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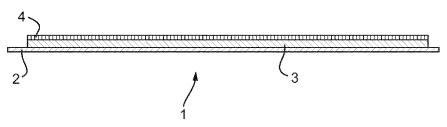
- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
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(54) Title: ORAL CARE DEVICE

Fig. 1



(57) **Abstract**: A delivery device for delivering a enamel regeneration system to the surfaces of teeth, the 5 delivery device comprising; a strip of an orally acceptable flexible material, having a strip surface capable of being applied to a tooth surface, the strip having the enamel regeneration system deposited upon the strip surface thereof, and/or impregnated into its structure.





ORAL CARE DEVICE

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Field of the Invention

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The invention relates to an oral care products for the remineralisation of teeth. The oral care products comprise a device and composition. Application of the composition using the device can lead to remineralisation, repair and in some cases whitening of the teeth.

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Background of the Invention

Calcium phosphate is the primary component of the enamel and dentin in the form of hydroxyapatite.

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In the mouth, there is a natural equilibrium between hydroxyapatite being dissolved from the enamel of teeth and hydroxyapatite being formed on or in the teeth from substances occurring naturally in the saliva. This equilibrium is shifting continuously. Among other factors, it is determined by diet and physical condition.

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If the equilibrium is such that hydroxyapatite is being dissolved, a cariogenic condition arises which is referred to as demineralisation. Exposure of the dental hard tissues to acid causes demineralisation, resulting in surface softening and a decrease in mineral density. Dental erosion (i.e. acid erosion or acid wear) is a surface phenomenon that involves demineralisation, and ultimately complete dissolution of the tooth surface by acids that are not of bacterial origin. Most commonly the acid will be of dietary origin.

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If the equilibrium is such that hydroxyapatite is being formed, this is referred to as remineralisation. Remineralisation hardens and strengthens the teeth, thereby providing protection from and treatment for dental erosion and/or tooth wear. It also reduces the likelihood of tooth decay and improves the appearance of the teeth, in particular their whiteness. The teeth may also appear smoother and shinier as a result.

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The presence of fluoride ions can enhance the natural remineralisation process and this is one of the accepted mechanisms by which fluoride toothpastes and rinses protect

against caries. Fluoride is most effective during the developmental years from childhood to young adulthood.

However, the ability of fluoride to promote remineralisation can be limited by the availability of calcium and phosphate ions in saliva. Accordingly, oral products utilising calcium and phosphate ions have been designed.

US 5,605,675 discloses a process for remineralisation of dental enamel by application of a two-phase composition; one phase containing a water-soluble calcium compound and one phase containing a water soluble inorganic phosphate and a water-soluble fluorine compound.

US 4,083,955 discloses a process for remineralisation of dental enamel by sequential application of two compositions, the first comprising calcium ions and second comprising phosphate ions, or vice versa.

However there remains the need for a simple and effective way to enable enamel regeneration of the teeth.

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Summary of the Invention

Accordingly the present invention relates to a delivery device for delivering a enamel regeneration system to the surfaces of teeth, the delivery device comprising plurality of layers comprising:

- i) a first layer comprising a strip of an orally acceptable flexible, non-aqueous dissolving material capable of being applied to a tooth surface;
- ii) a second layer comprising comprises a component of the enamel regeneration system,
- 30 iii) a third layer comprising a water soluble polymer film.

Detailed Description of the Invention

The delivery device of the invention comprises a strip of an orally acceptable flexible material. The surface of the strip is capable of being applied to a tooth surface.

Preferably the device has an elongate shape of a length sufficient that when placed against the front surface of a user's teeth it extends across a plurality of teeth, and of sufficient width that it extends at least from the gumline of the teeth to the crowns of the teeth. The elongate shape is such that it minimises the need for subsequent applications and time to cover all the users teeth.

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In a further embodiment the strip is such that it can be sufficient that when placed against the front surface of a user's teeth it extends across a plurality of teeth, and of sufficient width that it extends at least from the front gumline of the teeth to the crowns of the teeth and to the gumline behind the users teeth leading to total coverage of the teeth above the gumline.

Preferably the application device is rectangular in shape.

The strip/device has the enamel regeneration system deposited upon the strip surface thereof as a layer or more preferably multiple layers.

Preferably the device comprises at least three layers; one layer comprises a nondissolving backing film, a second layer comprises a component of the enamel regeneration system, and a third layer comprises a water soluble polymer film.

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It is preferable if the non-dissolving backing layer comprises materials such as polymers, natural and synthetic wovens, non-wovens, foil, paper, rubber, and combinations thereof. The strip of material may be a single layer of material or a laminate of more than one layer. Generally, the strip of material is substantially water impermeable. The material may be any type of polymer that is compatible with tooth whitening actives and is sufficiently flexible to be shaped and applied to the tooth surface. The material may comprise a single polymer or a mixtures of polymers. Suitable polymers include, but are not limited to, polyethylene, polypropylene, ethylvinylacetate, ethylvinyl alcohol, polyesters, polyamides, fluoroplastics and combinations thereof. Preferably, the material is polyethylene. The strip of material is generally less than about 1 mm thick, preferably

less than about 0.05 mm thick, and more preferably from about 0.001 to about 0.03 mm thick.

It is preferable the strip has a second layer comprising components of the enamel regeneration system. It is advantageous if the component of the enamel regeneration system is a water insoluble and/or slightly soluble calcium source.

Soluble and insoluble calcium source, as used herein, refers to the solubility of the calcium source in water. Soluble means a source that dissolves in water to give a solution with a concentration of at least 0.1 moles per litre at room temperature. Insoluble means a source that dissolves in water to give a solution with a concentration of less than 0.001 moles per litre at room temperature. Slightly soluble, therefore, is defined to mean a source that dissolves in water to give a solution with a concentration of greater than 0.001 moles per litre at room temperature and less than 0.1 moles per litre at room temperature. Substantially free of, as used herein, means less than 1.5%, and preferably, less than 1.0%, and most preferably, from 0.0 to 0.75% by weight, based on total weight of the oral care composition, including all ranges subsumed therein. The calcium source suitable for use in this invention is limited only to the extent that the same may be used in an oral cavity. In a preferred embodiment, the calcium source employed is insoluble or slightly soluble in water, but most preferably, insoluble in water.

Illustrative examples of the types of calcium source that may be used in this invention include, for example, calcium phosphate (i.e., added), calcium gluconate, calcium oxide, calcium lactate, calcium carbonate, calcium hydroxide, calcium sulfate, calcium carboxymethyl cellulose, calcium alginate, calcium salts of citric acid, calcium silicate, mixtures thereof or the like. In a preferred embodiment the calcium source is calcium silicate. In a more preferred embodiment, the calcium silicate used is (CaS_iO_3) whereby the same is made commercially available under the name Microcal ET by Ineos Silicas, Ltd.

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In yet another preferred embodiment, the calcium source is insoluble calcium silicate, present as the composite material calcium oxide-silica (CaO-SiO₂) as described in commonly-owned application Publication No. 2008/015117.

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When a calcium silicate composite material is employed, the ratio of calcium to silicon (Ca:Si) may be from 1:10 to 3:1. The Ca:Si ratio is preferably from 1:5 to 2:1, and more preferably, from 1:3 to 2:1, and most preferably, from about 1:2 to 2:1. The calcium silicate may comprise mono-calcium silicate, bi-calcium silicate, or tri-calcium silicate whereby ratios of calcium to silicon (Ca:Si) should be understood to be atom ratios.

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The calcium source employed in this invention may be in a crystalline or amorphous state, and preferably, the same is in an amorphous state. In an often preferred embodiment, the calcium source is in a mesoporous state, i.e. the source is a material having pores with diameters from 1 nm to 50 microns. Mesoporous calcium silicate (MCS) is often preferred.

The MCS which may be used in this invention can be made by combining a calcium salt, a silical precursor like silicate and a structure-directing agent to yield a solid suitable for calcinating. A more detailed description of the process that may be conducted to make the MCS suitable for use in this invention is described in the aforementioned commonly-owned application. Publication No. WO 2008/015117.

The amount of calcium source in the composition present as the second layer of this invention is typically from 0.1 to 50%, and preferably, from 1 to 30%, and most preferably, from 5 to 20% by weight of the oral care composition based on total weight of the oral care composition and including all ranges subsumed therein.

It is highly preferable if the second layer is non-aqueous, that is that the composition comprises less than 1 wt% of the total composition of the second layer of water, preferably less than 0.5 wt% of water.

It is highly preferable if the second layer is sandwiched between the first backing layer and a third layer.

It is preferable if the device comprises a third layer. The third layer comprises a water soluble polymer or polymers. Suitable water soluble polymers may be natural or synthetic. Suitable natural hydrocolloids and water soluble polymers include cellulosic material, a polysaccharide, a gum, a protein, a starch or a glucan. Examples include but are not limited to carboxymethyl cellulose, hydroxyl methyl cellulose, hydroxyethyl

cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, gum Arabic, xanthan gum, karaya gum, tragacanth, acacia, carrageenan, guar gum, locust bean gum, pectin, alginates, polydextrose, dextrin, dextran, amylose, chitin, chitosan, levan, elsinan, collagen, gelatin, zein, gluten, soy protein isolate, whey protein isolate, casein and pullan. Suitable water soluble synthetic polymers include but are not limited to poly(vinyl pyrrolidone), poly(vinyl alcohol), poly(acrylic acid), polyacrylates, Methylmethacrylate copolymer, carboxyvinyl polymer, polyethylene oxide and polyethylene glycol. The water soluble polymer layer is preferably a mixture of methylcellulose and hydroxypropyl methylcellulose.

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The third layer preferably further comprises a phosphate source. The phosphate source that may be used in this invention is limited only to the extent that the same may be used in a composition suitable for use in an oral cavity. Illustrative examples of the types of phosphate source suitable for use in this invention include monosodium phosphate, sodium dihydrogen phosphate, disodium hydrogen phosphate, sodium pyrophosphate, tetrasodium pyrophosphate, sodium tripolyphosphate, sodium hexametaphosphate, potassium dihydrogenphosphate, trisodium phosphate, tripotassium phosphate, mixtures thereof or the like. The phosphate source is preferably one which is water soluble.

Typically, the phosphate source makes up from 0.5 to 15%, and preferably, from 2 to 12%, and most preferably, from 4 to 9% by weight of the composition used in the third layer, based on total weight of the composition of the third layer and including all ranges subsumed therein. In a preferred embodiment, the phosphate source used is one which results in an oral care composition having a pH from 5.5 to 8, preferably from 6 to 7.5, and most preferably, about neutral. In a most preferred embodiment, the phosphate source used is trisodium phosphate and monosodium dihydrogen phosphate at a trisodium phosphate to monosodium dihydrogen phosphate weight ratio of 1:4 to 4:1, preferably 1:3 to 3:1, and most preferably, from 1:2 to 2:1, including all ratios subsumed

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therein.

It is preferable if the composition of the third layer comprises an aqueous base, that is that that the composition comprises greater than 50 wt% of the third composition of water, more preferably greater than 70 wt%.

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The advantage of having a water soluble layer and a non-water soluble layer is that in the mouth the water soluble layer dissolves in the saliva and the ingredients enclosed therein (the phosphate) can react with the ingredients in the second layer (silicate) to aid the insitu regeneration of enamel on the teeth. Thus the system provides an enamel regeneration system that can be used with the minimum of water, can be easily stored and is stable on storage.

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Preferably the composition of the invention comprise titanium dioxide. Preferably the titanium dioxide is present in the second layer. A preferred form of titanium dioxide is calcium silicate coated titanium dioxide. Examples of preferred forms of calcium silicate coated titanium dioxide are disclosed in WO2012/031786 and WO2012/03178.

It is preferable if the thickness of the first layer is less than about 1 mm thick, preferably less than about 0.05 mm thick, and more preferably from about 0.001 to about 0.03 mm thick, second layer is less than about 1 mm thick, preferably less than about 0.5 mm thick, and more preferably from about 0.001 to about 0.3 mm thick and third layer (if present) less than about 1 mm thick, preferably less than about 0.5 mm thick, and more preferably from about 0.001 to about 0.3 mm thick.

- The oral care composition forming the layers described herein may comprise ingredients which are common in the art, such as:
 - antimicrobial agents, e.g. Triclosan, chlorhexidine, copper-, zinc- and stannous salts such as zinc citrate, zinc sulphate, zinc glycinate, sodium zinc citrate and stannous pyrophosphate, sanguinarine extract, metronidazole, quaternary ammonium compounds, such as cetylpyridinium chloride; bis-guanides, such as chlorhexidine digluconate, hexetidine, octenidine, alexidine; and halogenated bisphenolic compounds such as 2,2' methylenebis-(4-chloro-6-bromophenol);
 - anti-inflammatory agents such as ibuprofen, flurbiprofen, aspirin, indomethacin, etc.;
- anti-caries agents such as sodium trimetaphosphate and casein;
 - plaque buffers such as urea, calcium lactate, calcium glycerophosphate and polyacrylates;
 - vitamins such as Vitamins A, C and E;
 - plant extracts;

- desensitizing agents, e.g. potassium citrate, potassium chloride, potassium tartrate, potassium bicarbonate, potassium oxalate, and potassium nitrate;
- anti-calculus agents, e.g. alkali-metal pyrophosphates, hypophosphite-containing polymers, organic phosphonates and phosphocitrates, etc.;
- 5 biomolecules, e.g. bacteriocins, antibodies, enzymes, etc;
 - flavors, e.g., peppermint and spearmint oils;
 - proteinaceous materials such as collagen;
 - preservatives;
 - opacifying agents;
- coloring agents like FD&C blue, yellow and/or red dyes/colorants;
 - pH-adjusting agents;
 - sweetening agents;
 - surfactants, such as anionic, cationic and zwitterionic or amphoteric surfactants
 (e.g., sodium lauryl sulfate, sodium dodecylbenzene sulfonate);
- particulate abrasive materials such as abrasive silicas, aluminas, calcium carbonates, zirconium silicate, polymethylmethacrylate, dicalciumphosphates, calcium pyrophosphates, hydroxyapatites, trimetaphosphates, insoluble hexametaphosphates as well as agglomerated particulate abrasive materials;
- fluoride sources like sodium fluoride, stannous fluoride, sodium
 monofluorophosphate, zinc ammonium fluoride, tin ammonium fluoride, calcium fluoride, cobalt ammonium fluoride or mixtures thereof;
 - polymeric compounds which can enhance the delivery of active ingredients such as antimicrobial agents can also be included. Examples of such polymers are copolymers of polyvinylmethylether with maleic anhydride and other similar delivery enhancing polymers, e.g., those described in DE-A03,942,643; buffers and salts to buffer the pH and ionic strength of the oral care compositions; and
 - other optional ingredients that may be included are, e.g., bleaching agents such as peroxy compound, e.g., potassium peroxydiphosphate, effervescing systems such as sodium bicarbonate/citric acid systems, color change systems, and the like.

Such ingredients common in the art typically and collectively make-up less than 20% by weight of the oral care composition, and preferably, from 0.0 to 15% by weight, and most preferably, from about 0.01 to about 12% by weight of the oral care composition, including all ranges subsumed therein.

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Suitable carrier humectants are preferably used in the oral care composition of the present invention and they include, for example, glycerin, sorbitol, propylene glycol, dipropylene glycol, diglycerol, triacetin, mineral oil, polyethylene glycol (preferably, PEG-400), alkane diols like butane diol and hexanediol, ethanol, pentylene glycol, or a mixture thereof. The carrier humectants should, in any case, be substantially free of water, and preferably, anhydrous. The same, for example, can be used in solid form, whereby glycerin is the preferred carrier humectant. Such carriers are particularly suitable in compositions used in the second layer.

The carrier humectant is used to take the balance of the compositions up to 100%, and the same may be present in the range of from 10 to 90% by weight of the oral care composition. Preferably, the carrier humectant makes up from 25 to 80%, and most preferably, from 45 to 70% by weight of the oral care composition, based on total weight of the oral care composition and including all ranges subsumed therein.

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The composition used in the layers of the invention are prepared by conventional methods of making oral care formulations. Such methods include mixing the ingredients under moderate shear and atmospheric pressure.

20 Mode of Use

The invention a provides a method of remineralising teeth, in which the oral care device as described above is applied to the surface of the teeth for sustained contact.

In the context of the present invention sustained contact means the product is preferably left on the teeth for 1 to 60 minutes, more preferably, for 5 to 45 minutes, most preferably from 10 to 30 minutes before being removed.

Preferably the application of the oral care product of the invention is carried out once daily for a period of several consecutive days, in addition to a regular regime of tooth brushing (preferably at least twice daily).

Typically, use (for a period of about two weeks to one month) of the device with the oral care composition of the present invention will result in a new hydroxyapatite layer on teeth that is from 0.5 to 20 microns, and preferably, from 0.75 to 5 microns, including all ranges subsumed therein.

Detailed Description of non-limiting embodiments

The invention, however, may be best understood by reference to the following description of some embodiments of the invention taken in conjunction with the accompanying drawing figure in which figure 1 is a cross sectional view of the strip.

Referring to figure 1, a device (1) of the invention is shown in section. The device comprises a strip (2) of insoluble backing material, this can be considered the bottom layer. Coated onto the insoluble backing material (2) is a second layer (3) comprising calcium silicate and titanium dioxide composite, a third layer (4) is present as the top layer in contact with the second layer. The third layer comprises a phosphate salt and water soluble polymer. In a preferred embodiment the phosphate salt comprises trisodium phosphate and monosodium dihydrogen phosphate and the polymer is a mixture of methylcellulose and hydroxypropyl methylcellulose.

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The invention will now be illustrated by the following non-limiting Examples:

Examples

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A simulated oral fluid was prepared by adding 1.9L of water to a glass beaker. The following materials were added one by one with continuous stirring, allowing sufficient time for each chemical to fully dissolve before adding the next. Sodium chloride 16.07g, sodium hydrogen carbonate 0.7g, potassium chloride 0.448g, potassium hydrogen phosphate 2.56g, magnesium chloride hexahydrate 0.622g, 1M hydrochloric acid 40ml, calcium chloride 0.1998g and sodium sulfate 0.1434g. The pH was adjusted to 7.0 using saturated TRIS buffer and the total volume made up to 2L using a volumetric flask.

Formulation and processing: Polymer film

Ingredient	%w/w
Glycerol	1.0
Monosodium phosphate	3.2
Trisodium phosphate	3.8
Hydroxypropyl cellulose	4.0
Methyl cellulose	4.0
Water	84
Total	100

The water and glycerol was weighed into a beaker. The polymers added slowly while under shear using a Silverson LR4 bench top mixer. When the polymer is fully dispersed (no lumps visible) the phosphates are added and mixed to disperse.

5 NB Air can become entrapped in the solution if required this can be removed using a desiccator.

To cast the film a quantity of the solution is poured on to a glass tile and using a pull down gauge the correct film height is achieved (micrometers on the gauge set at 15). The glass tiles are then placed in an oven at 50-60DegC over night to remove the water.

The following day the film can be removed from the tile and cut to the appropriate size.

Formulation and processing: Tio2/Cs Slurry

Ingredient	%w/w
Glycerol	75
Calcium Silicate	10
TiO2/CS	15
Total	100

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Glycerol was weighed into a suitable beaker then the two powders were added slowly while under shear using a Silverson LR4 bench top mixer. The slurry was mixed to remove any visible lumps.

20 The multilayer film was produced as follows.

Stage 1 a piece of plastic film was cut to the appropriate size.

Stage 2 using a four point balance 0.04g of Slurry was dispensed onto the film.

Stage 3 a rectangle shaped piece of the MSP/TSP polymer film (weighing approx. 0.04g) was cut and placed on top of the slurry and pressed evenly to dispersed the slurry equally under the film.

To a strip sample was added 0.5ml deionized water via auto-pipette and immediately three 6x6mm enamel block samples were placed on the surface. The samples were left in contact with the strip for 30 minutes with gentle agitation at 5 and 15 minutes. This procedure was completed twice, so n=6 enamel blocks were tested. After 30 minutes the bovine blocks were rinsed in 40 ml water and mixed gently for 1 minute. Samples were

then incubated in simulated oral fluid for 5 hours. The application process was repeated 5 times in total. Colour was measured via chromameter at baseline and after strip application and incubation. L*a*b* colour parameters were converted to WIO whiteness indices to allow comparison between samples. Colour change is expressed as Δ WIO = WIO(slurry application)-WIO(baseline).

	1 Application	3 Applications	5 Applications
Whitening Change	3.02 ± 0.69	4.35 ± 1.00	6.36 ± 0.74

CLAIMS

- 1. A delivery device for delivering a enamel regeneration system to the surfaces of teeth, the delivery device comprising plurality of layers comprising:
 - i) a first layer comprising a strip of an orally acceptable flexible, non-aqueous dissolving material capable of being applied to a tooth surface;
 - ii) a second layer comprising comprises a component of the enamel regeneration system,
 - iii) a third layer comprising a water soluble polymer film.

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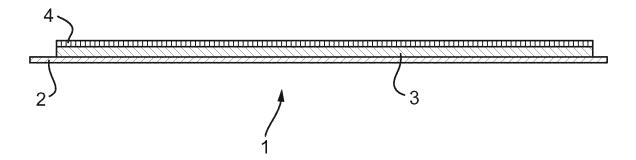
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- 2. A device according to claim 1 in which the enamel regeneration system of the second layer is a water insoluble and/or slightly soluble calcium source.
- 3. A device according to claim 2 in which calcium source of the enamel regenerationsystem is calcium silicate.
 - 4. A device according to any preceding claim in which the second layer comprises a non-aqueous base.
- 20 5. A device according to any preceding claim in which the third layer further comprises a phosphate source.
 - 6. A device according to claim 5 in which the phosphate source comprises trisodium phosphate, sodium dihydrogen phosphate or mixtures thereof.

- 7. A device according to any preceding claim in which the third layer comprises an aqueous base.
- 8. A device according to any preceding claim in which the water soluble polymer of the third layer comprises a cellulose.
 - 9. A device according to any one of the preceding claims further comprising a tooth whitening substance.

- 10. A device according to claim 9 in which the tooth whitening substance is titanium dioxide.
- 11. A device according to claim 9 or claim 10 in which the tooth whitening substance ispresent in the second layer together with the enamel regeneration component.
 - 12. A device according to any preceding claims having an elongate shape of a length sufficient that when placed against the front surface of a user's teeth it extends across a plurality of teeth, and of sufficient width that it extends at least from the gumline of the teeth to the crowns of the teeth.
 - 13. A device according to any preceding claim being substantially rectangular.

Fig. 1



INTERNATIONAL SEARCH REPORT

International application No PCT/EP2016/060124

A. CLASSIFICATION OF SUBJECT MATTER INV. A61K8/24 A61K8/25 A61Q11/00 A61C19/06 A61K8/02 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 A61C

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. DOCUM	ENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the re	levant passages	Relevant to claim No.
Y	US 2006/292092 A1 (SHARMA DEEPAK AL) 28 December 2006 (2006-12-28 page 1, paragraphs [0006],[0007] paragraph [0014] page 2, paragraphs [0020],[0022] paragraph [0023] page 3, paragraph [0037] - parag [0039] page 5; examples 1,2 claims	3) ,[0012] - -	1-13
X Furt	her documents are listed in the continuation of Box C.	X See patent family annex.	
"A" docume to be of "E" earlier of filing o "L" docume oited t specie "O" docume means "P" docume	ent which may throw doubts on priority claim(s) or which is o establish the publication date of another citation or other al reason (as specified) ent referring to an oral disclosure, use, exhibition or other	"T" later document published after the inter date and not in conflict with the application the principle or theory underlying the interpretation of particular relevance; the considered novel or cannot be considered novel or cannot be considered to involve an inventive stere on the sum of the same patent to the considered to the	ation but cited to understand invention laimed invention cannot be ered to involve an inventive e laimed invention cannot be by when the document is a documents, such combination e art
Date of the	actual completion of the international search	Date of mailing of the international sea	rch report
1	6 June 2016	24/06/2016	
Name and r	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 Pelli Wablat, B	

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