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(54) Titre : MATERIAU PREVU POUR L'UTILISATION PRINCIPALEMENT MEDICALE, IN VIVO A LONG TERME, ET
PROCEDE DE REALISATION

(54) Title: MATERIAL PRIMARILY FOR MEDICAL, LONG-TERM IN VIVO USE AND METHOD FOR ITS
MANUFACTURE

(57) **Abrégé/Abstract:**

The invention relates to a material that is used primarily for medical, long-term in vivo purposes, e.g. as a filling material in dentistry. The aim of the invention is to create a material primarily for medical, long-term in vivo use which does not have the disadvantages of materials used in prior art, is initiated without releasing active substances, and endures after the material has been removed or when the shape thereof is modified. Said aim is achieved by the fact that the material is made of polymers and filling agents which are embodied as polymer-coated, chemically modified particles that carry hydroxyl groups and are surrounded by a matrix of another polymer. The coating polymer develops an antimicrobial effect.



ABSTRACT

The invention relates to a material that is used primarily for medical, long-term *in vivo* purposes, e.g. as a filling material in dentistry. The aim of the invention is to create a material primarily for medical, long-term *in vivo* use which does not have the disadvantages of materials used in the prior art, is initiated without releasing active substances, and endures after the material has been removed or when the shape thereof is modified. Said aim is achieved by the fact that the material is made of polymers and filling agents which are embodied as polymer-coated, chemically modified particles that carry hydroxyl groups and are surrounded by a matrix of another polymer. The coating polymer develops an antimicrobial effect.

**MATERIAL PRIMARILY FOR MEDICAL, LONG-TERM *IN VIVO* USE AND
METHOD FOR ITS MANUFACTURE**

5 The invention relates to a material for the primary medical, long-term *in vivo* use, such as for example as filling materials for dental medicine as well as a process for its manufacture.

It is known that body foreign materials which are used in the body (for example in the oral cavity) or on the body (for example as a catheter) are subjected to the locally present microorganisms, or can promote the invasion of microorganisms into the body.

10 In the oral cavity, that is, for example, an anaerobic or aerobic mixed flora. The cavity causing *streptococcus mutans* [Hellwig E et al. Einführung in die Zahnerhaltung. Urban & Schwarzenberg Verlag, München 1995] and as a primary settler *streptococcus sanguis* belong to the bacterial strains most prevalent in that location.

Materials most often used in the oral cavity include metals, ceramics, polymers
15 or also mixed materials, so called composites [Eichner K. Zahnärztliche Werkstoffe und ihre Verarbeitung. Band 1, Band 2. Hüthig Verlag Heidelberg 1988 und Craig GC, Powers JM. Restorative Dental Materials. 11th ed. Mosby, St. Louis 2002].

Amongst all known dental materials, the composites, which are used as fastening material or filling materials have the reputation to especially promote bacterial accretion
20 in the oral cavity [Weitmann RT, Eames WB. Plaque accumulation on composite surfaces after various finishing procedures. J Am Dent Assoc 1975;91:101-106; Skorland KR, Sonju T. Effect of sucrose rinses on bacterial colonization on amalgam and composite. Acta Odontol Scand 1982;40:193-196 und Svanberg M, et al. Mutans streptococci in plaque from margins of amalgam, composite, and glass-ionmer
25 restorations. J Dent Res 1990;69:864]. Even worse, composites may shrink during polymerization, whereby microfine gaps can be created with fillings or cement grout between the tooth substance (dentine/enamel) and the composite. Bacteria can successfully colonize in this fine gap [Hellwig E et al. Einführung in die Zahnerhaltung. Urban & Schwarzenberg Verlag, München 1995].

30 Since these gaps largely elude the tooth cleaning action and the flushing action of the saliva, the bacteria multiply undisturbed and after a short amount of time lead to the creation of carious lesions. Bacteria cannot only grow on materials, they can also use

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the carbon components of the polymers for their metabolism, in part, and thereby contribute to the degradation of the composites [und Craig GC, Powers JM. Restorative Dental Materials. 11th ed. Mosby, St. Louis 2002].

Bacteria therefore are damaging in two different ways: their unchecked
5 multiplication on the one hand leads to cavities and on the other hand to the gradual destruction of the material.

The release of active ingredients from medically usable materials has been known for decades. Application locations are, among others, blood vessels (active ingredient release from coated stents for vessel enlargement) or bone (implantation upon
10 bone infection of a polymer bead chain of polymethylmethacrylate (Septopal ® of the company biometmerck) with the antibiotic gentamycin (Refobacin® of the company Merck)).

When artificial hip joints are implanted by way of cementing, the “cement” (hardening polymer material) is in this approach also admixed with an antibiotic.

15 While the releasing of restinose from the stents is to prevent overgrowth on the vessels, bead chains are used for an existing infection. In the case of a hip implantation, the antibiotic is used prophylactically in order to prevent the emergence of an infection.

Systems with active ingredients in the form of mouthwashes, toothpastes are used in the oral cavity [Lahdenperä MS, Puska MA, Alander PM, Waltimo T, Vallittu
20 PK. Release of chlorhexidine digugonate and flexural properties of glass fibre reinforced provisional fixed partial denture polymer. J Mat Sci Mat Med 2004;15:1349-1353; Imazato S. Influence of incorporation of antibacterial monomer on curing behaviour of a dental composite. J Dent 1999, 27:292-297; Imazato S, Torii M. Incorporation of bacterial inhibitor into resin composite, J Dent Res 1994; 73:1437-1444
25 und Addy M, Handley R. The effect of the incorporation of chlorhexidine acetate on some physical properties of polymerized and plasticized acrylics. J Oral Rehabil 1981;8.155-163].

One of the most prevalent oral antibacterial active ingredients is chlorhexidine-digluconate [Lahdenperä MS, Puska MA, Alander PM, Waltimo T, Vallittu PK. Release
30 of chlorhexidine digugonate and flexural properties of glass fibre reinforced provisional fixed partial denture polymer. J Mat Sci Mat Med 2004;15:1349-1353]. When used for

more than six weeks, mucous membrane discoloration and taste irritation occur, which is the reason why continuous medication is not wise.

It is known from dental amalgamates that the release of volatile components, for example copper in the filling gap renders the survival of microorganisms difficult or impossible [Skorland KR, Sonju T. Effect of sucrose rinses on bacterial colonization on amalgam and composite. *Acta Odontol Scand* 1982;40:193-196 und Svanberg M, et al. Mutans streptococci in plaque from margins of amalgam, composite, and glass-ionmer restorations. *J Dent Res* 1990;69:861-864].

Concepts are being discussed for composites in which by incorporation of releasable, bactericidally active substances the accumulation of plaque is to be reduced or even prevented [Imazato S. Influence of incorporation of antibacterial monomer on curing behaviour of a dental composite. *J Dent* 1999, 27:292-297; Imazato S, Torii M. Incorporation of bacterial inhibitor into resin composite, *J Dent Res* 1994; 73:1437-1444].

It is however a disadvantage of all preceding solutions that many of the principally applicable substances with antibiotic activity can have allergenic or toxic effects. Moreover, it must be ensured with the known materials (for example dental cement or filling) that a sufficient active ingredient level is guaranteed over the whole residence time of the material in the oral cavity.

Apart from the synthetically manufactured antibiotics, substances are also used as antibacterially active substances which are derived from natural products. These include, amongst others, chitsoan and its derivatives.

References EP 0339098 B1, EP 0389629 B1, EIP 1255576 B1 and EP 1237585 B1 disclose curable pastes of different oxides or phosphates with chitosan as binder, or the solubility of the chitosan is reduced by the alkaline properties of the oxides. The described use in the dental area refers to root filling materials, or because of the missing resistance to the pH in the oral cavity only provisional filling materials.

A compound made of chitosan and hydroxyl appetite is known from Japanese reference 02102165 A which as ceramic can however only be used after a sintering. It is a disadvantage of this solution, that the organic component acting as binder are pyrolized during the sintering.

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References EP 0287105 B1 and EP 1296726 B1 disclose a bone forming implant material of glycosaminoglycan with cationic polymers as matrix substances into which filler particles of a composition similar to bone are embedded. Although chitosan is a glycosaminoglycan, the mentioned references expressly describe a bone replacement material resorbable by the body, which can also be used in the jaw region.

The Japanese reference 07157434 A describes a proliferation inhibitor for bacteria in the oral cavity which is formed by chitosan and its derivatives.

The addition of metal ions to the amino groups of the chitosan or its derivatives is also known from the Japanese reference 10130427 A, whereby this system is used with hydroxyl apatite.

A similar material of chitosan derivatives and tin fluoride is disclosed in Japanese reference 05000930 A.

To date, chitosan was only used in connection with bioresorbable fillers, such as for example calcium phosphate and serves as a degradable bone filler material or as provisional tooth filling material. Chitosan is thereby used as a binder because of its pH dependent solubility.

It is a disadvantage of all known materials that they do not provide a consistent antimicrobial effect for the long term *in vivo* use.

It is therefore an object of the invention to provide a material for the primarily medical, long term *in vivo* use which avoids the disadvantages of the art and is initiated without an active ingredient release and remains consistent both after removal of the material or despite a change in the form of the material. Furthermore, a process for the manufacture of this material is to be provided.

This object is achieved in accordance with the invention by the characterizing features of the first claim and preferred embodiments are dealt with in the dependent claims.

The invention essentially consists in providing a material of polymeric basis, which during medical application in the oral cavity, for example, as dental filling or cement, develops an antimicrobial/antibacterial effect during the whole residence time, without being toxic or allergenic. This effect also remains even after material removal or after damage.

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The material preferably consists of filler bodies in the form of polymers, copolymers, composites, metals, glass-type compounds, ceramic in pure form or as mixtures of these materials, which are coated with a polymeric layer in the form of polysaccharides or their derivatives, whereby these polymeric coatings have an antimicrobial effect and the coated filler bodies are surrounded by a matrix consisting of a further polymer.

The polysaccharide is preferably chitosan.

According to the invention, the polymer, for example in the form of chitosan, is modified by a deacetylation in such a way that the deacetylated polymer, for example the chitosan, can be coupled to a modified silicone dioxide particle surface (terminal aldehyde groups on the particle surface) and a subsequent coupling of 3-vinylbenzaldehyde onto the polymer coated particles can be carried out.

This antimicrobially active coating can additionally be chemically modified such that carbon-carbon (double) bonds are introduced which participate during the hardening process in the chemical reaction (for example polymerization).

Furthermore, the additional chemical modification can be used to change the dispersion properties, to immobilize activateable starter molecules (initiators, which are activateable for example chemically, thermally or with UV light) on the surface or to immobilize additional reaction accelerators or controllers for the adjustment of the chain length which are necessary for the chemical reaction (for example the polymerization) on the surface.

The filler material activated in this way is dispersed in a liquid monomer mixture, for example bis-GMA, TEGDMA, UDMA, BPO, camphorquinone or ketones so that the material in accordance with the invention is created.

An antibacterial effect which is retained over long periods of time is generated with the coating in accordance with the invention of the polymer particles, whereby at the same time the bonding with the polymer matrix and the associated improved dispersion of the particle powder in the liquid phase is achieved.

During the dispersion, the terminal vinyl group of the particles (activated fillers) reacts with the monomers by hardening to a polymer matrix. The activated filler is therefore, because of the chemical binding, an integrated component of the material in accordance with the invention.

The invention is further described in the following by way of the exemplary embodiment.

1. Deacetylation of the Chitosan:

Deacetylation of the chitosan is carried out according to the known process
5 under reflux in hydrochloric acid. The chitosan deacetylated in this way is cleaned according to the state of the art by a dialysis process and transferred into a solid by freeze drying.

2. Coupling of Deacetylated Chitsoan onto Modified Silicone Dioxide-Particle
10 Surfaces/Coupling of 3-Vinylbenzaldehyde:

The hydroxyl groups of silicone dioxide particles are converted with aminopropyl-triethoxysilan in a mixture of ethanol/water at 45°C.

After purification of the particles/the filler bodies by flushing with ethanol, the amino groups are modified with glutaraldehyde at room temperature under the
15 formation of a Schiff base and subsequently flushed with water. This results in a terminal aldehyde group on the silicone dioxide particles/the filler bodies, which is converted with an aqueous solution of deacetylated chitosan at room temperature.

The particle surface/filler body surface modified with chitosan is converted with 3-vinylbenzaldehyde. The excess amino groups of the chitosan thereby react with the 3-
20 vinylbenzaldehyde under the formation of a Schiff base. The particles/filler bodies are cleaned of the non-covalently bonded 3-vinylbenzaldehyde by multiple washing with water and subsequently dried. Due to this process, the powder/filler bodies has/have covalently bonded chitosan on its/their surface, the amino groups of which are chemically modified in part by the reaction with 3-vinylbenzaldehyde.

25 For the manufacture of the material, the modified powder/filler bodies is/are dispersed in the monomer mixture (for example biz-GMA, TEGDMA, UDMA, BPO, camphorquinone or ketones). The terminal vinyl group of the particle/filler bodies reacts with the monomers during the reaction (hardening of the filler material) into the polymer matrix. The activated filler is thereby chemically bonded with the polymer and
30 forms therewith the material in accordance with the invention.

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3. Proof of the Antibacterial Effect was Provided through Bacteria Accretion Testing:

In order to verify the chemical integration of the filler bodies into the polymer matrix, dynamic-mechanical tests (DMA) as well as bending tests were carried out.

5 Test bodies (for example in the form of platelets) were therefor formed using the material in according with the invention.

A material with non-modified powder/filler bodies according to the art was used, for example, as reference. The portions of the powder/filler body in the filler material are thereby, as known, at 20 to 30% per volume.

10 The test bodies are subjected to a suspension of bacteria (for example *streptococcus sanguis*). The bacteria therefore have the possibility to attach to the specimen surface and to multiply. After 36 hours, the number of bacteria present on the surface are quantitatively determined for the material in accordance with the invention using fluorescence processes and by a scanning electron microscope and compared with the bacterial numbers of the reference.

15 All features included in the description and the following claims can be significant for the invention on their own in any combination with one another.

CLAIMS

1. Material for the primarily medical, long-term *in vivo* use consisting of polymers and filler bodies, characterized in that the filler bodies are chemically modified,
5 hydroxyl group carrying particles coated with a polymer which are surrounded by a matrix of a further polymer, whereby the coated polymer has antimicrobial activity.
2. Material according to claim 1, characterized in that the particles consist of polymers, copolymers, composites, metals, glass-type compositions, ceramic in pure
10 form or as mixtures of these materials.
3. Material according to claim 1, characterized in that the particles consist of silicone or titanium dioxide.
- 15 4. Material according to claim 1, characterized in that the polymer coating of the particles consists of polysaccharides.
5. Material according to claim 4, characterized in that the polymer coating of the particles consists of chitosan.
20
6. Material according to claim 1, characterized in that the chemical modification is formed by terminal aldehyde groups.
7. Material according to claim 6, characterized in that the aldehyde groups are 3-
25 vinylbenzaldehyde.
8. Material according to claim 1, characterized in that the polymer matrix consists of bis-GMA, TEGDEMA, UDMA, BPO, camhorchinone or ketones.
- 30 9. Material according to any one of the preceding claims, characterized in that additional chemical modifications are present on the particles which serve to change the dispersion properties, to immobilize activateable starter molecules on the surface or to

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immobilize reaction accelerators or controllers for the adjustment of the chain length which are necessary for the chemical reaction (for example the polymerization) on the surface.

- 5 10. Process for the manufacture of a material according to one or more of the preceding claims, comprising the following steps:
- reaction of 3-aminopropyl-triethoxysilane with hydroxyl group carrying silicone dioxide particles in a mixture of ethanol/water for the formation of amino groups,
 - 10 - reaction of glutaraldehyde under formation of a Schiff base for the formation of terminal aldehyde groups on the silicone dioxide particles,
 - coating of these particles with deacetylated chitosan,
 - reaction of the coated particles with 3-vinylbenzaldehyde for chemical modification,
 - 15 - dispersion of the chitosan coated chemically modified particle in a monomer mixture under formation of a curable phase for the formation of the polymer matrix.

Claims as Amended

1. Material for the primarily medical, long term *in vivo* use consisting of a polymer matrix and antimicrobial filler bodies, characterized in that the filler bodies are silicone dioxide particles coated with an antimicrobially active polysaccharide which particles have terminal vinyl groups by which the filler bodies are bonded into the polymer matrix.
2. Material according to claim 1, characterized in that the polymer coating of the particles consists of chitosan.
3. Material according to claim 1, characterized in that the polymer matrix is formed of bis-GMA, TEGDMA, UDMA, BPO, camphorquinone or ketones.
4. Process for the manufacture of a material according to claim 2 or 3, comprising the steps of
 - reaction of 3-aminopropyl-triethoxysilane with hydroxyl group carrying silicone dioxide particles in a mixture of ethanol/water for the formation of amino groups,
 - reaction of glutaraldehyde under formation of a Schiff base for the formation of terminal aldehyde groups on the silicone dioxide particles,
 - coating of these particles with deacetylated chitosan,
 - reaction of the coated particles with 3-vinylbenzaldehyde for chemical modification,
 - dispersion of the chitosan coated chemically modified particles in a monomer mixture under formation of a curable phase for the formation of the polymer matrix.