

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
25 August 2005 (25.08.2005)

PCT

(10) International Publication Number
WO 2005/077304 A1

(51) International Patent Classification⁷: **A61F 2/02**,
A61K 9/14

(21) International Application Number:
PCT/US2005/004045

(22) International Filing Date: 7 February 2005 (07.02.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/542,389 6 February 2004 (06.02.2004) US

(71) Applicant (for all designated States except US): **GEORGIA TECH RESEARCH CORPORATION** [US/US];
505 10th Street, NW, Atlanta, GA 30332-0415 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **BOYAN, Barbara, D.** [US/US]; 898 Byrnwyck Road N.E., Atlanta, GA 30319 (US). **GULDBERG, Robert, E.** [US/US]; 1204 Promontory Path, Marietta, GA 30062 (US). **KENNEDY, Stephen, J.** [IN/US]; 500 Mount Everest Way, Atlanta, GA 30022 (US). **KU, David, N.** [US/US]; 1943 Grist Stone Court N.E., Atlanta, Georgia 30307 (US).

(74) Agents: **WARREN, William, L.** et al.; Sutherland Asbill & Brennan LLP, 999 Peachtree Street, NE, Atlanta, GA 30309-3996 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: LOAD BEARING BIOCOMPATIBLE DEVICE

(57) Abstract: Implantable biomaterials, particularly hydrogel substrates with porous surfaces, and methods for enhancing the compatibility of biomaterials with living tissue, and for causing physical attachment between biomaterials and living tissues are provided. Also provided are implants suitable for load-bearing surfaces in hard tissue repair, replacement, or augmentation, and to methods of their use. One embodiment of the invention relates to an implantable spinal disc prosthesis.



WO 2005/077304 A1

5

LOAD BEARING BIOCOMPATIBLE DEVICE**CROSS REFERENCE TO RELATED APPLICATIONS**

[0001] The present invention claims the priority benefit of U.S. Provisional Patent
10 Application Serial No. 60/542,389 filed February 6, 2004, the entire contents of which
are hereby incorporated by reference.

BACKGROUND OF THE INVENTION15 **FIELD OF THE INVENTION**

[0002] The invention relates to spinal disc replacement devices, particularly
devices which mimic native spinal discs, for implantation which is compatible with
living tissue. The invention also relates to implants suitable for load-bearing surfaces
in the repair of tissue, replacement or augmentation, and methods of using such. One
20 embodiment of the invention relates to an implantable spinal disc prosthesis.

BACKGROUND ART

[0003] Materials used in the construction of implantable medical devices must be
nontoxic, nonantigenic, and noninflammatory. Hydrogels are a preferred type of
polymeric material for implantable devices. Because of their high water content,
25 analogous to living tissue, they are superior in biocompatibility to non-hydrous
polymeric materials.

[0004] U.S. Patent No. 5,981,826, issued to Ku et al., describes the preparation of polyvinyl alcohol hydrogels (PVA-H) by physically crosslinking an aqueous solution of polyvinyl alcohol (PVA) to produce a gel. The crosslinking is accomplished by subjecting the aqueous PVA solution to multiple cycles of freezing and thawing. One
5 limitation of the prior art is that the hydrogels produced are relatively nonporous and the pore size and degree of porosity, that is the density of the pores within the hydrogel, cannot vary independently of the mechanical properties or stiffness of the hydrogel.

[0005] Methods for producing certain porous hydrogels also exist in the art. U.S. Patent No. 6,268,405, issued to Yao et al., describes methods for creating porous PVA-
10 Hs by including immiscible materials in the polymerization process. After the hydrogel is polymerized, the included immiscible materials are washed out of the hydrogel by an appropriate solvent, yielding pores which are broadly distributed throughout the hydrogel. Controlling the size and density of the pores is accomplished by varying the molecular weight of the immiscible materials. A disadvantage of Yao et
15 al. is that the range of attainable pore sizes is limited. Moreover, the invention of Yao et al. is limited in that it can only produce hydrogels whose pores extend throughout the hydrogel. The pores in Yao et al. are intended to create vascularization of the hydrogel in soft or non-load bearing tissue. A further disadvantage of Yao et al. is that the pore sizes are broadly distributed about the average pore size.

20 [0006] Artificial discs intended for the replacement of a damaged intravertebral disc have been described. These are typically articulated devices comprising two rigid metal plates adhered to opposite ends of an elastomeric core. In use, the artificial disc is placed in the intervertebral space and the metal plates are secured to the surfaces of adjacent vertebrae. Various embodiments of artificial discs of this type are described in
25 U.S. Patent Nos. 5,674,296 and 6,156,067, issued to Bryan et al., U.S. Patent No. 5,824,094, issued to Serhan et al., U.S. Patent Nos. 6,402,785, issued to Zdeblick et al. More recent embodiments, e.g. U.S. Patent No. 6,419,704, issued to Ferree and U.S. Patent No. 6,482,234, issued to Weber et al., include descriptions of elastomeric cores that may be formed from materials with different elasticities to better mimic the native
30 structure of spinal discs.

[0007] Artificial discs have also been described wherein the disc is comprised of a flexible urethane silicone blend core and two identical rigid surfaces on either side of the core. U.S. Patent No. 6,607,558 to Kuras describes such a disc where nail like projections extend from the surface to fixate the disc between the vertebrae. Such a disc also possesses a different material for the end plates as for the elastic core.

[0008] The disadvantage of the artificial disc devices of the prior art are numerous. These prior art devices require the mechanical attachment of rigid artificial materials, such as titanium, directly to the bone with screws, staples, nails, cement, or other mechanical means. These rigid materials are only minimally compatible with natural, living bone and separation of the implant from the bone is often observed over long-term implantation. In addition, materials used in artificial discs of the prior art have physical and mechanical properties distinctly different from those of natural spinal discs and thus inadequately duplicate the desired properties of native spinal discs.

[0009] Vertebral fusion is still the most commonly performed procedure to treat debilitating pain associated with degenerative spinal disc disease or disc trauma, despite the fact that the procedure has many drawbacks. Vertebral fusion increases stress and strain on the discs adjacent to the fusion site, and it is now widely accepted that fusion is responsible for the accelerated degeneration of adjacent levels. Current multicomponent spinal disc prosthesis designs, elastomeric cores with metal plates on both the upper and lower surfaces, are susceptible to problems with interfacial bonding and wear. These designs have shown spontaneous device detachment due to retraction of bone tissue from the metal surface.

[0010] Bone ingrowth and attachment in the art has often required the use of bone promoting growth factors. For example, U.S. Patent No. 5,108,436, issued to Chu et al., describes using a porous implant for use in load bearing bone replacement which is used in combination with an osteogenic factor such as TGF- β .

[0011] Biomedical devices which are implanted in or around bone often fail because of fibrinogen encapsulation of the implant instead of cellular attachment to the implant itself. This encapsulation is a defensive reaction attempting to minimize

contact between the body and the implant and is considered a sign of implant incompatibility.

[0012] Moreover, the art of bone ingrowth onto implantable surface contains a multitude of examples relating to porous directed ingrowth where bone essentially grows into and around channels of the implant. For example, U.S. Patent No. 4,911,720, issued to Collier et al., discusses the ingrowth of bone into interconnecting pores which essentially locks bone into place. This method is disadvantageous in that bone does not actually attach itself to the material, instead bone attaches to other bone around the implant. In the unfortunate event that an implant must be removed, this type of Collier ingrowth results in large amounts of disruption to the surrounding bone tissue.

SUMMARY OF THE INVENTION

[0013] The present invention describes a hydrogel for implantation into a load bearing space within the body. The hydrogel has a textured surface on it which is comprised of superficial surface pores. Stated differently, the pores on the surface of the hydrogel substrate do not extend throughout the hydrogel but instead remain within a region near the surface. The pores on this hydrogel substrate can have an average diameter of between 1 and 100 micrometers. Preferably the average diameter of surface pores on the hydrogel substrate is between 5 and 50 micrometers, and preferably between 10 and 30 micrometers. The superficial pores of this hydrogel substrate can vary in size by less than 50%, preferably less than 30%, and preferably less than 10%. The hydrogel substrate of the present invention can be made up of polyvinyl alcohol and can have a water content of at least 5% w/w of the overall hydrogel. The hydrogel substrate of the present invention could be used in any load bearing implantable device application including, but not limited to, a spinal disc replacement. The present invention when used as a spinal disc replacement can possess the surface pores in the proper configuration and be additionally comprised of multiple regions of varying elasticities. It is also possible that the regions of varying elasticities

of the spinal disc replacement be comprised of multiple hydrogels as opposed to one hydrogel of varying elasticities.

[0014] The present invention also includes a method for making a hydrogel substrate with a textured surface for use in a load bearing biocompatible device. The hydrogel in liquid form is exposed to solid objects or to a mold which when polymerized or hardened results in a hydrogel with a textured surface. The solid objects used to impart the superficial pores may be made of polystyrene beads. Also, the solid objects used to impart the superficial pores may be grit, sand, silicon, silica, and ultra-fine particulate matter. The solid objects used to create the superficial pores can have a diameter of between 1 and 100 micrometers, preferably between 5 and 50 micrometers, and preferably between 10 and 30 micrometers. The solid objects used to create the superficial pores of this invention can be removed, for example, by use of an organic solvent or other washing means. This hydrogel substrate can be comprised of poly-vinyl alcohol possessing a water content of at least 5% w/w of the overall hydrogel.

BRIEF DESCRIPTION OF THE DRAWINGS

[0015] Figure 1 is an elevation view of spinal disc replacement made in accordance with one embodiment of the present invention.

[0016] Figure 2 is a schematic of a surface generated in accordance with one embodiment of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

[0017] The present invention is drawn to an implantable hydrogel substrate comprising a hydrogel surface having a plurality of superficial pores thereon. The pores on this hydrogel substrate can have an average diameter of between 1 and 100 micrometers. Preferably the average diameter of surface pores on the this hydrogel substrate is between 5 and 50 micrometers, and preferably between 10 and 30 micrometers. The superficial pores of this hydrogel substrate can vary in size by less than 50%, preferably less than 30%, and preferably by less than 10%. The hydrogel

substrate of the present invention can be made up of polyvinyl alcohol and can have a water content of at least 5% w/w of the overall hydrogel.

[0018] One embodiment of the present invention is an artificial disc for implantation into the spine comprising the hydrogel substrate described above. This artificial disc is a hydrogel possessing a plurality of regions having variable elasticity. Specifically, the disc is comprised of a surface region having a higher modulus of elasticity than an interior region. This disc can be prepared using multiple hydrogels with the elastic properties of the one disc with varying regions of elasticity.

[0019] The present invention also includes a method for making a hydrogel substrate comprising contacting solid objects with an aqueous hydrogel, allowing the hydrogel to polymerize and crosslink while the solid objects are at least partially immersed in the hydrogel, and removing those solid objects from the polymerized and crosslinked hydrogel to form superficial pores thereon. The solid objects used to impart the superficial pores may be polystyrene beads. Alternatively, the solid objects used to impart the superficial pores may be grit, sand, silicon, silica, and ultra-fine particulate matter. The solid objects used to create the superficial pores and therefore the pores themselves can have a diameter of between 1 and 100 micrometers, preferably between 5 and 50 micrometers, and preferably between 10 and 30 micrometers.

[0020] The solid objects used to create the superficial pores of this invention can be removed for example by use of an organic solvent or other washing means. This hydrogel substrate can be comprised of poly-vinyl alcohol possessing a water content of at least 5% w/w of the overall hydrogel.

[0021] Accordingly, the present invention is directed to an implantable hydrogel substrate product, a method of making that product, and a method of using that product which substantially improves upon the limitations existing in the art. To achieve these and other advantages in accordance with the purpose of the invention, as embodied and broadly described herein, the invention includes a load bearing biocompatible hydrogel for medical implantation that promotes bone attachment. The hydrogel substrate consists of a hydrogel surface component which has been optimized for implantation.

This is accomplished through pores on the surface having a controlled range in distribution of size. The surface pores are superficial and do not extend throughout the hydrogel.

[0022] Hydrogels are materials whose state is between that of a solid and of a liquid. Gels consist of polymeric, i.e. long chain, molecules linked together to form a three-dimensional network and are embedded in a liquid medium. In the case of hydrogels, the liquid medium comprises water. The polymer backbone of hydrogels is formed by hydrophilic monomer units and may be neutral or ionic. Examples of neutral and hydrophilic monomer units are ethylene oxide, vinyl alcohol, (meth)acrylamide, N-alkylated (meth)acrylamides, N-methylol(meth)acrylamide, N-vinylamides, N-vinylformamide, N-vinylacetamide, N-vinyl-N-methylacetamide, N-vinyl-N-methylformamide, hydroxyalkyl (meth)acrylates such as hydroxyethylmethacrylate, vinylpyrrolidone, (meth)acrylic esters of polyethylene glycol monoallyl ethers, allyl ethers, of polyethylene glycols, and sugar units such as glucose or galactose. Examples of cationic hydrophilic monomer units are ethyleneimine (in the protonated form), diallyldimethylammonium chloride and trimethylammonium propylmethacrylamide chloride. Examples of anionic monomer units are (meth)acrylic acid, crotonic acid, maleic acid, fumaric acid, itaconic acid, 2-acrylamido-2-methylpropanesulfonic acid, vinylsulfonic acid, vinylphosphonic acid, 2-methacryloyloxyethanesulfonic acid, 4-vinylbenzenesulfonic acid, allylsulfonic acid, vinyltoluenesulfonic acid and vinylbenzenephosphonic acid.

[0023] From the example listing above, a hydrogel for use in the present invention may be selected based upon its biocompatibility and stability at various hydration states. For the purposes of the present invention, a suitable hydrogel will have a moisture content of at least 5% w/w of the overall hydrogel, preferably at least 10%, 15%, 20%, 25%, 30%, 35%, 40%, 50%, 60%, 70%, or 80% w/w of the overall hydrogel.

[0024] Initial events following implantation of a biomaterial in an orthotropic surgical site include rapid adsorption of serum constituents onto the implant surface. The first cells that are likely to come into contact with the surface are polymorphonuclear cells, platelets, monocytes, and macrophages. These cells release

bioactive factors that promote mesenchymal cell migration to the wound site. In addition to these natural factors associated with wound healing, surgeons frequently use bone graft and bone graft substitutes to improve bone formation. Such materials include osteoinductive agents such as demineralized bone matrix and bone morphogenetic protein. If appropriate signals are present mesenchymal cells with an osteoprogenitor phenotype will continue to differentiate into osteoblasts; of these a subset will become osteocytes. Ultimately, the newly formed bone will be remodeled via osteoclastic resorption. The present invention also provides that well-known grafting agents may be incorporated into the hydrogel composition, which includes, but is not limited to growth factors, angiogenic agents, antibiotics, and the like.

[0025] Chemically modified or polar surfaces are generally known to be able to produce more reactive protein adsorption to the implant surface than unmodified or non-polar surfaces. The increased reactivity of the proteins adsorbed onto the polar surface is thought to promote cellular adhesion to that surface. Therefore, the invention provides that the hydrogel composition can possess chemically modified or polar surfaces.

[0026] In general, many materials are well-tolerated in bone, but the success of long-term or chronic implantation often depends on the intimacy of the interface between the material surface and the bone. Microarchitecture of the surface is an important determinant of cell response. It has been observed that osteoblast phenotypic expression is surface-dependent. As described herein, specific surface characteristics enhance osteoblast differentiation while permitting proliferation, leading to optimal cell response to the implantation.

[0027] The mechanical properties of the material must be appropriate for the application. When the mechanical properties of the material are similar to the mechanical properties of the tissue adjacent to the implant, tissue tolerance of the artificial material is enhanced. Polymeric and elastomeric biomaterials can be fabricated with a wide range of mechanical properties, making them suitable for many applications as implantable devices. Because of their high water content, similar to that of living tissue, hydrogels are superior in biocompatibility to non-hydrous polymeric materials. Poly-vinyl alcohol (PVA) is an example of a polymer that can be used to

form hydrogels, and has been studied extensively for its potential in biomedical applications. Poly-vinyl alcohol hydrogels (PVA-Hs) are biologically well tolerated and compatible with living cartilage tissue.

[0028] PVA-Hs can be produced from solution via repeated freezing and thawing cycles that increase the order of the microcrystalline regions, changing the dissolution properties, mesh size, and diffusion properties of the polymer. Also, PVA-Hs can be produced from solution via a slow and sustained transition through the freezing point of the solution. The mechanical properties of PVA-Hs can be varied over a wide range, and stable PVA gels can easily be produced to have an elastic modulus ranging from a few MPa, such as articular cartilage, to about 50 MPa, such as the stiffest portion of the annulus of spinal discs.

[0029] Increasing the porosity of a hydrogel substrate produces decreased mechanical strength. When porous hydrogels are used to provide the requisite surface of the present invention, it is advantageous that the porosity not extend throughout the hydrogel, but be limited to a relatively shallow depth below the surface. The thickness of the porous portion of the hydrogel is preferably less than 1 millimeter, less than 500 micrometers, and most preferable less than or equal to 200 micrometers.

[0030] The hydrogel substrates of the present invention can be used for implantation into any part of the body. One embodiment of this invention is an artificial intervertebral disc, comprising one or more hydrogels shaped substantially similarly to a natural intervertebral disc. The upper and lower surfaces of the hydrogel, or assembly of hydrogels, are constructed to have a rugose or textured surface with a defined porosity. That porosity depends primarily upon the size of a solid object used to create the surface texture. The surface texture is created by the distribution of pores that do not continue throughout the hydrogel, or, in other words, the pores are superficial. The size of the pores can be from 2 to 100 micrometers, preferably from 5 to 50 micrometers, and preferably, from 10 to 30 micrometers.

[0031] The porosity of the hydrogel surface embodied in this invention may be realized in a variety of ways. Molds may be constructed with patterning on the appropriate surfaces of the cavities in the mold. Alternatively, the porosity may be

produced by abrasion of a smooth hydrogel surface after molding. Abrading the surface with grit will result in a surface textured such as desired in this invention. Techniques for applying and using abrasives are well known to those of skill in the art.

[0032] One technique for producing the surface roughness of artificial discs of this invention involves providing solid objects having the size and shape of the required surface rugosity and then using these solid objects as a template for the construction of a mold. Alternatively, these solid objects may be embedded in the hydrogels of the present invention during the molding process and removed afterwards. Removal of the solid objects leaves behind on the surface of the hydrogel pores, cavities, and other invaginations required for the texture of the surface to be obtained.

[0033] One example of a material that can be used as solid objects to impart the surface texture on the hydrogels of the present invention is polystyrene. Polystyrene beads, commonly called latex beads, are commercially available in sizes ranging from 0.02 to 1000 micrometers, and can have a very narrow size distribution. Such a narrow size distribution is advantageous for applications requiring uniform surface roughness. For example, when using polystyrene beads with an average diameter of 20.3 μm an acceptable range for the distribution of bead size would be $\pm 0.6 \mu\text{m}$, preferably $\pm 0.5 \mu\text{m}$, and preferably $\pm 0.4 \mu\text{m}$. Polystyrene beads may be obtained having surface functional groups useful for covalent chemical attachment of various chemical entities to the surface of the beads. Polystyrene beads may also be obtained either crosslinked or uncrosslinked. The latter type of beads are insoluble in water, but freely soluble in many organic solvents. Thus, one method for removal of the beads after the molding process is the dissolution of the beads in appropriate organic solvents.

[0034] The pores on the textured surface in this embodiment enable the surface to resemble native bone which has undergone osteoclastic resorption. When surface textured hydrogels are used to provide the requisite surface porosity, it is advantageous for the pores not to extend throughout the hydrogel, but instead be limited to a relatively shallow depth below the textured surface. The thickness of the porous portion of the hydrogel surface is preferably less than 1 millimeter, preferably less than or equal to 500 micrometers, and preferably less than or equal to about 200 micrometers.

[0035] The hydrogels of the present invention may contain bioactive factors to further stimulate cell growth or differentiation. These factors, for instance attachment peptides, such as RGD containing peptides, and growth factors such as bone morphogenic proteins, insulin-like growth factor, platelet derived growth factor, 5 fibroblast growth factor, cartilage-derived growth factor, transforming growth factor-beta, and parathyroid hormone related peptide, as well as other regulatory chemicals such as statins, prostaglandins, and mineral ions well-known in the art. These factors may be included in the hydrogels of this invention singly or in combination, and they may be included with or without binding proteins.

10 [0036] The hydrogels of the present invention may also contain bone or cartilage forming cells (osteoblasts or chondrocytes) or precursor cells to bone and cartilage forming cells such as mesenchymal stem cells or osteoprogenitor cells. These precursor cells have the capacity to differentiate into bone and/or cartilage forming cells. Cells may be included in the hydrogels of the present invention alone or in 15 combination with bioactive factors to further stimulate cell growth or differentiation.

[0037] Natural intervertebral discs have a tough outer fibrocartilaginous ring called the annulus fibrosus and a soft, inner, highly elastic structure called the nucleus pulposus. The artificial discs of the present invention may contain an inner core constructed to mimic the physical and mechanical properties of the natural nucleus 20 pulposus, surrounded by an annular region constructed to mimic the physical and mechanical properties of the natural annulus fibrosus.

[0038] In one embodiment, these regions comprise hydrogels whose water content, degree of polymerization, and degree of crosslinking are adjusted to produce the requisite physical and mechanical properties. The hydrogel comprising the inner core 25 has a higher water content and/or a lower degree of polymerization and/or a lower degree of crosslinking to produce a relatively soft and elastic hydrogel. The hydrogel comprising the outer annular region has a lower water content and/or a higher degree of polymerization and/or crosslinking to produce a relatively hard outer hydrogel which mechanically is tough and stiff. The hydrogels comprising the upper and lower 30 surfaces may substantially resemble the hydrogel comprising the annular region in terms of physical and mechanical properties, water content, and degrees of crosslinking

and polymerization. The additional requirement, however, for the surfaces to be porous may allow or require a different combination of physical and mechanical properties in these hydrogels compared to the hydrogel comprising the outer annular region.

5 [0039] **Figure 1** shows a spinal disc replacement envisioned by the present invention. The spinal disc has an upper portion 1 and a lower portion 2. It is the hydrogel substrate surfaces of the upper portion 1 and lower portion 2 which possess the porous texture of the present invention. The upper portion 1 and lower portion 2 can be less elastic and more rigid than the inner region 4 which seeks to mimic the
10 nucleus pulposus. Likewise, the spinal disc may have an intermediate region of elasticity 3 which further aids in the function of the spinal disc. The intermediate region of elasticity 3 may or may not differ from the elasticity of either the inner region 4 or the upper portion 1 or lower portion 2.

[0040] **Figure 2** shows the upper portion 1 of the spinal disc of **Figure 1**
15 possessing superficial surface pores 10 of the present invention. The sizing of these pores as described herein promotes differentiation of cells into desired tissues, such as bone or bone-like cells, and induces the attachment of those cells to the surface.

[0041] In one embodiment, the superficial pores can be created with solid polystyrene beads of 20.7 μm to 19.9 μm of average diameter suspended in the
20 hydrogel solution, or coated on the appropriate surfaces of the mold prior to crosslinking of the hydrogel. After crosslinking, the polystyrene beads are removed by dissolving them in a solvent such as dimethyl formamide or its equivalent that does not dissolve the hydrogel. Such treatment produces porosity and surface roughness with dimensions approximately equal to the diameter of the polystyrene beads. The
25 invaginations left behind after removal of the polystyrene beads contribute to the controlled surface texture desired in the present invention. The polystyrene beads of this embodiment may also be adhered to a surface and used as a part of a mold, or as a template in the construction of a mold.

[0042] In another embodiment of this invention, the solid object used in the casting
30 of a rough hydrogel surface is grit. Grit can be any solid object that is small with a

narrow size distribution. Examples of grit include sand, silica particles, silicone particles, metal shot, etc. Those skilled in the art would recognize the need to match the grit used to the hydrogel along with the method of removing the grit leaving the rough or porous surface.

5 [0043] A silica grit of appropriate size can be used to impart the proper level of porosity on the surface of a hydrogel. As was seen with the polystyrene, the sand is placed in the bottom of a mold and the aqueous hydrogel is poured into the mold. The hydrogel is allowed to crosslink and polymerize and is then removed from the mold. The hydrogel is then washed to remove the grit leaving behind the invaginations and
10 pores which make up the textured surface of the hydrogel implant. Grit may also be adhered to a surface and used as a part of a mold, or as a template in the construction of a mold.

[0044] In yet another embodiment of the present invention, the mold used in the formation of the hydrogel substrate can be any type of material around which the
15 hydrogel forms. For example, the mold can be a series of beads, grit, filter screens, mesh, wires, glass tubing, and the equivalents of these materials or items. Once the hydrogel has been allowed to form around the mold element, the mold is removed from the hydrogel manually, chemically, or any other means which will allow the hydrogel to remain intact once the mold has been removed.

20 [0045] In yet another embodiment of the present invention, the hydrogel substrate can be a load bearing patch which can be used in the repair of partially or predominately damaged tissue. For example, the hydrogel substrate bearing the textured surface of the present invention can be relatively thin and small in diameter. That hydrogel substrate can then be placed where deteriorated, either acutely or
25 chronically, cartilage was removed.

[0046] In yet another embodiment of the present invention, the hydrogel substrate can be assembled outside the body in a malleable form. The malleable form of the hydrogel substrate can then be placed in the intended area, be it a spinal disc replacement, knee cartilage replacement, shoulder bursa repair, or other use one skilled
30 in the art would foresee. Once in the proper position, the malleable hydrogel substrate

could be hardened or polymerized via photopolymerization. Radiation curing or photopolymerization (photo-induced free radical polymerization) has become an important and useful technique for applying and curing coatings, inks and adhesives. Radiation-curable compositions typically comprise as essential components one or more radiation-curable monomers and a photoinitiator. The compositions are applied as a coating to various articles and surfaces and the monomers are polymerized to form a film by exposing the coating of the radiation-curable composition to radiation, typically ultraviolet (UV) or electron-beam radiation.

Examples

10 [0047] Example 1. Attachment of polystyrene objects to a surface.

[0048] To a suspension of carboxyl-modified polystyrene beads (20.3 μm +/- 0.43 μm diameter, Bangs Laboratories) in 20 mM MEW, pH 4.4 is added a 10-fold excess of water-soluble carbodiimide, 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride. After 15 minutes at room temperature, the beads are washed twice by centrifugation and suspension in 20 mM HEPES, pH 7.5 and then resuspended in the same buffer. The resulting suspension is added to the wells of a 24-well tissue culture plate made of polycarbonate, having an amino-modified surface (Nalge Nunc International). After 60 minutes at room temperature, the unreacted beads are decanted, and the wells are washed gently with deionized water. Microscopic analysis shows the bottom surface of the wells are covered with a monolayer of polystyrene beads at a density of approximately 50%.

[0049] The surface with attached polystyrene objects of the previous example may be used as a template to fabricate a mold for providing the desired porous surface of the hydrogels of the present invention. This may be accomplished by making a metallic replica of a surface comprising a plurality of polystyrene objects using sputtering and/or metal plating techniques and the like, all of which are well known to those of skill in the art. The metallic replica thus produced may be replicated again and reinforced with further metal or other components, again using methods well known to those skilled in the art. The result is a mold suitable for producing the surface texture of the hydrogels of the present invention.

[0050] The polystyrene objects of the foregoing example may also be included in the hydrogels of the present invention during the molding process. Subsequent removal of the polystyrene objects provides the controlled surface porosity provided for the hydrogels of the present invention. This is illustrated in the following example.

- 5 [0051] Example 2. Construction of a PVA-H with surface topography for implantation as a spinal disc prosthesis.

[0052] A two-part mold with inserts is used to produce the artificial disc depicted in Figure 1. The upper and lower halves of the mold are first separated to mold the upper and lower surface regions of the disc. The surface of each corresponding upper and lower surface is created by suspending in the aqueous hydrogel the objects for
10 creating the superficial pores. That suspension is then poured into the well of a mold at a depth no greater than the desired depth of the superficial pores. That layer of hydrogel is allowed to polymerize and crosslink. From that base layer creating the outermost layer of the corresponding surface, the remainder of the bulk of the hydrogel
15 substrate can be built up by adding additional depth of aqueous hydrogel.

[0053] A 30%w/w poly(vinyl alcohol) solution is prepared by mixing poly(vinyl alcohol) polymer (124,000 – 186,000 Av. MW, 99+% saponification, Aldrich Chemical Company) in sterile, deionized water. The polymer is dissolved by heating the mixture in an autoclave at 120°C for 30 minutes. To a portion of the viscous liquid
20 solution is added 30% w/w of the polystyrene objects from Example 1. This is mixed until a uniform suspension is obtained.. To each of the cavities in each half of the mold is added a sufficient amount of this suspension to coat the surfaces of the mold cavities to a thickness of 200 μ m. Inserts are placed in each cavity to spread the suspension across the surfaces of the cavities and maintain the 200 μ m thickness.

25 [0054] The two halves of the mold are then subjected to five cycles of freezing and thawing. In each cycle, the molds are placed in a freezer at about -20°C for approximately 12 hours then removed from the freezer and placed at room temperature for approximately 12 hours. The inserts defining the first 200 μ m thickness of the top portion of the upper surface and the bottom portion of the lower surface are removed
30 from the molds, and an additional amount of the 30% poly(vinyl alcohol) solution

(without polystyrene objects) is added to the mold cavities. The amount added is sufficient to increase the thickness of the top portion of the upper surface and the bottom portion of the lower surface to 1 mm. Inserts are placed in each cavity to spread the solution and maintain the 1 mm thickness.

5 [0055] The two halves of the mold are subjected to five additional cycles of freezing and thawing as above. The inserts defining the top portion of the upper surface and the bottom portion of the lower surface are removed from the molds, and annular inserts defining the shape of the core region are placed in the cavities of the lower half of the mold. A 20% w/w poly(vinyl alcohol) solution is prepared by mixing
10 poly(vinyl alcohol) polymer (89,000 – 98,000 Av. MW 99+% saponification, Aldrich Chemical Company) in sterile, deionized water and dissolving as above. The solution is filled into the annular inserts and the mold is subjected to five additional cycles of freezing and thawing. The annular inserts are removed, the two halves of the mold are assembled and clamped together, and the areas of the mold corresponding the annular
15 region are filled with 30% poly(vinyl alcohol) solution. The assembled mold is subjected to five more cycles of freezing and thawing. The molded artificial discs are removed from the mold and immersed in dimethyl formamide to dissolve the included polystyrene objects, the rinsed three times with deionized water.

[0056] The artificial disc produced by the forgoing example has a soft and elastic
20 inner core while the outer annular region and upper and lower surfaces are relatively hard, tough, and stiff. The surface of the artificial disc is smooth, except on the top portion of the upper surface and the bottom portion of the lower surface where the removal of the polystyrene objects produces a rough or rugose surface with a roughness of 20 μm . When artificial discs made according to this procedure are implanted into
25 the intervertebral spaces of dissectomized rabbits, extensive bone growth onto the surface occurs within 3 weeks.

[0057] Although the invention has been described with reference to a particular preferred embodiment with its constituent parts, features and the like, these are not intended to exhaust all possible arrangements, mechanical and electrical equivalents, or
30 features, and indeed many other modifications and variations will be ascertainable to those of skill in the art.

CLAIMS

What is claimed is:

- 5 1. An implantable hydrogel substrate comprising a hydrogel surface having a plurality of superficial pores thereon.
2. The hydrogel of claim 1 wherein the pores have an average diameter of between 1 and 100 micrometers.
3. The hydrogel of claim 1 wherein the pores have an average diameter of
10 between 5 to 50 micrometers.
4. The hydrogel of claim 1 wherein the pores have an average diameter of between 10 to 30 micrometers.
5. The hydrogel of claim 1 wherein the superficial pores vary in size by less than 30%.
- 15 6. The hydrogel of claim 1, wherein the superficial pores vary in size by less than 10%.
7. The hydrogel of claim 1, wherein the hydrogel is comprised of polyvinyl alcohol.
8. The hydrogel of claim 1, wherein the hydrogel contains a moisture
20 content of at least 5% w/w of the hydrogel.
9. The hydrogel of claim 1, wherein the hydrogel contains a moisture content of at least 30% w/w of the hydrogel.
10. An artificial disc for implantation into the spine comprising the hydrogel substrate of claim 1.

11. The artificial disc of claim 6, wherein the disc is a hydrogel comprising a plurality of regions having variably elasticity.
12. The artificial disc of claim 6, wherein the disc comprises a surface region having a lower modulus of elasticity than an interior region.
- 5 13. The artificial disc of claim 6, wherein the disc comprises more than one hydrogel.
14. The artificial disc of claim 9, wherein the disc comprises at least one surface region hydrogel having a higher modulus of elasticity than an interior region hydrogel.
- 10 15. A method of making a hydrogel substrate comprising:
 - a. contacting solid objects with a liquid hydrogel,
 - b. allowing the aqueous hydrogel to polymerize and crosslink while the solid objects are at least partially immersed in the surface region of the hydrogel, and
 - 15 c. removing said solid objects from the polymerized and crosslinked hydrogel to form superficial pores thereon.
16. The method of claim 15, wherein the solid objects are polystyrene beads.
17. The method of claim 15, wherein the solid objects are grit, sand, silicon,
20 silica, and ultra-fine particulate matter.
18. The method of claim 15, wherein the solid objects have an average diameter of between 1 to 100 micrometers.
19. The method of claim 15, wherein the solid objects have an average diameter of between 5 to 50 micrometers.

20. The method of claim 15, wherein the solid objects have an average diameter of between 10 and 30 micrometers.
21. The method of claim 15, wherein the solid objects are removed from the hydrogel by using an organic solvent or washing.
- 5 22. The method of claim 15, wherein the hydrogel is comprised of polyvinyl alcohol.
23. The method of claim 15, wherein the hydrogel contains a moisture content of at least 5% w/w of the hydrogel
- 10 24. The method of claim 15, wherein the hydrogel contains a moisture content of at least 30% w/w of the hydrogel.

15

1/2

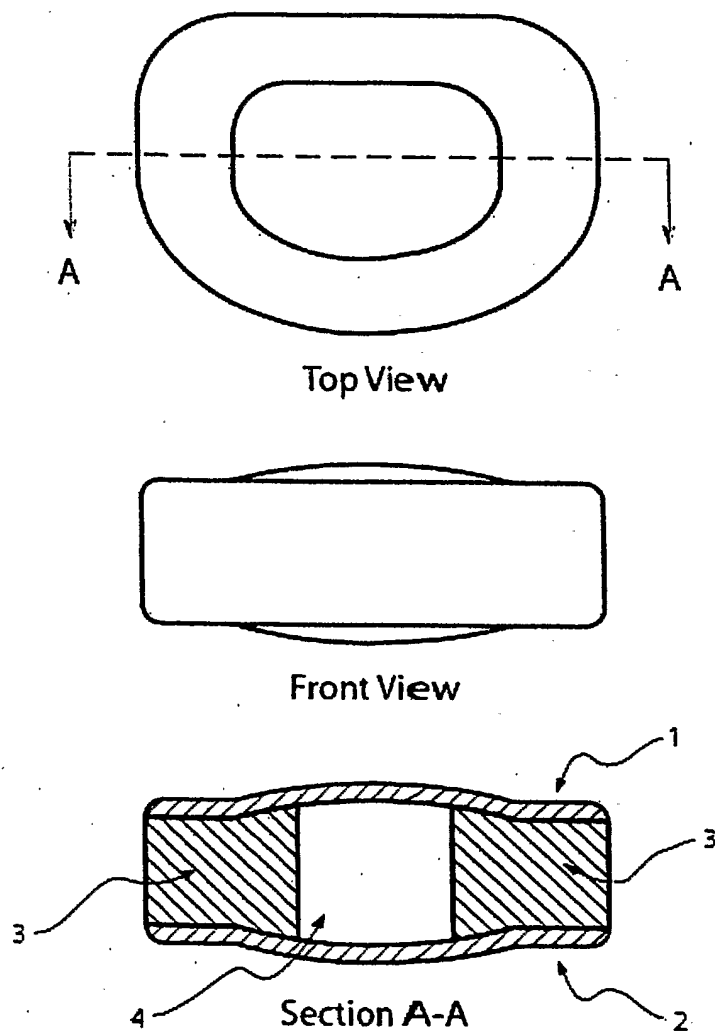
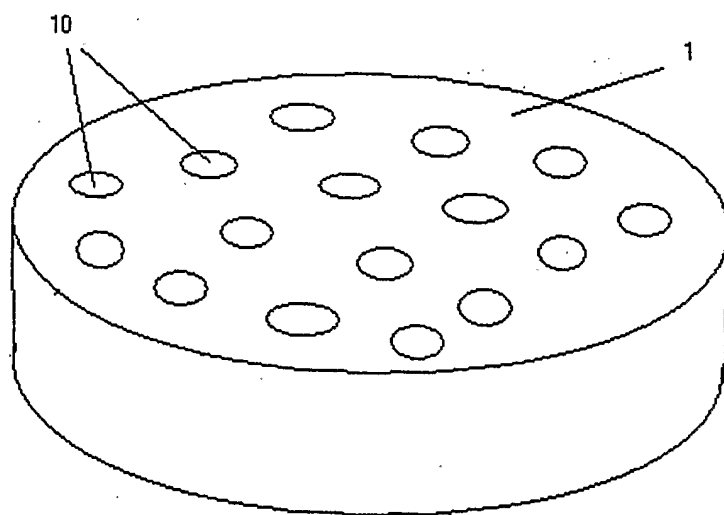


Figure 1

Figure 2



INTERNATIONAL SEARCH REPORT

International application

PCT/US05/04045¹

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61F 2/02; A61K 9/14

US CL : 424/423, 486

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)

U.S. : 424/423, 486

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6428,576 A (HALDIMANN) 06 August 2002 (06.08.2002), see column 6, lines 33-34, claims.	1-24

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent 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 when the document is taken alone

"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

Date of the actual completion of the international search

18 May 2005 (18.05.2005)

Date of mailing of the international search report

15 JUL 2005

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US

Commissioner for Patents

P.O. Box 1450

Alexandria, Virginia 22313-1450

Facsimile No. (703) 305-3230

Authorized officer

Carlos A. Azpuru

Telephone No. 1570 2572-1600