis and characterization of CAS

We have been found that for some specific chemical compositions of precipitated sodium aluminosilicates, their hydrothermal treatment results in the formation of sodium aluminosilicates having the spherically-shaped particles with exceptionally high specific surface area and ability to exchange of original sodium ions with other cations. Sodium aluminosilicate with spherically-shaped particles, SAS, was synthesized as follows:

(i) Preparation of sodium aluminosilicate suspension; The suspension is prepared by mixing of sodium aluminate solution (having appropriate chemical composition with respect to Na_2O , Al_2O_3 and H_2O) and sodium silicate solution (having appropriate chemical composition with respect to Na_2O , SiO_2 and H_2O) at temperatures (T_p) from room temperature (20°C) to 90°C . Thus obtained suspension contains:

7.586 – 11.695 wt. % Na_2O ,

4.229 – 9.379 wt. % Al_2O_3 ,

3.238 – 7.735 wt. % SiO_2 and

72.408 – 84.600 wt. % H_2O

(ii) Hydrothermal treatment of aluminosilicate suspensions: Hydrothermal treatment is carried out by heating of the aluminosilicate suspensions at temperatures (T_R) between $65 - 90^\circ\text{C}$, under stirring, until the solid phase of suspension is completely transformed into SAS ($t_R = 60 - 135$ min; depending on the chemical composition of starting suspension and reaction temperature, T_R);

(iii) Separation of product (SAS): SAS, obtained during hydrothermal treatment of suspension, as described in (ii), is separated from the liquid phase (mother liquor) by either centrifugation or vacuum filtration. The separated SAS is subjected to washing with several portions of demineralized water in order to remove all residual reagents (from the mother liquor) adsorbed on the product, until pH of filtrate is 9-10.

(iv) Drying of washed SAS is carried out at $80-150^\circ\text{C}$ for up to 24 h.

(v) The dry SAS was converted into calcium form (CAS) by ion-exchange of the sodium ions from SAS with the calcium ions from the calcium chloride (CaCl_2) solution, yielding pure calcium aluminosilicate with spherically-shaped particles (CAS).

This product is characterized as follows:

- (i) Chemical analysis of the product (contents of Na_2O , CaO , Al_2O_3 and SiO_2) is determined by atomic absorption spectroscopy. The content of water is determined from the mass difference before and after calcinations at 800°C for 2 hours.
- (ii) Shape of CAS particles is determined from scanning-electron microscope images (scanning-electron microscopy – SEM; Fig. 1).
- (iii) Particle size distribution curves of CAS were determined with Mastersizer 2000 (Malvern Instruments) laser light-scattering particle size analyzer.
- (iv) The external specific surface areas (RSP) of samples were measured by using Gemini 2360 (Micrometrics).

Properties of CAS

Chemically, CAS is hydrated calcium aluminosilicate having the chemical composition:

0.311 – 0.732 wt. % Na_2O ,

14.712 – 15.360 wt, % CaO ,

27.643 – 28.450 wt. % Al_2O_3 ,

33.248 – 35.193 wt. % SiO_2 and

20.446 – 23.273 wt. % H_2O ,

as it is determined by chemical analysis. Small variation in the chemical composition are caused either by variations of the chemical composition of starting sodium aluminosilicate suspension or by expected experimental errors of the applied method, including the expected errors during sample preparations. Small amount of Na_2O is a consequence of incomplete exchange of original sodium ions from SAS with the calcium ions from solution. Calcium ions in CAS are exchangeable and thus, they can be exchanged with other cations from solution.

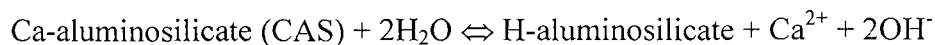
Particles of CAS have size in the range between $0.4\ \mu\text{m}$ and $4\ \mu\text{m}$ (see Fig. 2) and average particle size in the range between $1.237\ \mu\text{m}$ and $1.848\ \mu\text{m}$.

Particles of CAS, synthesized as individual ones, are characterized by unexpected spheroidal shape of each single particle. CAS is not composed of aggregates or accumulation of particles; see Fig.1. Also unexpectedly, CAS is characterized by expressed external surface roughness without distinguishing crystal faces (Fig.1b; SEM, magnification: 30.000×). The high external surface roughness of CAS is also indicated by unexpectedly high ratio between real specific surface area ratio (RSSA) determined by the Brunauer-Emmett-Teller (BET) method and geometrical specific surface area (GSSA) [A. Peiquey et al., *Carbon* **39** (2001) 507-514; K. Kaneko, C. Ishii, *Colloids and Surfaces* **67** (1992) 203-212] calculated from the corresponding particle size distribution curves of CAS ($RSSA/GSSA = 2.58 - 2.81$). These values of the ratio $RSSA/GSSA$ mean that the specific surface area of CAS is 2.58 – 2.81 times larger than the specific surface area of the material having the same particle size as CAS, but with flat surface.

Stabilizing ability of CSA

Solubility of mineral part of tooth (enamel, dentine) and thus its stability strongly depends on the pH in mouth cavity; solubility of hydroxyapatite, which is major part of enamel and dentine, decreases with increase of pH (see Fig. 3). In this way, pH is one of the most important factors for the control of stability of mineral parts of tooth and thus, for the control of caries development [M.E. Jensen, *Cariology* **43** (1999) 615.].

Due to hydrolytic reaction:



water suspension of CAS is alkaline. Depending on the amount of CAS in the suspension, pH of suspension is between 8 and 9. This makes CAS a perspective agent for the stabilization of teeth.

Mineralizing ability of CAS

Mineralizing ability of CAS is related to the exchangeable calcium ions in CAS. However, the rate of (re)mineralization is controlled by the rate of “releasing” of calcium ions from CAS. Calcium ions “released” from CAS, build oneself into surface of enamel at optimal pH (~ 8). This results in a gradual formation of hydroxyapatite on the teeth surfaces and thus, (re)mineralization the teeth surfaces without the formation of defect hydroxyapatite crystals and/or incrustations. These factors make CAS an ideal source of calcium ions needed for (re)mineralization.

Desensitizing ability of CAS

Dentin contains many thousands of microscopic tubular structures that radiate outwards from the pulp; these dentinal tubules are usually 0.5-2 micrometers in diameter (Fig. 4A.). Changes in the flow of the plasma-like biological fluid, present in the dentinal tubules can trigger mechanoreceptors present on nerves, thereby eliciting a pain response. The mentioned hydrodynamic flow can be increased by cold, air pressure, dryness, sugar, acids, or forces acting onto the tooth. One of the most efficient ways to prevent (hyper)sensitivity is physical occlusion of dentinal tubules by appropriate material. Due to: (i) its size (0.4 – 4 μm and 50 % of particles with the size less than 1.5 μm and 90 % of particles with the size less than 2.5 μm ; Fig. 2), which is comparable with the size of tubules (Fig. 4A), (ii) spherical shape (Fig. 1) which enables a “dense” packaging of CAS particles in tubules and thus, efficient occlusion of dentinal tubules (Figs. 4B and 4C) and (iii) chemical composition (insoluble aluminosilicate matrix and exchangeable calcium ions) makes CAS almost ideal candidate for desensitizing agent. Unexpectedly was shown that all oral compositions effectively occlude the dental tubules even during the short time application. Thus, application of CAS by expert is not necessary, but tubules will be occluded by application of the dental formulation related to this invention.

Polishing ability of CAS

Due to the principle that polishing of teeth should be completed with polishing particles less than 12 μm [E. Takanashi, R. Kishikawa, M. Ikeda, N. Inai, M. Otsuki, R.M. Foxton, J. Tagami, Influence of abrasive particles on surface properties of flowable compositions, *Dent. Mater. J.* 27 (2008)780-786.], CAS is, by its particles size, recognized as effective polishing agent.

Excipients and optional ingredients

One or more excipients and optional ingredients (75 – 99 wt. %) is required to produce a desired final dosage form: oral suspension (mouthwash), toothpaste, gel (denture adhesive), and chewing gum.

These ingredients are selected from the groups comprising excipients, diluents, fillers, humectants, thickeners (or binding agents), basic gums, softeners, sweeteners, flavors, surface active agents (foaming agents and solubilizers), preservatives, antioxidants, stabilizers, and other exquisite ingredients.

Diluents in oral suspensions and dentals gels are selected from the group containing purified water, ethanol, or their mixtures.

Fillers, abrasives and polishing agents can be the compounds such as microcrystalline cellulose, aluminum hydroxide $[\text{Al}(\text{OH})_3]$, calcium sulfate dihydrate ($\text{CaSO}_4 \cdot 2\text{H}_2\text{O}$), calcium carbonate (CaCO_3), calcium pyrophosphate ($\text{Ca}_2\text{P}_2\text{O}_7$), colloidal hydrated silicic acid ($\text{SiO}_2 \cdot x\text{H}_2\text{O}$), sorbitol, inulin, kaolin, talc, bentonite, magnesium carbonate (MgCO_3), basic magnesium carbonate $[(4\text{MgCO}_3 \cdot \text{Mg}(\text{OH})_2 \cdot 4\text{H}_2\text{O})]$, calcium silicate (CaSiO_3) and the mixtures of two or more of mentioned compounds, taking into consideration that the list of compounds is not completed and for the purpose of fillers, abrasives and polishing agents may also be used the compounds which are not listed here, but which are, to the average expert in the field, known as fillers, abrasives and polishing agents which are used in dental preparations.

Humectants are selected from the group comprising glycerol,

1,2-propylene-glycol, 1,3-propylene-glycol, liquid polyethylene-glycols, liquid polyglycerols, aqueous solutions of sorbitol, or their mixtures.

Thickeners, which in the formulations from the present invention: dental gel, oral suspension and toothpaste, serve also as binding agent, are selected from the group comprising polyacrylic acid, its co-polymers, or their sodium, or potassium salts; methylcellulose; sodium carboxy-methylcellulose; 2-hydroxy-ethyl-cellulose; 2-hydroxy-propyl-cellulose; 2-hydroxy-propyl methyl-cellulose, polyglycerols; polyethylene-glycols; agar agar; carrageenan's; gum Arabic; alginic acid and its sodium salt; tragacanth gum; karaya gum; bentonite; or their mixtures.

Basic gums as excipients in the formulation of chewing gums from the present invention are selected from the following group of compounds: poly-isoprene (natural rubber), isobutylene-isoprene copolymers (butyl elastomer; $M_w = 10.000-100.000$); styrene-butadiene copolymers (molar ratio 1:3 to 3:1; $M_w = 10.000-65.000$), polyvinyl acetate (PVA; $M_w = 2.000-90.000$); polyethylene; or their mixtures.

Softeners as excipients in chewing gums can be, for example, higher fatty acids like stearic, palmitic, or oleic acid; vegetable oils such as coconut, rapeseed, and sunflower seed oils; partially hydrogenated vegetable oils like hydrogenated castor oil; lecithin; mono- and diglycerides like glyceryl monostearate; waxes such as beeswax, Chinese wax, Candelilla wax, soybean wax, Jojoba oil, paraffin wax, microcrystalline wax; lanolin; esters of colophony; shellac; and mixtures of these substances.

Sweeteners are selected from the group consisting saccharose, fructose, glucose, glucose syrup, honey, sodium saccharin, acesulfame of potassium, sucralose, sodium or calcium cyclamate, xylitol, sorbitol, erythritol, maltitol, lactitol, glycyrrhizin, extract of Liquor-ice (*Glycyrrhiza glabra L.*) root, stevioside, rebaudioside A, extract of Stevia (*Stevia rebaudiana L.*), or their mixtures.

Flavors and accessory compounds are selected from the group of the compounds recognized as safe, edible natural compounds from the classes of:

- (i) organic acids (e.g. citric, malic, tartaric);
- (ii) pure terpenes (e.g. eucalyptol, L-menthol, limonene, camphor, citral, carvone);

- (iii) phenols and phenol ethers (e.g. thymol, methyl salicylate, eugenol, vanillin, ethyl vanillin, anethole);
- (iv) amino acids, usually as taste amplifier (e.g. sodium glutamate),
- (v) dry and liquid extracts, concentrates and essential oils of various herbs [e.g. peppermint (*Mentha piperita* L.), thyme (*Thymus vulgaris* L.), cinnamon (*Cinnamomum zeylanicum* L.), clove (*Syzygium aromaticum* L.), lemon balm (*Melissa officinalis* L.), lemon (*Citrus limonum*), sweet orange (*Citrus sinensis*), fennel (*Foeniculum vulgare* L.), anise (*Pimpinella anisum* L.), caraway (*Carum carvi* L.), green tea (*Camellia Sinensis* - epigallocatechin gallate) nutmeg (*Myristica fragrans* L.), etc.] and mixtures of these substances. It is known to those who are skilled in various uses of flavors, when they are applied in slightly increased amounts, can also exhibit accompanied effects such as odor-masking and disinfecting (antimicrobial) like thymol or eugenol.

Surface active substances (ionic and non-ionic tensides) which serve as foaming agents and solvents are selected from the group containing sodium lauryl sulfate, sodium lauryl ethylene glycol sulfate, sodium lauryl di-ethylene glycol sulfonate; sodium cocoamphodipropionate; disodium cocoamphodiacetate; dioctyl sodium sulphosuccinate; sodium laurylsulfoacetate; sodium laurylsarcosinate; ethoxylates of higher fatty alcohols like polyoxyethylene (23) laurylether, with H.L.B. value ≥ 10 ; ethoxylates of higher fatty acids like polyoxyethylene (23) oleate, with H.L.B. value ≥ 10 ; polyglyceryl derivatives of higher fatty alcohols with H.L.B. value ≥ 10 ; polyoxyethylene sorbitan esters of higher fatty acids like polyoxyethylene sorbitan monostearate, with H.L.B. value ≥ 10 ; or their mixtures.

Preservatives are selected from the group comprising of methyl 4-hydroxybenzoate, ethyl 4-hydroxybenzoate, propyl 4-hydroxybenzoate, butyl 4-hydroxybenzoate, sorbic acid, potassium sorbate, benzoic acid, sodium benzoate, 2-phenoxyethanol, 4-chloro-m-cresol, thymol, eugenol, or their mixtures.

Antioxidants are selected from the group comprising of 2,6-di-*tert*-butyl-4-hydroxytoluene (BHT), *tert*-butyl hydroxyanisole (BHA), EGCG,

tocopherol, tocopherol acetate, ascorbic acid, or their mixtures.

Stabilizers are selected from the group comprising of disodium citrate $[\text{Na}_2\text{C}(\text{OH})(\text{COOH})(\text{CH}_2\text{COO})_2]$, disodium ethylenediamine tetra acetate $(\text{Na}_2\text{EDTA}\cdot 2\text{H}_2\text{O})$, or their mixtures.

The ingredients chosen from the formulation of the present invention, serve as adjuvants, in order to achieve additional cosmetic and health effects. Here are included: sources of fluorides antimicrobials and astringents.

Fluorides as caries-preventing additives in dentifrices are selected from the group comprising of sodium fluoride (NaF), potassium fluoride (KF), sodium monofluorophosphate $(\text{Na}_2\text{PO}_3\text{F})$, stannous fluoride (SnF_2) , or their mixtures.

Antimicrobials are selected from the group comprising: boric acid or sodium borate; quaternary ammonium compounds such as cetylpyridinium chloride, benzalkonium chloride, or cetyltrimethylammonium bromide; carbamide, hydrogen peroxide; hexylresorcinol; hexachlorophene; triclosan; chlorhexidine gluconate or hydrochloride; hexetidine; iodine; sodium N-chloro tosyl amide; potassium chlorate; and compatible mixtures of these substances.

Astringents are selected from the group comprising zinc or aluminum salts such as zinc phosphate $[\text{Zn}_3(\text{PO}_4)_2]$, zinc chloride (ZnCl_2) , zinc iodide (ZnI_2) , zinc sulfate heptahydrate $(\text{ZnSO}_4\cdot 7\text{H}_2\text{O})$, zinc acetate dihydrate $[\text{Zn}(\text{CH}_3\text{COO})_2\cdot 2\text{H}_2\text{O}]$, aluminum sulfate octadecahydrate $[\text{Al}_2(\text{SO}_4)_3\cdot 18\text{H}_2\text{O}]$, aluminum acetate $[\text{Al}(\text{CH}_3\text{COO})_3]$, aluminum acetotartarate $[\text{Al}(\text{CH}_3\text{COO})(\text{CH}(\text{OH})\text{COO})_2]$, potassium aluminum sulfate dodecahydrate $[\text{Al}_2(\text{SO}_4)_3\cdot 12\text{H}_2\text{O}]$, or their mixtures, or pharmaceutically acceptable acids, or extracts of herbs with significant percentage of tannins such as Oak bark (*Cortex Quercus*), Witch hazel (*Hamamelis virginiana L.*), Peru balsam (*Mynoxylon balsamum L.*), Common sage (*Salvia officinalis L.*), walnut leaves (*folia Juglandis*) and Common Silverweed (*Argentina anserina L.*),

The formulations of this invention involve the final desired dosage and forms of oral suspension (mouthwash), toothpaste, dental gel (denture adhesive), and chewing gum. The formulations are produced by common procedures known to those skilled in the art of pharmaceutical technology [J. N. Ingle: *Encyclopaedia of Pharmaceutical*

Technology (2000) Marcel Dekker Inc., USA].

Oral suspension (mouthwash) is obtained by dispersion of CAS in purified water or its mixtures with ethanol in the presence of suitable thickener(s) which stabilize(s) final suspension in order to prevent precipitation. Finally the oral suspension is stabilized by addition of preservatives such as methyl- and propyl-4-hydroxybenzoate, antioxidant (e.g., BHT), stabilizer (e.g., Na₂EDTA), and eventually colors (e.g. brilliant blue FCF; E133).

Toothpaste is produced by mixing CAS with one or more fillers and suspension of thickener (herein as binder) and humectant in purified water. Thus obtained base paste is further processed by addition of chosen optional ingredients: antimicrobial agents (e.g. hexetidine) and/or astringents (e.g. zinc phosphate [Zn₃(PO₄)₂]), sweeteners (e.g. sodium saccharin), flavors (e.g. peppermint oil), preservatives (e.g. methyl 4-hydroxybenzoate), stabilizers (e.g. disodium citrate [Na₂C(OH)(COOH)(CH₂COO)₂]), and eventually certified colors.

Dental gel (denture adhesive) is prepared by vigorous mixing of purified water or aqueous ethanol and thickener, yielding the base gel which is then subjected to addition of CAS and other excipients such as sweetener, flavor, and eventually antimicrobial agent, and/or astringent, and certified colors.

Chewing gum is produced by melting of base gum at 110-120 °C, followed by addition of CAS, fillers, softeners, sweeteners, flavors, preservatives, and antioxidants, in the melted base gum. Such produced homogeneous mixture is poured into cooling belts yielding large pieces which are subsequently processed by extrusion and cutting (or rolling) into final shapes of chewing gums. Thereafter, such obtained form of chewing gum can be coated with suitable glazing agent. The latter is usually various waxes (e.g. paraffin wax), or mixtures of wax and certified colors.

The formulations from the present invention can also be produced by numerous variants of these and similar techniques, so that all possible forms of invention are not mentioned in the examples.

EXAMPLES

Example 1: Preparation of SAS

The synthesis suspensions are prepared by mixing of sodium aluminate solution (having appropriate chemical composition with respect to Na_2O , Al_2O_3 and H_2O) and sodium silicate solution (having appropriate chemical composition with respect to Na_2O , SiO_2 and H_2O) at temperature T_p . Such obtained suspensions contain:

7.586 wt. % Na_2O ; 4.425 wt. % Al_2O_3 ; 3.398 wt. % SiO_2 and 84.600 wt. % H_2O ; $T_p = 20\text{--}25\text{ }^\circ\text{C}$, for the synthesis of SAS by procedure **P#1 (SAS-P#1)**

11.695 wt. % Na_2O ; 4.229 wt. % Al_2O_3 ; 3.238 wt. % SiO_2 and 80.838 wt. % H_2O ; $T_p = 65\text{--}70\text{ }^\circ\text{C}$, for the synthesis of SAS by procedure **P#2 (SAS-P#2)**

10.249 wt. % Na_2O ; 6.485 wt. % Al_2O_3 ; 4.966 wt. % SiO_2 and 78.300 wt. % H_2O ; $T_p = 20\text{--}23\text{ }^\circ\text{C}$, for the synthesis of SAS by procedure **P#3 (SAS-P#3)**

9.945 wt. % Na_2O ; 8.251 wt. % Al_2O_3 ; 5.837 wt. % SiO_2 and 75.967 wt. % H_2O ; $T_p = 50\text{--}55\text{ }^\circ\text{C}$, for the synthesis of SAS by procedure **P#4 (SAS-P#4)**

10.478 wt. % Na_2O ; 9.379 wt. % Al_2O_3 ; 7.735 wt. % SiO_2 and 72.408 wt. % H_2O ; $T_p = 50\text{--}55\text{ }^\circ\text{C}$, for the synthesis of SAS by procedure **P#5 (SAS-P#5)**

Spherically-shaped sodium aluminosilicates are prepared by hydrothermal treatment of aluminosilicate suspension at:

$T_R = 85 - 90\text{ }^\circ\text{C}$ for the synthesis of SAS by procedure **P#1 (SAS-P#1)**

$T_R = 70 - 80\text{ }^\circ\text{C}$ for the synthesis of SAS by procedure **P#2 (SAS-P#2)**

$T_R = 65 - 75\text{ }^\circ\text{C}$ for the synthesis of SAS by procedure **P#3 (SAS-P#3)**

$T_R = 70 - 75\text{ }^\circ\text{C}$ for the synthesis of SAS by procedure **P#4 (SAS-P#4)**

$T_R = 75 - 80\text{ }^\circ\text{C}$ for the synthesis of SAS by procedure **P#5 (SAS-P#5)**

for:

$t_R = 135$ min for the synthesis of **SAS** by procedure #1 (**SAS-P#1**)

$t_R = 60$ min for the synthesis of **SAS** by procedure #2 (**SAS-P#2**)

$t_R = 120$ min for the synthesis of **SAS** by procedure #3 (**SAS-P#3**)

$t_R = 90$ min for the synthesis of **SAS** by procedure #4 (**SAS-P#4**)

$t_R = 60$ min for the synthesis of **SAS** by procedure #5 (**SAS-P#5**)

The product (**SAS**) is from the liquid phase separated by vacuum filtration and washed with several portions of demineralized water until pH of filtrate reached 9-10. The product is dried at 105 °C for 24 h. After drying, the product (**SAS**) appears in the form of white fine powder.

Example 2: Preparation of CAS by exchange of the sodium ions from SAS with calcium ions from solution

About 160 g of dry sample (**SAS**) is placed into a 1500 ml beaker containing 800 ml 1.1 M CaCl_2 solution preheated at 80 °C. Such obtained suspension, thermostated at 80 °C, is stirred for 2 h. Thereafter, the solid phase is separated from solution by centrifuging and washed with several portions of demineralized water. The wet washed solid phase is again placed into a 1500 ml beaker containing 800 ml of freshly prepared 1.1 M CaCl_2 solution preheated at 80 °C. The obtained suspension, thermostated at 80 °C, is stirred for 2 h. Once again, the solid phase (**CAS**) is separated from solution by centrifuging, and washed with several portions of demineralized water until negative reaction of filtrate on chloride ions. The washed product is dried at 105 °C overnight. Such obtained **CAS** appears in the form of fine white powder.

Example 3: Chemical analysis of CAS

Chemical compositions of the products (**CAS-P#1**, **CAS-P#2**, **CAS-P#3**, **CAS-P#4** and **CAS-P#5**), obtained by exchange of sodium ions from **SAS-P#1**, **SAS-P#2**, **SAS-P#3**, **SAS-P#4** and **SAS-P#5** with calcium ions from solution in accordance with Example 2, are determined as follows: The dried solid samples are kept in a desiccators with saturated NaCl solution for 96 h.

To determine a total content of water, a part of sample is equilibrated over saturated NaCl solution, weighed and then calcined at 800 °C for 2 h. After calcination, the sample is cooled down in desiccators over the dry silica gel. From the

weights of sample before (m_o) and after calcination (m_c), the total content of water, $((H_2O)_{tot}$ in wt. %), was calculated as:

$$(H_2O)_{tot} = 100(m_o - m_c)/m_o$$

Determination of the contents of calcium (Ca), sodium (Na), aluminum (Al) and silicon (Si) are conducted as follows: a given amount of calcined (waterless) sample is dissolved in 1:1 HCl solution. The solution is diluted with demineralized water to the concentration ranges available for measuring the concentrations of Na, Ca, Al and Si by atomic absorption spectroscopy (AAS). The contents of Na, Ca, Al and Si (in oxide forms; Na_2O , CaO , Al_2O_3 , SiO_2) in the samples are calculated from the measured concentrations of Na, Ca, Al, and Si in the solutions and quantity of the calcined sample dissolved in known volumes of solutions. The following results are obtained:

$Na_2O = 0.411$ wt.%; $CaO = 15.136$ wt.%; $Al_2O_3 = 28.207$ wt.%; $SiO_2 = 33.248$ wt.%; $H_2O = 22.998$ wt.% for CAS-P#1,

$Na_2O = 0.538$ wt.%; $CaO = 14.712$ wt.%; $Al_2O_3 = 27.643$ wt.%; $SiO_2 = 33.870$ wt.%; $H_2O = 23.237$ wt.% for CAS-P#2,

$Na_2O = 0.732$ wt.%; $CaO = 15.110$ wt.%; $Al_2O_3 = 28.670$ wt.%; $SiO_2 = 33.439$ wt.%; $H_2O = 22.049$ wt.% for CAS-P#3

$Na_2O = 0.311$ wt.%; $CaO = 15.360$ wt.%; $Al_2O_3 = 28.450$ wt.%; $SiO_2 = 35.193$ wt.%; $H_2O = 20.446$ wt.% for CAS-P#4 and

$Na_2O = 0.431$ wt.%; $CaO = 15.214$ wt.%; $Al_2O_3 = 28.381$ wt.%; $SiO_2 = 33.436$ wt.%; $H_2O = 22.538$ wt.% for CAS-P#5

Example 4: Morphology of CAS

Morphology of the particles of CAS is determined by scanning electron microscopy (SEM). SEM images of the particles of CAS (representative for all the samples prepared by the procedures described in the Examples 1 and 2) show that the particles of CAS have spheroidal shape (Fig. 1) without clearly expressed and recognizable crystal faces and that, surprisingly and unexpectedly appear in the form of face-less, spheroidal particles with high external surface roughness (Fig. 1B).

Example 5: Particle size distribution of CAS:

Particle size distribution curves of CAS are determined by the laser light scattering method using the apparatus Mastersizer 2000 (Malvern Instruments). For this purpose, water suspensions of CAS, containing ca. 1 % of CAS, are prepared. The suspensions are sonicated before the determination of particle size distribution. The particles of CAS have the sizes in micrometer range (about 0.4–4 μm , regardless to synthesis procedure used; see particle size distribution curve in Fig. 2) with:

50% of all particles lesser than 1.45 μm (D_{50}), 90% of all particles lesser than 2.35 μm (D_{90}) and average size, $D_{av} = 1.848 \mu\text{m}$ for CAS-P#1;

50% of all particles lesser than 1.10 μm (D_{50}), 90% of all particles lesser than 1.75 μm (D_{90}) and average size, $D_{av} = 1.235 \mu\text{m}$ for CAS-P#2;

50% of all particles lesser than 1.30 μm (D_{50}), 90% of all particles lesser than 2.75 μm (D_{90}) and average size, $D_{av} = 1.875 \mu\text{m}$ for CAS-P#3;

50% of all particles lesser than 1.10 μm (D_{50}), 90% of all particles lesser than 1.64 μm (D_{90}) and average size, $D_{av} = 1.20 \mu\text{m}$ for CAS-P#4;

50% of all particles lesser than 1.0 μm (D_{50}), 90% of all particles lesser than 1.5 μm (D_{90}) and average size, $D_{av} = 1.15$ for CAS-P#5;

Example 6: Real (BET) specific surface area (RSSA) of CAS:

The external real specific surface area (RSSA) of samples is determined by multiple BET method by using nitrogen as adsorbents at the temperature of liquid nitrogen (-195.6°C). Prior the analysis, the samples are dried at 105°C for one hour. The external real specific surface areas of the analyzed samples, calculated on the basis of BET isotherm are:

$\text{RSSA} = 2.375 \pm 0.025 \text{ m}^2/\text{g}$ for CAS-P#1;

$\text{RSSA} = 3.562 \pm 0.046 \text{ m}^2/\text{g}$ for CAS-P#2;

$\text{RSSA} = 4.433 \pm 0.061 \text{ m}^2/\text{g}$ for CAS-P#3;

RSSA = $2.970 \pm 0.036 \text{ m}^2/\text{g}$ for CAS-P#4 and

RSSA = $4.000 \pm 0.054 \text{ m}^2/\text{g}$ for CAS-P#5.

Example 7: Geometrical specific surface area (GSSA) of CAS:

The corresponding values of GSSA are determined from the corresponding particle size distribution data as:

$$\text{GSSA} = [0.524 \times \sum N_i \times (D_i)^2] / [3.145 \times \rho \times \sum N_i \times (D_i)^3]$$

where D is the diameter of CAS particles and N_i is the number frequency of the particles having the size (diameter) D . The corresponding values of GSSA are:

GSSA = $0.921 \text{ m}^2/\text{g}$ for CAS-P#1;

GSSA = $1.269 \text{ m}^2/\text{g}$ for CAS-P#2;

GSSA = $1.593 \text{ m}^2/\text{g}$ for CAS-P#3;

GSSA = $1.095 \text{ m}^2/\text{g}$ for CAS-P#4 and

GSSA = $1.431 \text{ m}^2/\text{g}$ for CAS-P#5.

The corresponding values of the ratio RSSA/GSSA ratios between real (RSSA; see Example 6) and geometrical (GSSA; see Example 7) specific surface areas are:

RSSA/GSSA = 2.58 for CAS-P#1;

RSSA/GSSA = 2.81 for CAS-P#2;

RSSA/GSSA = 2.78 for CAS-P#3;

RSSA/GSSA = 2.71 for CAS-P#4 and

RSSA/GSSA = 2.80 for CAS-P#5.

Example 8. Preparation of the formulation from the present invention in the form of oral suspension

Composition (1000 g of oral suspension): (a) calcium aluminosilicate with spherical particles - CAS (20.00 g; 2 wt. %), (b) 2-hydroxyethyl cellulose (12.00 g; 1.2 wt. %), (c) bentonite (20.00 g; 2% wt. %), (d) polyoxyethylene sorbitan monostearate (10.00 g; 1 wt. %), (e) sodium lauryl sulfate (8.00 g; 0.8 wt. %), (f) xylitol (15.00 g; 1.5 wt. %), (g) glycerol (25.00 g; 2.5 wt. %), (h) sorbitol (25.00 g of 70 % solution; 2.5 wt.%), (i) 1,2-propylene glycol (5.00 g; 0.5 wt. %); (j) peppermint oil (0.20 g; 0.02 wt. %), (k) thymol (0.10 g; 0.01 wt. %), (l) methyl salicylate (0.10 g; 0.01 wt. %),

(m) brilliant blue (10.00 g of 1% aqueous solution; 1 wt. %), (n) chlorhexidine di-hydrochloride (0.10 g; 0.01 wt. %), (p) purified water (849.5.00 g; 84.95 wt. %).

Procedure: Ingredients (d) and (e) are added into (p), and dissolved by mixing at room temperature (20-25 °C) during 15 minutes. Such obtained solution was heated to approx. 40-45 °C. Then (b) is added in portions and dissolved during mixing for 15 minutes. Ingredients (a) and (c) are added and then, the obtained mixture is homogenized for 5 minutes. Then, in such obtained mixture, the ingredients (f), (g), (h), (m), and (n) are added and then, the newly obtained mixture is homogenized by stirring for 15 minutes. Finally the separately prepared solutions of (j), (k), (l) and (i) are added to the previously prepared suspension, whereupon, the newly obtained suspension is homogenized by stirring for 30 minutes at room temperature. Such obtained product was a white liquid suspension of satisfied stability, and fresh, agreeable taste of mint.

Example 9a. Preparation of the formulation from the present invention, in the form of toothpaste

Composition (1000 g of toothpaste): (a) calcium aluminosilicate with spherical particles - CAS (40.00 g; 4 wt. %), (b) silica (100 g; 10 wt. %), (c) sodium carboxymethylcellulose (10.00 g; 1 wt. %), (d) sodium lauryl sulfate (12.00 g; 1.2 wt. %), (e) glycerol (400.00 g; 40 wt. %), (f) sorbitol (150.00 g of 70% solution; 15 wt. %), (g) peppermint oil (5.00 g; 0.5 wt. %), (h) L-menthol (2.00 g; 0.2 wt. %), (i) methyl salicylate (2.00 g; 0.2 wt. %), (j) sodium saccharin (1.20 g; 0.12 wt. %), (k) purified water (277.80 g; 27.78 wt. %).

Procedure: Ingredients (a) and (b) are added into previously prepared mixture of (k), (e), and (f), and stirred at room temperature (20-25 °C) during 30 minutes. Then, the ingredient (c) is added, whereupon the obtained mixture is stirred at room temperature for 1 h. Then, in such obtained viscous mixture, the ingredients (d), (g), (h), (i), and (j) are added, whereupon the obtained mixture is additionally homogenized for 1 h. The obtained product appears in the form of white paste of satisfied stability and agreeable taste. pH of the toothpaste, prepared by the above described procedure is 8.0

Example 9b. Preparation of the formulation from the present invention in the form of toothpaste

Composition (1000 g of toothpaste): (a) calcium aluminosilicate with spherical particles - CAS (50.00 g; 5 wt. %), (b) glycerin (200.00 g; 20 wt. %), (c) carbomer (22.00 g; 2.2 wt. %), (d) xylitol (0.5 g; 0.05 wt.%), (e) sodium lauryl sulfate (14.20 g; 1.42 wt. %), (f) hydrated silica (175 g; 17.5 wt. %), (g) silicate BLD (30.00 g; 3 wt. %), (h) sodium alginate (25.00 g; 2.5 wt. %), (i) flavor (7.00 g; 0.7 wt. %), (j) purified water (469.5 g; 46.95 wt. %) and (k) color (6.80 g; 0.68 wt. %).

Procedure: Carbomer (c) is slowly added into the vessel containing glycerin (b) , under gently mixing at room temperature until the mixture becomes homogeneous and then, the components (a), (h), (i), (j) and (k) are added to the homogeneous mixture and the newly prepared mixture is gently mixed until the mixture is homogeneous, whereupon the components (d), (e), (f) and (g) are added and the obtained mixture is additionally mixed to obtain a homogeneous paste. pH of the toothpaste, prepared by the above described procedure is 8.2

Example 9c. Preparation of the formulation from the present invention in the form of toothpaste

Composition (1000 g of toothpaste): (a) calcium aluminosilicate with spherical particles - CAS (20.00 g; 2 wt. %), (b) silica (100 g; 10 wt. %), (c) sodium carboxymethylcellulose (10.00 g; 1 wt.%), (d) sodium lauryl sulfate (12.00 g; 1.2 wt. %), (e) glycerol (420.00 g; 42 wt. %), (f) sorbitol (150.00 g 70 % solution; 15 wt. %), (g) peppermint oil (5.00 g; 0.5 wt. %), (h) L-menthol (2.00 g; 0.2 wt. %), (i) methyl salicylate (2.00 g; 0.2 wt. %), (j) sodium saccharine (1.20 g; 0.12 wt. %), (k) purified water (277.80 g; 27.78 wt. %).

Procedure: The components (a) and (b) are added to previously prepared mixture of (k), (e) and (f) and stirred at room temperature for 30 min. Then the component (c) is added, whereupon the obtained mixture is stirred at room temperature for 1 h. In such obtained viscose mixture are added components (d), (g), (i) and (j) and such obtained

mixture is homogenized for 1 h. The obtained product appears in the form of white paste of satisfied stability and agreeable taste.

Example 10. Preparation of the formulation from the present invention in the form of dental gel

Composition (1000 g of gel): (a) calcium aluminosilicate with spherical particles - CAS (50.00 g; 5 wt. %), (b) methyl cellulose (70.00 g; 7 wt. %), (c) sugar (200 g; 20 wt. %), (d) purified water (680.00 g; 68 wt. %).

Procedure: In a vacuum vessel containing water (d) is, under mixing, added sugar (c) and then CAS (a) and methyl cellulose (b).

The obtained mixture is mixed under vacuum for 20 min, i.e., until the reaction mixture becomes homogeneous. pH of the dental gel, prepared by the above described procedure is 8.2.

Example 11 Preparation of the formulation from the present invention in the form of chewing gum

Composition (1000 g of gel): (a) calcium aluminosilicate with spherical particles - CAS (20.90 g; 2.09 wt. %), (b) base gum (260.00 g; 26 wt. %); (c) sugar (560.00 g; 56 wt. %), (d) glucose syrup (159.00 g; 15.9 wt. %) and (e) flavor (1.00 g; 0.01%).

Procedure: Base gum is heated to the melting point when it becomes liquid and then is filtered. In the filtered base gum are, under stirring in vacuum vessel, added the components (a), (c), (d) and (e).

Obtained mixture of all ingredients is mixed until a homogeneous mass, having the density like a pastry, is obtained. Such obtained "pastry" is placed in the extruder or in the moulds where the chewing gum assumes the final shape.

Example 12: pH control

Five (5) persons were subjected to the measuring of pH at the teeth surfaces by using strips for pH measurement (Color pH AST, Merck EM Science), 10 minutes after consummation of different foods. In all the cases, the measured pH was between 6.5 and 6.8. 15 minutes after consummation of food, the tested persons were treated (brushed) the teeth by the preparation from Example 9b. pH on the teeth surface is

measured again 5 minutes after treatment. In all the cases, the measured pH was between 7.2 and 7.8. The measured pH did not change at least 4 hours after the treatment.

Example 13: Stabilization effect

Examination of the influence of CAS on the stabilization of tooth enamel was conducted on 12 intact human molars, extracted from orthodontic reason. Each tooth sample was divided in two parts. One moiety of each tooth was immersed in 10 ml of the corresponding suspension of CAS (0.1, 1 and 10 wt. %) thermostated at 37 °C and another moiety of each tooth was used as control. Times of contact of tooth with the suspension were $t = 10, 30, 60$ and 300 min. The moment of placing of tooth to suspension is used as the zero time ($t = 0$) of treatment. After the predetermined times of treatment, the treated moieties of teeth are washed with demineralized water and dried. Thereafter, each treated tooth and it's another, untreated moiety (control) were treated with 0.4 M acetic acid at 37 °C for 12 h (demineralization) under dynamic conditions. The ratio of the volume of tooth relative to the volume of 0.4 M solution of acetic acid was 1:1. After 12 h of treatment, samples of teeth were separated from the solutions and then, the concentration of calcium ions were determined in the solutions by atomic absorption spectrophotometry (AAS). The measured results, expressed as the percentage of the diminishing (%S) of the concentration of calcium ions in solution, caused by treatment, are shown in Fig. 5. The obtained results undoubtedly show that the treatment of teeth with the suspension of CAS in HV causes a considerable increasing of the stability of tooth enamel, as it was shown by the decrease of concentration of calcium ions in 0.4 M solution of acetic acid, as the consequence of the decreasing solubility of the tooth enamel after the treatment of teeth with the suspension of CAS in HV. Average value %S gradually increases from %S = 7 for $t = 10$ min, reaches the maxim value %S = 23 for $t = 60$ min and this value does not considerably change during the prolonged treatment. The presented results undoubtedly confirm that the stabilization of the tooth enamel is time-determined process. Or, in the other words, the toothpaste from the present invention possesses the prolonged effect relative to existing and generally known

preparations.

Example 14: (Re) mineralization effect

Demineralizing effect of the preparations containing CAS was examined by comparison of the scanning electron micrographs of demineralized teeth, before and after treatment with the preparation.

Segment of an intact tooth was treated by the preparation from the Example 9b, which contains 5 wt. % of CAS, for 20 seconds. Thereafter, the preparation was kept on the tooth for 80 seconds and then, the surface of tooth was rinsed with demineralized water. This procedure was repeated 4 times. After fourth repetition of the procedure, the tooth is rinsed and dried and the surface of such treated tooth was analyzed by scanning electron microscopy (SEM). The SEM micrograph in Fig. 6 clearly shows that the particles of CAS remained in the cracks on the tooth surface and even that the cracks are completely filled with the particles of CAS, after the treatment of tooth with the preparation.

A segment of the same tooth was demineralized in 0.4 M acetic acid at 37 °C for 6 hours. The surface of such demineralized tooth, with recognizable damaged enamel, is shown in the scanning electron micrograph in Fig. 7A. Another segment of the same tooth was, after demineralization, immersed in HV and kept in it for 20 minutes. Thereafter, the tooth was treated with the preparation from the Example 9b containing 5 wt. % of CAS, by rubbing with rotatory motions of a soft toothbrush for 30 seconds. Thereafter, the preparation was kept on the tooth for 80 seconds and then, the surface of tooth was rinsed with demineralized water. This procedure was repeated four times. After fourth repetition of the procedure, the tooth is rinsed and dried and the surface of such treated tooth was analyzed by scanning electron microscopy (SEM). Fig. 7B clearly shows that the damage of enamel is considerably lower after the treatment than before the treatment. The process of „evening“ of the surface of enamel is supported by remaining of the particles of CAS in the cracks on the tooth surface (Fig. 6). This enables that, in accordance with the remineralization ability of CAS, the

processes of (re)mineralization take place after brushing (till the next brushing; see Example 12). Since the process of remineralization is the most intense in the vicinity of the particles of CAS, it is quite undoubtedly that the hydroxyapatite, formed during this process, precipitates on the surfaces of the particles of CAS which are placed in intercrystalline spaces and fractures on the tooth surface as well as in natural (pits and fissures) and acquired (micro fractures) defects of hard tissues. In this way, the intercrystalline spaces and fractures are not only filled by the particles of CAS, but also completely covered by hydroxyapatite.

Example 15: Desensitization effect

15.1 Desensitization ability of CAS is examined so that a segment of intact human molars was fixed and polished off by grinding in order to expose the tooth tubules. The tooth with open tubules (Fig. 4A) was treated with 2.5-percent perchloric acid and then, rinsed with demineralized water. After rinsing, the tooth was treated with the preparation from Example 9b, which contains 5 wt. % CAS, for 20 seconds and thereafter, the preparation was kept on the tooth for 80 seconds and then, the surface of tooth was rinsed with demineralized water and dried. After rinsing and drying, the surface of the treated tooth was analyzed by scanning electron microscopy (SEM). The corresponding SEM photographs (Figs. 4B and 4C) show that dental tubules are filled (occluded) with the particles of CAS. This, in a large extent, prevents the irritation of the mechanoreceptors present on the nerves positioned in the peripherally parts of pulp. After the treatment with the preparation, the tooth is immersed in 5 ml of HV. After 6, 12, 18, and 24 h of contact with HV, the teeth were separated from the HV and the surfaces of teeth were rinsed with demineralized water and dried. After rinsing and drying, the surface of tooth was analyzed by scanning electron microscopy (SEM). Fig. 8 clearly shows a gradual formation of hydroxyapatite on the surfaces of the particles of CAS and complete mineralization of the openings of tubules. This shows that, after the tubules are filled with the particles of CAS, a part of calcium ions from CAS was released to HV by the processes of ion exchange between the calcium ions from CAS and the ions from HV. The released calcium ions react with the components of HV, which results in the formation of apatites. Because

of alkaline hydrolysis of CAS, the reaction between calcium ions and the components of HV takes place in alkaline medium, which stipulates the formation of hydroxyapatite. On the other hand, since the maximum concentration of calcium ions is expected on the surface (or near the surface) of the particles of CAS, the formed hydroxyapatite precipitates onto the particles of CAS, deposited in tubules. In this way, tubules are, not only filled with the particles of CAS (Fig. 4), but also completely filled with hydroxyapatite (Fig. 8). It is quite doubtless that the same processes take place under real conditions (in the mouth cavity).

15.2 Five persons with expressive hypersensitivity of teeth to outer irritations (cold, hot) used the preparation from the Example 9b for daily maintaining hygiene of teeth and mouth cavity. Two, of the mentioned five persons, felt a considerable decrease of hypersensitivity already after the first application of the preparation, and other three of them felt a considerable decrease of hypersensitivity after one to three days of application. In all the mentioned cases, the hypersensitivity of teeth completely disappeared after a week of application of the preparation.

Example 16: Polishing effect

Polishing effect of CAS can be clearly observed in Fig.7 from Example 14. Fig. 7A shows the surface of tooth with recognizable irregular „structure“ of enamel. After treatment of teeth by the procedure described in Example 14, the surface of tooth is not only „levelling“ (Fig. 7B), relative to the surface before treatment (Fig. 7A), but exhibits a high degree of smoothness.

Example 17: Stoppage of bleeding

The bleeding, caused by the injury of the mucous membrane in mouth cavity, was stopped 7 – 10 seconds after use of the preparations from Examples 8, 9a and 10. which resulted by bleeding,

17.1. The person L.K. bit her tongue. After application of the preparation from Example 10, the bleeding was stopped 10 seconds after the application.

17.2. The person R.F. hurt his gingiva by tooth-brush. After application of the preparation from Example 10, the bleeding was stopped 8 seconds after the application.

17.3. The person O.L. hurt the palate of mouth cavity by eating hard food. After application of the preparation from Example 9a, the bleeding was stopped 7 seconds after the application.

Example 18: Healing of Wounds

By application of preparations from Examples 8 and 10, healing of the wounds, originated by damage of epithelium tissue of mucous membrane in mouth cavity, can be shortened for to 3 – 6 days.

18.1 The person G.N. had aphotic ulcer with diameter of 3 mm on the mucous membrane of face. By application of the preparation from Example 8, three times per day during 5 days, the ulcerous mutation has been healed.

18.2 The person F.L. had hurt of gingiva around teeth with ceramic substitute, after stomatological application of hydrofluoric acid. By application of the preparation from Example 10, three times per day during 3 days, the hurt has been healed.

Example 19: Gingivitis and periodontitis

By brushing the teeth of five patients with gingivitis, three times per day, with the preparation from Example 9a, the index of bleeding of gingiva of all the five patients diminished from degree 4 to degree 2 after 3-5 days of treatment, to degree 1 after 5 – 7 days of treatment, and the bleeding was completely stopped after 10 days of treatment.

Example 20: Regulation of salivation

Increased secretion of estrogen and progesterone causes the hyper salivation during pregnancy. Also, because of decreased concentration of bicarbonate ions and increased amount of alpha amylase in saliva, pH and buffer capacity of saliva, respectively, decrease. The female person with expressed hyper salivation in the first quarter of pregnancy, were treated with the preparation from Example 9a during 3 weeks, whereupon the salivation was normalized.

20.1 The female person with expressed hyper salivation in the fourth week of pregnancy, was treated with the preparation from Example 9a during 3 weeks, whereupon the salivation was normalized.

20.2 The female person with expressed hyper salivation in the sixth week of pregnancy, was treated with the preparation from Example 9a during 3 weeks, whereupon the salivation was normalized.

Example 21: Mobile prosthetic substitutes and mobile and fixed orthodontic devices

Acrylate structure of mobile prosthetic substitutes and mobile and fixed orthodontic devices becomes porous and thus, a reservoir for *Candida albicans*, which results with the inflammation of mucous membrane at the place of contact with acrylate, substitutes during the time.

21.1 Inflammation of hard palate, *palatitis protetica*, was observed on the patient which had teen years old totally acrylate mobile prosthesis with porous structure. Complete withdrawal of the signs in the region caught by inflammation was observed after the application of the preparation from Example 10, 3 times per day during 10 days.

21.2 Accumulation of tooth plaque, especially in the region of metallic small hooks, was observed on a child. Complete withdrawal of the accumulation of tooth plaque, during the treatment, was observed after professional cleaning and everyday correct brushing of teeth with the preparation from Example 9a.

21.3 In female patient with fixed orthodontic device, which every day brushed the teeth with the preparation from Example 9a, increased accumulation of the plaque as well as the formation of caries lesions bellow the orthodontic little locks was not observed during the entire orthodontic treatment.

Example 22: Diabetes and oral complications

Periodontitis and diabetes mellitus are mutually interdependent states. Diabetes mellitus enhances the risk of the inception of periodontitis and, on the other hand, inflammatory processes of periodontium have a negative influence on the entire „picture“ of diabetes mellitus. In the patients with developed symptoms of diabetes mellitus of types 1 and 2 was observed decreased secretion of saliva, a decrease of the pH value, increased number of cariogenic bacteria, increased number of specific periodontal bacteria (*P. Intermedia* and *P. Gingivalis*) and thus, increased appearance

of caries, inflammation and destruction of periodontium and increased dentinal sensitivity.

In addition, the mentioned local pathological changes, there is negative systematic influence on the general state of diabetes mellitus.

22.1 Increased number of *S. Mutans*, decrease of pH value, decreased secretion of saliva, increased dentinal sensitivity and advanced periodontitis with bleeding of gingiva were observed in 5 patients with developed diabetes mellitus of type 2. Considerable diminishing of the mentioned symptoms was observed after brushing of teeth with the preparation from Example 9a, 3 times per day during 4 weeks.

22.2 Increased number of *S. Mutans*, decrease of pH value, decreased secretion of saliva, increased dentinal sensitivity and advanced periodontitis with bleeding of gingiva were observed in 5 patients with developed diabetes mellitus of type 1. Considerable diminishing of the mentioned symptoms was observed after brushing of teeth with the preparation from Example 9a, 3 times per day during 4 weeks.

Example 23: Native and acquired hypominerallization states of hard tooth tissues

In female patient with diagnosed amelogenesis imperfecta, hypominerallization type, with an expressive husking of enamel, the husking of enamel was stopped after application of the preparation from Example 9a, 3 times per day during 8 weeks, due to the newly risen process of remineralization of included regions.

Example 24: Effect on smokers

Smoking has a considerable role in the etiopathogenesis of different pathological states of mouth cavity. Due to decreased secretion of saliva, decrease of pH value, increased number of pathogenic bacteria (cariogenic and periodontal) and increased accumulation of plaque, appearance of caries and diseases of periodonta (gingivitis and periodontitis) are more frequent in smokers than in non-smokers.

24.1 In male patients (6) were obtained the symptoms of dry mouth and strong redolence. The mentioned symptoms were considerably reduced after brushing of teeth with the preparation from Example 9a, 3 times per day during 6 weeks. Dryness of mouth disappeared after 3 days, and redolence was completely disappeared after 6

days.

24.2 In female patients (7) was obtained a slight inflammation of gums and coating of tongue with pathological flora. By brushing of teeth with the preparation from Example 9b during 6 days, feeling of tongue was returned after 6 days, and inflammation of gums was alleviated between 7 and 9 days.

Example 25: Indirect and direct overlapping of pulp

25.1. A layer of preparation from Example 10 was applied to the patient V.L., with profundal caries, after removal of dentin infected by caries. After 6 weeks of the treatment, an efficient formation of the reparatory dentin was observed, by which is avoided the endodontic treatment of teeth.

25.2 A layer of preparation from Example 10 was applied to the patient B.S., with the fracture of tooth and exposition of pulp. After 6 weeks of the treatment, formation of a layer of the reparatory dentin and maintaining of the vitality of tooth were observed.

Example 26: Whitening of teeth, visual effect

To prove the effect of lighting and whitening of teeth, three groups of examinations are performed: *In Vivo*, *In Vitro* and SEM Studies are performed in order to examine the effect of CAS on the degree of lighting of teeth.

In vitro

Human teeth are used in tests. In the *in vitro* tests, each tooth was divided (catted) in two parts, so that each tooth is control to itself. One part of tooth is treated with the toothpaste from the Example 9a and another part is not treated. The starting values are measured on the parts of 20 teeth which are divided in two groups (20 moieties per group). The teeth are divided in the groups with respect to brightness of the teeth. The brightness is determined by Vitapan test – Vitapan key of color which is used to determine nuance-hue, lightness-value, saturation-chroma. After removing of tooth plaque, moieties of teeth are built up into neutral matrix and brushed with the tooth paste from Example 9a. Lighting Hue, Value and Chroma of teeth is again measured by the Vitapan method after 15 minutes of brushing and then, each treated moiety is compared with untreated one. Comparison has shown that the treated teeth is for 2 – 5 nuances brighter compared to the untreated ones.

In vivo

The study is performed on 10 persons (subjects) to whom is, at the start of test, measured the brightness of teeth by the Vitapan test – Vita Classical key of colors, standard method used for determination of the hue, value, and chroma of the tooth. Such determined values are used as starting values. The subjects use the toothpaste from the Example 9a, 2 times per day, during 30 days. After 30 days, the parameters are measured again by the Vitapan key of colors. Measuring of the nuance of teeth is performed as follows:

1. Comparing teeth are washed before measuring,
2. All strong and rich colors are removed from the horizon,
3. Subject is set to the plane of the examiner eyes so that the examiner looks at the teeth at an angle and under the conditions of daily social and business activities,
4. Color and nuances of teeth are examined under different sources of light such as sun, fluorescent light, common electric bulb
5. Examination of Hue, Value, Chroma
6. Plaque and surface dirtiness are removed from teeth
7. Teeth are kept moist during examination
8. Investigation of color is performed on the distance from 90 to 180 cm
9. In order to reject fatigue of eye as well as the potential visual defects of investigator, the examination is performed by two investigators which, after examination, compare the results of individual examinations

By comparison of teeth brightness before the use of toothpaste and after treatment of teeth with the toothpaste from Example 9a after 30 days, it is found that the teeth of the examined persons, after treatment, were for 2-7 nuances lighter relative to the starting values.

SEM

The teeth from the In Vitro test are examined by scanning-electron microscopy (SEM). The obtained photographs show that the particles of CAS are occluded in the micro-cracks of teeth and that the surface roughness is decreased (see Figure 6) Due

to reduced uneven spots and thus, reduced surface roughness, the teeth are smoother so that the reflection of light is more homogeneous and tooth looks lighter and whiter.

Example 27: Plaque, Bacterial sticking capability

Ivoclar Vivadent Plaque Test

Dental plaque is a central problem in stomatology because it is origin of the lytic changes on the tooth hard tissues as well as inflammatory changes in soft tissue, e.g. gingiva. Bacterial plaque induces not only the development of carries, but also periodontal and perio-implant diseases. The main cause of periodontitis is an insufficient hygiene of mouth cavity, existence of stratum – plaque on teeth and tartar. Bacteria of plaque penetrate to periodontal tissue causing an immunological response of organism, i.e., inflammation.

Plaque Test is a fluorescent liquid indicator for indication of plaque which is deposited on the teeth surface and then, illuminates with a polymerization's lamp. Under light, shines only the region of plaque as well as the spots of biofilm on teeth.

Way of testing

20 persons (subjects), 20 to 40 years old, are selected for the test. The amount of plaque on the teeth of all subjects, at the beginning of the test, is determined by deposition of fluorescent liquid indicator on the teeth surfaces and then, by illumination with a polymerization's lamp, which indicated the region of teeth encircled by plaque. Then, the plaque is removed by the standard stomatological – mechanical procedure. Duration of test was 30 days. All the subjects were provided with the identical tooth-brushes which they use for the brushing of teeth with the toothpaste from Example 9c, 3 minutes, 2 times per day. After thirty days, region of teeth encircled by plaque was determined by the same test. The test showed that the region (surface of teeth) encircled by plaque is 83 % lesser after use of toothpaste

during 30 days than before the start of the use of tooth paste.

Example 28: Filling of resorptive defects of teeth roots.

After every-day treatment of the patient, having an expressive lateral resorption of incisor, with the preparation from Example 9a, a good filling of lesion with normal lamina dura was, by a RTG control, observed after 3 months of treatment.

Example 29: Apexification of tooth root

Apexification of tooth root is a procedure of induction of formation of calcification barrier and closing the apex of one third of tooth root in the situations when an endodontic intervention on the teeth with incomplete growth of root is necessary.

Example 29.1: 11 year old girl needed endodontic intervention, because of trauma of crown of right middle incisor.

After extirpation of pulp and instrumentation of channels, channel is filled with the preparation from Example 9b. Then, cavity is closed by strengthened glass-ionomer cement. On the RTG snapshot, made after 3 months, was not observable periapex signs and symptoms of inflammation. Then a permanent obstruction of the root channel was started.

Example 30: Cariogenic bacteria

CRT Caries Risk Test

In order to examine the anti-cariogenic effect of tooth paste, the CRT Ivoclar Vivadent AG Test is applied. CRT is scientifically founded and widely known method, based on measuring of number of bacteria *Streptococcus mutans* and *Lactobacillus* in the sample of subject's saliva.

Method of testing

20 persons (subjects), from 20 to 40 years old, are chosen for test. The test lasts 30 days. All the subjects were provided with the identical tooth-brushes which they use for the brushing of teeth with the toothpaste from Example 9a, 3 minutes, 2 times per

day. Saliva has been taken from each of the subject in order to determine the starting status, i.e. quantity and number of bacteria before the use of toothpaste. Determination of the number of bacteria is done at 0th, 15th and 30th day of treatment. The results obtained after 30 days of the use of toothpaste have shown, on an average, for 61 % lower number of bacteria *Streptococcus mutans* and 38 % lower number of *Lactobacillus* bacteria.

Previously was shown that the dental formulation from the present invention is composed of calcium aluminosilicate with spherically shaped particles (CAS), one or more auxiliary compounds and, if necessary, optional compounds needed for the preparation of the product in final form, whereas the said dental formulation does not contain fluoride and phosphate ions. Amount of CAS in the formulation is from 1 to 10 wt. %, desirable from 2 to 7 wt. %, more desirable from 3 to 5 wt. % and most desirable 4 wt. %. pH of the dental formulation from the present invention is, in all its forms, toothpaste, dental powder, dental gel, oral suspension, chewing gum, or in some other product suitable for application in mouth cavity, desirably from 7.8 and 8.6 and most desirable, 8. The formulation keeps an optimal pH, at an average value of 7.6 – 7.8, in both the local environment and at the surfaces of teeth, even long time after the treatment. Auxiliary components of the dental formulation are selected from the groups comprising excipients, diluents, fillers, humectants, thickeners (or binding agents), basic gum, softeners, sweeteners, flavors, tensides (foaming compounds and diluents), preservatives, antioxidants, stabilizers, or mixtures of one or more of mentioned. The mentioned groups are only illustrative and thus, do not include the use of the auxiliary compounds which are not mentioned here. As such, dental formulation from the present invention is used as medicament. At the first, as a medicament against a number of the discomforts connected with teeth, gum and mouth cavity. More specific, the dental formulation is suitable as the medicament which can be used for desensitization of teeth, and/or stabilization of teeth, and/or mineralization of teeth and/or teeth polishing. More close, the said dental formulation uses as the medicament for the cure of inflammation of teeth and gum; especially in the cases of periodontitis and carries. Because of its properties, the said formulation is

suitable for the applications which demand the formation of reparatory dentin at the patients with carries. Moreover, the formulation from the present invention is very useful as a medium for the removal of dental plaque as well as for reparation of teeth, stoppage of bleeding, healing of hurts in different indications, especially for healing of ulcerative changes and for healing of damaged gingiva. In addition, the formulation from the present invention can be used for regulation of salivation in pregnancy.

It is necessary to mention that the formulation from the present invention is very efficient in the improvement of the sanitary conditions of inflammatory processes such as inflammation of teeth and gum, especially in the inflammations caused by use of prosthetic substitutes and mobile and fixed orthodontic devices. Furthermore, it is very efficient as the medicament for cure of the oral complications, such as periodontitis, originated as the consequence of diabetes mellitus type I and/or type II. The use of the dental formulation from the present invention has healing impact on the pathological conditions originated as the consequence of smoking; it is particularly efficient in the remove of bad odor and dryness of mouth. It was shown that the dental formulation is very efficient in prevention of peeling of tooth enamel at amelogenesis imperfecta, hypo-mineralization type. Furthermore, it is also useful in the apexification of tooth root. Besides the mentioned indications and symptoms, in which the dental formulation is very efficient, it can also be used for cosmetic purposes; at the first for whitening of teeth. Since the only active component of the dental formulation is calcium aluminosilicate with spherically shaped particles having maximum average size 1.848 μm , where at least 50 % of particles is lesser than 1.45 μm and at least 90 % of particles is lesser than 2.35 μm , the said dental formulation can be used as the medicament just for the indications which are mentioned for the dental formulation from the present invention.

CLAIMS

1. The dental formulation consisting of calcium aluminosilicate with the particles of spherical shape (CAS) and one or more excipients and optional compounds needed for preparation of the product in the final form of dosage, wherein the said dental formulation does not contain fluoride and phosphate ions.
2. The dental formulation according to the claim 1, **characterized by** amount of CAS is from 1 to 10 % by weight, desirable from 2 to 7 % by weight, more desirable from 3 to 5 % by weight and most desirable 4 % by weight.
3. The dental formulation according to the claim 2, **characterized by** pH of the said is in the range from 7.8 to 8.6.
4. The dental formulation according to the claim 3, **characterized by** pH of the said formulation is 8.
5. The dental formulation for desensitization, stabilization and mineralization of teeth claimed in any of claims 1 – 4, **characterized by** the auxiliary compound is selected from the group comprising excipients, diluents, fillers, humectants, thickeners (or binding agents), basic gum, softeners, sweeteners, flavors, tensides (foaming compounds and diluents), preservatives, antioxidants, stabilizers, or mixtures of one or more of mentioned.
6. The dental formulation according to the claim 5, **characterized by** the said formulation is prepared in the form of oral suspension, toothpaste, tooth powder, dental gel and chewing gum.

7. The dental formulation consisting of calcium aluminosilicate with the particles of spherical shape (CAS) and one or more excipients and optional compounds needed for preparation of the product in the final form of dosage for use as medicament.
8. The dental formulation according to the claim 7, for use in the procedures of desensitization of teeth, and/or stabilization of teeth; and/or mineralization of teeth; and/or polishing of teeth.
9. The dental formulation according to the claim 7, for use in therapy of inflammation of teeth and gums.
10. The dental formulation according to the claim 9, for use in a therapy of periodontitis and carries.
11. The dental formulation according to the claim 10, for use in procedures of reparatory dentin in patients with carries.
12. The dental formulation according to the claim 10, for use in removing of dental plaque.
13. The dental formulation according to the claims 8-10, for use in cases where reparation of teeth and/or, stoppage of bleeding and/or healing of hurts is needed.
14. The dental formulation according to the claim 13, for use in treatment of ulcerous changes, and for healing of damaged gingiva.
15. The dental formulation according to the claim 7, for use in regulation of salivation in the pregnancy.

16. The dental formulation according to the claim 9, for use in the procedures of improvement of the sanitary conditions of inflammatory processes caused by use of prosthetic substitutes and mobile and fixed orthodontic devices.
17. The dental formulation according to the claims 7-10, for use in the treatment of periodontitis and other oral complications originated as the consequence of diabetes mellitus type I and/or diabetes mellitus type II.
18. The dental formulation according to the claim 7, for use in the procedures of improvement of the sanitary conditions of the pathological states originated as the consequence of smoking.
19. The dental formulation according to the claim 7 or 18, for use in treatment of dryness of mouth, bad odour and in procedures of returning a sensation of tongue.
20. The dental formulation according to the claims 7-8, for use of apexifiksation prevention of husking of tooth enamel at amelogenesis imperfecta, hypo-mineralization type.
21. The dental formulation according to the claim 7, for use in procedures of apexification of the root of tooth.
22. The dental formulation consisting of calcium aluminosilicate with the particles of spherical shape (CAS) and one or more excipients and optional compounds needed for preparation of the product in the final form of dosage, for use in procedures of whitening of teeth.

23. Use of the dental formulation consisting of calcium aluminosilicate with the particles of spherical shape (CAS) and one or more excipients and optional compounds needed for preparation of the product in the final form of dosage for whitening of teeth.

24. Use of the dental formulation consisting of calcium aluminosilicate with the particles of spherical shape (CAS) and one or more excipients and optional compounds needed for preparation of the product in the final form of dosage as medicament.

25. Use of the dental formulation according to the claim 24, for desensitization of teeth, and/or stabilization of teeth, and/or mineralization of teeth, and/or polishing of teeth.

26. Use of the dental formulation according to the claim 24, for treatment of inflammation of teeth and gums.

27. Use of the dental formulation according to the claim 24, for treatment of periodontitis and carries.

28. Use of the dental formulation according to the any of claims 24 – 27, for treatment of periodontitis and other oral complications originated as the consequence of diabetes mellitus type I and diabetes mellitus type II.

29. Calcium aluminosilicate with spherically shaped particles having maximum average size 1.848 μm , where at least 50 % of particles is lesser than 1.45 μm and at least 90 % of particles is lesser than 2.35 μm for use as medicament.

30. Calcium aluminosilicate with spherically shaped particles according to the claim 29, for use in procedures of mineralization, calcification, stabilization and desenzibilization of teeth.
31. Calcium aluminosilicate with spherically shaped particles according to the claim 29, for treatment of inflammation of teeth and gum.
32. Calcium aluminosilicate with spherically shaped particles according to the claim 29, for treatment of periodontitis and caries.
33. Calcium aluminosilicate with spherically shaped particles according to the claim 32, for formation of reparatory dentin in the patients with caries.
34. Calcium aluminosilicate with spherically shaped particles according to the claim 32, for removal of dental plaque.
35. Calcium aluminosilicate with spherically shaped particles according to the claims 30-32, for reparation of teeth, stoppage of bleeding and healing of hurts.
36. Calcium aluminosilicate with spherically shaped particles according to the claim 35, for treatment of ulcerous changes and for healing of damaged gingiva.
37. Calcium aluminosilicate with spherically shaped particles according to the claim 29, for regulation of salivation in pregnancy.
38. Calcium aluminosilicate with spherically shaped particles according to the claim 31, for the improvement of the sanitary conditions of inflammatory processes caused by use of prosthetic substitutes and mobile and fixed orthodontic devices.

39. Calcium aluminosilicate with spherically shaped particles according to the claim 19, for treatment of periodontitis originated as the consequence of diabetes mellitus type I and diabetes mellitus type II.

40. Calcium aluminosilicate with spherically shaped particles according to the claim 29, for the improvement of sanitary of pathological states of mouth cavity originates as the consequence of smoking.

41. Calcium aluminosilicate with spherically shaped particles according to the claim 40, for removing the dryness of mouth, bad odour and returns the sensation of tongue.

42. Calcium aluminosilicate with spherically shaped particles according to the claims 29-30 for prevention of husking of tooth enamel at amelogenesis imperfecta, hypo-mineralization type.

43. Calcium aluminosilicate with spherically shaped particles claimed in claims 29, for apexification of the root of tooth.

44. Calcium aluminosilicate with spherically shaped particles having maximum average size 1.848 μm , where at least 50 % of particles is lesser than 1.45 μm and at least 90 % of particles is lesser than 2.35 μm , for whitening of teeth.

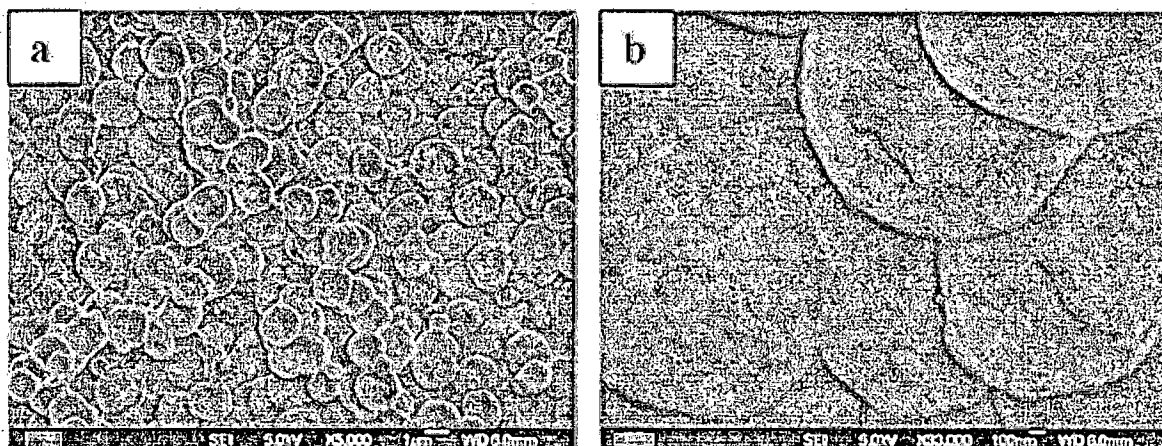


Figure 1

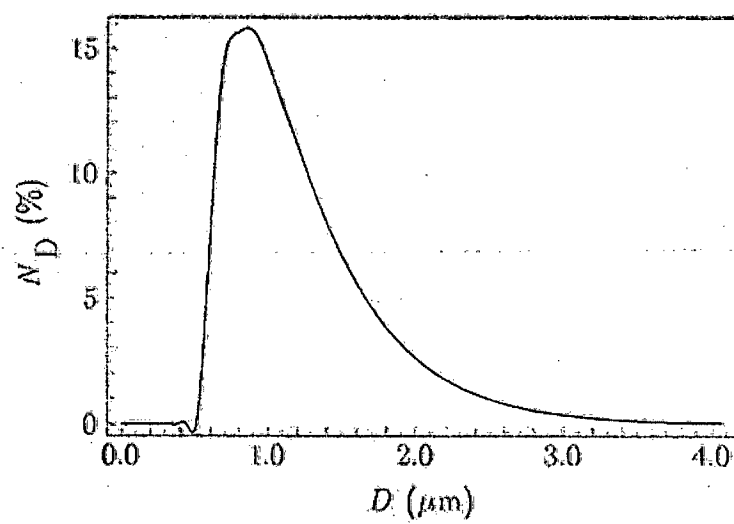


Figure 2

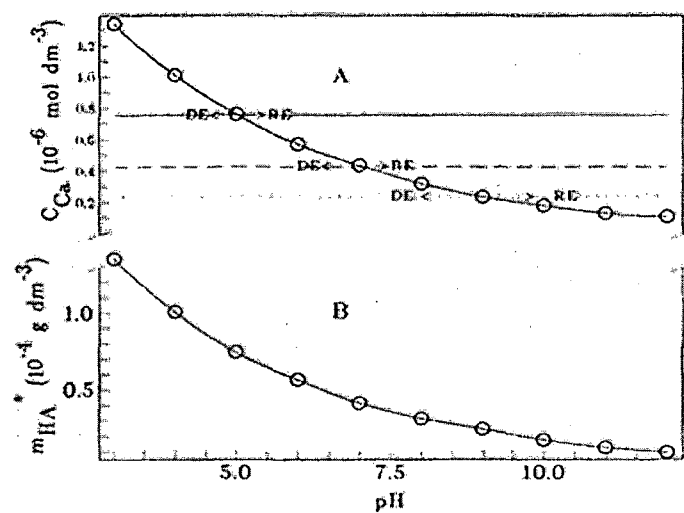


Figure 3

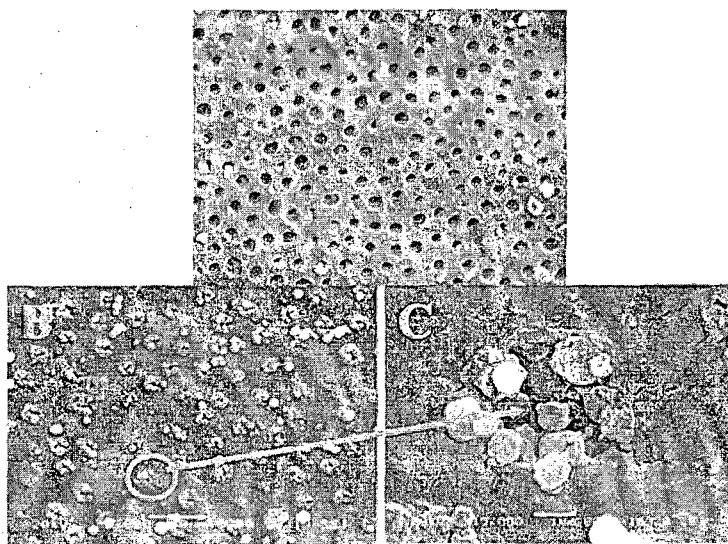


Figure 4

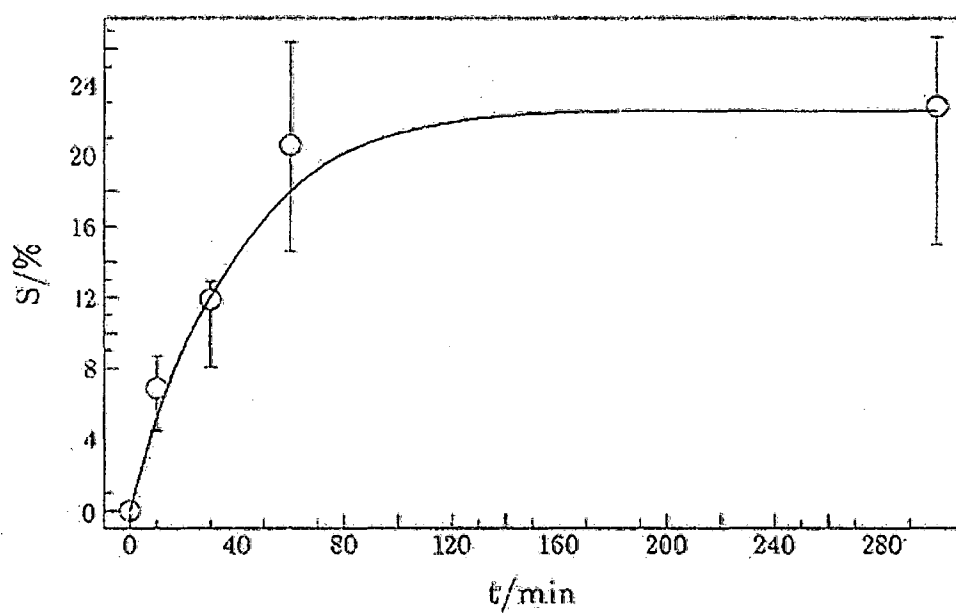


Figure 5

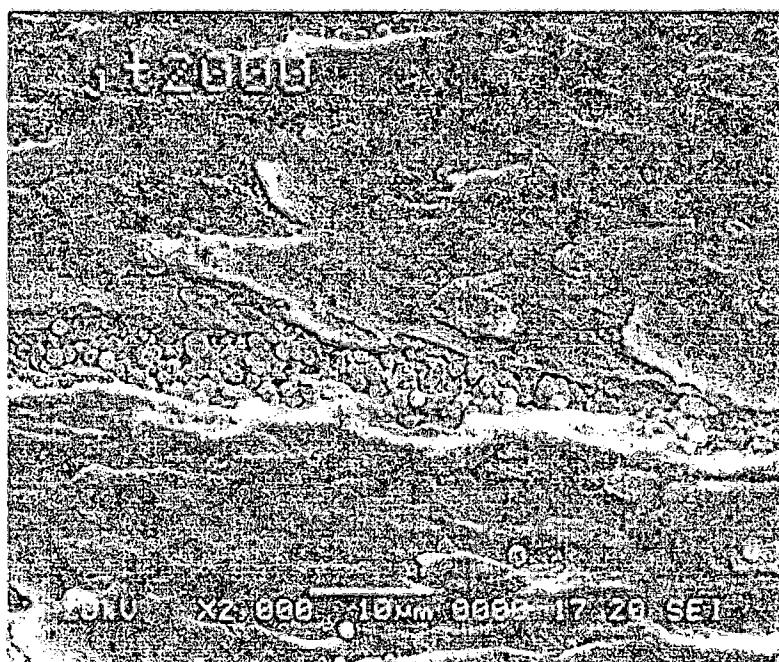


Figure 6

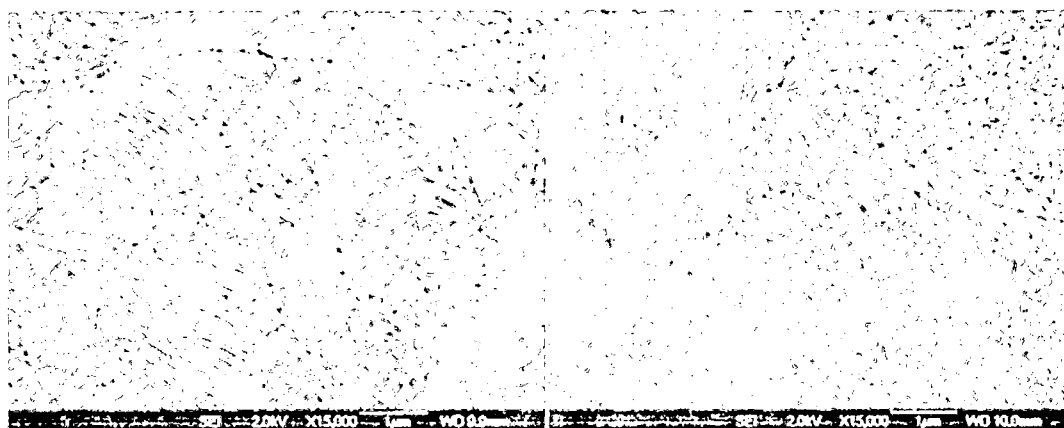


Figure 7

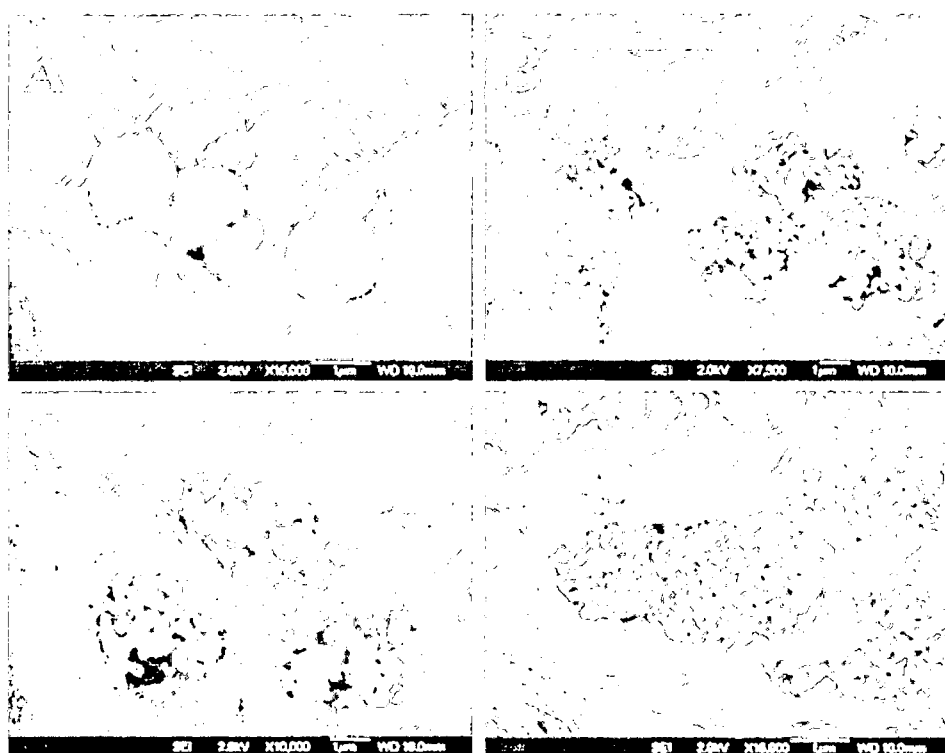


Figure 8

INTERNATIONAL SEARCH REPORT

International application No

PCT/HR2016/000009

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K8/25 A61Q11/00 A61K8/02 A61K8/19
ADD.

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 A61Q C01B

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 practicable, search terms used)

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 1 349 373 A (COLGATE PALMOLIVE CO) 3 April 1974 (1974-04-03)	1-6
Y	example 7	1-44
X	----- EP 2 438 010 A1 (BARCHEM LLC [US]) 11 April 2012 (2012-04-11) cited in the application the whole document & WO 2010/128342 A1 (BARCHEM LLC [US]; SUBOTIC BORIS [HR]; KOSANOVIC CLEO [HR]; BOSNAR SANJ) 11 November 2010 (2010-11-11)	7,24,29, 44
X	----- WO 2004/091564 A1 (BASIC ROBERT [HR]) 28 October 2004 (2004-10-28)	1-16, 25-27, 30-38
Y	Table on p.12ff (entries 1,13,38); the whole document	1-44
	----- -/-	



Further documents are listed in the continuation of Box C.



See patent family annex.

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Date of the actual completion of the international search

8 July 2016

Date of mailing of the international search report

19/07/2016

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Skulj, Primoz

INTERNATIONAL SEARCH REPORT

International application No

PCT/HR2016/000009

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2014/248322 A1 (KARLINSEY ROBERT L [US]) 4 September 2014 (2014-09-04) paragraphs [0017] - [0019], [0042] - [0043] -----	1-44
A	RU 2003 122223 A (NAT RES DEV CORP) 10 January 2005 (2005-01-10) -----	1
T	DATABASE MEDLINE [Online] US NATIONAL LIBRARY OF MEDICINE (NLM), BETHESDA, MD, US; 31 December 1948 (1948-12-31), "Typical hemostasis with methyl cellulose", XP002759631, Database accession no. NLM18894146 -----	
T	GRIGORIY E GURVITS: "Burning mouth syndrome", WORLD JOURNAL OF GASTROENTEROLOGY, vol. 19, no. 5, 1 January 2013 (2013-01-01), page 665, XP55286711, CN ISSN: 1007-9327, DOI: 10.3748/wjg.v19.i5.665 the whole document -----	
T	WEI XIA ET AL: "Bioactive Spheres: The Way of Treating Dentin Hypersensitivity", ACS BIOMATERIALS SCIENCE & ENGINEERING, vol. 2, no. 5, 9 May 2016 (2016-05-09), pages 734-740, XP55286737, ISSN: 2373-9878, DOI: 10.1021/acsbiomaterials.5b00499 -----	

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/HR2016/000009

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB 1349373	A	03-04-1974	NONE
EP 2438010	A1	11-04-2012	EP 2438010 A1 11-04-2012
		WO 2010128342	A1 11-11-2010
WO 2004091564	A1	28-10-2004	EP 1620064 A1 01-02-2006
		HR P20030304	A2 28-02-2005
		US 2006088480	A1 27-04-2006
		US 2008152598	A1 26-06-2008
		WO 2004091564	A1 28-10-2004
US 2014248322	A1	04-09-2014	NONE
RU 2003122223	A	10-01-2005	NONE