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(54) Title: BIOMEDICAL ADHESIVE

(57) Abstract: The biomedical adhesives of the invention provide a reactive surface to adhere or crosslink to tissue and may be used, for example, as ready-to-use corneal onlay in ophthalmic surgery. The invention provides a method for bonding a bulk material to a corresponding nucleophilic or electrophilic surface including attaching a multifunctionally activated bulk material compound to the bulk material and contacting a functional group of the compound with the surface under conditions permitting covalent linkage between the bulk material and the functional group.

BIOMEDICAL ADHESIVE

The present invention relates to a biomedical adhesive. Particularly, it relates to a ready-to-use adhesive for an organic or inorganic biocompatible bulk material in biological applications. One suitable use of the adhesive is binding a corneal onlay or inlay under ambient conditions to the corneal basement membrane or corneal stromal tissue.

It is desirable in many applications, especially in the biomaterial and medical field to adhere biomaterials and other biocompatible materials or devices to tissue. Tissue is defined as any part of the body, living or dead. A biomedical device that can be glued directly to tissue and attains sufficient interfacial bond strength is attractive because it may obviate the need for surgical methods such as suturing. Useful applications include the adhesion of drug delivery devices to the epidermis, the gluing of anti-adhesion barriers for surgery and the adhesion of synthetic onlays or inlays to the cornea. Conventional surgical adhesives are often not suitable for a wide range of adhesive applications. Currently cyanoacrylates and fibrin glues are used clinically as soft tissue adhesives. However the brittleness of the cured adhesives, the potential toxicity of their biodegradation products and the lack of control over cure time are the major drawbacks of cyanoacrylates. Slow curing, poor mechanical strength and infection risk are disadvantages of fibrin-based glues.

A variety of different methods for the bonding of devices to tissue have been disclosed in the prior art. For example, U.S. patent No. 5,354,336 describes a method for sealing lenticules onto a corneal surface comprising the steps of placing the lenticule to the correct position, applying a polymerizable collagen composition onto the lenticule and the corneal surface to form a collagen coating over the lenticule and the corneal surface and polymerizing the coating in the presence of an initiator thereby sealing the lenticule onto the corneal surface. However said glues have not yet proven satisfactory mainly because of severe handling problems. For example, the surgeon always has to mix the glue components shortly prior to use. Once the premixing has taken place, only a limited time period is available for using the glue depending on the glue's specific

curing time; this puts time-pressure on the surgeon. Following the attachment of the lenticule onto the cornea, excessive glue has to be removed carefully otherwise glue residues may inhibit the normal function of biological tissue. Further disadvantages of the known glues are, for example, insufficient mechanical stability and adhesive duration.

Reference to any prior art in the specification is not, and should not be taken as, an acknowledgment or any form of suggestion that this prior art forms part of the common general knowledge in Australia or any other country.

It will be understood that the term "comprises" or its grammatical variants as used in this specification and claims is equivalent to the term "includes" and is not to be taken as excluding the presence of other elements or features.

Biomedical adhesives may be given different names, including "bioadhesive", "biological adhesive" and "surgical adhesive" among others. In this specification, such terms are used interchangeably, and all refer to compositions which are biocompatible and which result in temporary or permanent bonding of two surfaces, where at least one of the surfaces is biological and/or bonding is in a biological environment.

The term "bulk material" is used in this specification to refer to biocompatible organic or inorganic material. This includes for example polymers from which biomedical devices are formed, prostheses, etc. The bulk material would usually be a solid phase.

Surprisingly, it now has been found that a biomedical adhesive can be formed with broad applicability and reduced adverse biological reaction.

The present invention therefore relates to a biomedical adhesive comprising multifunctionally activated functional groups.

In one form of the invention, there is provided a method for bonding a bulk material to a nucleophilic or electrophilic surface including attaching a multifunctionally activated functional group to the bulk material and then contacting

the functional group with the nucleophilic surface under conditions permitting covalent linkage between the surface and the functional group.

As would be appreciated, the compound and the surface can be either electrophilic or nucleophilic, as long as each is the opposite of the other so as to enable reaction between them – such a pair of reactive groups may be called "corresponding" (eg, an activated ester and an amino group).

The conditions are selected to be as convenient as possible. The temperature range is preferably between 0°C and 60°C, most preferably body temperature (ie, about 37°C). Ambient pressure is suitable. In some cases, there is also desirably sufficient surrounding fluid to facilitate or permit sufficient movement of the reactive groups (or the longer molecules to which they are attached) such that they come into close enough proximity for the covalent linkage to form.

The invention also provides a bioadhesive attached to a bulk material for bonding the bulk material to a biological surface, the bioadhesive comprising a multifunctionally activated compound reactable with nucleophilic or electrophilic functional groups.

The multifunctionally activated functional group is preferably an activated ester or amide.

The invention also provides a bioadhesive covalently linking a bulk material with a biological surface, the adhesive being formed by the curing of a multifunctionally activated functional group.

The invention also provides a biomedical device for attaching to a biological surface including a biocompatible organic or inorganic bulk material to which a multifunctionally activated compound has been bonded.

The invention is also directed towards a method of preparing a device comprising a bulk material combined with a bioadhesive which may be stored

anhydrously prior to use, comprising attaching the multifunctionally activated functional group to the bulk material and then dehydrating the device.

The invention also provides a process for applying a bioadhesive to a surface of a biomedical device comprising the steps of

providing a biomedical device comprising a biocompatible organic or inorganic bulk material

if the surface has inadequate functional groups on its surface, applying surface functional groups to the surface, and

covalently coupling a multifunctionally activated compound comprising at least one carboxy derivative group and at least one additional functional group that is co-reactive to the surface functional groups.

The invention is particularly directed towards a bioadhesive for *in vivo* use. The invention can be used to adhere, for example, synthetic materials to which the bioadhesive multifunctionally activated compound is attached to any appropriate nucleophilic or electrophilic surface of an animal (including humans). A common nucleophilic surface to which such articles may be attached is collagen, or any other lysine-rich polypeptide (whether natural or synthetic).

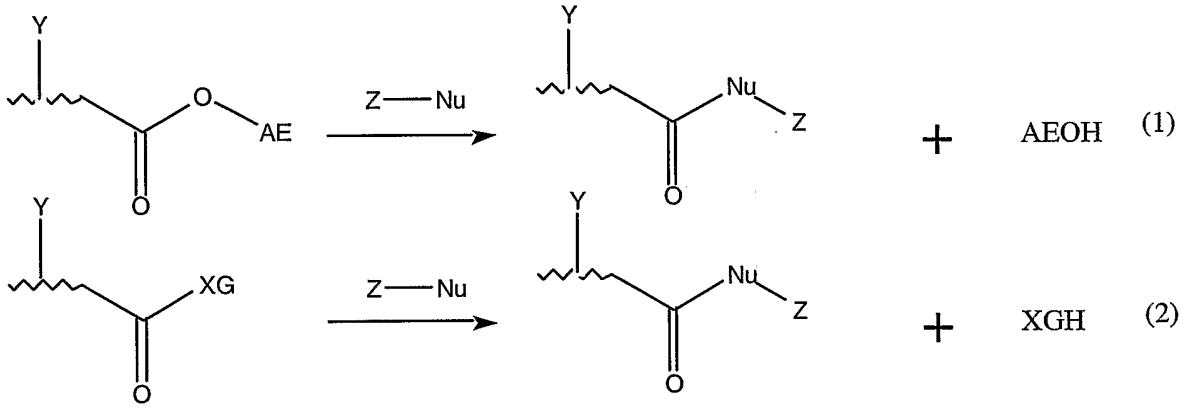
The incorporation of collagen into a device according to the invention is optional. Collagen may confer other properties on the biomedical device useful or desirable for its intended purpose. Collagen may be bonded to the biomedical device of the invention by the same surface functional groups as bind the multifunctionally activated compound or otherwise.

The invention has particular application to biomedical devices made from a bulk material which is strongly hydrophobic. Such materials are known to be difficult to adhere in a biological environment. As detailed in a preferred embodiment, hydrophobic surfaces may first be treated by the addition of surface functional groups (such as aldehydes) by known processes (such as plasma deposition).

Suitable multifunctionally activated functional groups include carboxy derivative groups, such as, for example, carboxylic halides, for example -COCl or -COBr; carboxylic anhydrides; lactones; carboxylic amides; or preferably carboxylic esters. A preferred group of carboxy derivative groups are esters, in particular activated esters or amides.

The reactive groups may be selected from a class of esters, which are highly reactive towards nucleophiles. Active esters or other reactive groups derived from carboxylic acids or amides undergo elimination reactions with nucleophiles to form stable adducts as follows:

General reaction (1) describes the elimination reaction of nucleophiles (Nu) with an active ester (AE). General reaction (2) describes the elimination reaction of nucleophiles (Nu) with a reactive group (XG).



in which

X= halogen;

Y= H, alkyl, or optionally active ester or reactive group;

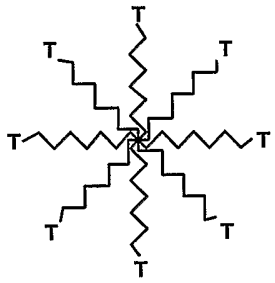
Nu = nucleophile (e.g. amine, thiol)

These reactions can be applied as a curing reaction for adhesives, when di- or poly-functional reagents are used. Thus, if Z contains more than one nucleophilic group and Y contains more than one active ester or reactive group,

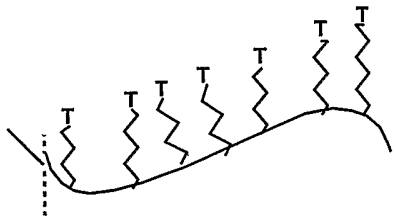
then a cross-linked polymer results that has the properties of an adhesive. If the substrate to be glued contains nucleophilic groups (e.g. amines in collagen-coated articles or ophthalmic tissue), then direct bonding to the active ester or reactive group can occur and the formulation acts as a bioadhesive.

The reactive groups can be in the form of a multifunctional dendritic polymer, a multifunctionalized comb like polymer, the terminating ends of a linear polymer or other multifunctional polymer where there is at least one reactive group per polymer chain as follows:

Linear polymer



Dendrimeric polymer



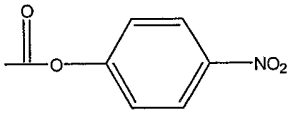
Comb like polymer

T = reactive group

= optional spacer

Careful choice in the spacer component enables the synthesis of a bioadhesive that supports or inhibits cell growth, or is biodegradable or non-biodegradable. The bioadhesives can also contain other materials, such as inert biocompatible fillers, to improve the viscosity and to result in porosity after leaching.

An activated ester or amide is, for example, a radical of formula



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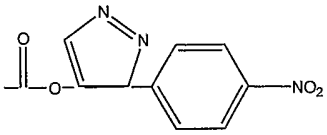

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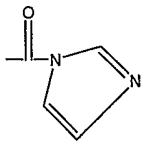

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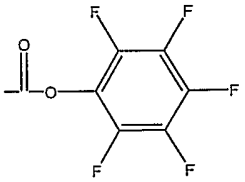

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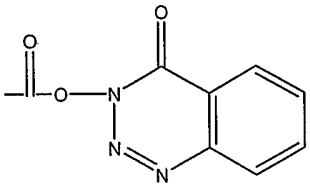
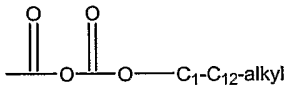
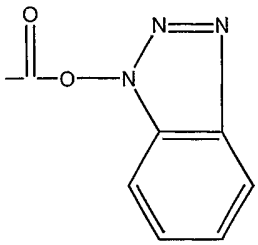


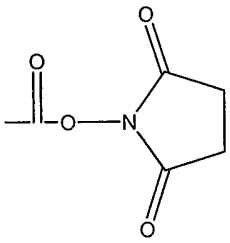
(e)



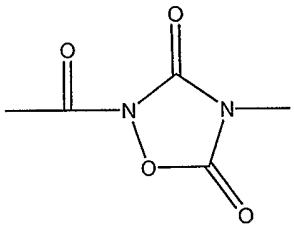
(f)



(g)



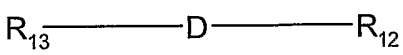
(h)



(i)

A preferred carboxy derivative group according to the invention is an activated ester group of formula (g), (e) or, in particular, of formula (h).

Multifunctionally activated compounds are, for example, compounds of formula



(j),

wherein

D is a bivalent organic radical, which may be substituted, for example, by one or more carboxy or carboxy derivative groups;

R_{12} is a carboxy derivative group; and

R_{13} is a further reactive group, for example a carboxy, a carboxy derivative, isocyanato, isothiocyanato or epoxy group.

Examples of bivalent organic radicals D are, for example, an optionally branched C_1-C_{12}-alkylene; a radical of dendrimer or star bust polymer; a radical of a polyethylene glycol; a radical of a polyvinyl alcohol, for example, a polyvinyl alcohol with pendant polymerisable groups as described in WO 96/24075; or a radical of a hyperbranched polyester resin as described by M. Johansson and A. Hult in Journal of Coatings Technology, 67, No. 849, 35 (1995). D is preferably a bivalent radical of a polyethylene glycol, for example a radical of formula $-CH_2-CH_2-(O-CH_2-CH_2)_f-$, wherein f is an integer of, for example, from 2 to 250.

R_{12} is a carboxy derivative group, wherein the above given meanings and preferences apply. R_{13} is independently preferably a carboxy derivative group, wherein the above given meanings and preferences apply. Most preferably, R_{12} and R_{13} are identical.

In one embodiment, the multifunctionally activated compound is polyethylene glycol that is di-substituted with succinimidyl propionate, succinimidyl succinate or succinimidyl succinimide, or the known derivatives of these functional groups.

The method of attaching a multifunctional compound of formula (j) to a bulk material surface provided with a natural or synthetic polymer comprising co-reactive functional groups depends on the nature of the reactive groups being present in compound (j) and at the natural or synthetic polymer. The reactions are known per se, for example, from textbooks of organic chemistry.

For example, in case that a compound of formula (j) with a carboxy, amide or ester group R_{13} is to be coupled to a natural or synthetic polymer containing amino, thiol or hydroxy groups, the reaction may be carried out under the conditions that are customary for ester or amide formation. It is preferred to carry

out the esterification or amidation reaction in the presence of an activating agent, for example N-ethyl-N'-(3-dimethyl aminopropyl)carbodiimide (EDC), N-hydroxy succinimide (NHS) or N,N'-dicyclohexyl carbodiimide (DCC).

In case that a compound of formula (j) with an anhydride group R_{13} is to be coupled to a natural or synthetic polymer containing amino, thiol or hydroxy groups the reaction may be carried out as described in organic textbooks, for example in an aprotic solvent, for example one of the above-mentioned aprotic solvents, at a temperature from room temperature to about 100°C.

In case that a compound of formula (j) with an activated ester or amide group R_{13} is to be coupled to the surface of a bulk material or to a natural or synthetic polymer containing amino, thiol or hydroxy groups, the reaction may be carried out, for example, at room temperature or at elevated temperature, for example at about 20 to 100°C, in an aprotic medium.

In case that a compound of formula (j) with an isocyanato group R_{13} is to be coupled to a natural or synthetic polymer containing amino or hydroxy groups, the reaction may be carried out in an inert organic solvent such as acetonitrile, an optionally halogenated hydrocarbon, for example petroleum ether, methylcyclohexane, toluene, chloroform, methylene chloride and the like, or an ether, for example diethyl ether, tetrahydrofurane, dioxane, or a more polar solvent such as DMSO, DMA, N-methylpyrrolidone or even a lower alcohol or water, at a temperature of from 0 to 100°C, preferably from 0 to 50°C and particularly preferably at room temperature, optionally in the presence of a catalyst, for example a tertiary amine such as triethylamine or tri-n-butylamine, 1,4-diazabicyclooctane, or a tin compound such as dibutyltin dilaurate or tin dioctanoate. In addition, the reaction of the isocyanato groups with amino groups may also be carried out in an aqueous solution in the absence of a catalyst. It is advantageous to carry out the above reactions under an inert atmosphere, for example under a nitrogen or argon atmosphere.

In case that a compound of formula (j) with an epoxy group R_{13} is to be coupled to a natural or synthetic polymer containing amino, thiol or hydroxy

groups, the reaction may be carried out, for example, at room temperature or at elevated temperature, for example at about 20 to 100°C, in an aprotic medium using a base catalyst, for example $Al(O\text{-}C_1\text{-}C_6\text{-alkyl})_3$ or $Ti(O\text{-}C_1\text{-}C_6\text{-alkyl})_4$.

In a preferred embodiment of the invention, the bulk material forms a biomedical device. The device may be obtainable by a process comprising the steps of

providing a biomedical device comprising a biocompatible organic bulk material and having surface functional groups on its surface, and

covalently coupling the surface functional groups with a natural or synthetic polymer comprising co-reactive groups, and

covalently coupling a multifunctionally activated compound comprising at least one carboxy derivative group and at least one additional functional group that is co-reactive to the co-reactive groups of the natural or synthetic polymer.

Examples of bulk materials that may be coated according to the process of the invention are natural or synthetic organic polymers, or laminates, composites or blends of said materials. Some examples of polymers are polyaddition and polycondensation polymers (polyurethanes, epoxy resins, polyethers, polyesters, polyamides, polycarbonates and polyimides); vinyl polymers (polyacrylates, polymethacrylates, polystyrene, polyethylene, polyacrylamides and halogenated derivatives thereof, polyvinyl acetate and polyacrylonitrile); elastomers (silicones, polybutadiene and polyisoprene); or modified or unmodified biopolymers (collagen, cellulose, chitosan and the like).

Another preferred group of bulk materials are those conventionally used for the manufacture of biomedical devices, e.g. contact lenses, intraocular lenses or artificial cornea, which are not hydrophilic per se. Such materials are known to the skilled artisan and may comprise for example polysiloxanes, perfluoropolyethers (PFPE), fluorinated poly(meth)acrylates or equivalent fluorinated polymers derived

e.g. from other polymerizable carboxylic acids, polyalkyl (meth)acrylates or equivalent alkylester polymers derived from other polymerizable carboxylic acids, or fluorinated polyolefines, such as fluorinated ethylene propylene, or tetrafluoroethylene, preferably in combination with specific dioxols, such as perfluoro-2,2-dimethyl-1,3-dioxol. Examples of suitable bulk materials are e.g. Lotrafilcon A, Neofocon, Pasifocon, Telefocon, Fluorsilfocon, Paflufocon, Silafocon, Elastofilcon, Fluorofocon or Teflon AF materials, such as Teflon AF 1600 or Teflon AF 2400 which are copolymers of about 63 to 73 mol % of perfluoro-2,2-dimethyl-1,3-dioxol and about 37 to 27 mol % of tetrafluoroethylene, or of about 80 to 90 mol % of perfluoro-2,2-dimethyl-1,3-dioxol and about 20 to 10 mol % of tetrafluoroethylene.

Another preferred group of biocompatible polymers are those being conventionally used for the manufacture of biomedical devices, e.g. contact lenses, which are hydrophilic per se, since hydrophilic groups, e.g. carboxy, carbamoyl, sulfate, sulfonate, phosphate, amine, ammonium or hydroxy groups, are inherently present in the material. Such materials are known to the skilled artisan and comprise for example polyhydroxyethyl acrylate, polyhydroxyethyl methacrylate (HEMA), polyvinyl pyrrolidone (PVP), polyacrylic acid, polymeth-acrylic acid, polyacrylamide, poly-N,N-dimethyl acrylamide (DMA), polyvinyl alcohol, copolymers for example from two or more monomers from the group hydroxyethyl acrylate, hydroxyethyl methacrylate, N-vinyl pyrrolidone, acrylic acid, methacrylic acid, acrylamide, N,N-dimethyl acrylamide, vinyl alcohol, vinyl acetate and the like, polyalkylene glycols such as polyethylene glycols, polypropylene glycols or polyethylene/polypropylene glycol block copolymers. Typical examples are e.g. Polymacon, Tefilcon, Methafilcon, Deltafilcon, Bufilcon, Phemfilcon, Ocufilcon, Focofilcon, Etafilcon, Hefilcon, Vifilcon, Tetrafilcon, Perfilcon, Droxifilcon, Dimefilcon, Isofilcon, Mafilcon, Nelfilcon or Atlafilcon.

An even more preferred group of bulk materials are, for example, porous polymers with improved wettability and cell growth ability as described in US 6015609, WO 97/35906, WO 97/35905, WO 00/49058 or in WO 00/15686. Polymers incorporating charged units or zwitterions (such as described WO 00/15686) are also useful in this invention, and the contents of that specification

are herein incorporated by reference. Additional examples are provided in European Patent Application no. 02011173.8, the contents of which are herein incorporated by reference. PFPE macromonomers and the synthesis of polymers therefrom are known e.g. from PCT applications WO 96/31546 or WO 97/35906.

The bulk material network can, if desired, be reinforced by addition of a crosslinking agent, that is not a PFPE polymer, for example by a polyunsaturated crosslinking comonomer. Examples of typical crosslinking comonomers are allyl (meth)acrylate, lower alkylene glycol di(meth)acrylate, poly(lower alkylene) glycol di(meth)acrylate, lower alkylene di(meth)acrylate, divinyl ether, divinyl sulfone, di- and trivinylbenzene, trimethylolpropane tri(meth)acrylate, pentaerythritol tetra(meth)acrylate, bisphenol A di(meth)acrylate, methylenebis(meth)acrylamide, triallyl phthalate and diallyl phthalate. Polyunsaturated perfluoroalkyl crosslinkers of formula

$$Q - CH_2 - (CF_2)_q - CH_2 - Q \qquad (k),$$

wherein for Q the above given meanings and preferences apply, and q is an integer of, for example, from 1 to 20 and preferably from 1 to 12, are the preferred additional crosslinking comonomers. If a crosslinking comonomer is used, the amount used is in the range of from 0.01 to 40 % of the expected total weight of polymer, preferably the comonomer is in the range of 0.1 to 30 %, and more preferably in the range of 0.1 to 20 %. Preferably the polymerization mixture does not contain a crosslinking monomer.

The preferred bulk materials of the invention may be obtained by copolymerizing one or more PFPE macromonomers, one or more charged monomers or a suitable precursor thereof and optional further comonomers and/or additives to afford a transparent polymer in the presence of a suitable initiator. Standard methods well known in the art for effecting polymerization may be utilized, with free radical polymerization being preferred. Free radical polymerization can be simply carried out by radiating (using ultra-violet light) monomer mixtures containing a UV initiator, such as benzoin methylether, in an appropriate container or vessel. The mixture is irradiated for a sufficient time to

enable polymerization between monomers to take place. Alternatively, thermal initiation using a thermal initiator such as azobisisobutyronitrile, can be employed. If a precursor of the zwitter-ionic monomer is used, the copolymer after the irradiation may be treated with a suitable reagent in order to convert the precursor units into zwitter-ionic units.

The polymerization mixture can be converted to a polymer neat or in the presence of one or more solvents. While the structure of the components of the polymerization mixture has the most significant effect on the resulting modulus, the choice of solvent and comonomer also has an effect. Useful solvents include those selected from the following classes: esters, alcohols, ethers, and halogenated solvents. Fluorinated solvents are particularly useful and their use in combination with other solvents (in ratios varying from 1:9 to 9:1) from the classes above is especially desirable. Solvent concentrations of between 0-70% w/w, particularly 30-80% w/w, especially 55% in the polymerization mixture are desirable. Preferred solvents include acetates, particularly isopropyl acetate and tert-butyl acetate, 2-(trifluoromethyl)-2-propanol, chlorofluoroalkanes, particularly trichlorotrifluoroethane, and perfluorinated alkanes, such as perfluoro-1,3-dimethylcyclohexane, 2,2,3,3-tetrafluor-1-propanol, 2',3',4',5',6'-pentafluoroacetophenone, 1,1,1-trifluoro-3,4-pentadione, 2',3',4',5',6'-pentafluorobenzyl alcohol and the like. A particular preferred solvent is water or an aqueous solution comprising, for example, one or more organic solvents, for example a C_1-C_4-alkanol such as methanol or ethanol, or a fluorinated alkane. Water may be 1 to 70 % w/w, preferably 2 to 50 % w/w and particularly preferably 3 to 30 % w/w, in each case based on the entire formulation.

The bulk materials may form porous substrates. Porosity may be provided by the inherent porosity of the material. Alternatively, pores may be introduced into the polymers by various procedures such as those disclosed in PCT applications WO 00/15686. In case of porous bulk materials, a polar solvent, for example water, a C_1-C_4-alkanol, and/or a surfactant, preferably a fluorinated surfactant, may be incorporated into the polymerization mixture. The use of surfactants is an effective means of controlling the size and density of the pores. Non-ionic surfactants containing fluorine are preferred. Particularly preferred surfactants

include commercially available fluorinated surfactants such as Zonyl (DuPont) and Fluorad (3M). Zonyl surfactants, which are made of a perfluorinated hydrophobic tail and hydrophilic poly(ethylene oxide) head group, are a particularly preferred surfactant for use in the process of the present invention.

Suitable bulk materials are those obtainable by copolymerizing one or more macromonomers comprising at least one PFPE unit, wherein the above-given meanings and preferences apply, and at least one zwitter-ionic monomer or a precursor thereof, wherein again the above-given meanings and preferences apply, in an aqueous solution and, if a zwitter-ionic monomer precursor has been used, converting the precursor units into charged units after the copolymerization reaction. A particular preferred reaction medium in this context is an aqueous solution comprising a C_1-C_4-alkanol, in particular methanol or ethanol, a fluorinated surfactant and optionally a fluorinated alkane.

The surface of the bulk material may inherently contain functional groups or may be provided with covalently attached functional groups, for example, by plasma deposition, particularly if it is hydrophobic. The method of coating a surface by plasma deposition is known to the skilled artisan and is described in, e.g. WO 98/52620 and WO 00/29548. Typical examples of reactive groups being introduced to the surface of the bulk material by plasma surface preparation include aldehyde groups, amino groups, hydroxy groups, carboxy groups, carbonyl groups, sulfonic acid groups, sulfonyl chloride groups and groups able to be replaced by amino or hydroxy groups, such as halo groups. Aldehyde groups, thiol groups, amino groups, hydroxy groups and carboxy groups are preferred.

Examples of the natural or synthetic polymer used are cell-adhesive glycoproteins like collagens (various types), fibronectin, vitronectin, laminin, poly(ethyl imine), amino dextran, PAMAM dendrimers, poly(allyl amine), poly(vinyl alcohol), poly(arylic acid) and poly(methacrylic acid). Collagen and collagen-like proteins are preferred. The coupling of cell-adhesive glycoproteins to plasma polymers covalently bound to the underlying bulk material is known and described, for example, in WO 00/29548.

Moreover, biomedical devices according to the invention comprising a preferred bulk material, that is a bulk material obtainable by copolymerizing a macromonomer comprising at least one PFPE unit and a zwitter-ionic monomer in an aqueous solution, offer the additional advantage, that unlike other hydrophobic materials, for example those disclosed in WO 00/15686, they may be hydrated very easily. Accordingly, the biomedical devices of the invention may be dehydrated after their preparation and stored for extended periods without loss of adhesive activity. Such a biomedical device, for example an onlay, is then immediately ready for use, by just placing it in water for a short period, typically for about 1 to 10 minutes and particularly for about 2 minutes, which is sufficient to re-hydrate both the bulk material and the coating (so as to re-activate the hydrolytically unstable functional groups of the multifunctionally activated compound). All of these advantages naturally apply not only to contact lenses but also to other biomedical mouldings according to the invention as mentioned before.

In a further preferred form of the invention, biomedical devices (such as corneal inlays and onlays or lenticules) are formed from a polymer as described above, and then dried and stored in anhydrous conditions. This maintains the multifunctionally activated compounds' unreacted reactive groups such that they can bond to tissue upon implantation or affixation of the device to tissue, after re-hydration to increase polymer chain mobility.

The biomedical devices of the present invention such as in particular corneal onlays and inlays may be fixed on the cornea by just placing the device in intimate contact with the corneal tissue for a certain time period, for example for about 5 to 30 minutes and especially for 10 to 20 minutes. Such onlays and inlays are easier to handle, since the use thereof does not involve, for example, a premixing of glue components or time pressure upon the surgeon due to specific curing times of the glue components. In addition, no tedious removal of excess glue after fixing onto the cornea is necessary, and the previous problem of inhibition of overgrowth by glue residues does not exist.

Preferably, the cornea is previously prepared for the attachment of an onlay, for example, by removing the epithelial cell layers of the cornea by scraping and/or washing the eye, for example, with ethanol/water mixtures. Ideally the cornea surface and the lenticule are dried with surgical sponges or the like. It is desirable to minimise the fluid and air between the lenticule and the cornea surface. Excess fluid and air may be removed by applying pressure across the membrane using a rolling action with a surgical instrument. Such onlays provide a new route towards implanting a corneal onlay onto a cornea which is easy to perform, does not affect the wearers vision, and is safe. In particular, a mechanically stable fixation of the implant on the cornea is obtained which lasts for a period of time sufficient for normal biological function to recover after surgery. This may include the chance to allow the epithelial cells to recover, grow over the implant and thus fix it in a persistent manner.

The invention is particularly suitable for corneal inlays where cell growth ability is less important. Cell growth ability may be impeded by higher charged unit content, such as over 10% w/w, although this may be overcome by surface modification of the inlay (eg collagen attachment). The inlay may be implanted using known techniques. For example, an incision may be made in the stroma, into which the re-hydrated inlay is placed. The inlay then attaches to the stroma through reaction of the re-activated functional groups of the multifunctionally activated compound with no additional material being required. Polymers with charged unit content of around 20% are useful for this application.

The present invention is further described by the following non-limiting examples. If not specified otherwise, all parts are by weight. Temperatures are in degree Celsius.

Example 1: Preparation of a self-hydrating PFPE material

The following formulation was prepared in a glass vial furnished with a stirrer. The components were added in order of decreasing hydrophilicity and mixed well, prior to the addition of the photoinitiator. After the addition of the

photoinitiator (Darocur 1173), the mixing was continued for a further five minutes. The resulting solution was then placed in polypropylene moulds and polymerised for 3 hours under the irradiation of broad spectrum UV lamps (1 mW/cm^{-2}). The polymers (20 mm diameter disc 50 to 250 microns thick) were removed from the mold and placed through a general extraction procedure to remove any unpolymerised components. This procedure consists of a 2 x 24 h soaking in a fluorinated solvent such as Vertrel XF (DuPont), TCTFE (Aldrich) or HFE 7100 (3M), then 2 x 24 hr immersion in isopropyl acetate and subsequent immersion for 2 x 24 h in methanol. The polymers were then hydrated by a graded solvent change from methanol to ethanol (2 x 24 hr), 75% ethanol/water (2 x 24 hr), 50% ethanol/water (2 x 24 hr), 25% ethanol/water (2 x 24 hr), then pure water or saline (2 x 24 hr). This assists in extracting unpolymerised monomers/solvents/surfactants.

Examples 1 to 4 used a combination of Part A and Part B for polymerisation as follows:

Part A consisted of (parts by weight):

PFPE macromonomer #1	4.5
PFPE macromonomer #2	0.5
Ethanol	2.5
PFDMCH	3.0

Part B consisted of a 50% (w/w) solution of [2-(methacryloyloxy)ethyl]dimethyl(3-sulfopropyl)-ammonium inner salt (zwitterion) in water.

Component	Amount
Part A	1.749
Part B	0.143
Surfactant	Zonyl FSK 0.1841
Darocur 1173	0.0024

EWC (%)	27.5
Optical Clarity (%)	95.6
Porosity (A_{280})	0.815

Explanation of abbreviations:

PFPE macromonomer #1: perfluorinated macromer obtained by endcapping a perfluoropolyether diol (Ausimont, Italy, M_w = 2000) with isocyanatoethyl methacrylate as described in Chaouk H. et al., J.Appl.Polym.Sci., 2001, **80**, 1756;

PFPE macromonomer #2: perfluorinated macromer obtained by endcapping a perfluoropolyether diol (Ausimont, Italy, M_w = 1000) with isocyanatoethyl methacrylate as described in Chaouk H. et al., J.Appl.Polym.Sci., 2001, **80**, 1756;

Zonyl FSK, FSA, FSO100 and FSN100 = non-ionic fluorinated surfactants (DuPont);

Darocur®1173 = photoinitiator (Ciba Speciality Chemicals).

PFDMCH = perfluorodimethylcyclohexane

Equilibrium water contents (EWC) (expressed as percentages) and porosity measurements are measured as reported by Chaouk H. *et al, J. Appl. Polym. Sci.*, 2001, **80**, 1756.

Optical haze (%) is measured using a Gardner PG-5500 digital photometric unit. Optical clarity is calculated by subtracting optical haze from 100%.

Example 2: Surface modification of a "self-hydrating" bulk material

The formulation of Example 1 was covalently coated, both sides, with type 1 collagen according to the procedure disclosed in WO 00/29548. The collagen

coated materials were then exchanged from phosphate buffered saline (PBS) to MilliQ water, then 100% ethanol and finally acetonitrile. The acetonitrile was then replaced by dry acetonitrile. 250 µl of poly(ethylene glycol) di(succinimidyl propionate) solution (582 mg, Shearwater Polymers, dissolved in 1.2 ml of dry acetonitrile) were added to each of the acetonitrile equilibrated collagen coated self-hydrating polymer samples in separate vials. After 20 minutes of incubation, 3 samples (samples 1,2,3) were evaporated to dryness using a rotary evaporator. Another 3 samples (4,5,6) had the excess crosslinker solution removed with a pipette. Dry acetonitrile (2 ml) was added to these vials and they were gently shaken before removing excess acetonitrile solution with a pipette. The three samples (samples 4,5,6) were then evaporated to dryness using a rotary evaporator. All samples were stored under vacuum over P_2O_5 until used, in this case seven days later, although lenticules made in this manner could be stored much longer.

Example 3: Adhesive testing of a "self-hydrating" biomedical device

The dried surface-modified lenticules of Example 45 are hydrated by placing them in water. The use of hot water sped up the hydration process. The hydration process may be performed using PBS instead of water or aqueous mixtures. Once hydrated, the lenticules were surface dried using lint-free tissue paper and then placed on a freshly debrided bovine cornea. Excess fluid and bubbles were expelled from under the lenticule by gently wiping across the anterior surface of the lenticule. The lenticule was allowed to cure for 15 to 19 minutes before the adhesion was assessed using a vacuum tester (a detachment threshold > 5.5 means that the adhesion is greater than what was able to be tested using the vacuum tester):

Sample	hydration time (minutes)	cure time (minutes)	detachment threshold
1	2	16	> 5.5
2	2	15	> 5.5
3	2	15	> 5.5

4	2	15	> 5.5
5	2	17	3.5
6	2	19	> 5.5

Example 4: Adhesive modification prior to implantation

Poly(ethylene glycol) di(succinimidyl propionate) (50 mg, Shearwater Polymers) was dissolved in water for irrigation (125 µl, Baxter products) within 30 seconds by vigorous mixing. A hydrated but surface dried double sided collagen coated perfluoropolyether lenticule was cast in a contact lens mould. The concave cup of the lenticule was filled with poly(ethylene glycol) di(succinimidyl propionate) solution. After two minutes the solution was removed by pipettor and the excess poly(ethylene glycol) di(succinimidyl propionate) solution was removed by washing the modified lenticule for 4 minutes in water (for irrigation, 25 ml, Baxter products). The lenticules were then surface dried using lint free tissue paper. The modified lenticules were then placed on a freshly debrided feline cornea. Excess fluid and bubbles were expelled from under the lenticule by gently wiping across the face of the lenticule. The lenticules were allowed to cure for 10 minutes before antibacterial cream is applied to the eyes and the cat is allowed to gain consciousness. Six lenticules adhered to feline cornea for between 14 and 90 days. In one case, the epithelium completely covered the lenticule by day 12 post-implantation. The lenticule remained adhered to the cornea and fully epithelized beyond day 90. After adhesive failure the wound beds re-epithelized within a normal time period indicating the adhesive did not induce permanent damage to the cornea.

It will be understood that the invention disclosed and defined herein extends to all alternative combinations of two or more of the individual features mentioned or evidence from the text or drawings. All of these different combinations constitute various alternative aspects of the invention.

Claims:

1 A method for bonding an inorganic or organic bulk material to a nucleophilic or electrophilic surface including:

attaching a multifunctionally activated compound to the bulk material, the compound selected to be electrophilic or nucleophilic opposite to the surface;

contacting the bulk material with the surface under conditions permitting covalent linkage between the surface and the bulk material.

2 A method according to claim 1 in which the conditions include temperature between 0°C and 60°C and ambient pressure.

3 A method according to claim 1 or 2 in which the multifunctionally activated compound includes an activated ester or amide.

4 A method according to any one of the claims 1 to 3, wherein the multifunctionally activated compound is of formula

$$R_{13}\text{———}D\text{———}R_{12}$$

wherein

D is a bivalent organic radical, which is unsubstituted or substituted by one or more carboxy or carboxy derivative groups;

R_{12} is a carboxy derivative group; and

R_{13} is a further reactive group selected from the group consisting of a carboxy, carboxy derivative, isocyanato, isothiocyanato and epoxy group.

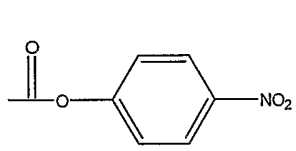
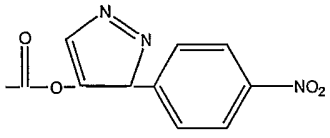
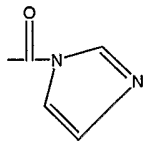
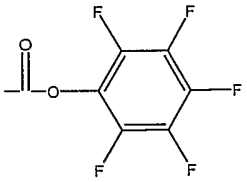
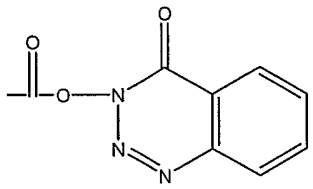
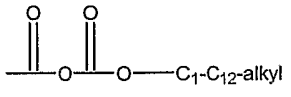
5 A method according to claim 4, wherein D is an optionally branched C_1-C_{12}-alkylene; a radical of a dendrimer or star-bust polymer; a radical of a

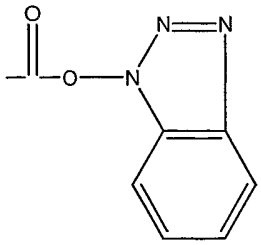
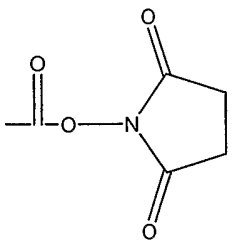
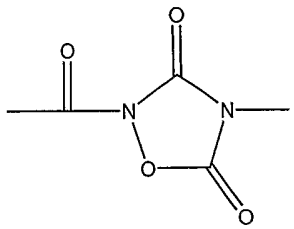
polyethylene glycol; a radical of a polyvinyl alcohol; or a radical of a hyperbranched polyester resin, preferably the radical of a polyethylene glycol.

6 A method according to claim 4 or 5, wherein R_{12} and R_{13} are each an activated ester group.

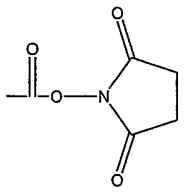
7 A method according to claim 1 or 2 wherein the multifunctionally activated compound is polyethylene glycol that is di-substituted with succinimidyl propionate, succinimidyl succinate or succinimidyl succinamide, and is first reacted with nucleophilic groups on the surface of the bulk material.

8 A method according to claim 1, 2, 4 or 5 in which the multifunctionally activated compound includes a carboxy derivative group selected from a group consisting of:

9 A method according to claim 8 in which the carboxy derivative group is



10 A method according to any one of claims 1 to 9 in which a natural or synthetic polymer comprising co-reactive groups is first bonded to the bulk material.

11 A method according to claim 10 in which the natural or synthetic polymer is selected from the group consisting of cell-adhesive glycoproteins like collagens (various types), fibronectin, vitronectin, laminin, poly(ethyl imine), amino dextran, PAMAM dendrimers, poly(allyl amine), poly(vinyl alcohol), poly(arylic acid) and poly(methacrylic acid).

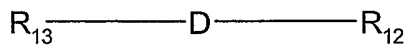
12 A method according to claim 10 in which the natural or synthetic polymer is collagen.

13 A bioadhesive attached to a bulk material for bonding the bulk material to a biological surface, the bioadhesive comprising a multifunctionally activated compound reactable with nucleophilic or electrophilic functional groups.

14 A bioadhesive according to claim 13 in which the multifunctionally activated compound is bound to a natural or synthetic polymer bound to the bulk material.

15 A bioadhesive comprising a multifunctionally activated compound for covalently linking an inorganic or organic bulk material to a nucleophilic or electrophilic surface by reaction of the multifunctionally activated compound with the bulk material and the surface.

16 A bioadhesive according to claim 15 in which the multifunctionally activated compound is of formula



(j)

wherein

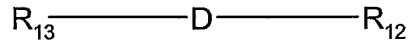
D is a bivalent organic radical, which is unsubstituted or substituted by one or more carboxy or carboxy derivative groups;

R_{12} is a carboxy derivative group; and

R_{13} is a further reactive group selected from the group consisting of a carboxy, carboxy derivative, isocyanato, isothiocyanato and epoxy group.

17 A biomedical device for attaching to a biological surface by a bioadhesive including a biocompatible organic or inorganic bulk material to which a multifunctionally activated compound has been bound.

18 A biomedical device according to claim 17 in which the multifunctionally activated compound is of formula



(j)

wherein

D is a bivalent organic radical, which is unsubstituted or substituted by one or more carboxy or carboxy derivative groups;

R_{12} is a carboxy derivative group; and

R_{13} is a further reactive group selected from the group consisting of a carboxy, carboxy derivative, isocyanato, isothiocyanato and epoxy group, one or more of the groups being hydralytically unstable.

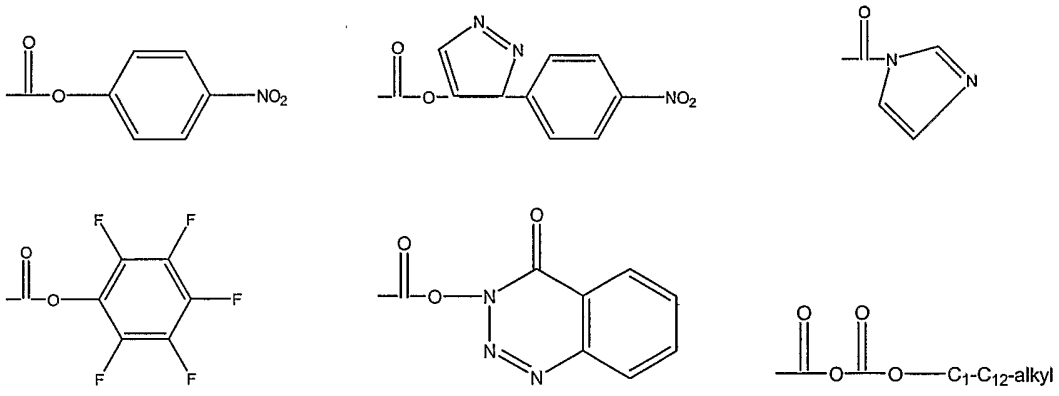
19 A biomedical device according to claim 17 or 18 further comprising a natural or synthetic polymer having co-reactive groups.

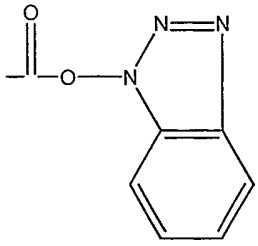
20 A biomedical device according to claim 18 or 19, wherein D is an optionally branched C_1-C_{12}-alkylene; a radical of a dendrimer or star bust polymer; a radical of a polyethylene glycol; a radical of a polyvinyl alcohol; or a radical of a hyperbranched polyester resin, preferably the radical of a polyethylene glycol.

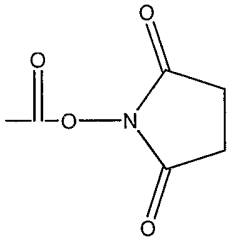
21 A biomedical device according to any one of claims 18 to 20, wherein R_{12} and R_{13} are each an activated ester group.

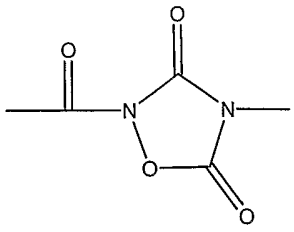
22 A biomedical device according to claim 17 or 19 wherein the multifunctionally activated compound is polyethylene glycol that is di-substituted with succinimidyl propionate, succinimidyl succinate or succinimidyl succinamide, and is first reacted with nucleophilic groups on the surface of the bulk material.

23 A biomedical device according to any one of claims 17, 19 or 20 in which the multifunctionally activated compound includes a carboxy derivative group selected from a group consisting of:

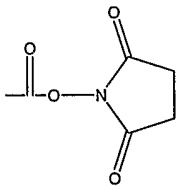








24 A biomedical device according to claim 23 in which the carboxy derivative group is



25 A biomedical device according to any one of claims 17 to 24 further comprising a natural or synthetic polymer.

26 A biomedical device according to any one of claims 17 to 25 stored anhydrously prior to use wherein one or more of the groups of the multifunctionally activated compound are unreacted.

27 A biomedical device according to any one of claims 17 to 26, the device being an opthalmic device, a contact lens, a corneal onlay, a corneal inlay, a lenticule or an intraocular lens.

28 A process for applying a bioadhesive to a surface of a biomedical device comprising a biocompatible organic or inorganic bulk material including the steps of

if the surface is not nucleophilic or electrophilic, applying nucleophilic or electrophilic functional groups to the surface, and

covalently bonding to the surface a multifunctionally activated compound, the compound selected to be electrophilic or nucleophilic opposite to the functional groups.

29 A process for applying a bioadhesive to a surface of a biomedical device comprising a biocompatible organic or inorganic bulk material including the steps of

if the surface is not nucleophilic or electrophilic, applying nucleophilic or electrophilic functional groups to the surface,

covalently bonding the functional groups to a natural or synthetic polymer comprising co-reactive groups,

covalently coupling to the natural or synthetic polymer a multifunctionally activated compound, the compound selected to be electrophilic or nucleophilic opposite to the co-reactive groups.

30 A process according to claim 28 or 29, wherein the multifunctional compound is of formula

$$R_{13}\text{——}D\text{——}R_{12} \qquad \text{(j)}$$

wherein

D is a bivalent organic radical, which is unsubstituted or substituted by one or more carboxy or carboxy derivative groups;

R_{12} is a carboxy derivative group; and

R_{13} is a further reactive group selected from the group consisting of a carboxy, carboxy derivative, isocyanato, isothiocyanato and epoxy group.

31 A process according to any one of claims 28 to 30, wherein the biocompatible organic or inorganic bulk material is a PFPE polymer.

32 The use of a biomedical device according to any one of claims 17 to 27 as an intraocular lens for the implantation into or onto the cornea.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU03/00612

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl. [7]: C09J 171/02; A61L 24/04

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)

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)
WPAT JAPIO USPTO (Keywords:- PEG, adhesive, succinimidyl, bifunctional, activated ester and similar terms)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5744545 A (Rhee et al.) 28 April 1998 Examples 9-11	1-32
X	US 6326025 B1 (Sigler et al.) 4 December 2001 Column 6 lines 27-56, Examples 1 & 2	1-5, 13-16, 28-30
X	US 5583114 A (Barrows et al.) 10 December 1996 Examples 1-10	1-5, 13-16, 28-30

[X] Further documents are listed in the continuation of Box C [X] 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 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 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	Date of mailing of the international search report
10 June 2003	19 JUN 2003
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized officer **N.L. KING** Telephone No : (02) 6283 2150

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU03/00612

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	AU 200038629 A (UAB Research Foundation) 21 September 2000 Pages 9, 10, 35	13-16
X	US 20010003126 A (Rhee et al.) 7 June 2001 Pages 10, 11; Claims 32, 44	1-9, 13-24, 28-32
A	AU 199894021 A (Becton, Dickinson and Company) 23 April 1999 Entire document	1-32

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/AU03/00612

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
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		WO	9005755				
US	6326025	WO	9933419	AU	19502/99	EP	1047363
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END OF ANNEX