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(54) Title: FUNCTIONALISED POLYMERIC MATERIALS

(57) **Abstract:** A method of functionalising a polymer of a type which includes, in the polymer backbone, phenyl moieties; carbonyl and/or sulphone moieties; and ether and/or thioether moieties; wherein the method includes treating the polymer to functionalise the carbonyl and/or sulphone moieties to provide functionalities which have a lower electron withdrawing effect of phenyl moieties in said polymer backbone than the carbonyl and/or sulphone moieties they replace; and treating the polymeric material prepared in order to functionalise said activated phenyl moieties. Preferred embodiments relate to the preparation of a bio-compatible polymeric material for use in medical applications by functionalising the polymer (e.g. of polyetheretherketone or polyetherketone) and treating it with bio-compatible moieties.



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Functionalised Polymeric Materials

This invention relates to functionalised polymeric materials. Particularly, although not exclusively, the invention relates to bio-compatible polymeric materials and provides such a material per se, a method of producing such a material and the use of the material in medical treatment, for example in a prosthesis.

10 Much research is being directed to the provision of materials to meet the growing need for prosthetic devices such as orthopaedic, dental or maxillofacial implants. For example, nearly half a million patients receive bone implants each year in the US with the majority being
15 artificial hip and knee joints made from titanium or colbalt-chrome alloys. However, these materials are too stiff leading to bone resorption, loosening of the implant and, consequently, have lifetimes of less than 10 years. Additionally, medical devices or prostheses such as
20 pacemakers, vascular grafts, stents, heart valves, catheters and dental implants that contact body tissues or fluids of living persons or animals have been developed and used clinically.

25 A major problem with medical devices such as those described is the susceptibility to foreign body reaction and possible rejection. Consequently, it is of great interest to the medical industry to develop materials from which medical devices can be made which are less prone to
30 adverse biological reactions that typically accompany introduction of medical devices into humans or animals.

It is known to functionalise polymers with bio-compatible moieties. However, known functionalised polymers tend to have a relatively low concentration of associated bio-compatible moieties.

5

It is an object of the present invention to address the abovedescribed problems.

According to a first aspect of the present invention,
10 there is provided a method of functionalising a polymer of
~~a type which includes, in the polymer backbone:~~

- (A) phenyl moieties;
- (B) carbonyl and/or sulphone moieties; and
- 15 (C) ether and/or thioether moieties;

the method including:

- (1) treating the polymer to functionalise said carbonyl
20 and/or sulphone moieties to provide functionalities
which have a lower electron withdrawing effect on
phenyl moieties (hereinafter referred to as
"activated phenyl moieties") in said polymer backbone
than the carbonyl and/or sulphone moieties they
25 replace; and
- (2) treating the polymeric material prepared in (1) in
order to functionalise said activated phenyl
moieties.

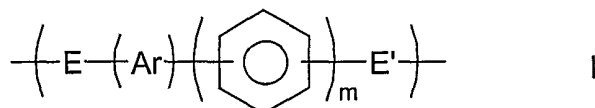
30 Except where otherwise stated, throughout this
specification, any alkyl, akenyl or alkynyl moiety
suitably has up to 8, preferably up to 6, more preferably
up to 4, especially up to 2, carbon atoms and may be of

straight chain or, where possible, of branched chain structure. Generally, methyl and ethyl are preferred alkyl groups and C₂ alkenyl and alkynyl groups are preferred.

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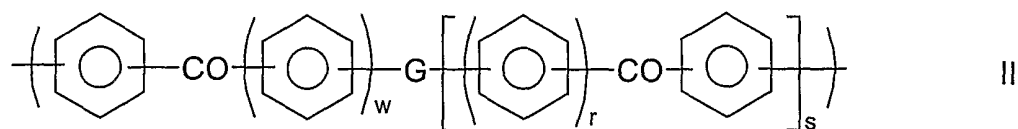
Except where otherwise stated in this specification, optional substituents of an alkyl group may include halogen atoms, for example fluorine, chlorine, bromine and iodine atoms, and nitro, cyano, alkoxy, hydroxy, amino, alkylamino, sulphinyl, alkylsulphinyl, sulphonyl, 10 alkylsulphonyl, amido, alkylamido, alkoxycarbonyl, haloalkoxycarbonyl and haloalkyl groups. Preferably, optionally substituted alkyl groups are unsubstituted.

15 Preferably, said polymer has a moiety of formula



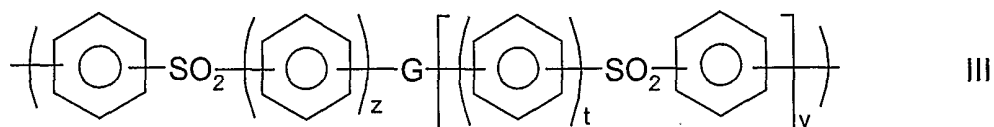
and/or a moiety of formula

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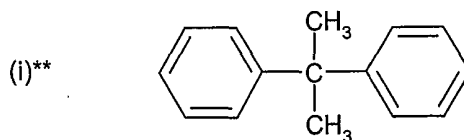


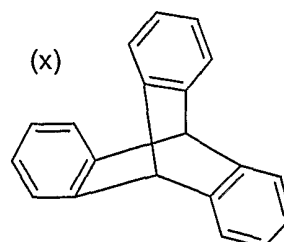
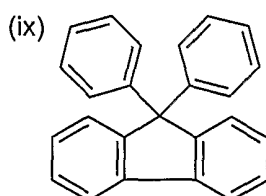
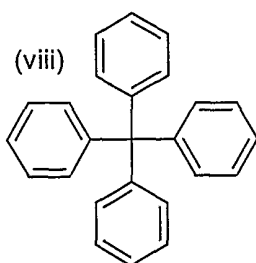
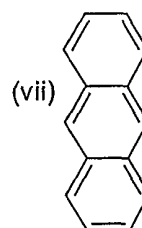
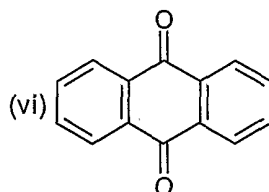
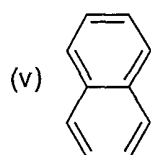
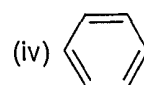
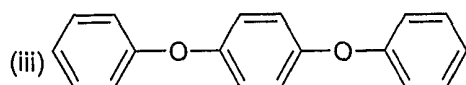
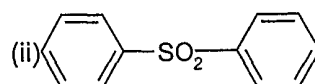
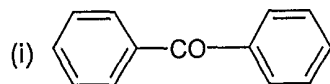
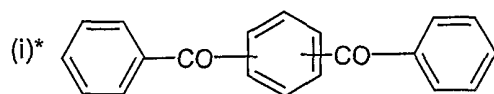
and/or a moiety of formula

25



wherein the phenyl moieties in units I, II, and III are independently optionally substituted and optionally cross-linked; and wherein m,r,s,t,v,w and z independently
 5 represent zero or a positive integer, E and E' independently represent an oxygen or a sulphur atom or a direct link, G represents an oxygen or sulphur atom, a direct link or a -O-Ph-O- moiety where Ph represents a phenyl group and Ar is selected from one of the following
 10 moieties (i)*, (i)**, (i) to (x) which is bonded via one or more of its phenyl moieties to adjacent moieties





Unless otherwise stated in this specification, a phenyl moiety may have 1,4- or 1,3-, especially 1,4-, linkages to
5 moieties to which it is bonded.

Said polymer may include more than one different type of repeat unit of formula I; more than one different type of repeat unit of formula II; and more than one different
10 type of repeat unit of formula III. Preferably, however,

only one type of repeat unit of formula I, II and/or III is provided.

Said moieties I, II and III are suitably repeat units.
5 In the polymer, units I, II and/or III are suitably bonded to one another - that is, with no other atoms or groups being bonded between units I, II, and III.

Where the phenyl moieties in units I, II or III are
10 optionally substituted, they may be optionally substituted by one or more halogen, especially fluorine and chlorine, atoms or alkyl, cycloalkyl or phenyl groups. Preferred alkyl groups are C₁₋₁₀, especially C₁₋₄, alkyl groups. Preferred cycloalkyl groups include cyclohexyl and
15 multicyclic groups, for example adamantyl.

Another group of optional substituents of the phenyl moieties in units I, II or III include alkyls, halogens, C_yF_{2y+1} where y is an integer greater than zero, O-R^q (where
20 R^q is selected from the group consisting of alkyls, perfluoralkyls and aryls), CF=CF₂, CN, NO₂ and OH. Trifluormethylated phenyl moieties may be preferred in some circumstances.

25 Preferably, said phenyl moieties are not optionally-substituted as described.

Where said polymer is cross-linked, it is suitably cross-linked so as to improve its properties. Any suitable
30 means may be used to effect cross-linking. For example, where E represents a sulphur atom, cross-linking between polymer chains may be effected via sulphur atoms on

respective chains. Preferably, said polymer is not optionally cross-linked as described.

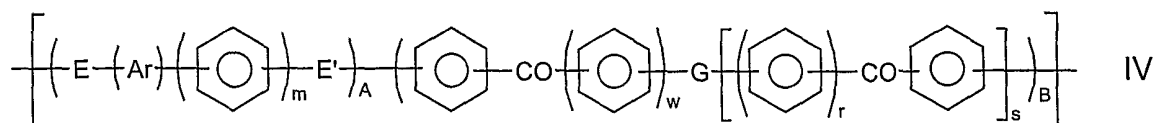
Where w and/or z is/are greater than zero, the
5 respective phenylene moieties may independently have 1,4- or 1,3-linkages to the other moieties in the repeat units of formulae II and/or III. Preferably, said phenylene moieties have 1,4- linkages.

10 Preferably, the polymeric chain of the polymer does not include a -S- moiety. Preferably, G represents a direct link.

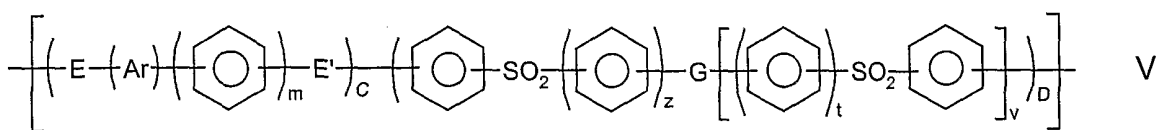
Suitably, "a" represents the mole % of units of formula
15 I in said polymer, suitably wherein each unit I is the same; "b" represents the mole % of units of formula II in said polymer, suitably wherein each unit II is the same; and "c" represents the mole % of units of formula III in said polymer, suitably wherein each unit III is the same.
20 Preferably, a is in the range 45-100, more preferably in the range 45-55, especially in the range 48-52. Preferably, the sum of b and c is in the range 0-55, more preferably in the range 45-55, especially in the range 48-52. Preferably, the ratio of a to the sum of b and c is in
25 the range 0.9 to 1.1 and, more preferably, is about 1. Suitably, the sum of a, b and c is at least 90, preferably at least 95, more preferably at least 99, especially about 100. Preferably, said polymer consists essentially of moieties I, II and/or III.

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Said polymer may be a homopolymer having a repeat unit of general formula



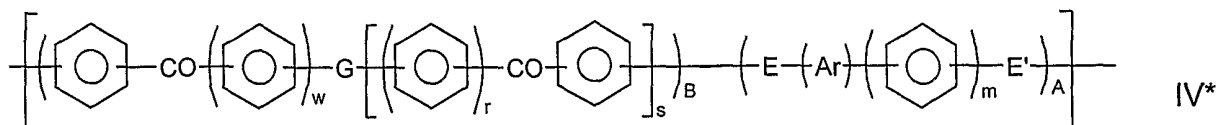
or a homopolymer having a repeat unit of general formula



5 or a random or block copolymer of at least two different units of IV and/or V

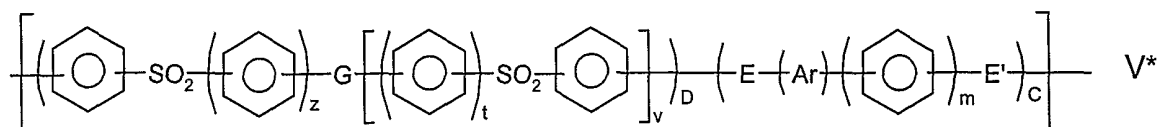
wherein A, B, C and D independently represent 0 or 1 and E, E', G, Ar, m, r, s, t, v, w and z are as described in any
10 statement herein.

As an alternative to a polymer comprising units IV and/or V discussed above, said polymer may be a homopolymer having a repeat unit of general formula



15

or a homopolymer having a repeat unit of general formula



or a random or block copolymer of at least two different units of IV* and/or V*, wherein A, B, C, and D independently represent 0 or 1 and E, E', G, Ar, m, r, s, t, v, w and z are as described in any statement herein.

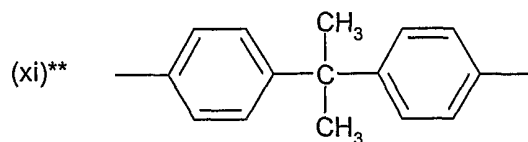
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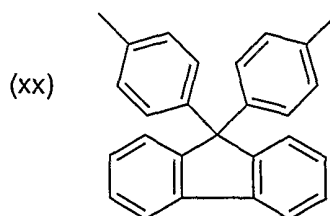
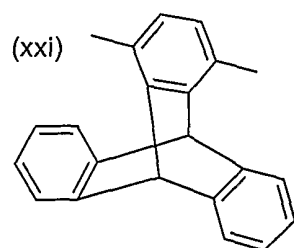
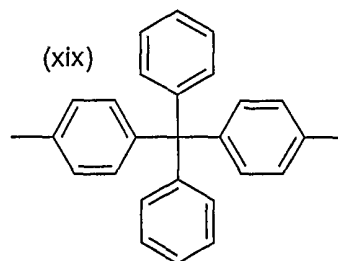
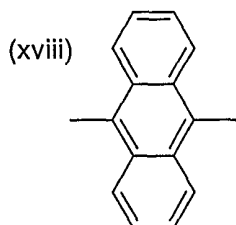
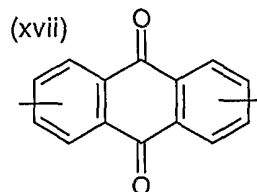
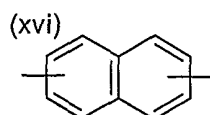
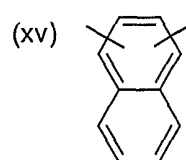
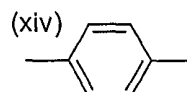
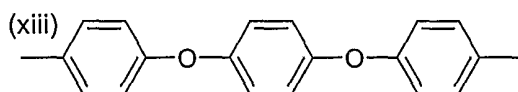
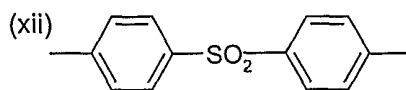
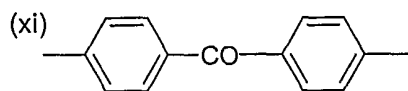
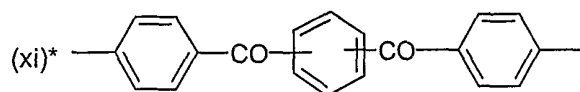
Preferably, m is in the range 0-3, more preferably 0-2, especially 0-1. Preferably, r is in the range 0-3, more preferably 0-2, especially 0-1. Preferably t is in the range 0-3, more preferably 0-2, especially 0-1.
 10 Preferably, s is 0 or 1. Preferably v is 0 or 1. Preferably, w is 0 or 1. Preferably z is 0 or 1.

Preferably, said polymer is a homopolymer having a repeat unit of general formula IV.

15

Preferably Ar is selected from the following moieties (xi)*, (xi)**, (xi) to (xxi):





In (xi)*, the middle phenyl may be 1,4- or 1,3-substituted.

Preferably, (xv) is selected from a 1,2-, 1,3-, or a 1,5- moiety; (xvi) is selected from a 1,6-, 2,3-, 2,6- or a 2,7- moiety; and (xvii) is selected from a 1,2-, 1,4-, 1,5-, 1,8- or a 2,6- moiety.

5

One preferred class of polymers does not include any moieties of formula III, but suitably only includes moieties of formulae I and/or II. Where said polymer is a homopolymer or random or block copolymer as described, said homopolymer or copolymer suitably includes a repeat unit of general formula IV. Such a polymer may, in some embodiments, not include any repeat unit of general formula V.

15 Suitable moieties Ar are moieties (i)*, (i), (ii), (iii) and (iv) and, of these, moieties (i)*, (i) and (iv) are preferred. Other preferred moieties Ar are moieties (xi)*, (xii), (xi), (xiii) and (xiv) and, of these, moieties (xi)*, (xi) and (xiv) are especially preferred.

20

An especially preferred class of polymers are polymers (or copolymers) which consist essentially of phenyl moieties in conjunction with ketone and/or ether moieties. That is, in the preferred class, the polymer does not include repeat units which include -S-, -SO₂- or aromatic groups other than phenyl. Preferred polymers of the type described include:

(a) a polymer consisting essentially of units of formula IV wherein Ar represents moiety (iv), E and E' represent oxygen atoms, m represents 0, w represents 1, G represents a direct link, s

30

represents 0, and A and B represent 1 (i.e. polyetheretherketone).

5 (b) a polymer consisting essentially of units of formula IV wherein E represents an oxygen atom, E' represents a direct link, Ar represents a moiety of structure (i), m represents 0, A represents 1, B represents 0 (i.e. polyetherketone);

10 (c) a polymer consisting essentially of units of formula IV wherein E represents an oxygen atom, Ar represents moiety (i)*, m represents 0, E' represents a direct link, A represents 1, B represents 0, (i.e. polyetherketoneketone).

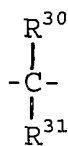
15 (d) a polymer consisting essentially of units of formula IV wherein Ar represents moiety (i), E and E' represent oxygen atoms, G represents a direct link, m represents 0, w represents 1, r represents 0, s represents 1 and A and B represent 1. (i.e. polyetherketoneetherketoneketone).

20

(e) a polymer consisting essentially of units of formula IV, wherein Ar represents moiety (iv), E and E' represents oxygen atoms, G represents a direct link, m represents 0, w represents 0, s, r, A and B represent 1 (i.e. polyetheretherketoneketone).

25

30 In stage (1), ketone moieties may be functionalised to provide a moiety



5 or a moiety



10 wherein the groups $-CR^{30}R^{31}-$ and $-CR^{32}-$ have a lower electron withdrawing effect on groups adjacent the carbon atom thereof compared to the ketone groups they replace.

15 R^{30} and R^{31} may represent any groups which enable $-CR^{30}R^{31}-$ to have the lower electron withdrawing effect described.

The atom in R^{30} which links it to the moiety $-C-$ may be a hydrogen (where R^{30} represents a hydrogen atom), carbon or oxygen atom. A said carbon atom may be bonded to or a component of an optionally-substituted, saturated, unsaturated, linear, branched, acyclic and/or cyclic moiety. Examples of acyclic moieties include alkyl, alkenyl and alkynyl moieties. Examples of cyclic moieties include cycloalkyl, cycloalkenyl, cycloalkynyl, heterocycloalkyl, heterocycloalkenyl, aryl and heteroaryl moieties. An oxygen atom may be part of a hydroxy group or may be bonded to or a component of an optionally-substituted saturated, unsaturated, linear, branched, acyclic and/or cyclic moiety. Examples of acyclic and cyclic moieties may be as described above for said carbon atom.

The atom in R^{31} which links it to the moiety -C- may be as described above for R^{30} .

5 The atom in group R^{32} which links R^{32} to the moiety -C- is preferably a nitrogen atom so that R^{32} defines an imine with the moiety -C-. Said nitrogen atom may be bonded to an optionally-substituted, saturated, unsaturated, linear, branched, acyclic and/or cyclic moiety. Examples of such moieties are as described above for R^{30} and/or R^{31} .

10

In the method, the polymer may be subjected to one or a series of treatments prior to functionalisation of activated phenyl moieties in stage (2). For example, in stage (1), the polymer may be functionalised to provide
15 functionalities which have a lower electron withdrawing effect and such functionalities may be further functionalised, prior to stage (2), to provide moieties which may participate in treatments or reactions which may be undertaken after functionalisation of said active
20 phenyl moieties. Alternatively, the polymer may be treated to provide said activated phenyl moieties; said activated phenyl moieties may be functionalised; and, optionally, there may then be further functionalisation of the functionalities which have a lower electron withdrawing
25 effect and/or functionalised activated phenyl moieties.

Where ketone moieties are functionalised to provide a moiety $-CR^{30}R^{31}-$ as described, said polymer which includes moieties described in (A), (B) and (C) may be subjected to
30 a first treatment which is a reduction reaction for reducing carbonyl moieties. Any suitable type of reducing agent may be used as described in the examples hereinafter. Preferred reducing agents supply hydride ions

or otherwise supply a nucleophile which can react with the carbonyl group. Examples include the use of lithium aluminium hydride or sodium borohydride and organometallic compounds, for example 4-lithiobenzonitrile, arranged to
5 supply organic nucleophiles.

A said first treatment may result in the functionalisation of carbonyl moieties to form a moiety $-CR^{30}R^{31}-$ wherein R^{30} represents a hydrogen atom or a
10 nucleophilic residue of the reducing agent used, for example a nucleophilic residue of an organometallic compound such as a benzonitrile moiety.

Where ketone moieties are functionalised to provide a
15 moiety $-CR^{32}-$ as described, said polymer which includes moieties described in (A), (B), and (C) may be subjected to an addition-elimination reaction, suitably by treatment with ammonia or, especially, a primary amine.

20 A first treatment of a polymer which includes phenyl moieties, sulphone moieties and ether or thioether moieties may be the reduction of the sulphone moieties, suitably to sulphide moieties.

25 After said first treatments described (suitably without any further functionalisation of the moieties which have replaced the carbonyl or sulphone moieties), said polymer may be treated to functionalise phenyl moieties thereof as described in stage (2). Treatment is
30 preferably undertaken using reagents and/or conditions which could not be used to functionalise said phenyl moieties if the carbonyl and/or sulphone moieties had not been previously treated as described in stage (1).

Preferably stage (2) involves an electrophilic aromatic substitution reaction of said activated phenyl moieties. Any type of electrophilic aromatic substitution
5 reaction may be used, including Friedel-Crafts, alkylation, acylation, nitration, sulphonation, halogenation, chloromethylation, phosphorylation and lithiation reactions.

10 After stage (2) as described, the functionalised polymer may be further functionalised as may be desired. In this regard, functional groups on said activated phenyl moieties or functional groups which have replaced carbonyl or sulphone moieties may be functionalised. In some
15 cases, it may be possible to assemble a polymer wherein functional groups, for example phenyl groups, which are pendent from said activated phenyl moieties and functional groups which have replaced carbonyl or sulphone moieties may be functionalised at the same time and/or under the
20 same reaction conditions.

Preferably, the method involves functionalising the polymer at or adjacent a surface thereof, such that the bulk of the polymer is not substantially functionalised.
25 Thus, the method preferably involves functionalising phenyl moieties of said polymer such that the concentration of non-functionalised phenyl moieties (i.e. phenyl moieties not functionalised in the method) present within the bulk of the functionalised polymer is greater
30 than the concentration of non-functionalised phenyl moieties present at or adjacent the surface. Put another way, the concentration of carbonyl or sulphone moieties (whichever is/are in the polymer) in the bulk of the

functionalised polymer is preferably greater than at the surface of the polymer.

Preferably, said polymer functionalised in the method
5 is presented as a solid, suitably shaped so as to represent at least part of a device for use in medical applications, and then functionalised in the method. For example, said device may be a component of an implant for a human or animal body, for example an orthopaedic or
10 dental implant or vascular graft. Said solid may be provided in a desired shape by any suitable means, for example by injection or compression moulding or by film formation techniques or extrusion. Thus, preferably, stages (1) and (2) of said method according to said first
15 aspect are undertaken on said polymer in solid form, suitably so as to preferentially functionalise a surface region of said solid.

The method preferably includes the step of treating
20 said polymer after functionalisation of said activated phenyl moieties with a material for providing bio-compatible moieties (hereinafter "BCM material"). Said BCM material may be arranged to provide any of the bio-compatible moieties described hereinafter. Said polymer
25 may be provided as a solid. Suitably, said bio-compatible moieties are caused to become associated with a surface of said solid, preferably with functional groups pendent from said activated phenyl moieties at a surface of said solid. They could, additionally, be caused to become associated
30 with functional groups that have replaced carbonyl or sulphone moieties. Said solid is preferably shaped so as to represent at least a part of a device for use in medical applications, as described above. Preferably,

after association with said bio-compatible moieties, the bio-compatible material formed (referred to as "bio-compatible polymeric material") is not engineered or otherwise treated in a manner which may result in
5 substantial depletion of the bio-compatible moieties associated with its surface.

In the scientific literature there is inconsistency in the use of descriptions such as "bio-compatible", "bio-
10 active" and "bio-materials". In the context of the present specification, the term "bio-compatible" has generally been used to refer to a material which is compatible with use in medical applications, for example by not being toxic or otherwise harmful to living
15 materials. It also encompasses materials which have a biological or physiological effect when associated with living materials.

Preferably, said bio-compatible polymeric material has
20 improved or enhanced bio-compatibility compared to said polymer prior to functionalisation in the method.

Bio-compatible moieties suitably include moieties arranged to reduce adverse biological reactions when the
25 bio-compatible polymeric material is introduced into (or otherwise associated with) a human or animal body. For example, adverse biological reactions associated with introduction into a human or animal body of said polymer having said bio-compatible moieties may be less compared
30 to use of the same polymer but which does not include associated bio-compatible moieties.

"Bio-compatible moieties" referred to herein suitably refer to moieties which are compatible with use in medical applications, for example by not being toxic or otherwise harmful to living material. Such bio-compatible moieties
5 may be arranged to bond (for example to form ionic or covalent bonds) or otherwise interact with materials present in human or animal bodies in order to improve their integration and acceptance by such bodies.

10 A said bio-compatible moiety may be selected from an anticoagulant agent such as heparin and heparin sulfate, an antithrombotic agent, a clotting agent, a platelet agent, an anti-inflammatory agent, an antibody, an antigen, an immunoglobulin, a defence agent, an enzyme, a
15 hormone, a growth factor, a neurotransmitter, a cytokine, a blood agent, a regulatory agent, a transport agent, a fibrous agent, a protein such as avidin, a glycoprotein, a globular protein, a structural protein, a membrane protein and a cell attachment protein, a peptide such as a
20 glycopeptide, a structural peptide, a membrane peptide and a cell attachment peptide, a proteoglycan, a toxin, an antibiotic agent, an antibacterial agent, an antimicrobial agent such as penicillin, ticarcillin, carbenicillin, ampicillin, oxacillin, cefazolin, bacitracin,
25 cephalosporin, cephalothin, cefuroxime, cefoxitin, norfloxacin, perfloxacin and sulfadiazine, hyaluronic acid, a polysaccharide, a carbohydrate, a fatty acid, a catalyst, a drug, biotin, a vitamin, a DNA segment, a RNA segment, a nucleic acid, a nucleotide, a polynucleotide, a
30 nucleoside, a lectin, a ligand and a dye (which acts as a biological ligand), a radioisotope, a chelated radioisotope, a chelated metal, a metal salt, a sulphonic acid or salt thereof, a steroid, a non-steroid, a non-

steroidal anti-inflammatory, an analgesic, an anti-histamine, a receptor binding agent, a chemotherapeutic agent, a hydrophilic polymer (e.g. poly(ethylene glycol) (PEG), poly(ethylene oxide) (PEO), ethylene oxide-
5 propylene oxide block co-polymers, poly(N-vinyl-2-pyrrolidone) (PNVP), poly(2-hydroxyethyl methacrylate) (pHEMA), HEMA co-polymers, poly(vinyl alcohol) (PVA), polyacrylamide, its derivatives, poly(methyl methacrylate) (PMMA), suitably having a PEG chain on each of the side
10 groups, polysiloxanes (e.g. polydimethylsiloxanes (PDMS)), ionic water-soluble polymers like poly(acrylic acid) (PAAc)) and a polyurethane. Examples of some of the aforesaid are provided in US5958430, US5925552, US5278063 and US5330911 and the contents of the aforementioned
15 specifications are incorporated herein by reference.

In one embodiment, said bio-compatible moieties may comprise bone morphogenic protein (BMP) as described in US4563489 and patents cited therein and the contents of
20 the aforesaid are incorporated herein. Said BMP may be provided in combination, for example in admixture, with a physiologically acceptable biodegradable organic polymer and said biodegradable polymer may be associated with said at least two moieties of said polymer of said bio-
25 compatible polymeric material, for example by being covalently bonded to said at least two moieties. Thus, in this case, the combination of said biodegradable polymer and BMP defines said bio-compatible moieties. Said biodegradable polymer is preferably a biodegradable
30 polylactic acid; or alternatively, other physiologically acceptable biodegradable organic polymers which are structurally equivalent to polylactic acid can be used as the delivery system for BMP. Examples include

poly(hydroxy organic carboxylic acids) e.g. poly(hydroxy aliphatic carboxylic acids), polyglycollic acid, polyglactin, polyglactic acid and poly adonic acids.

5 In another embodiment, said bio-compatible moieties may be selected from inorganic crystalline structures, inorganic amorphous structures, organic crystalline structures and organic amorphous structures. Preferred
10 bio-compatible moieties are phosphorous based ceramics, for example calcium-phosphorous ceramics. Phosphates in general are suitable but calcium phosphates and calcium apatite are preferred. Especially preferred is hydroxyapatite, a synthetic Ca-P ceramic.

15 Whilst said bio-compatible moieties may be associated by any suitable means with the functionalised polymer, for example by covalent bond(s), hydrogen bond(s), encapsulation in a matrix which is bonded to or otherwise interacts with said functionalised groups, or by ionic
20 interaction(s), it is preferred that there are covalent bonds between the bio-compatible moieties and said polymer or there are ionic interactions between said bio-compatible moieties and said polymer.

25 Thus, the invention extends to a method of making a bio-compatible polymeric material for use in medical applications, the method including associating bio-compatible moieties with a functionalised polymer of a type or when prepared as described according to said first
30 aspect.

Said functionalised polymer preferably includes functional groups arranged to become associated with

suitable functional groups provided by BCM material. Said polymer may include functional groups selected from the following: -OH, -CHO, -NR¹⁰₂, preferably -NH₂ or -NHR¹⁰, -SH, -CONH₂, -CONHR¹⁰, -COOH, -COCl or
5 -COOR¹⁰ group, a halogen atom, especially a fluorine, chlorine, bromine or iodine atom, -NO₂, -SO₃M, -SO₂R¹¹, -SO₂NHR¹⁰, -SO₂NR¹⁰₂ or -COOM groups, an anhydride, an epoxide, a cyanate, -CN, an isocyanate, a carbon-carbon double bond, for example a group -CR¹⁰=CR¹⁰₂ or a (C₀-C₁₀alk)
10 acrylate (wherein "alk" refers to an alkyl group) such as =COOC(CH₃)CH₂ and -COOCHCH₂, a carbon-carbon triple bond, for example a group -CR¹⁰ or an azide, wherein R¹⁰ represents a hydrogen atom or an optionally substituted alkyl group, wherein M represents a hydrogen atom or an
15 alkali metal and R¹¹ represents a halogen, especially a chlorine, atom.

Preferably, said functional groups are components of moieties pendent from activated phenyl moieties of said
20 polymer. Said functional groups could be components of groups that have replaced carbonyl or sulphone moieties of said polymer.

BCM material may include any suitable functional group
25 that is arranged to become associated with functional groups of said functionalised polymer and may be selected from any of the functional groups referred to above for said functionalised polymer provided that a selected functional group on said functionalised polymer is capable
30 of becoming associated with, suitably reacting with, a selected functional group provided by BCM material.

In some cases a bio-compatible moiety may be provided by reaction of said functionalised polymer with more than one functional group. For example a bio-compatible moiety may be a polyurethane which may be prepared: when said
5 functionalised polymer provides a hydroxy group and said BCM material provides a diisocyanate and a diol; or wherein said functionalised polymer provides an isocyanate group and said BCM material provides a diisocyanate and a diol. Thus, in both cases, said BCM material may provide
10 two different compounds.

In some cases, BCM material may be provided by a monomer or monomers having a functional group arranged to react with said functionalised polymer and being arranged
15 to polymerise to provide a polymeric bio-compatible moiety.

In one embodiment, said functionalised polymer may include ionic functional groups, for example -COOM or -
20 SO₃M, and such groups may be arranged to ionically associate with an ionic moiety provided by BCM material.

In other embodiments, an amide bond may be formed between said functionalised polymer and BCM material.
25

In some cases, said functionalised polymer may be multi-functional, thereby enabling it to associate with a plurality of bio-compatible moieties. For example, multi-functionality may be provided by dendritic or
30 hyperbranched end groups.

The invention extends to a functionalised polymeric material, preferably a bio-compatible polymeric material,

wherein the bulk of said material comprises a polymer of a type which includes, in the polymer backbone, the following:

- 5 (A) phenyl moieties;
(B) carbonyl and/or sulphone moieties; and
(C) ether and/or thioether moieties;

wherein a surface of said material comprises a
10 functionalised derivative of said polymer present in the bulk which derivative has a lower concentration of carbonyl and/or sulphone moieties compared to the concentration of carbonyl and/or sulphone moieties in the bulk.

15

Preferably, a surface of said material comprises a greater concentration of functionalised phenyl moieties compared to the concentration of functionalised phenyl moieties in the bulk. The surface may include a greater
20 concentration of functionalised carbonyl and/or sulphone moieties compared to the concentration of functionalised carbonyl and/or sulphone moieties in the bulk.

Since said functionalised polymeric material is
25 suitably only functionalised at or adjacent its surface and functionalised polymer represents only a small fraction of the total weight of the polymer, the existence of functionalised polymer may have a limited effect on the bulk properties of the polymeric material.

30

The glass transition temperature (T_g) of said polymer, suitably the bulk thereof, (in the absence of associated bio-compatible moieties) may be at least 135°C, suitably at

least 150°C, preferably at least 154°C, more preferably at least 160°C, especially at least 164°C. In some cases, the Tg may be at least 170°C, or at least 190°C or greater than 250°C or even 300°C.

5

Said polymer, suitably the bulk thereof, (in the absence of associated bio-compatible moieties) may have an inherent viscosity (IV) of at least 0.1, suitably at least 0.3, preferably at least 0.4, more preferably at least 0.6, especially at least 0.7 (which corresponds to a reduced viscosity (RV) of least 0.8) wherein RV is measured at 25°C on a solution of the polymer in concentrated sulphuric acid of density 1.84gcm⁻³, said solution containing 1g of polymer per 100cm³ of solution. IV is measured at 25°C on a solution of polymer in concentrated sulphuric acid of density 1.84gcm³, said solution containing 0.1g of polymer per 100cm³ of solution.

The measurements of both RV and IV both suitably employ a viscometer having a solvent flow time of approximately 2 minutes.

The main peak of the melting endotherm (Tm) for said polymer, suitably the bulk thereof, (if crystalline) may be at least 300°C.

Preferably, said polymer, suitably the bulk thereof, (in the absence of associated bio-compatible moieties) has at least some crystallinity or is crystallisable. The existence and/or extent of crystallinity in a polymer is preferably measured by wide angle X-ray diffraction, for example as described by Blundell and Osborn (Polymer 24,

953, 1983). Alternatively, crystallinity may be assessed by Differential Scanning Calorimetry (DSC).

Said polymer suitably the bulk thereof, (in the
5 absence of associated bio-compatible moieties) may have a number average molecular weight in the range 2000-80000. Preferably said molecular weight is at least 14,000. The molecular weight may be less than 60,000.

10 Said bio-compatible polymeric material suitably has a tensile strength (according to ISO R527) of at least 80, preferably at least 90, especially at least 95 MPa. The tensile strength may be less than 360, suitably less than 250, preferably less than 140 MPa. It preferably has an
15 elongate at break (according to ISO R527) of at least 40, preferably at least 50%. It preferably has a tensile modulus (according to ISO R527) of greater than 2.5, preferably greater than 3, especially greater than 3.5 GPa. The tensile modulus may be less than 40, suitably
20 less than 30, preferably less than 20, more preferably less than 10 GPa. It preferably has a flexural strength (according to ASTM D695) of at least 100, more preferably at least 110, especially at least 115 MPa. The flexural strength may be less than 650, preferably less than 400,
25 more preferably less than 260, especially less than 200 MPa. It preferably has a flexural modulus (according to ISO R178) of at least 3, preferably at least 3.5, especially at least 4 GPa. The flexural modulus may be less than 60, suitably less than 25, preferably less than
30 20, especially less than 10 GPa. Advantageously, the aforementioned properties can be adjusted by appropriate selection of polymers and/or any reinforcement means included in said support material to suit particular

applications. For example, a continuous carbon fibre polyetheretherketone may typically have a tensile strength of about 350 MPa, a tensile modulus of 36 GPa, an elongation of 2%, a flexural modulus of 50 GPa and a flexural strength of 620 MPa. A polyaryetherketone with 30% of high performance fibres may typically have a tensile strength of 224 MPa, a tensile modulus of 13 GPa, a tensile elongation of 2%, a flexural modulus of 20 GPa and a flexural strength of 250 MPa.

10

Said bio-compatible polymeric material may include one or more fillers for providing desired properties. Said material preferably incorporates an X-ray contrast medium. Fillers and/or said X-ray contrast medium is/are preferably distributed substantially uniformly throughout said material.

Where an X-ray contrast medium is provided it suitably comprises less than 25wt%, preferably less than 20wt%, more preferably less than 15wt%, especially less than 10wt% of said bio-compatible material. Where it is provided, at least 2wt% may be included. Preferred X-ray contrast mediums are particulate and preferably are inorganic. They preferably have low solubility in body fluids. They preferably also have a sufficient density compared to that of the polymer to create an image if a compounded mixture of the polymer and contrast medium are X-ray imaged. Barium sulphate and zirconium oxide are examples. Said particulate material is suitably physically held in position by entrapment within the polymer.

Preferably, said functionalised and/or bio-compatible polymeric material includes a major amount of said

polymer, especially one having moieties I, II and/or III, described according to said first aspect.

In the context of this specification, a "major" amount
5 may mean greater than 50 wt%, suitably greater than 65 wt%, preferably greater than 80 wt%, more preferably greater than 95 wt%, especially greater than 98 wt% of the referenced material is present relative to the total weight of relevant material present.

10

The invention further extends to a bio-compatible polymeric material comprising a polymer having bio-compatible moieties associated with its surface and a lower concentration of bio-compatible moieties associated
15 with its bulk, wherein the bulk comprises a polymer of a type which includes, in the polymer backbone, the following:

- (A) phenyl moieties;
- 20 (B) carbonyl and/or sulphone moieties; and
- (C) ether and/or thioether moieties.

Preferably, said bio-compatible moieties are associated with moieties which are pendent from phenyl
25 moieties of the polymer at or adjacent the surface thereof. Bio-compatible moieties may, optionally, be associated with moieties pendent from -C- moieties which are components of the polymer backbone, suitably at or near the surface of the polymer.

30

Polymers as described herein may be prepared as described in PCT/GB99/02833.

According to a third aspect of the present invention, there is provided a device for use in medical applications, wherein said device comprises a bio-compatible polymeric material according to said first
5 aspect or made in a method according to said second aspect or as described in any invention described herein.

Said device is preferably a prosthetic device, for example an implant such as an orthopaedic, dental or
10 maxillofacial implant or a component thereof; or a device, for example a catheter, which is arranged to be temporarily associated with a human or animal body. Said device is preferably a prosthetic device as described. An orthopaedic device may be an implant for a body joint, for
15 example a knee or hip joint or spine fusion device.

A said device may include a part or parts made out of said bio-compatible polymeric material and a part or parts made out of other materials. Suitably, however, said
20 device includes at least 50wt%, preferably at least 65wt%, more preferably at least 80wt%, especially at least 95wt% of said bio-compatible polymeric material. In some embodiments said device may consist essentially of said bio-compatible polymeric material.

25

According to a fourth aspect, there is provided a method of making a device according to the third aspect, the method comprising: forming a material into a shape which represents or is a precursor of a device or a part
30 of a device for use in medical applications wherein said material comprises a polymer which includes moieties (A), (B) and (C) of the first aspect; functionalising said polymer in said shape (preferably the surface thereof) as

described according to said first aspect; and causing bio-compatible moieties to associate with said functionalised polymer.

5 The invention extends to the use of a functionalised polymer as described herein in the manufacture of a device for use in a medical treatment, for example in surgery.

10 Any feature of any aspect of any invention or embodiment described herein may be combined with any feature of any aspect of any other invention or embodiment described herein.

15 Specific embodiments of the invention will now be described, by way of example.

 All chemicals referred to were used as received from Sigma-Aldrich Chemical Company, Dorset, U.K., unless otherwise stated.

20

 The following materials are referred to hereinafter:

25 PEEK (Trade Mark)-polyetheretherketone obtained from Victrex Plc of England and/or prepared as described herein;

 PEK (Trade Mark)-polyetherketone obtained from Victrex Plc or prepared as described herein;

 PEES - polyetherethersulphone

30 In the following examples, polyaryletherketone films of approximately 120 μ m thick were used. The film samples were prepared from samples of Victrex PEEKTM (Melt Viscosity 0.45kNsm⁻², at 1000sec⁻¹ at 400°C) and of Victrex

PEK™ (Melt Viscosity 0.22kNsm^{-2} , at 1000sec^{-1} at 400°C) powder which was compression moulded between metal plates using a Moore laboratory hot press at 400°C for between 5 and 10 minutes. The PEEK™ and PEK™ melt was quenched in
5 ice-cold water in order to obtain $120\mu\text{m}$ thick amorphous samples. The film samples were refluxed in acetone for 72h prior to use.

Example 1 Reduction of PEEK™ film.

10

Dimethylsulfoxide (300ml) and sodium borohydride (2.4g, 63.5mmol) were introduced to a 500ml reaction flask and the solution stirred at 120°C . A PEEK™ film sample (2 x 10cm) was totally immersed in the reaction solution and
15 stirred at 120°C for 6h. The film was then removed and washed successively with methanol, water and ethanol. The sample was then dried at room temperature overnight; XPS analysis C_{1s} (85.11%): 284.7eV (C-C, C-H), 286.1eV (C-O), 286.9eV (C=O), 291.6eV (π); O_{1s} (14.89%): 531.4eV (O=C),
20 532.2eV (O-H), 533.3eV (O-C), 539.6eV ($\pi-\pi^*$).

Example 2 Reduction of PEK™ film

Dimethylsulfoxide (300ml) and sodium borohydride
25 (2.4g, 63.5mmol) were introduced to a 500ml reaction flask and the solution stirred at 120°C . A PEK™ film sample (2 x 10cm) was totally immersed in the reaction solution and stirred at 120°C for 6h. The film was then removed and washed successively with methanol, water and ethanol. The
30 sample was then dried at room temperature overnight.

Example 3 Friedel Crafts propylation of modified PEEK™ film

A solution of 1,3-propane sultone (7.32g, 60mmol) and
5 aluminium chloride (0.15g, 1.1mmol) was prepared in a
boiling tube, under a nitrogen atmosphere. A sample of
PEEK™ film from example 1 was then immersed in the
solution and the solution heated to 40°C for 24h. The
film was then removed and washed with methanol and
10 distilled water followed by acetone.

Example 4 Reaction of Modified PEEK™ film with diaminopentane

15 A solution of 1,5-diaminopentane (2.66g, 26mmol) in
acetic acid (50ml) was introduced into a 100ml round
bottomed flask. A sample of modified PEEK™ film from
example 3 was immersed in the reactive solution and
stirred, at room temperature, for 3 days. The film sample
20 was then removed and rinsed with acetic acid before being
dried under vacuum for 6 hours.

Example 5 Reaction of Modified PEEK™ film containing amino and sulphonic acid groups with GRGDS.

25

The surface modified PEEK™ from Example 4 was stirred
at 10°C for 1 hr under an atmosphere of nitrogen in an
aqueous solution of the water soluble carbodiimide, 1-
ethyl-3-(3-dimethylaminopropyl)-carbodiimide) (0.4g)
30 dissolved in buffer at pH 4.5 (0.1M 2-(N-
morpholino)ethanesulphonic acid) (40ml). The sample of
PEEK™ was removed and washed with buffer solution.

The sample was stirred at 20°C for 24 hr under an atmosphere of nitrogen in a solution of the peptide GRGDS (160mg) in phosphate-buffered saline solution (40ml) (Na₂HPO₄ 1.15g; KH₂PO₄, 0.2g; NaCl, 8g; KCl, 0.2g; MgCl₂, 0.1g; CaCl₂, 0.1g in 1 litre of distilled water). The functionalised PEEKTM was washed successively with phosphate buffer and distilled water.

10 Example 6 Friedel Crafts propylation of modified PEKTM film

A solution of 1,3-propane sultone (7.32g, 60mmol) and aluminium chloride (0.15g, 1.1mmol) was prepared in a boiling tube, under a nitrogen atmosphere. A sample of 15 PEKTM film from example 2 was then immersed in the solution and the solution heated to 40°C for 24h. The film was then removed and washed with methanol and distilled water followed by acetone.

20 Example 7 Reaction of modified PEKTM film with p-aminobenzoic acid

A solution of 4-aminobenzoic acid (3.6g, 26mmol) in acetic acid (50ml) was introduced into a 100ml round 25 bottomed flask. A sample of modified PEKTM film from example 6 was immersed in the reactive solution and stirred, at room temperature, for 3 days. The film sample was then removed and rinsed with acetic acid and acetone before being dried under vacuum for 6 hours.

30

Example 8 N-protection of p-aminobenzoic acid

A mixture of dioxane (20ml), water (10ml) and 1M sodium hydroxide (10ml) and p-aminobenzoic acid (5.75g) was stirred and cooled in an ice water bath. Di-t-butyl pyrocarbonate (9.6g, 44mmol) was added and stirring
5 continued for 30 minutes at room temperature. The reactive solution was concentrated *in vacuo* to about 10-15ml, cooled in an ice water bath, covered with a layer of ethyl acetate (30ml) and acidified with dilute aqueous potassium hydrogen sulphate solution. The aqueous phase
10 was extracted with ethyl acetate. The combined extracts were washed with water and dried over anhydrous magnesium sulphate and evaporated *in vacuo*.

Example 9 Reaction of N-protected p-aminobenzoic acid
15 with ethyl chloroformate

para N-Boc protected benzoic acid (9.44g, 40mmol) from example 8 was dissolved in 10ml of 4M sodium hydroxide solution and cooled to 0°C in an ice bath. Ethyl
20 chloroformate (4.45g, 41mmol) and sodium hydroxide (10ml of 4.0M) was added alternately, with shaking and cooling, over 30minutes. The mixture was allowed to warm to room temperature over 1h, then extracted with ether. The aqueous phase was acidified with dilute hydrochloric acid.
25 The liberated oil was extracted with ether, the combined extracts were washed dried over magnesium sulphate and the solvent removed by evaporation, to yield the desired activated ester.

30 Example 10 Friedel Crafts reaction of modified PEEKTM film
with N-protected activated ester of p-aminobenzoic acid

The *N*-protected activated ester of *p*-aminobenzoic acid from example 9 (6.18g, 20mmol) and aluminium chloride (0.15g, 1.1mmol) were dissolved in freshly distilled dichloromethane in a boiling tube, under a nitrogen atmosphere. A sample of PEEKTM film from example 1 was then immersed in the solution and the solution heated to 40°C for 24h. The film was then removed and washed with methanol and distilled water followed by acetone.

10 Example 11 Reaction of surface modified PEEKTM from example 10 with *p*-aminobenzoic acid

A solution of 4-aminobenzoic acid (3.6g, 26mmol) in acetic acid (50ml) was introduced into a 100ml round bottomed flask. A sample of modified PEEKTM film from example 10 was immersed in the reactive solution and stirred, at room temperature, for 3 days. The film sample was then removed and rinsed with acetic acid and acetone before being dried under vacuum for 6 hours.

20

Example 12 C-Protection of *p*-amino benzoic acid

p-Amino benzoic acid (30g, 220mmol) was added to a 500ml reaction flask and dissolved in absolute methanol. Concentrated sulphuric acid (5g) was added and the solution boiled gently for 6h. The excess alcohol was removed by distillation. The methyl ester was then extracted with ether and the combined extracts washed with sodium hydrogen carbonate solution and water. The combined extracts were dried over magnesium sulphate and the ether removed by evaporation to afford the methyl ester.

Example 13 Reaction of surface modified PEEK™ from example 10 with C protected p-aminobenzoic acid

A solution of C-protected 4-aminobenzoic acid (3.92g, 26mmol), in which the carboxylic group has been protected as the methyl ester in the standard fashion, in acetic acid (50ml) was introduced into a 100ml round bottomed flask. A sample of modified PEEK™ film from example 10 was immersed in the reactive solution and stirred, at room temperature, for 3 days. The film sample was then removed and rinsed with acetic acid and acetone before being dried under vacuum for 6 hours.

Example 14 Reaction of modified PEK™ film with C-protected p-aminobenzoic acid

A solution of C-protected 4-aminobenzoic acid (3.92g, 26mmol), in which the carboxylic group has been protected as the methyl ester in the standard fashion, in acetic acid (50ml) was introduced into a 100ml round bottomed flask. A sample of modified PEK™ film from example 6 was immersed in the reactive solution and stirred, at room temperature, for 3 days. The film sample was then removed and rinsed with acetic acid and acetone before being dried under vacuum for 6 hours.

Example 15 Calcium Phosphate Deposition on modified PEK™ film from example 14

A supersaturated calcium phosphate solution containing 5mM CaCl_2 , 1.5mM KH_2PO_4 and 1.5mM Na_2HPO_4 was prepared by mixing 1.5ml of 0.1M Na_2HPO_4 stock solution into 92ml of deionised water, followed by the slow addition of 5.0ml of

0.1M CaCl_2 solution. The combined solution was stirred for 3 minutes and modified PEK™ film (example 14) was immersed in the solution and taken out just before the solution precipitated (1 hour). The films were then
5 rinsed with deionised water and blown dry with nitrogen. The process can be repeated several times to achieve a desired thickness.

Example 16 Deprotection of Modified PEK™ sample from
10 Example 15

A sample of modified PEK™ film from example 15 was immersed into a 100ml solution of 10 per cent sodium hydroxide and refluxed for 12 hours. The sample was
15 removed and washed thoroughly with dilute sulphuric acid followed by distilled water. The sample was then removed and dried overnight at room temperature.

Example 17 Reaction of surface modified PEK™ with the
20 peptide GRGDS

The surface modified PEK™ from Example 16 was stirred at 10°C for 1 hr under an atmosphere of nitrogen in an aqueous solution of the water soluble carbodiimide, 1-
25 ethyl-3-(3-dimethylaminopropyl)-carbodiimide) (0.4g) dissolved in buffer at pH 4.5 (0.1M 2-(N-morpholino)ethanesulphonic acid) (40ml). The sample of PEK™ was removed and washed with buffer solution.

30 The sample was stirred at 20°C for 24 hr under an atmosphere of nitrogen in a solution of the peptide GRGDS (160mg) in phosphate-buffered saline solution (40ml) (Na_2HPO_4 , 1.15g; KH_2PO_4 , 0.2g; NaCl, 8g; KCl, 0.2g; MgCl_2 ,

0.1g; CaCl_2 , 0.1g in 1 litre of distilled water). The functionalised PEEKTM was washed successively with phosphate buffer and distilled water.

5 Example 18 Reaction of surface modified PEEKTM containing free carboxyl groups and a protected amino group with the peptide GRGDS

The surface modified PEEKTM from Example 11 was stirred
10 at 10°C for 1 hr under an atmosphere of nitrogen in an aqueous solution of the water soluble carbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide) (0.4g) dissolved in buffer at pH 4.5 (0.1M 2-(N-morpholino)ethanesulphonic acid) (40ml). The sample of
15 PEEKTM was removed and washed with buffer solution.

The sample was stirred at 20°C for 24 hr under an atmosphere of nitrogen in a solution of the peptide GRGDS (160mg) in phosphate-buffered saline solution (40ml)
20 (Na_2HPO_4 , 1.15g; KH_2PO_4 , 0.2g; NaCl , 8g; KCl , 0.2g; MgCl_2 , 0.1g; CaCl_2 , 0.1g in 1 litre of distilled water). The functionalised PEEKTM was washed successively with phosphate buffer and distilled water.

25 Example 19 Deprotection of the surface modified PEEKTM film from example 18.

A 1M solution of hydrogen chloride in acetic acid was stirred in a 100ml reaction flask at room temperature. A
30 sample of modified PEEKTM film from example 18 was added and the solution stirred for a further 6 hours. The film sample was used directly in example 20.

Example 20 Reaction of modified PEEK™ film from example 19 with the peptide sequence KRSR

The modified PEEK™ sample from example 19 was placed
5 in a 250ml round-bottomed flask fitted with a magnetic
follower and a nitrogen inlet and outlet and containing
N,N-dimethylacetamide (60ml), and disuccinimidylsuberate
(300mg). The contents were stirred under an atmosphere of
nitrogen at room temperature for 2hrs. The specimen was
10 removed, washed with ether and dried in vacuo for 10hrs at
50°C. The dried sample was stirred at 20°C for 24 hr
under an atmosphere of nitrogen in a solution of the
peptide KRSR(160mg) in an aqueous buffer solution (40ml),
pH 9. The functionalised PEEK™ was washed successively
15 with the buffer solution and ether.

Example 21 Reaction of modified PEEK™ film from example 11 with aspartic acid

20 The surface modified PEEK™ from Example 11 was stirred
at 10°C for 1 hr under an atmosphere of nitrogen in an
aqueous solution of the water soluble carbodiimide, 1-
ethyl-3-(3-dimethylaminopropyl)-carbodiimide) (0.4g)
dissolved in buffer at pH 4.5 (0.1M 2-(N-
25 morpholino)ethanesulphonic acid) (40ml). The sample of
PEEK™ was removed and washed with buffer solution. The
sample was stirred at 20°C for 24 hr under an atmosphere
of nitrogen in a solution of aspartic acid in phosphate-
buffered saline solution (40ml) (Na₂HPO₄, 1.15g; KH₂PO₄,
30 0.2g; NaCl, 8g; KCl, 0.2g; MgCl₂, 0.1g; CaCl₂, 0.1g in 1
litre of distilled water). The functionalised PEEK™ was
washed successively with phosphate buffer and distilled
water.

Example 22 Deprotection of the surface modified PEEK™ film from example 21.

5 A 1M solution of hydrogen chloride in acetic acid was stirred in a 100ml reaction flask at room temperature. A sample of modified PEEK™ film from example 21 was added and the solution stirred for a further 6 hours. The film sample was removed and used directly in example 23.

10

Example 23 Reaction of modified PEEK™ film from example 22 with arginine.

15 The modified PEEK™ sample from example 22 was placed in a 250ml round-bottomed flask fitted with a magnetic follower and a nitrogen inlet and outlet and containing N,N-dimethylacetamide (60ml), and disuccinimidylsuberate (300mg). The contents were stirred under an atmosphere of nitrogen at room temperature for 2hrs. The specimen was
20 removed, washed with ether and dried in vacuo for 10hrs at 50°C. The dried sample was stirred at 20°C for 24 hr under an atmosphere of nitrogen in a solution of arginine in an aqueous buffer solution (40ml), pH 9. The functionalised PEEK™ was washed successively with the
25 buffer solution and ether.

Example 24 Deprotection/Coupling of modified PEEK™ sample from example 19.

30 The surface modified PEEK™ from Example 19 was stirred at 10°C for 1 hr under an atmosphere of nitrogen in an aqueous solution of the water soluble carbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (0.4g)

dissolved in buffer at pH 4.5 (0.1M 2-(N-morpholino)ethanesulphonic acid) (40ml). The sample of PEEK™ was removed and washed with buffer solution.

The sample was stirred at 20°C for 24 hr under an atmosphere of nitrogen in phosphate-buffered saline solution (40ml) (Na₂HPO₄, 1.15g; KH₂PO₄, 0.2g; NaCl, 8g; KCl, 0.2g; MgCl₂, 0.1g; CaCl₂, 0.1g in 1 litre of distilled water). The functionalised PEEK™ was washed successively with phosphate buffer and distilled water.

10

Example 25 Preparation of a polyetheretherketone/PEES (70/30) co-polymer

A 250ml, 3 necked, round-bottomed flask fitted with a stirrer/stirrer guide, nitrogen inlet and outlet and a thermocouple was charged with hydroquinone (55.05g, 0.5mol), 4,4'-dichlorodiphenylsulphone (34.46g, 0.12g), 4,4'-difluorobenzophenone (84.00g, 0.385mol) and DPS (285.91g, 1.3mol) and purged with nitrogen for more than 1 hour. The contents were then heated to between 140 and 150°C to form an almost colourless solution. While maintaining a nitrogen blanket, dried potassium carbonate (72.56g, 0.525mol) was added. The temperature was raised to 175°C and held for 120 min; heated to 200°C, held for 30 min; heated to 320°C and held for 120 minutes. The reaction mixture was allowed to cool, milled and washed with acetone and water. The resulting polymer was dried in an air oven at 120°C. The polymer had an RV of 1.03. Tg = 159°C and Tm = 306°C.

30

Example 26 Surface Reduction of a polyetheretherketone/PEES (70/30) co-polymer with Dibal-H

A sample of polyetheretherketone/PEES (70/30) co-polymer from example 25 was immersed in 200ml of a 1.0M solution of diisobutylaluminium hydride (Dibal-H) in toluene. The mixture was then refluxed under nitrogen for 96hours and eventually cooled to room temperature. The sample was removed and washed with ethanol (100ml), followed by water (200ml), and concentrated hydrochloric acid (100ml). The sample was then rinsed with water and allowed to dry at room temperature overnight.

10

Example 27- Friedel- Crafts propylation of modified polyetheretherketone/PEES film

A solution of 1,3-propane sultone (7.32g, 60mmol) and aluminium chloride (0.15g, 1.1mmol) was prepared in a boiling tube at 60°C, under a nitrogen atmosphere. A sample of modified polyetheretherketone/PEES (70/30) film was then immersed in the solution and stirred at 60°C for 24h. The film was then removed and washed with methanol and distilled water followed by acetone.

The reader's attention is directed to all papers and documents which are filed concurrently with or previous to this specification in connection with this application and which are open to public inspection with this specification, and the contents of all such papers and documents are incorporated herein by reference.

All of the features disclosed in this specification (including any accompanying claims, abstract and drawings), and/or all of the steps of any method or process so disclosed, may be combined in any combination,

except combinations where at least some of such features and/or steps are mutually exclusive.

Each feature disclosed in this specification
5 (including any accompanying claims, abstract and drawings), may be replaced by alternative features serving the same, equivalent or similar purpose, unless expressly stated otherwise. Thus, unless expressly stated otherwise, each feature disclosed is one example only of a generic
10 series of equivalent or similar features.

The invention is not restricted to the details of the foregoing embodiment(s). The invention extend to any novel one, or any novel combination, of the features disclosed
15 in this specification (including any accompanying claims, abstract and drawings), or to any novel one, or any novel combination, of the steps of any method or process so disclosed.

CLAIMS

1. A method of functionalising a polymer of a type which includes:

5

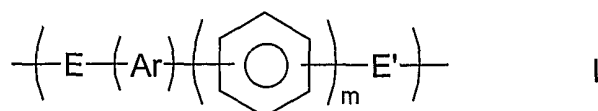
- (A) phenyl moieties;
- (B) carbonyl and/or sulphone moieties;
- (C) ether and/or thioether moieties;

10 the method including:

- (1) treating the polymer to functionalise said carbonyl and/or sulphone moieties to provide functionalities which have a lower electron withdrawing effect on phenyl moieties (hereinafter referred to as "activated phenyl moieties") in said polymer backbone than the carbonyl and/or sulphone moieties they replace; and
 - (2) treating the polymeric material prepared in
- 15
- 20 (1) in order to functionalise said activated phenyl moieties.

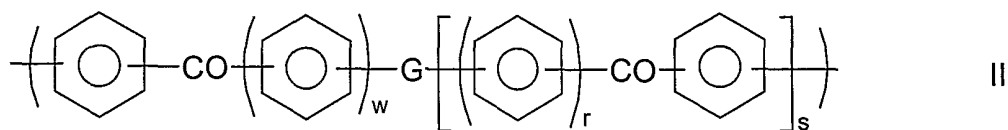
2. A method according to claim 1, wherein said polymer has a moiety of formula

25

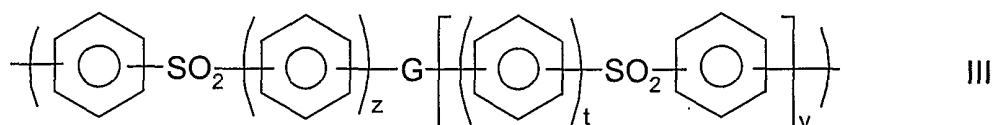


and/or a moiety of formula

30

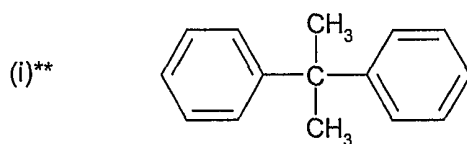


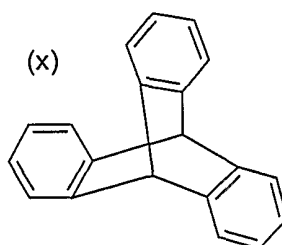
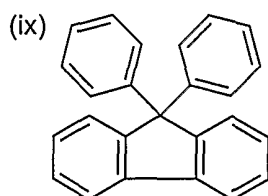
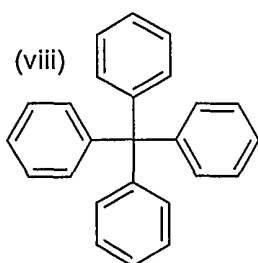
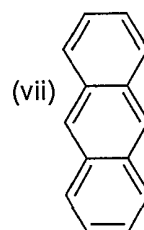
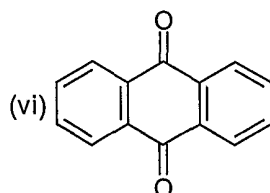
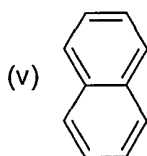
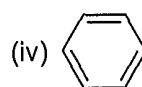
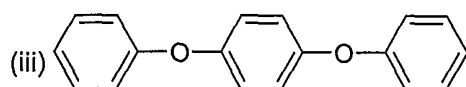
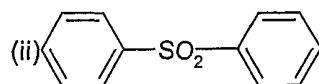
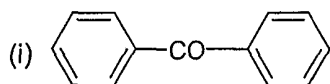
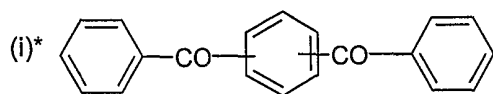
and/or a moiety of formula



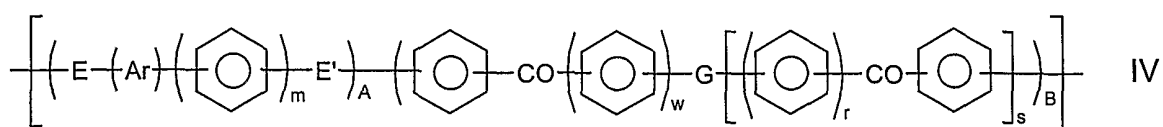
5

wherein the phenyl moieties in units I, II, and III are independently optionally substituted and optionally cross-linked; and wherein m,r,s,t,v,w and z independently represent zero or a positive integer, E and E' independently represent an oxygen or a sulphur atom or a direct link, G represents an oxygen or sulphur atom, a direct link or a -O-Ph-O- moiety where Ph represents a phenyl group and Ar is selected from one of the following moieties (i)*, (i)**, (i) to (x) which is bonded via one or
 10 more of its phenyl moieties to adjacent moieties
 15

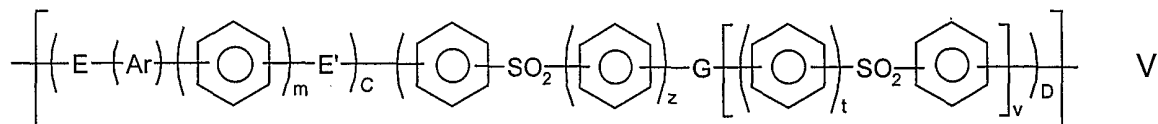




3. A method according to claim 1 or claim 2, wherein said polymer is a homopolymer having a repeat unit of general
5 formula



or a homopolymer having a repeat unit of general formula

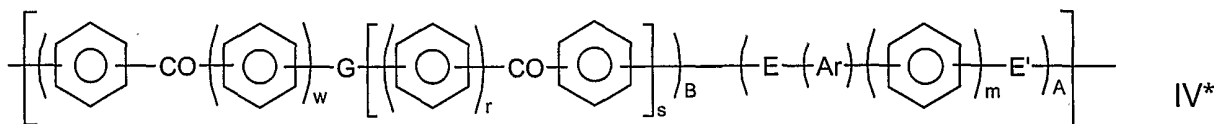


or a random or block copolymer of at least two
5 different units of IV and/or V

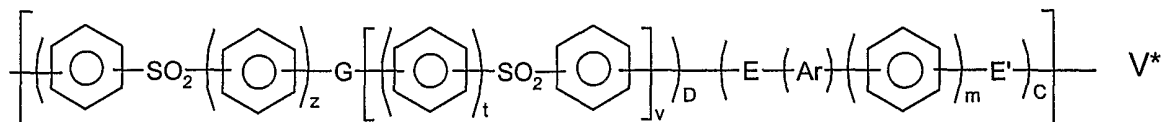
wherein A, B, C and D independently represent 0 or 1
and E, E', G, Ar, m, r, s, t, v, w and z are as described in claim
2; or

10

said polymer is a homopolymer having a repeat unit of
general formula



or a homopolymer having a repeat unit of general
15 formula



or a random or block copolymer of at least two different
units of IV* and/or V*, wherein A, B, C, and D
20 independently represent 0 or 1 and E, E', G, Ar, m, r, s,
t, v, w and z are as described in claim 2.

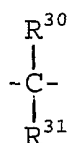
4. A method according to any preceding claim, wherein
 said polymer is selected from polyetheretherketone,
 polyetherketone, polyetherketoneketone,
 5 polyetherketoneetherketoneketone and
 polyetheretherketoneketone.

5. A method according to any preceding claim, wherein
 said polymer is polyetheretherketone.

10

6. A method according to any preceding claim, wherein in
 stage (1), ketone moieties are functionalised to provide a
 moiety

15



or a moiety

20



wherein the groups $-CR^{30}R^{31}-$ and $-CR^{32}-$ have a lower
 electron withdrawing effect on groups adjacent the carbon
 25 atom thereof compared to the ketone groups they replace.

7. A method according to claim 6, wherein the atom of
 R^{30} which links it to the moiety $-C-$ is a hydrogen, carbon
 or oxygen atom.

30

8. A method according to claim 7, wherein a said carbon
 atom is bonded to or is a component of an optionally
 substituted saturated, unsaturated, linear, branched,

acyclic and/or cyclic moiety; and an oxygen atom is part of a hydroxy group or is bonded to or a component of an optionally substituted saturated, unsaturated, linear, branched, acyclic and/or cyclic moiety.

5

9. A method according to claim 7 or claim 8, wherein the atom of R^{31} which links it to the moiety -C- represents an atom or group which independently is as described for R^{30} .

10 10. A method according to claim 6, wherein the atom in group R^{32} which links R^{32} to the moiety -C- is a nitrogen atom so that R^{32} defines an imine with the moiety -C-.

11. A method according to any of claims 6 to 9, wherein
15 ketone moieties are functionalised to provide a moiety $-CR^{30}R^{31}-$ and said polymer which includes moieties described in (A), (B) and (C) is subjected to a first treatment which is a reduction reaction for reducing carbonyl moieties.

20

12. A method according to claim 6 or claim 11, wherein ketone moieties are functionalised to provide a moiety $-CR^{32}-$ and said polymer which includes moieties described in (A), (B) and (C) is subjected to an
25 addition-elimination reaction.

13. A method according to any preceding claim, wherein stage (2) involves an electrophilic aromatic substitution reaction of said activated phenyl moieties.

30

14. A method according to any preceding claim, wherein the method involves functionalising the polymer at or adjacent

a surface thereof, such that the bulk of the polymer is not substantially functionalised.

15. A method according to any preceding claim, wherein the
5 method involves functionalising phenyl moieties of said polymer such that the concentration of non-functionalised phenyl moieties present within the bulk of the functionalised polymer is greater than the concentration of non-functionalised phenyl moieties present at or
10 adjacent to a surface thereof.

16. A method according to any preceding claim, wherein said polymer functionalised in the method is presented as a solid and is then functionalised in the method.

15 17. A method according to any preceding claim, which includes the step of treating said polymer after functionalisation of said activated phenyl moieties with a material for providing bio-compatible moieties.

20 18. A method of making a bio-compatible polymeric material for use in medical applications, the method including associating bio-compatible moieties with a functionalised polymer of a type or when prepared as described according
25 to any preceding claim.

19. A functionalised polymeric material, wherein the bulk of said material comprises a polymer of a type which includes, in the polymer backbone, the following:

30

- (A) phenyl moieties;
- (B) carbonyl and/or sulphone moieties; and
- (C) ether and/or thioether moieties;

wherein a surface of said material comprises a functionalised derivative of said polymer present in the bulk which derivative has a lower concentration of
5 carbonyl and/or sulphone moieties compared to the concentration of carbonyl and/or sulphone moieties in the bulk.

20. A bio-compatible polymeric material which includes a
10 polymer of a type which includes, in the polymer backbone,

- (A) phenyl moieties;
- (B) carbonyl and/or sulphone moieties;
- (C) ether and/or thioether moieties;

15

wherein some carbonyl or sulphone moieties of the polymer have been substituted with functionalities which have a lower electron withdrawing effect on phenyl moieties (hereinafter referred to as "activated phenyl moieties")
20 in said polymer backbone than the carbonyl and/or sulphone moieties they replace and wherein bio-compatible moieties are associated with said activated phenyl moieties.

21. A bio-compatible polymeric material comprising a
25 polymer having bio-compatible moieties associated with its surface and a lower concentration of bio-compatible moieties associated with its bulk, wherein the bulk comprise a polymer of a type which includes, in the polymer backbone, the following:

30

- (A) phenyl moieties;
- (B) carbonyl and/or sulphone moieties; and
- (C) ether and/or thioether moieties.

22. A device for use in medical applications, wherein said device comprises a bio-compatible polymeric material according to claims 20 or claim 21 or made in the method
5 according to claim 17 or claim 18.

23. A method of making a device, the method comprising:
forming a material into a shape which represents or is a precursor of a device or a part of a device for use in
10 medical applications, wherein said material comprises a polymer which includes phenyl moieties, carbonyl and/or sulphone moieties, and ether and/or thioether moieties;
functionalising said polymer in said shape as described in any of claims 1 to 18; and causing bio-compatible moieties
15 to associate with said functionalised polymer.

24. The use of a functionalised polymer as described in any of the claims 19 to 21 in the manufacture of a device for use in a medical treatment.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 01/02790

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C08G65/48 A61L27/18

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)

IPC 7 C08G A61L

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 practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	US 6 117 967 A (LIMBURG WILLIAM W ET AL) 12 September 2000 (2000-09-12) examples XIV,XV	1-4,6,7, 9,11
X	MARCHANT-BRYNAERT J. : "Surface modifications and reactivity assays of polymer films etc" REC. DEV. POLYM. SCI., vol. 2, 1998, pages 335-362, XP001032906 page 346 -page 358 -/--	19-22,24

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents:

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Date of the actual completion of the international search

24 October 2001

Date of mailing of the international search report

02/11/2001

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O'Sullivan, T

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 01/02790

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	THOMPSON S A ET AL: "A NOVEL METHOD FOR CROSSLINKING POLYETHERETHERKETONE" JOURNAL OF APPLIED POLYMER SCIENCE, JOHN WILEY AND SONS INC. NEW YORK, US, vol. 36, no. 5, 20 August 1988 (1988-08-20), pages 1113-1120, XP000149412 ISSN: 0021-8995 figure 1 -----	1-24
A	US 4 764 566 A (SWEDO RAYMOND J) 16 August 1988 (1988-08-16) claim 1 column 2A, line 101-24 -column 3, line 20 -----	1-24
A	LINDFORS B E ET AL: "HETEROGENEOUS HYDROLYSIS OF POLY(ARYL ETHER KETIMINE)S-AN ALTERNATIVE SYNTHETIC ROUTE TO SEMICRYSTALLINE POLY(ARYL ETHER KETONE)S" MAKROMOLEKULARE CHEMIE, RAPID COMMUNICATIONS, HUTHIG UND WEPF VERLAG. BASEL, CH, vol. 12, no. 6, 1 June 1991 (1991-06-01), pages 337-345, XP000232516 table 1 -----	1-24

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 01/02790

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 6117967	A	12-09-2000	JP 2001019761 A	23-01-2001
			US 6194111 B1	27-02-2001
US 4764566	A	16-08-1988	NONE	