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(54) Title: BIOACTIVE CEMENT (57) Abstract A bioactive cement comprises a filler consisting of nonalkali glass powder containing Ca, monomer containing hydrophilic dimethacrylate, a polymerization starter, and a polymerization promoter. The nonalkali glass powder containing Ca comprises a composition by weight of 40-50 % CaO, 30-40 % SiO₂, 10-20 % P₂O₅, 0-10 % MgO, and 0-2 % CaF₂. The hydrophilic dimethacrylate is 2,2-bis[4-(3-methacryloxy-2-hydroxy propoxy)phenyl] propane. The bioactive cement is capable of forming a hydroxyapatite layer on a surface of a hardened cement body when the hardened cement body is brought into contact with body fluid.		

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DESCRIPTION

BIOACTIVE CEMENT

Background of the Invention:

This invention relates to a bioactive cement for bonding or fixing an implant material used in orthopedic and dental fields.

5 In the orthopedic field, a bone defect due to fracture, bone tumor, or any other disease is dealt with. In some cases, a part of a bone is resected in a surgical operation. In the dental field, a defect of a jawbone may result from extraction of a tooth, a Riggs' disease,
10 and so on. In order to repair such bone defect and to reconstruct the part which has been resected, use is made of an implant material comprising a substance selected from metal, ceramics, and crystallized glass.

 It is desired that such implant material is
15 quickly and adaptively embedded and fixed in a repair part to be repaired. For this purpose, the implant material must be ground or worked into a shape adapted to the repair part. However, it is extremely difficult to perform such grinding or working with a high precision.

In view of the above, a biocement is generally used together with the implant material in order to bond and fix the implant material to a living bone. For example, in the orthopedic field, a polymethyl-
5 methacrylate (PMMA) cement has been widely used. In the dental field, use has been made of a zinc phosphate cement or a carboxylate cement.

The above-mentioned biocements of various types can make a strong bond with the implant material.
10 However, those biocements may possibly be loosened from the living bone and frequently induce an inflammatory reaction in a surrounding tissue.

Under the circumstances, various proposals have been made of the improvement of the biocement which
15 contains a bioactive substance as a filler so as to provide a chemical bond with the living bone. For example, Japanese Patent Publication No. 42384/1979 discloses a biocement comprising a combination of polymethylmethacrylate (PMAA) and $K_2O-Na_2O-CaO-MgO-SiO_2-P_2O_5$
20 P_2O_5 crystallized glass powder.

Japanese Patent Prepublication No. 503148/1987 discloses another biocement comprising a combination of 2,2-bis[4-(3-methacryloxy-2-hydroxy propoxy)phenyl] propane (hereinafter referred to as Bis-GMA) base monomer
25 and apatite powder with bioglass powder added as an optional component.

However, the conventional biocements described above are not yet satisfactory in bonding condition with

the living bone, bonding strength, mechanical strength, and chemical stability of a hardened cement body itself which is obtained after completion of a hardening process.

5 For example, the biocement disclosed in Japanese Patent Publication No. 42384/1979 is disadvantageous in that the bonding strength with the living bone is insufficient. As a result of thorough investigation, the present inventors have found out that, once this cement
10 is hardened, body fluid such as cerebrospinal fluid, lymph, and saliva is not allowed to filtrate into the interior of the hardened cement body and therefore the crystallized glass powder can not exhibit bioactivity. It has also been found out that this is because the
15 biocement uses the monomer (methylemethacrylate, hereinafter abbreviated to MMA) which is substantially non-hydrophilic.

 In addition, the hardened cement body itself has a reduced mechanical strength because of two-dimensional
20 polymerization of the above-mentioned MMA.

 Furthermore, the biocement disclosed in Japanese Patent Publication No. 42384/1979 comprises, as a filler, the crystallized glass powder containing alkali components such as Na_2O and K_2O . Accordingly, chemical
25 durability is not excellent and bioactivity is insufficient.

 On the other hand, the biocement disclosed in Japanese Patent Prepublication No. 503148/1987 employs,

as a hardening agent, Bis-GMA which is highly hydrophilic. In accordance with our findings described above, it is supposed that the body fluid can easily filtrate in the interior of the hardened cement body and therefore the biocement can form a chemical bond with the living bone. However, the present inventors has practically confirmed that a sufficient bonding strength can not be achieved with this biocement. This is because the biocement uses a filler comprising apatite which has low bioactivity.

10 In case when the apatite powder is exclusively used as the filler, the bonding rate is rather slow and the bonding strength is weak. When the bioglass powder is additionally used, the bonding rate is increased. However, a silica gel layer, which is thick and fragile,

15 is formed on the surface of the bioglass powder because Na_2O contained in the glass is easily precipitated in the form of Na^+ ion. As a result, a strong bond with the living bone is difficult to obtain. In addition, the precipitated Na^+ ion increases the pH value of the body

20 fluid. Accordingly, the surrounding tissue may possibly be adversely affected. Furthermore, the bioglass has a low chemical durability. If this biocement is embedded in contact with the body fluid for a long time, the glass powder is broken. This results in deterioration of the

25 mechanical strength of the hardened cement body.

Summary of the Invention:

It is an object of this invention to provide a bioactive cement which can be quickly auto-hardened to

bond and fix an artificial biomaterial (implant material), which forms a chemical bond with a living bone, which has a stability in a living body for a long time, and which can get rid of deterioration of a mechanical strength.

As a result of extensive research and various experiments, the present inventors found out that the above-mentioned object is accomplished by a combination of (1) nonalkali glass powder and/or nonalkali crystallized glass powder containing Ca, and (2) hydrophilic dimethacrylate.

Specifically, a bioactive cement according to this invention comprises a filler consisting of nonalkali glass powder and/or nonalkali crystallized glass powder containing Ca, a monomer containing hydrophilic dimethacrylate, a polymerization starter, and a polymerization promoter and is capable of forming a hydroxyapatite layer on a surface of a hardened cement body when the hardened cement body is brought into contact with body fluid.

The nonalkali glass powder and the nonalkali crystallized glass powder containing Ca must be able to precipitate Ca^{2+} ion in a living body. In this connection, the glass powder or the crystallized glass powder has a composition consisting by weight of 20-60% CaO , 20-50% SiO_2 , 0-30% P_2O_5 , 0-20% MgO , and 0-5% CaF_2 , preferably, 40-50% CaO , 30-40% SiO_2 , 10-20% P_2O_5 , 0-10% MgO , and 0-2% CaF_2 .

The composition is restricted as specified above because of the grounds which will presently be described. When CaO is less than 20%, Ca^{2+} ion is difficult to be precipitated. This results in degradation of bioactivity. When CaO is more than 60%, chemical durability is deteriorated. When SiO_2 is less than 20%, chemical durability is deteriorated. When SiO_2 is more than 50%, uniform glass is difficult to obtain. When P_2O_5 and MgO are more than 30% and 20%, respectively, chemical durability is deteriorated. When CaF_2 is more than 5%, devitrification is increased. This makes it difficult to obtain uniform glass.

In order to provide the hardened cement body having a greater strength and to obtain high bioactivity, it is desirable that the glass powder or the crystallized glass powder has a smaller particle size. Preferably, the particle size is not greater than 65 μm .

The glass powder and the crystallized glass powder are restricted to those containing no alkali component because of the grounds which will presently be described. When the glass powder or the crystallized glass powder contains any alkali component, the chemical durability of the glass is considerably degraded. This causes destruction of the glass during long-term embedment in the living body. As a result, the hardened cement body itself is also deteriorated in strength. In addition, the alkali component is precipitated and increases the pH value of the body fluid. In this event,

the surrounding tissue may be adversely affected.

Furthermore, when the alkali component is precipitated, a thick and fragile silica gel layer is formed on the surface of the glass powder or the crystallized glass powder. As a result, it is impossible to obtain a strong bond with the living bone.

In order to provide a stronger bond with polymer, it is preferable to subject the surface of the glass powder or the crystallized glass powder to a silane coupling treatment. As a silane coupling agent, use is generally made of 3-methacryloxy propyl trimethoxy silane, 3-aminoethyl aminopropyl trimethoxy silane, 3-glycidoxy propyl trimethoxy silane, and so on.

The hydrophilic monomer used in this invention includes hydrophilic dimethacrylate. The dimethacrylate is a multifunctional monomer and forms a cross-link polymerization structure. Accordingly, the resultant polymer has a high mechanical strength. It is noted here that the hydrophilic monomer is defined as those containing a hydrophilic group such as an OH group and allowing the body fluid to enter into the interior of the material (hardened cement body). One preferred example of the hydrophilic dimethacrylate is Bis-GMA. Bis-GMA is adapted for use in the living body because it is readily available and harmless in the living body. However, as described above, use may be made of any other monomer which contains a hydrophilic group such as an OH group and allows the body fluid to readily enter into the

interior of the material.

If necessary, other monomer may be contained in addition to the hydrophilic dimethacrylate. When Bis-GMA is exclusively used, the biocement is often difficult to handle because of high viscosity. In this connection, it is preferable to use the additional monomer such as triethylene glycol dimethacrylate (TEGDMA), diethylene glycol dimethacrylate (DEGDMA), and ethylene glycol dimethacrylate (EGDMA). Furthermore, substantially non-hydrophilic monomer may be added on demand. Addition of the substantially non-hydrophilic monomer is to control a hydrophilic property on the surface of the hardened cement body. As such a control agent, use is made of 2,2-bis(4-methacryloxy phenyl)propane (BPDMA), 2,2-bis(4-methacryloxy ethoxy phenyl)propane (Bis-MEPP), 2,2-bis(4-methacryloxy polyethoxy phenyl)propane (Bis-MPEPP), or the like.

It is possible to mix the glass powder and the crystallized glass powder with the monomer at any mixing ratio. However, taking the workability in kneading operation into account, the mixing ratio of the powder to the monomer is desirably within a range between 30:70 and 90:10 by weight.

As the polymerization starter, use may be made of benzoyl peroxide, tri-n-butylborane, or the like. It is possible to induce photo polymerization by the use of a sensitizer such as dl-camphorquinone. The polymerization starter may be contained in various manners. The content

of the polymerization starter is selected within a range of 0.01-2 wt% with respect to the total amount of the cement. When the content is less than 0.01 wt%, the progress of polymerization is very slow. This results in
5 increase of a hardening time. Thus, workability in kneading operation is deteriorated. On the other hand, when the content is greater than 2 wt%, the progress of polymerization is very rapid and the hardening time becomes too short. Thus, in this case also, the
10 workability in kneading operation is deteriorated.

As the polymerization promoter, use may be made of tertiary amine such as dimethyl-p-toluidine, diethyl-p-toluidine, and dimethyl aniline. The polymerization promoter may be contained in various
15 manners. The content of the polymerization promoter is selected within a range of 0.01-2 wt% with respect to the total amount of the cement. When the content is less than 0.01 wt%, the progress of polymerization is very slow. This results in increase of a hardening time.
20 Thus, workability in kneading operation is deteriorated as described above in the case of the polymerization starter. On the other hand, when the content is greater than 2 wt%, the progress of polymerization is very rapid and the hardening time becomes too short. Thus, the
25 workability in kneading operation is deteriorated also.

The bioactive cement according to this invention is supplied to a user in the supply form selected from a powder-liquid phase comprising a powder phase material

and a liquid phase material and a two-paste phase comprising two paste phase materials. In the powder-liquid phase, the powder phase material includes glass powder and/or crystallized glass powder, and the polymerization starter while the liquid phase material includes the monomer and the polymerization promoter. In the two-paste phase, one paste material includes glass powder and/or crystallized glass powder, the monomer, and the polymerization starter while the other paste material includes glass powder and/or crystallized glass powder, the monomer, and the polymerization promoter. In use, the user mixes the powder phase material and the liquid phase material or two paste phase materials with each other. Taking various conditions into consideration, one of the above-mentioned supply forms will be selected. Generally, the two-paste phase is desired if a large amount of the powder component is contained. This is because workability in kneading operation is deteriorated when such a large amount of the powder component is kneaded with the hardening liquid. In the bioactive cement according to this invention, it is found out that the two-paste phase is desired when the amount of the powder component is not smaller than 80wt%.

When the filler comprising nonalkali glass powder and/or nonalkali crystallized glass powder containing Ca, the monomer containing the hydrophilic dimethacrylate, the polymerization starter, and the polymerization promoter are mixed together at an appropriate mixing

ratio, polymerization occurs and the mixture is hardened in a short time within a range between 3 and 15 minutes.

As a result, a hardened cement body with a high mechanical strength is obtained.

5 In response to the body fluid filtrating through the surface of the hardened cement body, Ca^{2+} ion is precipitated from the glass powder and the crystallized glass powder. The precipitated Ca^{2+} ion reacts with PO_4^{4-} ion contained in the body fluid. As a result, a
10 hydroxyapatite layer similar to the component of the living bone is formed on the surface of the hardened cement body. Thus, the hardened cement body can be tightly and readily bonded with the living bone. Since no Na^+ ion is precipitated, a thick and fragile silica
15 gel layer is never produced on the surface. Accordingly, a bonding strength with the living bone is never decreased.

Description of the Preferred Embodiment:

Now, description will be made as regards a
20 bioactive cement according to several embodiments of this invention.

Table 1 shows various examples (Samples Nos. 1-16) according to this invention while Table 2 shows comparative examples (Samples Nos. 17-24).

Table 1-(1)

Sample No.			1	2	3	4	5	6	7	8
Powder (wt%)	Glass	A B C	100	100	100	100	100	100	100	100
	Crystal- lized Glass	A B D								
	Hydroxy- apatite									
Monomer (wt%)	Bis-GMA		50	50	40	30	30	30	50	50
	Bis-MEPP					20				
	Bis-MPEPP						20			
	BPDMA							20		
	TEGDMA		50	50	60	50	50	50		
	DECDMA								50	
	ECDMA									50
	MMA									
Mixing Ratio of Powder/Monomer (wt%/wt%)			85/15	70/30	74/26	77/23	77/23	77/23	70/30	70/30
Compressive Strength (MPa)			180	170	160	170	170	170	165	160
Bonding Strength with Living Bone			High	High	High	High	High	High	High	High
Hardening Time (Minutes)			5	7	6	5	4	4	7	8

A: $\text{CaO-MgO-SiO}_2\text{-P}_2\text{O}_5$ B: $\text{CaO-SiO}_2\text{-P}_2\text{O}_5$ C: $\text{Na}_2\text{O-CaO-SiO}_2\text{-P}_2\text{O}_5$ D: $\text{K}_2\text{O-Na}_2\text{O-CaO-MgO-SiO}_2\text{-P}_2\text{O}_5$

Table 1-(2)

Sample No.			9	10	11	12	13	14	15	16
Powder (wt%)	Glass	A B C	100	100	100	50	30	50		
	Crystal- lized Glass	A B D				50	70	50	100	100
	Hydroxy- apatite									
Monomer (wt%)	Bis-GMA		40	50	50	50	50	50	50	50
	Bis-MEPP									
	Bis-MPEPP									
	BPDMA									
	TEGDMA		30	50	50	50	50	50	50	50
	DECDMA		30							
	ECDMA									
	MMA									
Mixing Ratio of Powder/Monomer (wt%/wt%)			74/26	35/65	83/17	87/13	77/23	83/17	87/13	83/17
Compressive Strength (MPa)			165	160	160	185	160	165	190	165
Bonding Strength with Living Bone			High	High	High	High	High	High	High	High
Hardening Time (Minutes)			6	10	5	7	7	8	8	10

A: $\text{CaO-MgO-SiO}_2\text{-P}_2\text{O}_5$ B: $\text{CaO-SiO}_2\text{-P}_2\text{O}_5$ C: $\text{Na}_2\text{O-CaO-SiO}_2\text{-P}_2\text{O}_5$ D: $\text{K}_2\text{O-Na}_2\text{O-CaO-MgO-SiO}_2\text{-P}_2\text{O}_5$

Table 2

Sample No.			17	18	19	20	21	22	23	24
Powder (wt%)	Glass	A B C	100							
			100	100	50					
	Crystal- lized Glass	A B D					100	100		
	Hydroxy- apatite				50			100	100	
Monomer (wt%)	Bis-GMA			50		50	50		50	
	Bis-MEPP									
	Bis-MPEPP									
	BPDMA									
	TEGDMA			50		50	50		50	
	DECDMA									
	ECDMA									
	MMA		100		100			100		100
Mixing Ratio of Powder/Monomer (wt%/wt%)			70/30	70/30	70/30	70/30	70/30	70/30	70/30	70/30
Compressive Strength (MPa)			50	100	40	110	110	50	115	60
Bonding Strength with Living Bone			Null	Low	Null	Low	Low	Null	Low	Null
Hardening Time (Minutes)			8	6	8	7	6	8	8	10

A: $\text{CaO-MgO-SiO}_2\text{-P}_2\text{O}_5$ B: $\text{CaO-SiO}_2\text{-P}_2\text{O}_5$ C: $\text{Na}_2\text{O-CaO-SiO}_2\text{-P}_2\text{O}_5$ D: $\text{K}_2\text{O-Na}_2\text{O-CaO-MgO-SiO}_2\text{-P}_2\text{O}_5$

Those samples were prepared in the manner which will now be described.

A mixture having a composition consisting by weight of 44.7% CaO, 4.6% MgO, 34.0% SiO₂, 16.2% P₂O₅,
5 and 0.5% CaF₂ was prepared. The mixture was melted and vitrified at 1500°C for two hours into a vitrified product. Then, the vitrified product was rolled into a compact glass body. The compact glass body was pulverized in a ball mill and classified or sieved to
10 obtain glass powder having a maximum particle size of 65 μm. On the other hand, another compact glass body similarly formed was fired at 1050°C for four hours, pulverized in a ball mill, and classified to obtain crystallized glass powder having a maximum particle size
15 of 65 μm. Each of the glass powder and the crystallized glass powder was added into aqueous solution of acetic acid containing 1wt% of 3-methacryloxy propyl trimethoxy silane. The solution was heated and agitated, and then dried at 120°C for two hours. Thus, the glass powder A
20 and the crystallized glass powder A with a silane treatment were obtained.

Likewise, each of the glass powder B and the crystallized glass powder B with a silane treatment was obtained from a mixture having a composition consisting
25 by weight of 46.5% CaO, 36.0% SiO₂, 17.0% P₂O₅, and 0.5% CaF₂.

Furthermore, a mixture having a composition consisting by weight of 25.0% Na₂O, 25.0% CaO, 45.0%

SiO_2 , and 5.0% P_2O_5 was processed in the manner similar to the glass powder A to obtain the glass powder C with a silane treatment.

Finally, a mixture having a composition
5 consisting by weight of 5.0% Na_2O , 0.5% K_2O , 3.0% MgO , 34.0% CaO , 46.0% SiO_2 , and 11.5% P_2O_5 was processed in the similar manner to the crystallized glass powder A to obtain the crystallized glass powder D with a silane treatment.

10 In the comparative examples, the hydroxyapatite powder having a maximum particle size of 65 μm was used.

Each sample was prepared by the use of the glass powder and the crystallized glass powder thus obtained. The powder-liquid phase was used in Samples Nos. 2-10 and
15 13 and Comparative Samples Nos. 17-24 while the two-paste phase was used in Samples Nos. 1, 11, 12, and 14-16.

In each of the powder-liquid phase samples, 0.4wt% of benzoyl peroxide was added with respect to the total amount of the glass powder and the crystallized
20 glass powder. On the other hand, 0.2wt% of dimethyl-p-toluidine was added with respect to the amount of the monomer. The powder phase material and the liquid phase material thus obtained were kneaded with each other to obtain the samples.

25 In each of the two-paste phase samples, the glass powder and/or the crystallized glass powder was kneaded with the monomer at the mixing ratio indicated in Table 1 and equally divided into two paste materials. In one of

the paste materials, 0.6wt% of benzoyl peroxide was added with respect to the amount of the one paste material. In the other paste material, 0.2wt% of dimethyl-p-toluidine was added with respect to the amount of the other paste material. The two paste materials thus obtained were kneaded with each other to obtain the samples.

Each of those samples was evaluated with respect to a compressive strength for fixation and a bond with the living bone. The results were shown in Tables 1 and 2.

The compressive strength was measured according to the Japanese Industrial Standard Test JIS-T 6602 (for a dental zinc phosphate cement). Each sample was thoroughly kneaded, poured into a desired mold, cured for one hour to be hardened, and taken out from the mold. The hardened cement body was immersed in a simulated body fluid for 24 hours. Then, wet compression strength was measured.

The bond with the living bone was measured as follows. A hole of 2 x 16mm was bored in a tibia condyle of a rabbit. Each sample was kneaded, hardened, and formed into a piece of 10 x 15 x 2mm. The sample piece was embedded in the hole. After ten weeks, the rabbit was killed to extract the hardened cement body and the surrounding tissue. Then, separation of the cement body and the surrounding tissue was tried. It is noted here that the bonding strength is represented as "high", "low", and "null" when manual separation was impossible,

when the bond was formed but could be manually separated, and when no bond was observed.

The hardening time was measured according to JIS-T 6602. A needle having a weight of 300g and a sectional area of 1mm^2 was dropped onto the kneaded mixture of each sample. The hardening time was measured as a time duration until no trace of the needle was formed any longer.

As a result, Samples Nos. 1-16 according to the embodiments of this invention exhibited the high compressive strength between 160 and 190 MPa. In addition, those samples were very tightly bonded with the surrounding bone and could not easily be separated by manual force. No inflammation was observed in the surrounding living tissue. Auto-hardening was performed in a short time between 4 and 10 minutes.

On the other hand, Comparative Samples Nos. 17-24 were hardened in a short time between 6 and 10 minutes. However, the compressive strength was not greater than 115 MPa. As regards the bonding strength with the living bone, no bond was observed and, if a bond was formed, the bond was easily separated by manual force. More in detail, Comparative Samples Nos. 17, 19, 22, and 24 using methylmethacrylate (MMA) as the monomer exhibited the very low compressive strength between 40 and 60 MPa. As regards the bond with the surrounding bone, no bond was formed even in Sample No. 17 using nonalkali glass powder A. Comparative Samples Nos. 18, 20, 21, and 23 using

Bis-GMA as the monomer exhibited more favorable results than those using MMA. However, in comparison with Samples according to this invention using nonalkali glass powder or nonalkali crystallized glass powder, the
5 compressive strength and the bonding strength were obviously low.

The above-mentioned facts indicate that a biocement having high strength and high bioactivity can be obtained by combination of nonalkali glass powder
10 and/or nonalkali crystallized glass powder and hydrophilic dimethacrylate.

As thus far been described, a bioactive cement according to this invention can be quickly auto-hardened to bond and fix an implant material without inducing any
15 inflammatory reaction in a living tissue. In addition, the bioactive cement can be chemically bonded with a living bone and has a high mechanical strength. Therefore, it is stable for a long-term use.

Thus, the bioactive cement is useful for bonding
20 and fixing various kinds of implant materials. In addition, the bioactive cement is also useful as a filler itself for filling a bone defect.

Furthermore, the bioactive cement according to this invention may be preliminarily hardened for use as
25 an implant material which can be ground and worked.

CLAIMS

1. A bioactive cement comprising a filler consisting of nonalkali glass powder containing Ca, monomer containing hydrophilic dimethacrylate, a polymerization starter for starting polymerization of
5 said monomer, and a polymerization promoter for promoting polymerization of said monomer, said bioactive cement being capable of forming a hydroxyapatite layer on a surface of a hardened cement body when said hardened cement body is brought into contact with body fluid.

2. A bioactive cement as claimed in Claim 1, wherein said nonalkali glass powder containing Ca comprises a composition consisting by weight of 20-60% CaO, 20-50% SiO₂, 0-30% P₂O₅, 0-20% MgO, and 0-5% CaF₂.

3. A bioactive cement as claimed in Claim 1, wherein said nonalkali glass powder containing Ca comprises a composition by weight of 40-50% CaO, 30-40% SiO₂, 10-20% P₂O₅, 0-10% MgO, and 0-2% CaF₂.

4. A bioactive cement as claimed in Claim 1, wherein said nonalkali glass powder containing Ca is subjected to a silane coupling treatment.

5. A bioactive cement as claimed in Claim 1, wherein said hydrophilic dimethacrylate is 2,2-bis[4-(3-methacryloxy-2-hydroxy propoxy)phenyl] propane.

6. A bioactive cement as claimed in Claim 5,
wherein said monomer contains, in addition to said
hydrophilic dimethacrylate, at least one of triethylene
glycol dimethacrylate (TEGDMA), diethylene glycol
5 dimethacrylate (DEGDMA), and ethylene glycol
dimethacrylate (EGDMA).

7. A bioactive cement as claimed in Claim 5,
wherein said monomer contains, in addition to said
hydrophilic dimethacrylate, at least one of
2,2-bis(4-methacryloxy phenyl)propane (BPDMA),
5 2,2-bis(4-methacryloxy ethoxy phenyl)propane (Bis-MEPP),
and 2,2-bis(4-methacryloxy polyethoxy phenyl)propane
(Bis-MPEPP).

8. A bioactive cement comprising a filler
consisting of nonalkali crystallized glass powder
containing Ca, monomer containing hydrophilic
dimethacrylate, a polymerization starter for starting
5 polymerization of said monomer, and a polymerization
promoter for promoting polymerization of said monomer,
said bioactive cement being capable of forming a
hydroxyapatite layer on a surface of a hardened cement
body when said hardened cement body is brought into
10 contact with body fluid.

9. A bioactive cement as claimed in Claim 8,
wherein said nonalkali crystallized glass powder
containing Ca comprises a composition consisting by
weight of 20-60% CaO, 20-50% SiO₂, 0-30% P₂O₅, 0-20% MgO,
5 and 0-5% CaF₂.

10. A bioactive cement as claimed in Claim 8,
wherein said nonalkali crystallized glass powder
containing Ca comprises a composition consisting by
weight of 40-50% CaO, 30-40% SiO₂, 10-20% P₂O₅, 0-10%
5 MgO, and 0-2% CaF₂.

11. A bioactive cement as claimed in Claim 8,
wherein said nonalkali crystallized glass powder
containing Ca is subjected to a silane coupling
treatment.

12. A bioactive cement as claimed in Claim 8,
wherein said hydrophilic dimethacrylate is
2,2-bis[4-(3-methacryloxy-2-hydroxy propoxy)phenyl]
propane.

13. A bioactive cement as claimed in Claim 12,
wherein said monomer contains, in addition to said
hydrophilic dimethacrylate, at least one of triethylene
glycol dimethacrylate (TEGDMA), diethylene glycol
5 dimethacrylate (DEGDMA), and ethylene glycol
dimethacrylate (EGDMA).

14. A bioactive cement as claimed in Claim 12,
wherein said monomer contains, in addition to said
hydrophilic dimethacrylate, at least one of
2,2-bis(4-methacryloxy phenyl)propane (BPDMA),
5 2,2-bis(4-methacryloxy ethoxy phenyl)propane (Bis-MEPP),
and 2,2-bis(4-methacryloxy polyethoxy phenyl)propane
(Bis-MPEPP).

INTERNATIONAL SEARCH REPORT

International Application No

PCT/JP 93/00249

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC Int.Cl. 5 A61L25/00		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
Int.Cl. 5	A61L	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
X	WO,A,8 700 058 (LUSUARDE WERTHER ET AL.) 15 January 1987 see page 7, line 4 - line 20; claims ---	1
Y	US,A,4 156 766 (RAYMOND J. FELDT) 29 May 1979 see column 4, line 38 - line 65; examples ---	1-14
Y	DATABASE WPIL Week 9128, Derwent Publications Ltd., London, GB; AN 91-205158 & JP,A,3 131 263 (NIPPON ELECTRIC GLASS) 4 June 1991 see abstract ----- -/--	1-14
¹⁰ Special categories of cited documents :¹⁰ "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "&" document member of the same patent family		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search 17 MAY 1993		Date of Mailing of this International Search Report 02.06.99
International Searching Authority EUROPEAN PATENT OFFICE		Signature of Authorized Officer M. ESPINOSA

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category ^a	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	US,A,3 853 962 (ROBERT JOHNS GANDER) 10 December 1974 see column 3, line 25 - line 60 see column 4, line 13 - line 38; examples 1-3 ---	1-14
A	WO,A,9 117 965 (UNIVERSITY OF FLORIDA) 28 November 1991 see claims -----	1

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.**

JP 9300249
SA 70558

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

17/05/93

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		AU-A- 5994386	30-01-87
		DE-A- 3681429	17-10-91
		EP-A, B 0229771	29-07-87
		JP-T- 62503148	17-12-87

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		US-A- 3845009	29-10-74

WO-A-9117965	28-11-91	US-A- 5074916	24-12-91
