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Dental materials equipped with active anti-plaque substance(s)

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Abstract

Dental materials equipped with active anti-plaque substance(s)

Molecularly dispersely distributed octenidine salts or dequalinium salts are used for equipping dental material with anti-plaque properties. Dental material equipped with active anti-plaque substance contains at least one molecularly dispersely distributed octenidine salt or dequalinium salt. Furthermore, a process for equipping dental material based on (meth)acrylate with anti-plaque properties is described in the case of which at least one octenidine salt or dequalinium salt is distributed in a molecularly dispersed manner in a (meth)acrylate monomer before polymerisation.

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COMPLETE SPECIFICATION

FOR A STANDARD PATENT

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Invention Title:	Dental materials equipped with active anti-plaque substance(s)

The following statement is a full description of this invention, including the best method of performing it known to me/us:

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Dental materials equipped with active anti-plaque substance(s)

The invention relates to dental materials equipped with active anti-plaque substance(s).

Background

Polymeric dental materials, in particular those based on acrylate/methacrylate, which are introduced into the oral cavity to remain there permanently tend to become colonised by plaque on the material surface in the case of lack of oral hygiene.

Plaque is composed of various bacteria which become anchored firmly to surfaces such as e.g. teeth or dental materials by proteins and carbohydrates. Further bacteria can then settle on this first bacteria layer thus forming a three-dimensional colony. As a result of certain substances released by the bacteria, this "biofilm" is almost immune to attack by antibiotics.

Apart from the hygiene aspect, plaque leads, in the advanced stage, also to strong discolouration resulting in aesthetically adverse effects.

State of the art

A reduction of plaque colonisation can be effected either by biocides or by a hydrophobic coating on the dental material preventing the adhesion of the bacteria on the material.

The use of quaternary ammonium salts as antimicrobial additives has been known for a long time. Thus silane with quaternary ammonium groups as functional group is made by Microbeshield, for example, and is marketed for antibacterial finishing of filters, textiles and wound substrates. Moreover, silver-containing types of glass, salts or zeolites have been proposed as antimicrobial additives.

Task in hand

It is the purpose of the present invention to provide a process by means of which the colonisation by plaque on dental materials can be permanently prevented or delayed without the product properties of the dental material being negatively influenced.

In this respect, the following core requirements are of importance:

- A homogeneous distribution of the active substances within the interior of the material (bulk) and on the material surface should be guaranteed, i.e. conversely: a spot-type distribution must be avoided.
- The material must not exhibit any micro-pores and macro-pores following the release of the active substance (aesthetics, cracking, starting point and new colonisation).

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- The inactivation of the active substance on the surface should be made difficult by subsequent diffusion from the interior (bulk).
- A wide spectrum of effectiveness against typical oral germs should be the aim.
- The active substance should be released in a delayed manner.
- The active substance should have such a high rate of release that an antimicrobial effectiveness arises while no toxic or irritating/sensitising effects occur.
- The active substance must not interfere with the polymerisation of the product or have a negative effect on the properties of the material; in particular, no phase separation (plasticizer effect) must occur.
- Only a low probability resistance formation of the typical oral germs vis-à-vis the active substance ought to arise.

Octenidine, its manufacture and its anti-plaque effect are known as such (Merck Index 14th ed. 2006, Monograph number: 0006754). The compound is used predominantly in mouth rinses. In US 4,206,215, it is also recommended to use the antimicrobial active substances described therein in varnishes or coatings.

Invention

According to the invention, dental material equipped with active anti-plaque substance is proposed according to claim 1 which material contains at least one molecularly dispersely distributed octenidine salt or dequalinium salt. Further preferred embodiments are indicated in the dependent claims. The invention also relates to a process according to claim 20 and a use according to claim 19.

In this case, octenidine salt should be understood to be a compound with the basic dicationic bipyridinium structure according to CAS No. 70775-75-6. This should include also slight modifications to the basic chemical structure, e.g. with a variation of the central alkyl chain (n = 7 – 13), a variation of the terminal alkyl chains (n = 4 – 12), and a variation of the anions. Instead of the octenidine salt, dequalinium salts with a similar structure can be involved.

Suitable anions of such salts are the non free radical polymerisable anions (e.g. fatty acid anions, carboxylic acid anions, alkyl sulphonic acids and aryl sulphonic acids, alkyl sulphates and aryl sulphates). Examples of these are hexanoates, dodecylates, stearates and dodecyl sulphates.

Such octenidine salts exhibit a certain mobility/migratability in the dental material.

Free radical polymerisable anions of unsaturated fatty acids (e.g. oleates, sorbates) can also be used. During hardening of the dental material, these can be incorpo-

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rated by polymerisation and are immobile, whereas the cationic portion can be mobilised. A combination of salts with anions of both groups is also possible. In this way, the release, via migration, of the salts or the cations from the dental material is possible at different rates. Finally, a release of residual substance is possible as a result of the abrasion of the material.

Dental materials equipped with active anti-plaque substance according to the invention consist e.g. of filling composites, mixed composites, prosthesis materials, materials for artificial teeth, moulding compounds, protective varnishes, fissure sealants, cements, adhesives or dentin bondings. Veterinary materials such as hoof material are also suitable.

The octenidine salt or dequalinium salt is present in the dental material preferably in quantities of less than 10% by weight. This means in particular that the release of active substance occurs in non-toxic, non-irritant and non-sensitising but antimicrobially effective quantities. In addition, the quantities should be chosen in such a way that the active substance is liberated in odour and taste neutral amounts. The possibility of discolouration of the dental material should also be excluded by the selection of the quantity. Octenidine salt and/or dequalinium salt is present in the dental material e.g. in quantities of <5, 3 or <1% by weight.

For incorporation by polymerisation or homogeneous distribution in the dental material, the salt is appropriately added to the corresponding monomer or monomer mixture. Examples of suitable monomers are those common in the dental sector such as e.g. monomeric (meth)acrylates such as ethylene glycol dimethacrylate EDMA, diethylene glycol dimethacrylate, triethylene glycol dimethacrylate TEGDMA, glycerol dimethacrylate GDMA, glycerol trimethacrylate, trimethylol propane trimethacrylate, pentaerythritol dimethacrylate, pentaerythritol trimethacrylate, pentaerythritol tetramethacrylate, derivatives of bisphenol A such as bisphenol A dimethacrylate and bisphenol A diglycol dimethacrylate, urethane methacrylate obtainable from diisocyanates and hydroxyalkyl methacrylates as well as reaction products of polyols, diisocyanates and hydroxyalkyl methacrylates according to DE 37 03 080 A1 or DE 37 03 120 A1; C_{1-12} alkyl methacrylates, preferably C_{1-4} alkyl methacrylates such as methyl methacrylate, ethyl methacrylate, n-propyl methacrylate, isopropyl methacrylate, n-butyl methacrylate and t-butyl methacrylate, hydroxyalkyl C_{1-4} methacrylates such as 2-hydroxyethyl methacrylate, 2-hydroxypropyl methacrylate, diethylene glycol monomethacrylate, triethylene glycol monomethacrylate, alkoxy C_{1-4} alkyl methacrylates such as 2-methoxyethyl methacrylate, 3-methoxybutyl methacrylate and ethyl triglycol methacrylate. Suitable

monomers of these are, respectively, the monomers themselves, polymerisable prepolymers produced therefrom and mixtures thereof.

Suitable fillers are in particular quartz powder and glass ceramic powders, aluminium oxides and/or silicon oxides. These include the so-called microfillers whose grain size is in the nm range, such as highly disperse, finely particulate pyrogenic or precipitated silicic acid and the so-called macrofillers whose grain size is in the micrometer range, in particular granular silicic acid or ground types of dental glass. The types of glass are e.g. barium glass powder, barium silicate glass powder, lithium powder or aluminium silicate glass powder, preferably aluminium silicate glass which may be doped with barium, strontium or rare earths (compare DE-PS 24 58 380). Finely ground types of glass or quartz with mean particle sizes of between approximately 1 and 10 micrometers and highly disperse SiO_2 with mean particle sizes of between approximately 10 and 400 nm are preferred.

Depending on the type of polymerisation initiator used, curing of the dental compositions may take place by thermal, photochemical or redox-induced radical polymerisation.

Preferred examples of thermal initiators are the known peroxides such as e.g. dibenzoyl peroxide, dilauryl peroxide, tert-butyl peroctoate or tert-butyl perbenzoate and azobisisobutyroethyl ester, azobisisobutyronitrile, azobis-(2-methyl propionamidine) dihydrochloride, benzpinakol or 2,2-dimethyl benzpinakol.

Benzophenone, benzoine and their derivatives or alpha-diketones or their derivatives such as 9,10-phenanthrene quinone, diacetyl or 4,4-dichlorobenzyl are preferred photoinitiators. Camphor quinone and 2,2-dimethoxy-2-phenyl acetophenone are particularly preferred and alpha-diketones in combination with amines as reducing agents such as e.g. 4-(N,N-dimethylamino) benzoic acid ester, N,N-dimethyl aminoethyl methacrylate, N,N-dimethyl sym.-xylidine or triethanol amine are used particularly preferably. In addition, acyl phosphines such as e.g. 2,4,6-trimethyl benzoyl diphenyl- or bis(2,6-dichlorobenzoyl)-4-N-propylphenyl phosphine oxide are particularly suitable.

Redox initiator combinations such as e.g. combinations of benzoyl peroxide or lauryl peroxide with N,N-dimethyl-sym.-xylidine or N,N-dimethyl-p-toluidine are preferably used as initiators for polymerisation carried out at room temperature.

The following examples illustrate the invention in further detail. Information concerning parts and percentages relate here and in the remaining description to the weight, unless indicated otherwise.

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Practical examples

Production of octenidine palmitate

100 ml of methanol are placed into a round-bottomed flask, a stoichiometric quantity of NaOH is added and dissolution is carried out at room temperature with stirring. After adding the corresponding molar quantity of octenidine dihydrochloride, stirring is carried out for 10 min and a stoichiometric quantity of palmitic acid is added. After stirring for approximately 30 min, filtration is carried out and the solvent is drawn off.

Production of a dental composite with homogenously molecularly dispersely distributed octenidine palmitate

Octenidine palmitate is added to a 70:30 mixture of bis-GMA and TEDMA in such an amount that the end concentration of octenidine palmitate is 3 or 6% by weight. Stirring is carried out with light heating until the octenidine palmitate is completely dissolved.

The addition of the usual photoinitiators and stabilisers as well as 65% by weight of dental glass with a grain size of ~ 1 µm and approximately 8% by weight of pyrogenic silicic acid Aerosil OX50 for adjusting the rheology completes the filling composite. If necessary, colour pigments are added for colour adjustment.

Hardening to form test specimens

The composite Venus® (Heraeus Kulzer) to which the antimicrobial additive has been added is processed to form test panels with a diameter of 20 mm and a thickness of 1 mm by spreading it into a steel mould. On exposure to the light of the dentist lamp Translux Energy® (Heraeus Kulzer) in line with the specifications contained in ISO4049, the test specimen is cured.

Test of the antimicrobial effect

The following sterile specimens were placed into flow chambers:

Venus® reference material without active substance,

Venus® with 3% active substance,

Venus® with 6% active substance,

1 x titanium (control).

Subsequently, the flow chambers were connected to a bioreactor which contained a freshly prepared bacterial mixed culture (Streptococcus mutans, Streptococcus sanguinis, Actinomyces viscosus, Fusobacterium nucleatum, Veillonella parvula) in the logarithmic growth phase with defined proportions of the individual bacteria species for the execution of the plaque adherence tests. The incubation of the mixed culture took place in line with a continuous culture management anaerobically at 37°C, pH=7.2 and 5.0 g/l sucrose as source of C. By means of hose pumps, the bacterial mixed culture was

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passed through the flow chambers over the material surface. Testing of the biofilm formation took place over a period of 5 days. After removing the specimens from the flow chambers, rinsing of the specimens was carried to remove non-adhering bacteria.

Analyses:

The analysis of the bacteria adhesion on the specimen surfaces was carried out following selective fluorescence staining of adhering living and dead microorganisms.

Results:

The addition of the active substance has a marked effect on the quantity of adhering bacteria and in particular on the vitality of the adhering bacteria population. Fig. 1 shows the adhesion of plaque bacteria (mixed culture, 5 species) after 5 days of dynamic cultivation (flow chamber) on polymer materials (composite Venus®, Heraeus Kulzer) with and without active substance. A reduction of the bacteria count by approximately 80% was observed.

The non-modified polymer material exhibits a distribution of living and dead bacteria of approximately 50:50 (compare Fig. 1). As a result of the addition of active substance, the ratio is markedly displaced in the direction of dead bacteria (10% living, 90% dead). This is clear proof of the antibacterial effectiveness of the additive used.

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The claims defining the invention are as follows:

1. Dental material equipped with active anti-plaque substance characterised in that it contains at least one molecularly dispersely distributed octenidine salt or dequalinium salt, the salt being present in the dissolved form molelcularly dispersed in one or several of the monomers common in the dental sector and based on (meth)acrylate and the salt exhibiting at least one anion from the group consisting of fatty acid anions, carboxylic acid anions, alkyl sulphonic acids and aryl sulphonic acids, alkyl sulphates and aryl sulphates.

2. Dental material according to claim 1 containing one or several monomer(s) common in the dental sector; at least one molecularly dispersed dissolved octenidine salt or dequalinium salt and at least one substance from the group of polymerisation initiators, stabilisers and fillers.

3. Dental material according to claim 1 or 2 in which the salt is present in a concentration of < 10% by weight.

4. Dental material according to any one of the preceding claims in which the salt is temperature stable in the region up to an upper limit of 100 °C.

5. Dental material according to any one of the preceding claims in which the salt exhibits at least one non free radical polymerisable anion.

6. Dental material according to any one of the preceding claims characterised in that the salt is capable of migration in the dental material within a temperature range of 15-40°C.

7. Dental material according to any one of the preceding claims containing the salt with a solubilising, free radical polymerisable anion.

8. Dental material according to claim 7 containing additionally at least one octenidine salt or dequalinium salt with a solubilising, non free radical polymerisable anion.

9. Dental material according to claim 7 or 8, it being possible to incorporate the anions by polymerisation.

10. Dental material according to one of the preceding claims characterised in that the total quantity of octenidine salt and/or dequalinium salt amounts to < 5% by weight.

11. Dental material according to claim 10 characterised in that the quantity amounts to < 3% by weight.

12. Dental material according to claim 10 characterised in that the quantity amounts to < 1% by weight.

13. Dental material according to any one of the preceding claims containing a further antimicrobial component.

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14. Dental material according to claim 13 the further component of the group consisting of monocationic antiseptics, dicationic antiseptics, oligomeric or polymeric cationic antiseptics and antiseptic heavy metal compounds.

15. Use of octenidine salts or dequalinium salts molecularly dispersely distributed in a (meth)acrylate monomer for equipping dental material with anti-plaque properties, the salt exhibiting at least one anion from the group consisting of fatty acid anions, carboxylic acid anions, alkyl sulphonic acids and aryl sulphonic acids, alkyl sulphates and aryl sulphates.

16. Process for equipping dental material based on (meth-)acrylate with anti-plaque properties in the case of which at least one octenidine salt or dequalinium salt is distributed in a molecularly dispersed manner in a (meth-)acrylate monomer before polymerisation, the salt exhibiting at least one anion from the group consisting of fatty acid anions, carboxylic acid anions, alkyl sulphonic acids and aryl sulphonic acids, alkyl sulphates and aryl sulphates.

17. Dental material equipped with active anti-plaque substance, substantially as hereinbefore described with reference to any one of the examples and/or the accompanying drawing.

18. Use according to claim 15, substantially as hereinbefore described with reference to any one of the examples and/or the accompanying drawing.

19. Process according to claim 16, substantially as hereinbefore described with reference to any one of the examples and/or the accompanying drawing.

Dated 8 April, 2009
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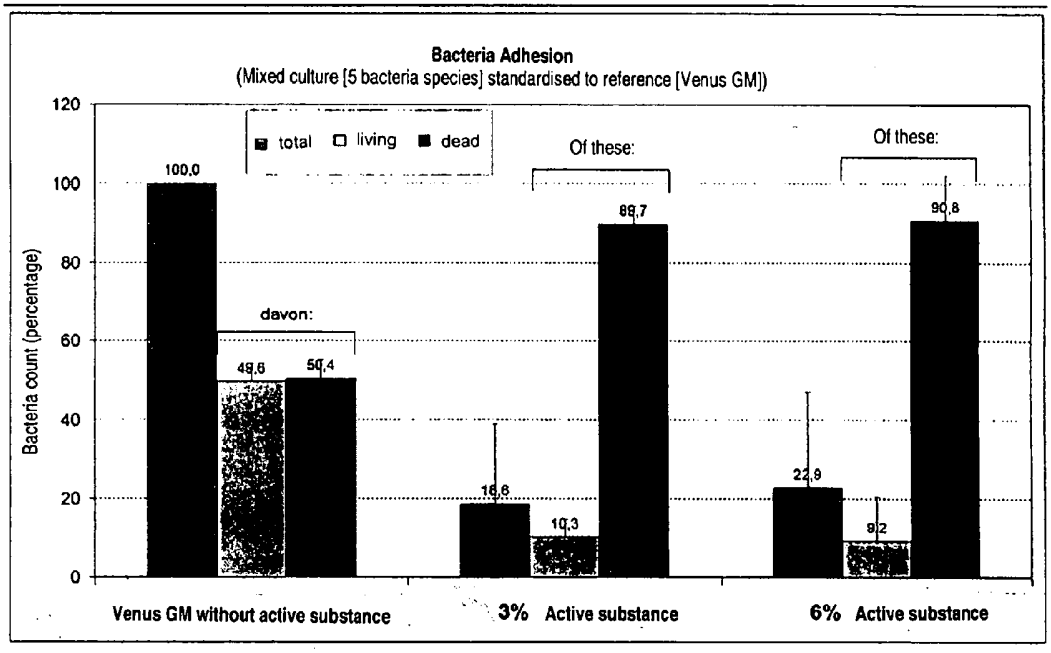
(FIG 1)



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