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(54) Title: A COMPOSITE, ITS PREPARATION AND USE

(57) **Abstract:** The invention relates to a process for producing a polymer composite comprising the steps of a) dissolving a water insoluble polymer and optionally a reinforcing filler thereof into a water soluble solvent, b) mixing water optionally containing a reinforcing filler onto the solution obtained in step a) thus forming an emulsion between the dissolved polymer and the reinforcing filler thereof and the solvent-water solution, c) allowing said solvent to evaporate simultaneously with the solidification of the polymer thus creating a porous reinforced polymer, d) covering said porous reinforced polymer with a polymerizable monomer system, and e) polymerizing said monomer system thus creating a polymer composite, provided that reinforcing fillers are present either in step a) or in step b). The invention further relates to the composite obtainable by the process and the use thereof.

## A COMPOSITE, ITS PREPARATION AND USE

### FIELD OF THE INVENTION

The present invention relates to a process for producing a composite, the composite  
5 obtained by said process and the use of said composite.

### BACKGROUND OF THE INVENTION

The use of porous biomaterials in applications such as bone augmentation and bone  
implants is based on the phenomenon that bone can grow into the porous structure  
of the biomaterial if the pore size of the material varies between 100 to 400  $\mu\text{m}$ .  
10 Several techniques have been used to produce porous polymers. Such techniques  
are described for example in US patent 4,076,656, where polymer particles are  
dispersed in water-soluble liquid to form a network of channels in a polymer. A  
similar technique is also shown in US patent 4,954,381 involving combination of  
water-soluble polymer and an organic solvent soluble polymer.

15 Document US 4,834,747 presents a method of producing a device having a porous  
surface by preparing a polymer solution, by coating the device with the solution and  
by evaporating the solvent. Document US 5,238,636 discloses a similar method for  
producing porous films and document US 4,384,047 a similar method for producing  
porous membranes. The porous material obtained by these techniques is however  
20 quite weak and soft. The applicants are not aware of any materials having a porous  
yet stronger structure and being suitable for medical use.

### OBJECT OF THE INVENTION

An object of the present invention is to provide a composite based on a porous  
structure but being stronger than the prior art structures and at the same time  
25 preferably being suitable for medical use.

Another object of the invention is to provide a process for preparing such a  
composite. A yet further object of the invention is the use of such a composite in  
different medical applications.

## SUMMARY OF THE INVENTION

The invention relates to a process for producing a polymer composite comprising the steps of

- 5 a) dissolving a water insoluble polymer and optionally a reinforcing filler thereof into a water soluble solvent,
- b) mixing water optionally containing a reinforcing filler onto the solution obtained in step a) thus forming an emulsion between the dissolved polymer and the reinforcing filler thereof and the solvent-water solution,
- 10 c) allowing said solvent to evaporate simultaneously with the solidification of the polymer thus creating a porous reinforced polymer,
- d) covering said porous reinforced polymer with a polymerizable monomer system, and
- e) polymerizing said monomer system thus creating a polymer composite,

provided that reinforcing fillers are present either in step a) or in step b).

- 15 The invention further relates to a composite obtainable by the inventive process as well to its use in biomaterial applications, structural engineering material applications, dental or orthopedic implants, coatings of fiber reinforced composite implants, as bone augmentation material and bone fixation material, as tissue guiding material, as tissue and cell culturing material, as a drug releasing vehicle
- 20 material, as absorbing substrate material and/or as construction material.

## BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a scanning electron microscope (SEM) micrograph of a porous polymethyl methacrylate (PMMA) specimen at 1000x magnification showing a honeycomb-like structure.

- 25 Figure 2 shows a SEM micrograph of a porous PMMA having macroscopic (400–100  $\mu\text{m}$ ) void structure on the surface and a micro porous PMMA structure as shown in Fig. 1.

Figure 3 shows a stiff fiber-reinforced composite PMMA core having scale porous PMMA surface.

Figure 4 shows a SEM micrograph of a porous PMMA film having a thickness of approximately 150  $\mu\text{m}$ .

Figure 5 shows a SEM micrograph of a fiber-reinforced porous PMMA material.

Figure 6 shows a SEM micrograph of a fiber-reinforced porous PMMA material after coating the porous polymer with dimethacrylate monomer.

Figure 7 shows a solid fiber-reinforced composite device having a porous surface according to the invention.

#### DETAILED DESCRIPTION OF THE INVENTION

By "polymerizing" in this application it is meant both polymerizing and crosslinking.

Furthermore, by dendrimers large spherical hyper-branched polymers are meant.

The invention is characterized by the enclosed claims.

The invention relates to a process for producing a polymer composite comprising the steps of

- 15 a) dissolving a water insoluble polymer and optionally a reinforcing filler thereof into a water soluble solvent,
- b) mixing water optionally containing a reinforcing filler onto the solution obtained in step a) thus forming an emulsion between the dissolved polymer and the reinforcing filler thereof and the solvent-water solution,
- 20 c) allowing said solvent to evaporate simultaneously with the solidification of the polymer thus creating a porous reinforced polymer,
- d) covering said porous reinforced polymer with a polymerizable monomer system, and
- e) polymerizing said monomer system thus creating a polymer composite,
- 25 provided that reinforcing fillers are present either in step a) or in step b).

In the process according to the invention a water-insoluble polymer and a reinforcing filler thereof is dissolved into a water-soluble solvent. After this water is mixed with the formed solution of solvent and dissolved polymer and reinforcing

filler thereof. As the solvent itself is water-soluble it will mix with the water and the solvent and water will form a homogenous mixture. The polymer and reinforcing filler thereof are water-insoluble, so they will solidify when they come into contact with water. As the solvent evaporates, a highly porous polymer structure is formed.

5 After drying, the porous polymer is ready for the next step of the process, i.e. covering the polymer with a monomer system and polymerizing said monomer system.

The objects of the invention are thus fulfilled with the inventive process and composite. Indeed, the present composite is based on a porous structure but yet it is

10 stronger than the prior art structures since it has been reinforced with filler(s). Attempts have previously been made to reinforce and to harden a composite by incorporating reinforcing fibers or particles. The problem encountered in these attempts has however been the poor adhesion of the fibers or particles to the porous material, whereas in the invention, the fillers adhere well to the surrounding

15 material due to the additional coating performed by covering the porous reinforced polymer with a reactive monomer and by further polymerizing it.

According to an embodiment of the invention, the materials (polymer, filler, solvent and monomer) used in the process are biocompatible. It is also obvious to a person skilled in the art that the materials are compatible with each other. The materials of

20 the composite may also be resorbables or not and furthermore, they may be bioresorbables and/or biodegradables or not.

According to a further embodiment of the invention, said filler is present only in the water soluble solvent of step a). According to a yet further embodiment of the invention, said filler is present only in the water of step b). According to a still

25 further embodiment of the invention, said filler is present both in the water soluble solvent of step a) and in the water of step b).

Using the process according to the invention the pore size of the formed polymer is easily controlled by controlling the temperature of the water, which is poured onto the solution of solvent and dissolved polymer and reinforcing filler thereof. Use of

30 warmed water will result in faster evaporation of the solvent from the emulsion and thus a smaller pore size of the polymer structure. Porosity, pore size, void volume and surface structure obtained are functions of the molecular size of the polymer, the solvent, the temperature, the evaporation rate as well as the shape, size and nature of the filler.

Suitable polymers used in the method according to the invention are different water-insoluble thermoplastic polymers. They can be selected from the group of polymethyl methacrylate (PMMA), polylactide, polycaprolactone, polyamide, polyurethane, polyethylene, polypropylene, other polyolefins and polyvinyl chloride (PVC).

According to an embodiment of the invention, said polymerizable monomer system is a monomer or a mixture of monomers having low viscosity. Suitable monomers are monomethacrylates and dimethacrylates as well as methacrylate functionalized dendrimers or other methacrylated hyperbranched polymers. The monomer may for example be ethylene glycoldimethacrylate (EGDMA) or triethylene glycoldimethacrylate (TEGDMA). The same monomer may also be used in step a) as the solvent.

According to another embodiment of the invention, the solvent is selected from the group consisting of tetrahydrofuran (THF), acetone and chloroform. The monomer system used in step d) may also be used in step a) as the solvent.

In the process according to the invention different fillers are added into the polymer structure. The addition of fillers is done at the stage of dissolving the polymer, i.e. before solidification of the polymer resulting in a porous composite of the polymer and the filler. Fillers can be in the form of fibers or particulate materials and they can also be bioactive agents, such as bioactive glass.

Suitable fibers that can be used as filler in the process according to the invention can be selected from a group consisting of inert glass fibers, bioactive glass fibers, carbon/graphite fibers, aramid fibers, polyethylene fibers, collagen and natural fibers. Examples of suitable natural fibers are cellulose and modified cellulose fibers.

Particulate material that can be used as filler in the process according to the invention can be selected from a group consisting of inert glass, bioactive glass, silica gel, titanium gel, carbon, graphite, aramid, polyethylene, gypsum and hydroxyapatite, as well as different mixtures of these materials. It is also obvious to a person skilled in the art that the composite may contain both fibrous and particulate filler materials.

Different pharmaceutically active agents can be incorporated in the composite produced by the process according to the invention. Such agents can be added for example when a porous composite according to the invention is used in bone

augmentation and implant applications. The pharmaceutically active agent can be added to the composite before solidification of the polymer structure, or alternatively, they can be incorporated into the porous structure after the solidification of the porous composite by further impregnation, before the step of  
5 coating of the porous polymer. It is obvious that the composite according to the invention may contain one or more of such active agents.

By pharmaceutically active agents it is meant different drugs, biologically active substances and therapeutically active substances. The pharmaceutically active agent can be selected for example from the group consisting of bone morphogenic  
10 proteins (BMPs), interferons, corticosteroids, biphosphonates, cytostatics, anabolic hormones, vitamins, anti-inflammatory drugs, antimicrobials, disinfectants and combinations and mixtures thereof. This is to be taken as a non-limiting list of examples and a person skilled in the art is able to find more examples of suitable active agents.

15 The pharmaceutically active agents can be released from the porous polymeric structure by diffusion. As the pore size is an important variable in control of the diffusion, the porous polymers and composites produced according the invention are extremely suitable as the pore size can be optimized. The pore size of the composites can be optimized so that there is both macro pores and micro pores.  
20 Macro pores of size 100–1000  $\mu\text{m}$  will contribute e.g. bone growth when the material is used as implants. Micro pores, with size in nanometer scale, are important for controlled diffusion of active agents and drugs. Optionally the nanometer scale pore size can be obtained by adding fillers containing nanometer size pores into the porous polymer. Such fillers can be made of polymers like  
25 dendrimers, or of inorganic material like  $\text{SiO}_2$ .

A further use of the present inventive process is the coating of an existing device with the composite according to the invention. Indeed, the inventive process gives an advantageous method for producing materials consisting of several layers, wherein the different layers have a good adhesion to each other. The device to be  
30 coated may be any suitable device such as an implant, a fixation nail, a polymer block or a composite and it may be manufactured from any material such as bioactive glass or a polymer, bioactive or not.

The thickness of the porous surface layer can be determined by the dissolving time of the solid surface in the solvent. The pore size can also here be modified by the

process conditions: water temperature and pressure, used solvent and polymer and molecular size of the polymer as well as the properties of the filler material.

A device may be coated in two different ways. Indeed, it may be coated by covering it with a solution of water insoluble polymer and a filler followed by the steps b) to  
5 e) of the present process. This leads to a coating having a more marked interface between the device and the coating than the second inventive way, which consists on dissolving the surface of the device consisting of a polymer or reinforced polymer followed by the treatment of the partly diluted surface with water and  
10 further the steps c) to e) of the present process. This second way leads to a coating having a less marked interface between the device and the coating and also improved adhesion of the coating due to the penetration of the materials of the coating to the materials of the device, i.e. increased interdiffusion bonding.

The invention further relates to the composite obtainable according to the present process. The composite according to the invention is based on a porous polymer. In  
15 the finished composite, the pores may be either totally or partially filled with the polymerized monomer of the monomer system of step d). Preferably, the pores are from 100 to 1000  $\mu\text{m}$  in size.

The invention also relates to the use of the inventive composite. Indeed, the composite according to the invention can be used in different biological applications  
20 (as a biomaterial, for example) or in structural engineering applications. It can be used for example in dental or orthopedic implants, coatings for FRC implants, as bone augmentation material and fixing material, as tissue guiding and cell culturing material or as a drug releasing vehicle material.

The composite according to the invention can also be used in the fabrication of  
25 porous ceramic device or implant by replica technique. By replica technique it is meant that porous polymer structure is copied by ceramic powder which is then sintered at elevated temperature to form a solid ceramic of porous structure. In this embodiment, the replica technique allows to production of a ceramic device or implant that has the same porous structure of the polymer, i.e. the porous structure  
30 of the polymer is copied to the ceramic material. Said ceramic material may be for example aluminium oxide or the like.

The composite according to the invention can also be used in other technical applications such in filters, absorbing substrate or construction material.



It will be appreciated that the essence of the present invention can be incorporated in the form of a variety of embodiments, only a few of which are disclosed herein. It will be apparent for the specialist in the field that other embodiments exist and do not depart from the spirit of the invention. Thus, the described embodiments are illustrative and should not be construed as restrictive.

#### EXPERIMENTAL PART

Examples 1a to 1c disclose the preparation of micrometer and nanometer scale porous polymer to be used in the preparation of a composite according to the invention. Example 2 discloses the preparation of the porous PMMA having macroscopic scale void structure and example 3 presents the preparation of a fiber reinforced composite (FRC) core having a micrometer scale porous PMMA surface. Example 4 discloses the preparation of a microscopic scale porous PMMA film to be used in a composite according to the invention. Example 5 presents the preparation of porous PMMA containing silica fillers. Example 6 shows the preparation of PMMA containing glass fibers. Examples 7 and 8 disclose the preparation of a composite according to the invention.

##### Example 1a

2.00 g of polymethyl methacrylate (PMMA) was dissolved in 5 ml of tetrahydrofuran (THF). After the PMMA gel was formed, 0.2 g of glass fiber wool was added into the mixture. Warmed (50 °C) water was poured onto the obtained mixture causing PMMA to coagulate. Channels were formed in the polymer structure by evaporation of the THF, as illustrated in Figure 1. A porosity/void percentage of 51 vol-% was achieved.

##### Example 1b

2.00 g of polymethyl methacrylate (PMMA) was dissolved in 5 ml of tetrahydrofuran (THF). After the PMMA gel was formed, 0.2 g of glass fiber wool was added into the mixture. Boiling water (100 °C) was poured onto the obtained mixture causing PMMA to coagulate. Channels were formed in the polymer structure by evaporation of the THF. A porosity/void percentage of 72 vol-% was achieved.

Example 1c

2.00 g of polymethyl methacrylate (PMMA) was dissolved in 5 ml of acetone. After the PMMA gel was formed, 0.4 g of glass fiber wool was added into mixture. Boiling water (100 °C) was poured onto the obtained mixture causing PMMA to solidify. Channels were formed in the polymer structure by evaporation of the acetone. A porosity/void percentage of 81 vol-% was achieved.

Example 2

2.0 g of polymethyl methacrylate (PMMA) was dissolved in 5 ml of tetrahydrofuran (THF). After the PMMA gel was formed, cold water (8 °C) was poured onto the obtained mixture causing PMMA to solidify slowly. Micro pores and macro voids were formed slowly during the first 24 hours by evaporation of the THF, as shown in Figure 2.

When low water temperature was used, PMMA formed more complex surface structure with macroscopic voids.

Example 3

A PMMA pre-core was manufactured using PalaPress (provided by Heraus Kulzer, Germany) according to the manufacturer's recommendations. Continuous E-glass fiber reinforcement (Stick™ by StickTech Oy, Finland) was added into a polymethyl methacrylate/ methyl methacrylate mixture (PMMA/MMA). Stiff FRC-PMMA core was cured in a pressure-curing device at a pressure of 2 bar and temperature of 55 °C (Ivomat®, by Schaan, Liechtenstein). After the FRC-PMMA specimen was cured, it was inserted into THF for 5 hours in order to obtain a PMMA-gel on the surface of the specimen. The specimen was then inserted into warm water (50 °C) and a porous PMMA surface was obtained having a strong FRC-core, as illustrated in Figure 3.

Example 4

2.0 g of polymethyl methacrylate (PMMA) was dissolved in 5 ml of tetrahydrofuran (THF). After the PMMA gel was formed, it was inserted into a syringe. The gel was injected onto a glass plate so that a film was formed. Warm water (50 °C) was poured onto the mixture causing PMMA to solidify. Evaporation channels were formed by the evaporation of the THF and porous PMMA film was obtained.

Alternatively the PMMA gel was injected onto warm water so that a thin PMMA film is formed onto the water surface, as presented in Figure 4.

#### Example 5

7,0 g of polymethyl methacrylate (Palapress Clear, PMMA-fillers) was dissolved in  
5 100 ml of tetrahydrofuran (THF). 100 ml of water, 20 ml of tetraethylene  
orthosilane (TEOS), 100 ml of ethanol and 2 ml of 1.0 M HCl were mixed in order  
to prepare a sol-gel silica. After 24 hours, water containing said sol-gel silica was  
poured into PMMA/THF causing porous PMMA having silica particles to be formed.  
The porous specimen was then dipped to EGDMA containing 2 wt-% of benzoyl  
10 peroxide (BPO) and polymerized.

#### Example 6

50 ml of PMMA was dissolved in 120 ml of THF. 20 ml of short glass fibers (E-  
glass, length 2 mm) were mixed into the PMMA/THF-gel. The obtained mixture  
was poured into warm water and a fiber reinforced porous PMMA was obtained, as  
15 illustrated in Figure 5.

#### Example 7

The porous fiber reinforced PMMA obtained in Example 6 was dipped in ethylene  
glycol dimethacrylate (EGDMA) monomer containing 2 wt-% of benzoylperoxide  
as an initiator. The porous PMMA was then polymerized together with EGDMA by  
20 heating the material at 70 °C for 2 hours. A reinforced and EGDMA-coated  
composite was obtained as a result, and illustrated in Figure 6.

#### Example 8

A glass fiber reinforced composite prepared according to known methods and  
having a linear PMMA matrix was inserted to a mixture of THF and PMMA for one  
25 (1) minute. Short glass fibers as the filler component of a porous surface were  
mixed to the THF-PMMA-gel. Water was poured into the THF-PMMA-gel with  
fiber material. A solid material having a porous surface layer with interdiffusion  
bonding was obtained. The porous surface layer containing the short glass fibers  
was coated with EGDMA monomer containing 2 wt-% of benzoylperoxide as an  
30 initiator and polymerized heating the material at 70 °C for 2 hours. Furthermore,  
Figure 7 shows schematically a composite according to an embodiment of the

present invention. The Figure shows the short glass fibers 1, the fiber reinforced composite 3 and the porous layer 2 at the surface of the composite 3.

#### Example 9

5 The example 8 was repeated except that instead of the glass fibers, nanometer scale porous silica ( $\text{SiO}_2$ ) fillers of size 0,5 to 50  $\mu\text{m}$  containing biphosphonate were mixed to the THF-PMMA-gel.

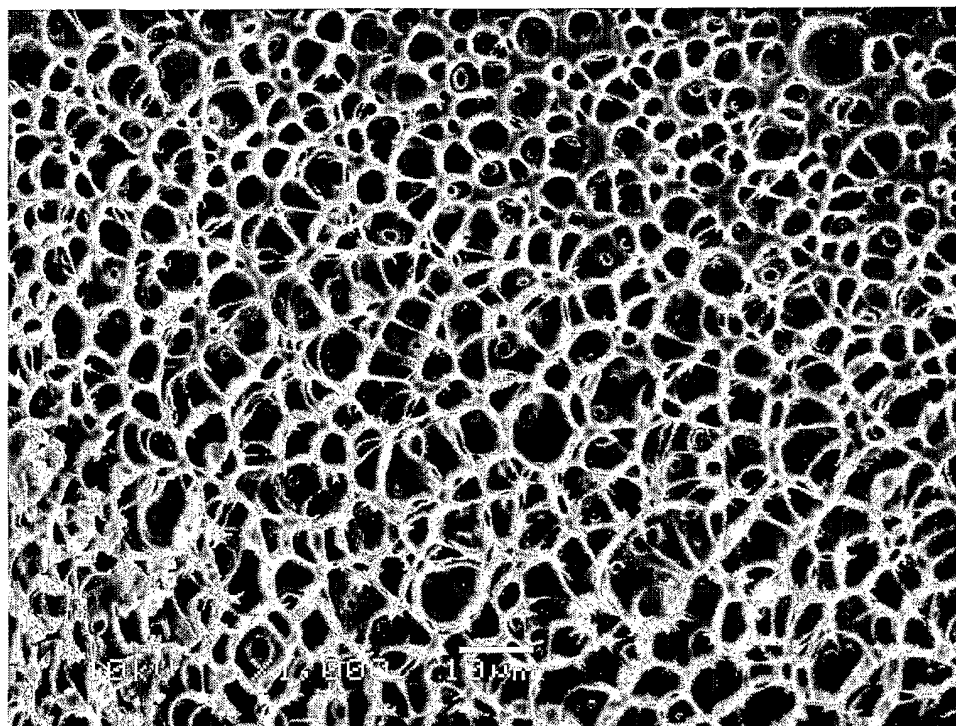
## Claims

1. A process for producing a polymer composite comprising the steps of
  - a) dissolving a water insoluble polymer and optionally a reinforcing filler thereof into a water soluble solvent,
  - 5 b) mixing water optionally containing a reinforcing filler onto the solution obtained in step a) thus forming an emulsion between the dissolved polymer and the reinforcing filler thereof and the solvent-water solution,
  - c) allowing said solvent to evaporate simultaneously with the solidification of the polymer thus creating a porous reinforced polymer,
  - 10 d) covering said porous reinforced polymer with a polymerizable monomer system, and
  - e) polymerizing said monomer system thus creating a polymer composite,provided that reinforcing fillers are present either in step a) or in step b).
2. The process according to claim 1, **characterized** in that said polymer is  
15 selected from the group consisting of polymethyl methacrylate, polylactide, polycaprolactone, polyamide, polyethylene, polypropylene, polyurethane and polyvinyl chloride.
3. The process according to claim 1 or 2, **characterized** in that said solvent is  
20 selected from the group consisting of tetrahydrofuran, acetone, chloroform and mixtures thereof.
4. The process according to any of the preceding claims, **characterized** in that said polymerizable monomer system is selected from the group consisting of monomethacrylate, dimethacrylate, methacrylate functionalized dendrimers and mixtures thereof.
- 25 5. The process according to any of the preceding claims, **characterized** in that said filler is present only in the water soluble solvent of step a).
6. The process according to any of the claims 1 to 4, **characterized** in that said filler is present only in the water of step b).

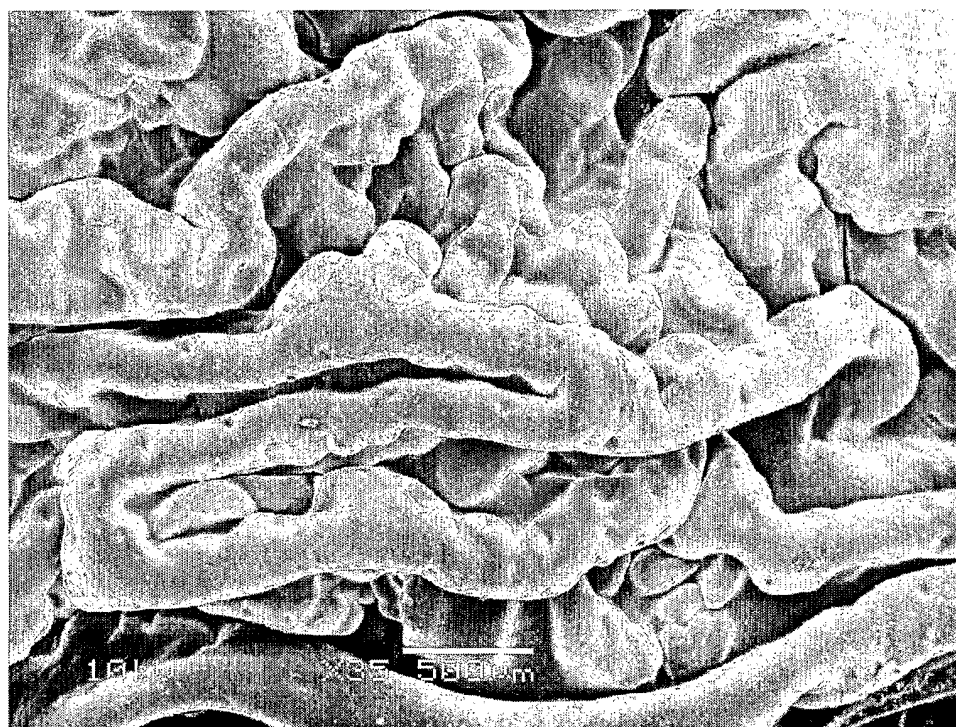
7. The process according to any of the claims 1 to 4, **characterized** in that said filler is present both in the water soluble solvent of step a) and in the water of step b).
8. The process according to any of the preceding claims, **characterized** in that  
5 said filler is a fiber or a particulate material.
9. The process according to claim 8, **characterized** in that said filler is a fiber and is selected from the group consisting of inert glass fibers, bioactive glass fibers, carbon/graphite fibers, aramid fibers, polyethylene fibers, collagen, natural fibers and mixtures thereof.
- 10 10. The process according to claim 8, **characterized** in that said filler is a particulate material, the material being selected from the group consisting of inert glass, bioactive glass, silica gel, titanium gel, carbon, graphite, aramid, polyethylene, gypsum, hydroxyapatite, silicium oxide and mixtures thereof.
11. The process according to any of the preceding claims, **characterized** in that a  
15 pharmaceutically active agent has been added before or after solidification of the polymer.
12. The process according to claim 11, **characterized** in that said pharmaceutically active agent is selected from the group consisting of bone morphogenetic proteins, interferons, corticosteroids, biphosphonates, cytostatics,  
20 anabolic hormones, vitamins, anti-inflammatory drugs, antimicrobial agents, disinfectants and mixtures thereof.
13. A composite obtainable by the process according to any of claims 1 to 12.
14. The composite according to claim 13, **characterized** in that it is biocompatible.
- 25 15. Use of the composite according to claim 14 in biomaterial applications or in structural engineering material applications.
16. Use of the composite according to claim 14 in dental or orthopedic implants, coatings of fiber reinforced composite implants, as bone augmentation material and bone fixation material, as tissue guiding material, as tissue and cell culturing  
30 material or as a drug releasing vehicle material.

17. Use of the composite according to claim 13 or 14 in the fabrication of porous ceramic device or implant by replica technique.

18. Use of the composite according to claim 13 or 14 in filters, as absorbing substrate material or as construction material.

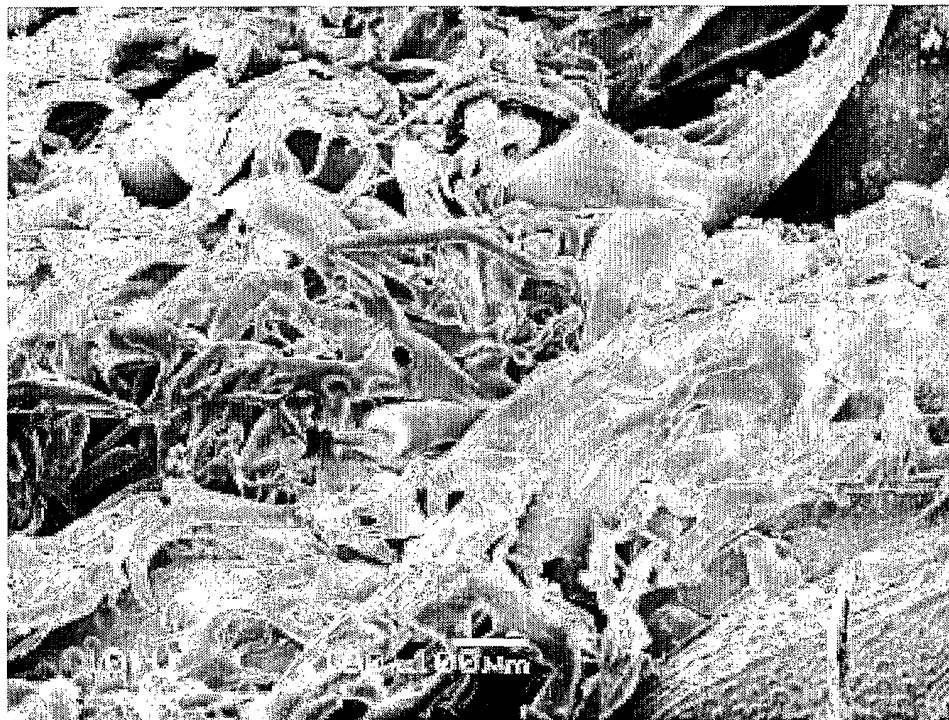


**FIG. 1**

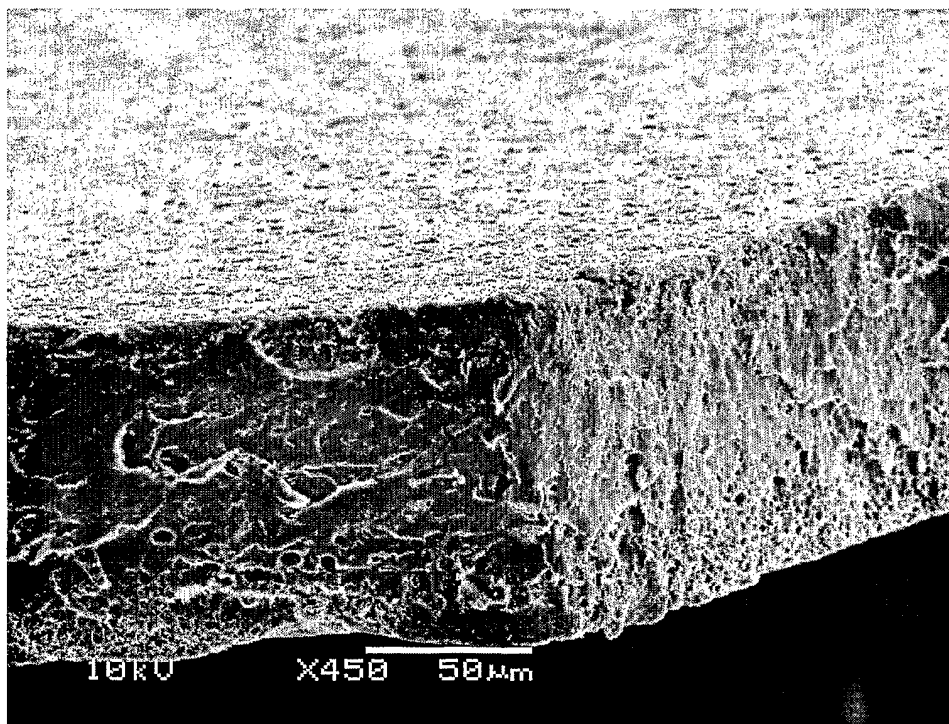


**FIG. 2**





**FIG. 3**



**FIG. 4**

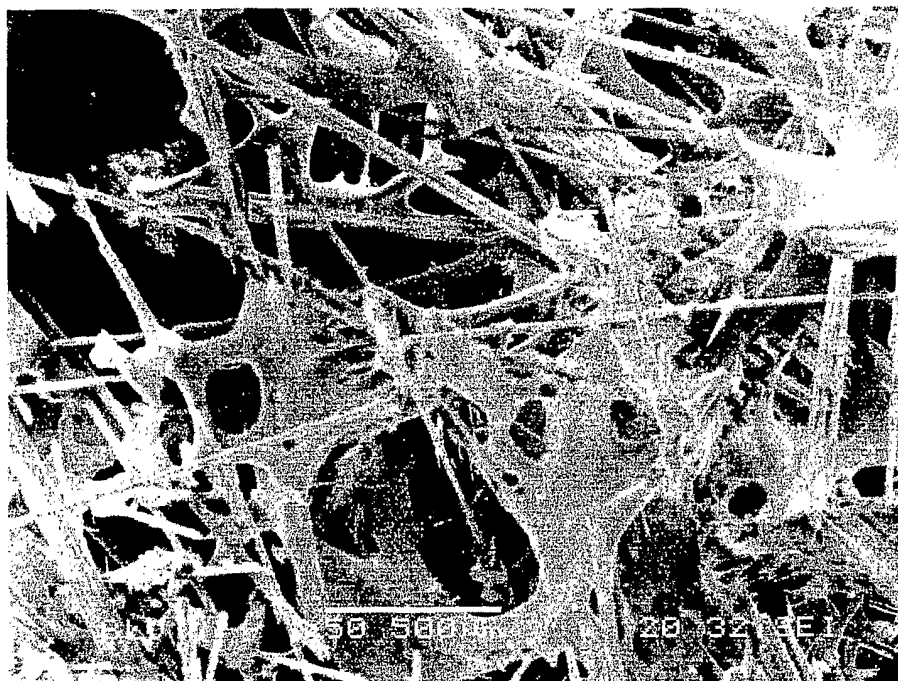


FIG. 5

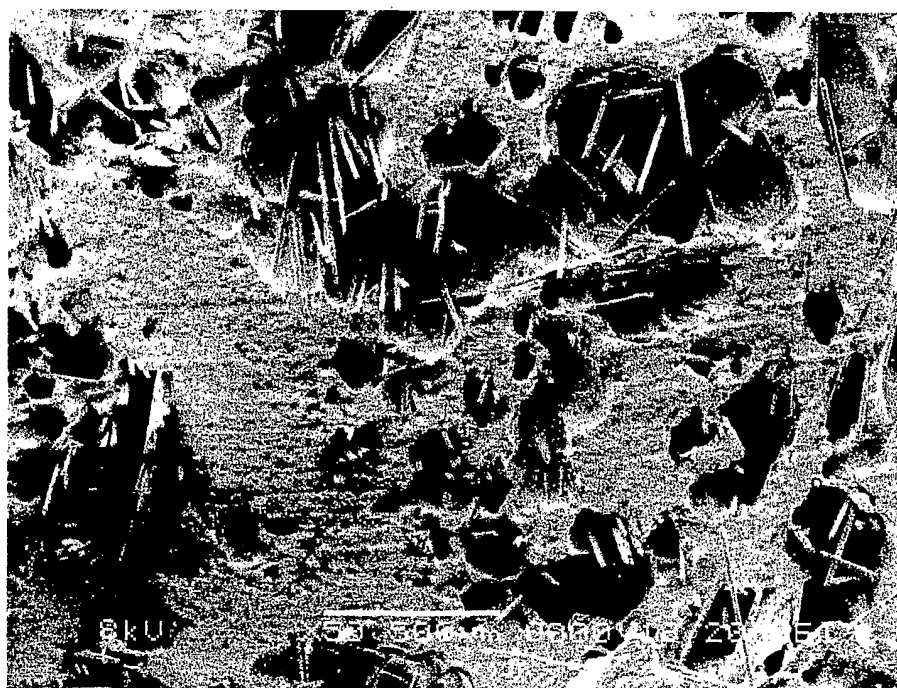


FIG. 6

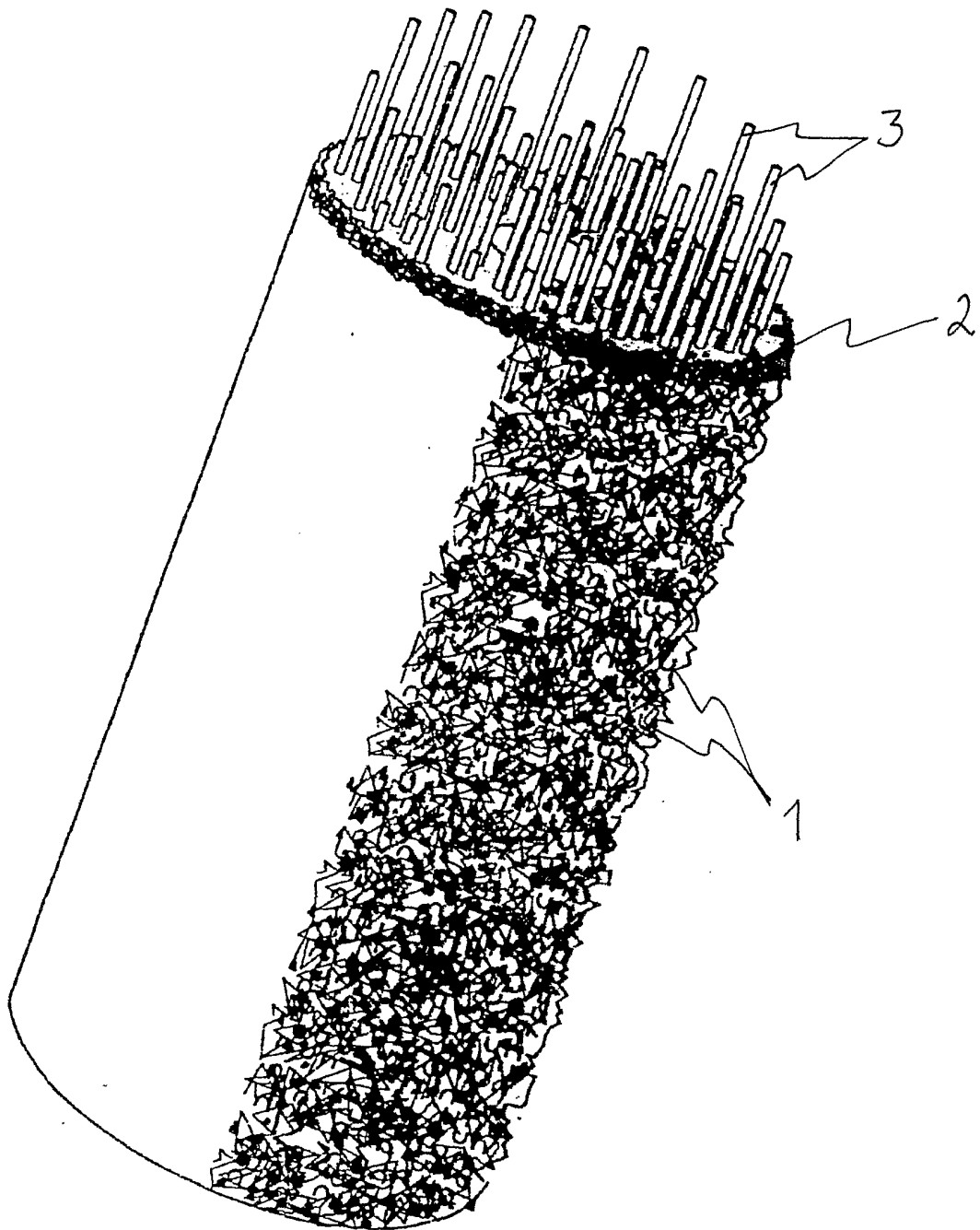


FIG. 7

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/FI 02/00158

## A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C08J 9/28, C08J 7/06, A61L 27/56

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)

IPC7: C08J, A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5397572 A (ALLAN G.A. COOMBES ET AL), 14 March 1995 (14.03.95), column 5, line 57 - column 7, line 4; column 8, line 32 - line 34; column 9, line 13 - line 17, abstract  --	1-18
A	File WPI, Derwent accession no. 1996-250331, ELECTROLUX AB, "Reverse osmosis membranes for purifying water - comprising a porous base membrane and a semi-permeable surface layer of new poly:ethylene glycol acrylate prepd. by in situ radical polymerisation", SE,A,9402890, 19960301, DW199625  --	1-18

 Further documents are listed in the continuation of Box C. See patent family annex.

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International application No.

PCT/FI 02/00158

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