



(51) International Patent Classification:

A61L 31/06 (2006.01) **C08G 63/60** (2006.01)
A61L 31/14 (2006.01)

(21) International Application Number:

PCT/GB2009/002646

(22) International Filing Date:

12 November 2009 (12.11.2009)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

0820682.3 12 November 2008 (12.11.2008) GB

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

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report (Art. 21(3))

(54) Title: NOVEL POLYMERIC MATERIALS

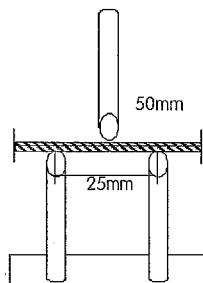


Figure 5

(57) Abstract: The invention provides a degradable polymeric material comprising monomer units derived from (a) a dicarboxylic acid, (b) a first hydroxybenzoic acid derivative, (c) a diol -comprising at least two phenyl rings and (d) a second hydroxybenzoic acid derivative, wherein the combined content of units of the first and second hydroxybenzoic acid derivatives (b) and (d) is greater than 55%, expressed as a mole fraction. The polymers can be formed into fibres and the polymers and fibres according to the invention are bioresorbable and/or biodegradable and are therefore suitable for use in medical devices that will be used in the human body.

NOVEL POLYMERIC MATERIALS

RELATED APPLICATIONS

5 This application claims priority from UK provisional application No. 0820682.3 entitled
"Novel Polymeric Materials" filed on 12 November 2008, which is herein incorporated in
its entirety.

FIELD OF THE INVENTION

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The present invention relates to novel polymeric materials and compositions and their
uses in the medical field. More specifically, the invention is concerned with polymer
compositions having good mechanical and degradative properties which are of use in
orthopaedic applications.

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BACKGROUND TO THE INVENTION

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Orthopaedic surgery frequently requires the implantation of materials that must be both
biocompatible and capable of bearing high loads. Conventionally, metals such as
titanium and its alloys have been employed for such purposes, but these materials suffer
a number of disadvantages. More recently, biocompatible, bioresorbable polymers have
been developed that aim to overcome the deficiencies associated with the use of metals
in orthopaedic applications. However, well known bioresorbable polymers, often require
extensive processing in order to achieve the strength required for load-bearing
orthopaedic applications, and these materials are generally not stiff enough to resist
deformation under high load.

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Thus, biomaterials with adequate strength retention during degradation for bone fracture
and fixation are currently not available. Specifically, poly(glycolic acid) (PGA) fibres have
modulus and strength of 25 GPa and 1.5 GPa, respectively, but lose their mechanical
properties during degradation in simulated body fluid in less than two weeks. On the
other hand, poly(lactic acid) (PLA) based polymers do not have adequate mechanical
properties for long bone fracture repair, although they do retain their mechanical
properties for sufficient time during fracture repair.

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Mechanical properties, and their retention during degradation, can to some extent be tailored by the preparation of PGA-PLA based copolymers. However, whilst these copolymers show relatively good mechanical property retention during degradation, they have at most one third the modulus of cortical bone (20-30 GPa).

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WO-A-2007/110609 discloses polymer compositions and artefacts which comprise bioresorbable polymers having high mechanical strength and modulus. Monomer mixtures comprising sulphonyl diphenol compounds, hydroxybenzoic acid derivatives and dicarboxylic acids are used in the preparation of the claimed polymers, which are successfully employed for the manufacture of load bearing medical devices suitable for implantation within the body. However, the present inventors have now found that improved performance may be achieved by the use of certain liquid crystal polymers.

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The prior art provides numerous disclosures of liquid crystal polymers. However, for present purposes, it is necessary that said polymers should be degradable, and disclosures of such materials are very limited. Thus, US-A-7182884 describes a degradable liquid crystal polymer obtained from tissue derived compounds which is biocompatible and is based on polyhydroxycinnamic acid, whilst WO-A-97/48782 discloses thermotropic polymers, which are typically aromatic poly(ester-anhydride)s, having high modulus and biodegradability, and which find use as bone fixative materials, as well as in the construction of prosthetic devices and the filling of other bone defects.

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In addition, EP-A-350127 is concerned with orthopaedic devices for replacing or connecting fragments of human or animal bone, the orthopaedic devices being based on liquid-crystalline polymers comprising aromatic chains and having a modulus of elasticity of at least 15 GPa in longitudinal direction and at least 10 GPa in transverse direction. However, the disclosed polymers are non-degradable and, therefore unsuited to present purposes. Similarly, US-A-4664972, US-A-5006402, EP-A-305683, EP-A-226847, EP-A-225539 and US-A-4746721 all relate to liquid crystal polymer formulations which are non-degradable.

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Thus, the present inventors have sought to provide liquid crystal polymer compositions which are degradable, and also provide the requisite physical properties in terms of strength and resilience and have established that suitable materials may be obtained from a range of condensation polymers.

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SUMMARY OF THE INVENTION

Thus, according to a first aspect of the present invention, there is provided a degradable polymeric material comprising monomer units derived from (a) a dicarboxylic acid, (b) a first hydroxybenzoic acid derivative, (c) a diol comprising at least two phenyl rings and (d) a second hydroxybenzoic acid derivative, wherein the combined content of units of the first and second hydroxybenzoic acid derivatives (b) and (d) is greater than 55%, expressed as a mole fraction.

10 In one embodiment of the invention, the combined content of units of the first and second hydroxybenzoic acid derivatives (b) and (d) is greater than 57%, expressed as a mole fraction. In a further embodiment of the invention, the combined content of units of the first and second hydroxybenzoic acid derivatives (b) and (d) is greater than 59%, expressed as a mole fraction. In a still further embodiment of the invention, the combined content of units of the first and second hydroxybenzoic acid derivatives (b) and (d) is greater than 61%, expressed as a mole fraction. In another embodiment of the invention, the combined content of units of the first and second hydroxybenzoic acid derivatives (b) and (d) is greater than 63%, expressed as a mole fraction. In yet another embodiment of the invention, the combined content of units of the first and second hydroxybenzoic acid derivatives (b) and (d) is greater than 65%, expressed as a mole fraction. Preferably, the combined content of these components is in the region of 75% of the total.

Suitable dicarboxylic acid derivatives may be either aliphatic or aromatic dicarboxylic acids. However, the dicarboxylic acids are preferably aliphatic dicarboxylic acids.

Preferred first and second hydroxybenzoic acid derivatives are derivatives of 4-hydroxybenzoic acid. The first and second hydroxybenzoic acid derivatives may be the same or different. However, in the most preferred embodiments, the first and second hydroxybenzoic acid derivatives are different.

The diol comprising at least two phenyl rings preferably contains either two or three phenyl rings, most preferably two phenyl rings. Said phenyl rings may be linked together by means of a direct bond or a linking group, such as an alkyl or ether group or, more preferably, a sulphone group. Alternatively, said phenyl rings may be directly fused together into a polycyclic ring system, such as an anthracene or phenanthrene system

or, more preferably, a naphthalene system, or the rings may be linked by more than one direct bond or linking group, so as to form a further ring system.

According to a second aspect of the present invention, there is provided a method of manufacturing a degradable polymer, said method comprising the steps of mixing (a) a dicarboxylic acid, (b) a first hydroxybenzoic acid derivative, (c) a diol comprising at least two phenyl rings and (d) a second hydroxybenzoic acid derivative in a solvent, heating the mixture to approximately 80°C, adding Vilsmeier reagent, and precipitating the resultant polymer out of the solution, wherein the combined content of units of the first and second hydroxybenzoic acid derivatives (b) and (d) is greater than 55%, expressed as a mole fraction. The polymer may be further purified using methods known to those skilled in the art. In alternative embodiments of the invention, the combined content of units of the first and second hydroxybenzoic acid derivatives (b) and (d) may be greater than 57%, or greater than 59% or greater than 61%, or greater than 63%, or greater than 65%, expressed as a mole fraction.

The resultant polymers are typically melt processable, with a melting point of less than 200°C, preferably approximately 180°C, more preferably about 150°C, and may show birefringence under crossed polarised light. Furthermore they are preferably capable of being injection moulded and can be gamma sterilized without significant molar mass loss.

The polymers can be formed into fibres that typically have a tensile strength of at least 150 MPa and a tensile modulus of at least 3 GPa, although fibres with a tensile strength of at least 200 MPa, preferably at least 250 MPa, more preferably at least 500 MPa, and a tensile modulus of at least 7 GPa, preferably at least 12 GPa are preferable for certain high-strength applications. The fibres are semi-crystalline in nature. In some cases, the strength and tensile modulus of the fibres can be further enhanced by annealing the fibres at a temperature of at least 100°C.

Thus, according to a third aspect of the present invention, there is provided a degradable polymeric material comprising monomer units derived from (a) a dicarboxylic acid, (b) a first hydroxybenzoic acid derivative, (c) a diol comprising at least two phenyl rings and (d) a second hydroxybenzoic acid derivative which has been processed into a fibre, wherein the combined content of units of the first and second hydroxybenzoic acid derivatives (b) and (d) in the polymer is greater than 55%, expressed as a mole fraction. In alternative embodiments of the invention, the combined content of units of the first and

second hydroxybenzoic acid derivatives (b) and (d) may be greater than 57%, or greater than 59% or greater than 61%, or greater than 63%, or greater than 65%, expressed as a mole fraction.

- 5 The polymers and fibres according to the invention are biocompatible and preferably bioresorbable and/or biodegradable, and are therefore suitable for use in medical devices that will be used in the human body. Such devices include plates, rods, screws, pins, anchors, staples, arrows, and spinal devices (such as a spinal interbody fusion cage), medical device coatings, and composite devices or other such items. Such
10 devices may be made by injection moulding. Injection moulded devices may have a modulus of at least 4 GPa. Devices comprising polymers and fibres according to the invention are particularly suitable for use in applications which require good mechanical properties, for example bone fixation repairs, particularly to high load bearing bones such as the tibia and fibula, where moduli of at least 20 GPa are often required.

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- Alternatively, fibres are embedded within a polymer matrix to create a fibre-reinforced composite. Thus according to a fourth aspect of the present invention, there is provided a composite device comprising (i) a degradable polymer comprising monomer units derived from (a) a dicarboxylic acid, (b) a first hydroxybenzoic acid derivative, (c) a diol
20 comprising at least two phenyl rings and (d) a second hydroxybenzoic acid derivative, and (ii) a polymer matrix, wherein the combined content of units of the first and second hydroxybenzoic acid derivatives (b) and (d) in the polymer is greater than 55%, expressed as a mole fraction. In alternative embodiments of the invention, the combined content of units of the first and second hydroxybenzoic acid derivatives (b) and (d) may
25 be greater than 57%, or greater than 59% or greater than 61%, or greater than 63%, or greater than 65%, expressed as a mole fraction.

- Preferably in such an arrangement, the fibres are oriented substantially in one direction in order to improve the strength of the composite. Suitable polymer matrix materials
30 include poly(ϵ -caprolactone) or other polymers known to those skilled in the art.

BRIEF DESCRIPTION OF THE DRAWINGS

- The invention will now be further illustrated by reference to specific embodiments and the
35 accompanying drawings, which illustrate particular embodiments of the present invention that assist in gaining an understanding of the principles, characteristics, and features of the invention. In the drawings:

Figure 1 shows the effect of increasing the combined content of the first and second hydroxybenzoic acid derivatives (b) and (d) in polymers according to the invention on the tensile modulus of the polymer;

5 Figure 2 shows the effect of increasing the combined content of the first and second hydroxybenzoic acid derivatives (b) and (d) in polymers according to the invention on the accelerated degradation properties of the polymers at 80°C;

10 Figure 3 shows the effect of increasing the combined content of the first and second hydroxybenzoic acid derivatives (b) and (d) in polymers according to the invention on the accelerated degradation properties of the polymers at 70°C.;

15 Figure 4 shows the effect of increasing the combined content of the first and second hydroxybenzoic acid derivatives (b) and (d) in polymers according to the invention on the accelerated degradation properties of the polymers at 37°C; and

Figure 5 is a schematic of the equipment used for determining flexural properties.

DESCRIPTION OF THE INVENTION

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The invention provides a polymer comprising monomer units derived from (a) a dicarboxylic acid, (b) a first hydroxybenzoic acid derivative, (c) a diol comprising at least two phenyl rings and (d) a second hydroxybenzoic acid derivative.

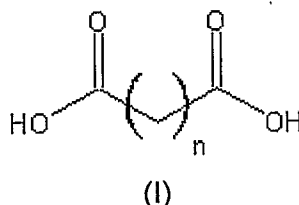
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The dicarboxylic acid component (a) may be either an aliphatic or an aromatic dicarboxylic acid. Suitable aliphatic dicarboxylic acids include sebacic acid, suberic acid, dodecanoic acid, adipic acid, diglycolic acid and 3,6-dioxaoctanedioic acid, whilst suitable aromatic dicarboxylic acids include meta-, iso- or para-arylenes which may additionally contain one or more substituents such as halogens or lower alkyl radicals.

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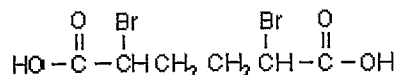
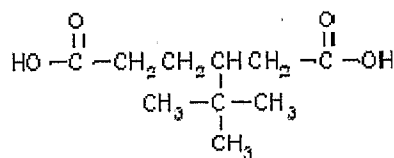
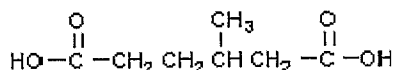
Terephthalic acid is a particularly suitable aromatic dicarboxylic acid.

Preferably, however, the dicarboxylic acid is an aliphatic dicarboxylic acid having the general formula (I):

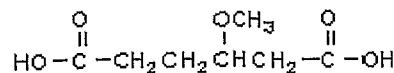


wherein n is a positive integer which is preferably in the range of from 1 to 10, and the carbon atoms in the chain may be substituted with hydrogen atoms or some or all of the carbon atoms may carry one or more alternative substituents with other possible substituents including alkyl groups, such as methyl or ethyl groups, alkoxy groups, for example methoxy and ethoxy groups, or halogen atoms, such as fluorine, chlorine, bromine or iodine. In some embodiments, one or more CH₂ groups along the hydrocarbon backbone (the length of which is represented by n) may be substituted with oxygen to form an ether group. In other embodiments, one or more of the said CH₂ groups may be substituted with an ester group.

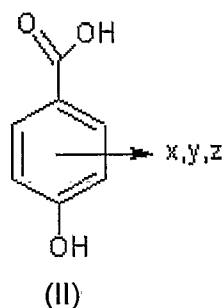
Thus, typical examples of suitable dicarboxylic acids could include the following derivatives:



or



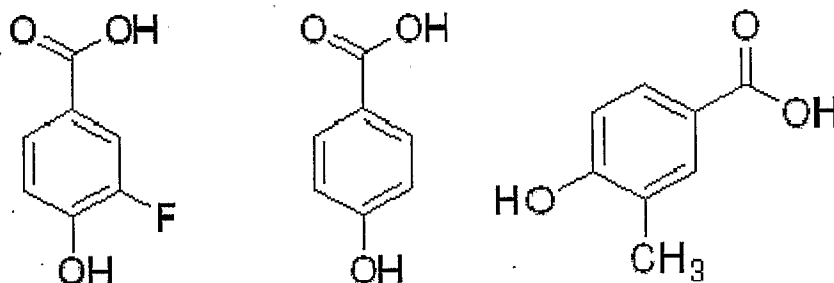
The first and second hydroxybenzoic acid derivatives may be the same or different. In certain preferred embodiments, these derivatives are different but in other preferred embodiments these derivatives may be the same. Suitable derivatives are preferably 4-hydroxybenzoic acid derivatives having the general formula (II):



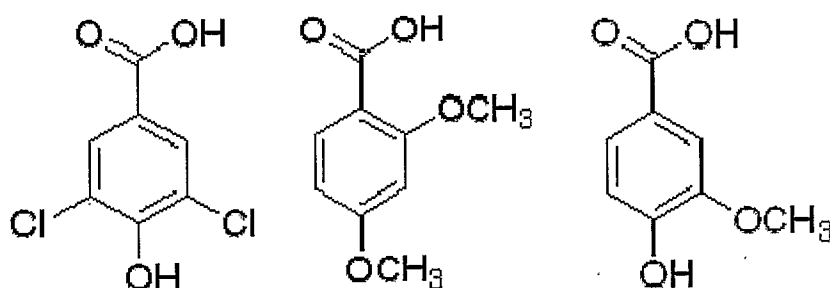
5 wherein x, y and z represent optional substituents which may be present at any vacant position on the aromatic ring. Preferred substituents x, y and z may be selected from:

- 1) straight or branched chain alkyl groups, such as methyl, ethyl and the like;
- 2) straight or branched chain alkoxy groups, for example methoxy and
10 ethoxy groups; and
- 3) halogen groups, typically fluoro, chloro, bromo or iodo groups.

Typical examples of suitable hydroxybenzoic acid derivatives could include the following
15 compounds:



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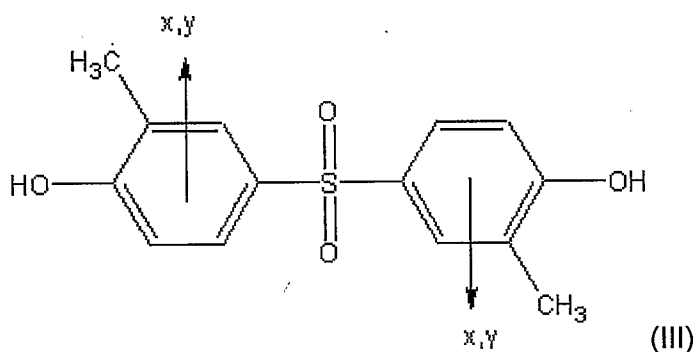


In preferred embodiments of the invention, the first hydroxybenzoic acid derivative (b) comprises 4-hydroxybenzoic acid, wherein each of the substituents x, y and z represents hydrogen.

- 5 Furthermore, in preferred embodiments of the invention, the second hydroxybenzoic acid derivative (d) comprises a derivative of 4-hydroxybenzoic acid wherein one of the substituents x, y and z represents a methoxy group, whilst the other two substituents comprise hydrogen. Most preferably, the second hydroxybenzoic acid derivative (d) comprises 4-hydroxy-3-methoxybenzoic acid (vanillic acid).

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The diol component (c) comprising at least two phenyl rings may most preferably contains two phenyl rings which are linked together by means of a linking group. Most preferably, said linking group comprises a sulphone group, and said diol component has the general formula (III):



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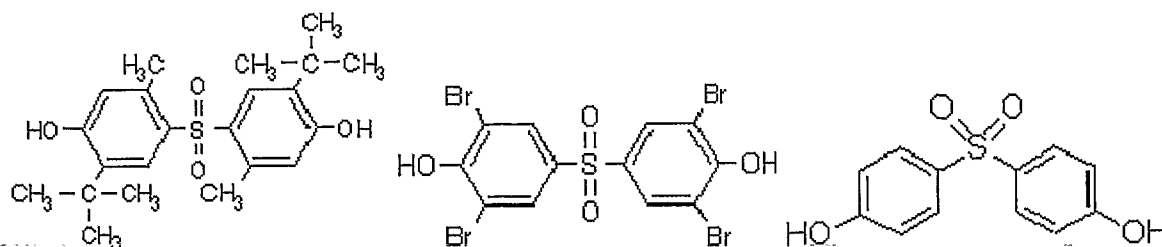
wherein x, y and z represent optional substituents which may be present at any vacant position on the aromatic ring. Preferred substituents x, y and z may be selected from:

- 20
- 1) straight or branched chain alkyl groups, such as methyl, ethyl and the like;
 - 2) straight or branched chain alkoxy groups, for example methoxy and ethoxy groups; and
 - 3) halogen groups, typically fluoro, chloro, bromo or iodo groups.

- 25
- In further embodiments, the methyl groups which are shown *ortho* to the hydroxyl moiety on each ring may also occupy the *meta* position. In still further embodiments one or both of the depicted methyl groups may be absent.

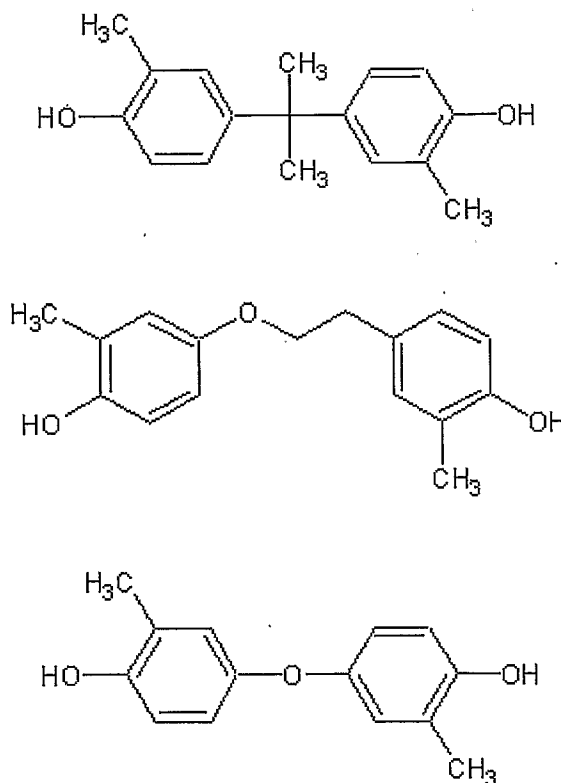
Examples of preferred diol components include the following:

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Alternative embodiments of the invention envisage diol components wherein the linking group may comprise an alkyl, alkyl ether or ether linkage, as in the following derivatives:

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In further alternative embodiments, said phenyl rings may be directly fused together into a polycyclic ring system, such as a naphthalene system, which may be optionally substituted with, for example methyl groups, as in the following derivatives:

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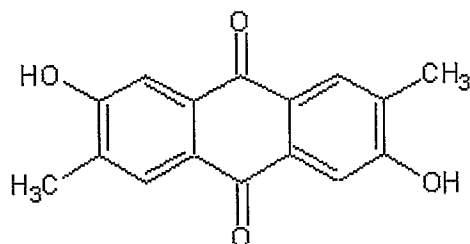


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In still further alternative embodiments of the invention, the at least two phenyl rings may be linked by more than one direct bond or linking group, so as to form a further ring system. Preferably, in such embodiments, two phenyl rings are linked by two linking

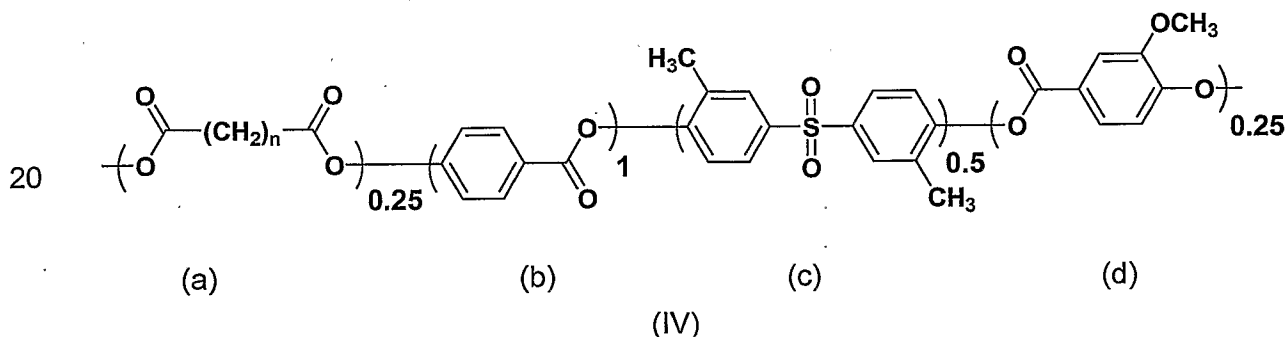
groups. Suitable linking groups may, for example, include straight or branched chain alkyl groups, ether groups or carbonyl groups. In a specific example, two phenyl ring systems may be linked by two carbonyl groups to form an anthraquinone derivative having the following formula:

5



In a particularly preferred embodiment of the first aspect of the invention, the polymer comprises monomer units derived from (a) an aliphatic dicarboxylic acid, (b) 4-hydroxybenzoic acid, (c) 4,4-sulphonylbis(2-methylphenol) and (d) 4-hydroxy-3-methylbenzoic acid (vanillic acid). In one such embodiment, the monomers are combined in the ratio of 0.25:1.0:0.25:0.5 ((a):(b):(c):(d)) and the polymer is of the formula (IV):

15



25 wherein n is a positive integer which is preferably in the range of from 1 to 10.

The present inventors have shown that by including a dicarboxylic acid unit (a) in combination with a diol unit (c) in the formulation of random aromatic polyesters it is possible to make degradable polymers with liquid crystalline properties and good mechanical properties. Moreover, it is seen that that the formation of a liquid crystalline phase having a higher degree of crystallinity is enhanced by increasing the aromaticity mole fraction relating to the units of the first hydroxybenzoic acid derivative (b) and the

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second hydroxybenzoic acid derivative (d) in the polymer, thereby resulting in a polymers having even better mechanical properties. However, increasing crystallinity also results in slower degradation rates, and the control of the degree of crystallinity by suitably adjusting the aromaticity of the polymeric material is a key feature of the invention and allows polymeric materials to be prepared which are tailored to specific end uses. Thus, aromaticity may be increased in those instances where good mechanical properties are of particular importance, whilst lower aromaticity contents are useful when mechanical properties are of somewhat less importance, but better degradability is desirable.

- 10 Hence, a key feature of the present invention relates to the control of the aromatic content, and changing the degree of aromaticity in the copolymer facilitates the synthesis of materials with different molecular structures, mechanical properties and degradation rates. Specifically, it has been found that by adjusting the proportions of the first hydroxybenzoic acid derivative (b) and the second hydroxybenzoic acid derivative (d) in the polymer, it is possible to obtain a range of degradable polymers with adjustable degradation rates.

The polymers according to the invention may be manufactured by mixing the monomers in a solvent, heating the mixture to approximately 80°C, adding Vilsmeier reagent, and precipitating the resultant polymer out of the solution. Suitable solvents include mixtures of pyridine and dimethylformamide, which may be combined in almost any possible ratio, although it is noted that lower yields are obtained when mixtures approaching pure solvents are used.

- 25 Many methods for the preparation of Vilsmeier reagent are available, and these will be well known to those skilled in the art. By way of illustration, a suitable Vilsmeier reagent composition may comprise the following:

Reagent	Mol ratio
Dimethylformamide	2
Pyridine	5
Tosyl chloride	1.35

- 30 In this formulation, the ratio of tosyl chloride to carboxylic acid in the polymer formulation is typically 1.35:1 (i.e. tosyl chloride is in excess).

Referring now to the drawings, polymers have been prepared wherein the dicarboxylic acid comprises adipic acid, and the polymer comprises units of (a) adipic acid, (b) 4-hydroxybenzoic acid, (c) 4,4-sulphonylbis(2-methylphenol) and (d) 4-hydroxy-3-methylbenzoic acid (vanillic acid) in the ratio of Y:X:Y:X/2 ((a):(b):(c):(d)), wherein $3X/2 + 2Y = 100\%$. Thus, polymers with different degrees of aromaticity (i.e. different combined contents of 4-hydroxybenzoic acid and vanillic acid) have been synthesised, and injection moulded bars suitable for degradation studies and mechanical testing have been prepared therefrom.

10 THE EFFECT OF VARYING CONTENTS OF 4-HYDROXYBENZOIC ACID PLUS VANILIC ACID ON TENSILE MODULUS OF INJECTION MOULDED BARS

With specific reference to Figure 1, there is shown the effect on tensile modulus of the injection moulded bars of varying contents of 4-hydroxybenzoic acid plus vanillic acid, and it is seen that the tensile modulus of the polymer increases with the combined 4-hydroxybenzoic acid plus vanillic acid content for bars prepared by injection moulding at 190°C and 210°C. Thus, the polymers comprising 65% and 75% combined 4-hydroxybenzoic acid plus vanillic acid showed successively better mechanical properties when compared with the polymer comprising 55% combined 4-hydroxybenzoic acid plus vanillic acid. Wide angle X-rays scattering analysis of these polymers has shown that the polymer with 55% mole fraction of 4-hydroxybenzoic acid plus vanillic acid is completely amorphous whereas the other three polymers with higher levels of aromaticity are partially crystalline.

25 THE EFFECT OF VARYING CONTENTS OF 4-HYDROXYBENZOIC ACID PLUS VANILIC ACID ON ACCELERATED DEGRADATION OF INJECTION MOULDED BARS

Figure 2 illustrates the effect on accelerated degradation of the injection moulded bars of varying contents of 4-hydroxybenzoic acid plus vanillic acid, with testing of polymers comprising 55%, 65% and 75% mole fractions of combined 4-hydroxybenzoic acid plus vanillic acid contents having been carried out at 80°C, and it is clear that the amorphous polymer with 55% combined content degrades considerably faster than the other two polymers. Indeed, this polymer loses around 85% of its molecular weight in about 0.5 of a week, whilst the polymer comprising 65% combined content degrades to around the same extent in approximately 1.75 weeks, and after more than 2 weeks the polymer comprising 75% combined content has only lost around 75% of its molecular weight.

From Figure 3 can be gleaned the effect on accelerated degradation of the injection moulded bars of varying contents of 4-hydroxybenzoic acid plus vanillic acid, with testing of polymers comprising 55%, 65% and 75% mole fractions of combined 4-hydroxybenzoic acid plus vanillic acid contents having been carried out at 70°C, and it is
5 again clear that the amorphous polymer with 55% combined content degrades considerably faster than the other two polymers. Thus, it is apparent that this polymer loses around 90% of its molecular weight in about 1.5 weeks, whilst the polymer comprising 65% combined content degrades to around the same extent in approximately 6 weeks, and after the same 6 week period the polymer comprising 75% combined
10 content has only lost just over 80% of its molecular weight.

Figure 4 illustrates the effect on accelerated degradation at 37°C and it is again clear that the amorphous polymer with 55% combined content degrades considerably faster than the other two polymers.

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THREE-POINT BEND TESTING OF A LIQUID CRYSTAL POLYMER PROCESSED AT VARIOUS TEMPERATURES

Material

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The LCP comprising monomer units derived from (a) adipic acid, (b) 4-hydroxybenzoic acid, (c) 4,4-sulphonylbis(2-methylphenol) and (d) 4-hydroxy-3-methylbenzoic acid (vanillic acid) as described above was processed at 210°C, 230°C, 250°C, 270°C or at 290°C (3 samples supplied for each processing temperature).

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Sample dimensions: length: 50mm, width: 25mm, thickness:1.6mm

Mechanical testing

30 Three-point (3pt) bend testing was carried out on an Instron 5569 with 10kN load cell and flexural testing fixtures.

The 3pt bend samples were placed on the lower two prongs of the test fixture set with a span of 25mm, and centred. Once the samples were central, the upper prong was
35 lowered until it just touched the upper surface of the polymer samples; at this point the gauge length was reset. The diagram in Fig 5 shows the 3pt bend fixture set up and sample placement.

Testing was carried out at a rate of 0.8mm/min and was directed to end when the load dropped below 40% of the peak load, once over 3N. This drop in load was deemed to be sensitive enough to detect sample failure.

5 Results

The average flexural properties of the LCP's processed at different temperatures can be found in Table 1.

10

Samples	Processing Temperature (°C)	Modulus (GPa)	Flexure stress @ break (MPa)	Flexure strain @ break (%)
1	210	3.29 ± 1.55	46.72 ± 30.41	4.46 ± 2.66
2	230	4.88 ± 0.07	96.22 ± 13.91	2.44 ± 0.48
2	230	4.88 ± 0.07	96.22 ± 13.91	2.44 ± 0.48
3	250	5.11 ± 0.14	93.46 ± 9.87	2.27 ± 0.28
4	270	5.08 ± 0.50	102.80 ± 18.23	2.36 ± 0.75
5	290	4.56 ± 1.48	89.41 ± 8.83	2.16 ± 0.33

TABLE 1: Average flexural properties of LCP's processed at a various temperatures

The samples processed at the lowest temperature (210°C) had notably poorer properties than those processed at the higher temperatures. The LCP's processed at this temperature also show larger deviations in the results than typically seen at the other processing temperatures.

The peak flexural modulus value was obtained at a processing temperature of 250°C and the peak flexural stress value was obtained at a processing temperature of 270°C. Flexural strain does not differ greatly between these two processing temperatures. Based on this data, the processing temperature that would achieve the peak mechanical properties is considered to be between about 250°C and about 270°C.

25 THE FLEXURAL PROPERTIES OF SAMPLES OF LCP POLYMER PROCESSED WITH DIFFERENT FILLERS

The LCP comprising monomer units derived from (a) adipic acid (b) 4-hydroxybenzoic acid, (c) 4,4-sulphonylbis(2-methylphenol) and (d) 4-hydroxy-3-methylbenzoic acid (vanillic acid) as described above was processed with different fillers.

Sample 1 – LCP + CaCO₃

Sample 2 – LCP + HA

Sample 3 – LCP + Phosphate glass fibre

Sample 4 – LCP + Hygroscopic glass fibre

5 (2 samples supplied for each filler)

Sample dimensions: length: 50mm, width: 25mm, thickness: 1.6mm

Mechanical testing

10

Three-point (3pt) bend testing was carried out as described above.

Results

15 The average flexural properties of the LCP's with different fillers can be found in Table.2.

Samples	Filler	Modulus (GPa)	Flexure stress @ break (MPa)	Flexure strain @ break (%)
Sample 1	CaCO ₃	5.27±0.25	84.65±5.87	1.99±0.31
Sample 2	HA	5.42±0.25	95.79±12.92	2.80±0.74
Sample 3	Phosphate glass fibre	6.72±0.42	118±0.71	2.15±0.17
Sample 4	Hygroscopic glass fibre	6.02±0.94	116±4.95	2.22±0.28

Table 2: Average flexural properties of LCP's with different fillers

20 The two glass fibre fillers produced the stiffest composite samples with peak flexural stresses greater than those obtained by the CaCO₃ and HA fillers. The flexural strain at break of the glass fibre composites is lower than measured for the HA samples but greater than the CaCO₃ filled polymer. Of the two different types of glass fibres used, the phosphate glass shows the greatest stiffness and strength.

25

The amount of filler used was about 35% of the total composite.

30

MECHANICAL TESTING OF DUMBBELLS AND RECTANGULAR SHEETS

Method

- 5 The tensile modulus and strength at break of injection moulded polymer dumbbells were measured using an Instron 5566.

For tensile modulus measurements a digital static extensometer was used and the reported modulus values are calculated using the secant and tangent at a strain of
 10 0.25%. The reported flexural modulus in contrast is the Young's modulus at 0.15%-0.25% of strain. For flexural properties and tensile modulus 5 samples were tested in each case and for tensile strength 7 specimens were tested.

Material: HBA₅₀, VA₂₅, d-BPS_{12.5}, Adipic_{12.5}

15

Results

The flexural and tensile mechanical properties are shown in Table 3. The flexural
 20 (5.3±0.3GPa) and tensile (5.7±0.2GPa) modulus agree well with each other, confirming comparable stiffness to injection moulded PGA (6GPa) [1] and superior stiffness compared to injection moulded PLLA (3-4GPa) [1] and PEEK (4.5GPa) [2]. The material has a flexural strength of 92±12MPa. The bending strain at break of 1.9±0.3% is comparable to other LCPs such as Vectra [3]. Increasing the modulus of this LCP is still
 25 plausible by optimising the molecular orientation achieved during injection moulding.

	Modulus (GPa)	Strength (MPa)	Strain at break (%)
Flexural	5.3±0.3	92±12	1.9±0.3
Tensile	5.7±0.2	37±18	3.4±2

Table 3: Tensile and flexural properties of injection moulded HBA₅₀, VA₂₅, d-BPS_{12.5}, Adipic_{12.5}

30 BIOCOMPATIBILITY

It has also been demonstrated that the formulation having an aromatic content (4-hydroxybenzoic acid plus vanillic acid) of 75% is biocompatible. MC3T3 E1 viable cells were seen growing on the polymer after 7 days, suggesting that the polymer provides a
 35 biocompatible surface for cell proliferation. Viable cells growing right up to the edge of the samples indicated that no cytotoxic compounds were leached out in 4 days.

Throughout the description and claims of this specification, the words “comprise” and “contain” and variations of the words, for example “comprising” and “comprises”, means “including but not limited to”, and is not intended to (and does not) exclude other moieties, additives, components, integers or steps.

5

Throughout the description and claims of this specification, the singular encompasses the plural unless the context otherwise requires. In particular, where the indefinite article is used, the specification is to be understood as contemplating plurality as well as singularity, unless the context requires otherwise.

10

Features, integers, characteristics, compounds, chemical moieties or groups described in conjunction with a particular aspect, embodiment or example of the invention are to be understood to be applicable to any other aspect, embodiment or example described herein unless incompatible therewith.

15

REFERENCES

- 1] Middleton JC, Tipton AJ. Biomaterials; 21 2335 (2000)
- 20 [2] Kurtz SM, Devine JN. Biomaterials; 28, 4845 (2007)
- [3] www.goodfellow.com/csp/active/STATIC/A/Vectra_A_-Liquid_Crystal_Polyester.HTML

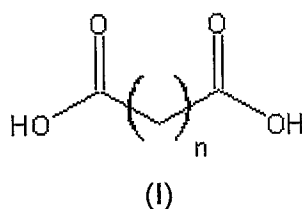
CLAIMS

1. A degradable polymeric material comprising monomer units derived from (a) a dicarboxylic acid, (b) a first hydroxybenzoic acid derivative, (c) a diol comprising at least two phenyl rings and (d) a second hydroxybenzoic acid derivative, wherein the combined content of units of the first and second hydroxybenzoic acid derivatives (b) and (d) is greater than 55%, expressed as a mole fraction.
2. A polymeric material as claimed in claim 1 wherein the combined content of units of the first and second hydroxybenzoic acid derivatives (b) and (d) is greater than 57%, expressed as a mole fraction.
3. A polymeric material as claimed in claim 1 or 2 wherein the combined content of units of the first and second hydroxybenzoic acid derivatives (b) and (d) is greater than 59%, expressed as a mole fraction.
4. A polymeric material as claimed in claim 1, 2 or 3 wherein the combined content of units of the first and second hydroxybenzoic acid derivatives (b) and (d) is greater than 61%, expressed as a mole fraction.
5. A polymeric material as claimed in any one of claims 1 to 4 wherein the combined content of units of the first and second hydroxybenzoic acid derivatives (b) and (d) is greater than 63%, expressed as a mole fraction.
6. A polymeric material as claimed in any preceding claim wherein the combined content of units of the first and second hydroxybenzoic acid derivatives (b) and (d) is greater than 65%, expressed as a mole fraction.
7. A polymeric material as claimed in any preceding claim wherein said combined content of units of the first and second hydroxybenzoic acid derivatives (b) and (d) is in the region of 75% of the total.
8. A polymeric material as claimed in any preceding claim wherein said dicarboxylic acid derivatives are aromatic dicarboxylic acids.
9. A polymeric material as claimed in claim 8 wherein said aromatic dicarboxylic acid comprises terephthalic acid is a particularly suitable aromatic dicarboxylic acid.

10. A polymeric material as claimed in any one of claims 1 to 7 wherein said dicarboxylic acids are aliphatic dicarboxylic acids.

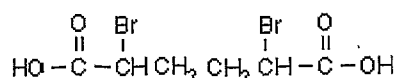
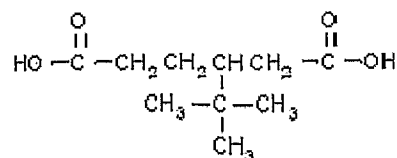
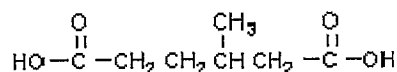
11. A polymeric material as claimed in claim 10 wherein said aliphatic dicarboxylic acid comprises sebacic acid, suberic acid, dodecanoic acid, adipic acid, diglycolic acid and 3,6-dioxaoctanedioic acid.

12. A polymeric material as claimed in claim 10 wherein said aliphatic dicarboxylic acid has the general formula (I):

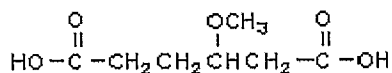


wherein n is a positive integer which is preferably in the range of from 1 to 10, and the carbon atoms in the chain may be substituted with hydrogen atoms or some or all of the carbon atoms may carry one or more alternative substituents including alkyl groups, alkoxy groups or halogen atoms, and one or more CH₂ groups along the hydrocarbon backbone may be substituted with oxygen to form an ether group, or may be substituted with an ester group.

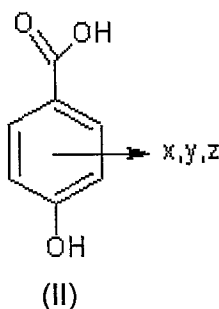
13. A polymeric material as claimed in claim 12 wherein said aliphatic dicarboxylic acid comprises a compound of the formula:



or

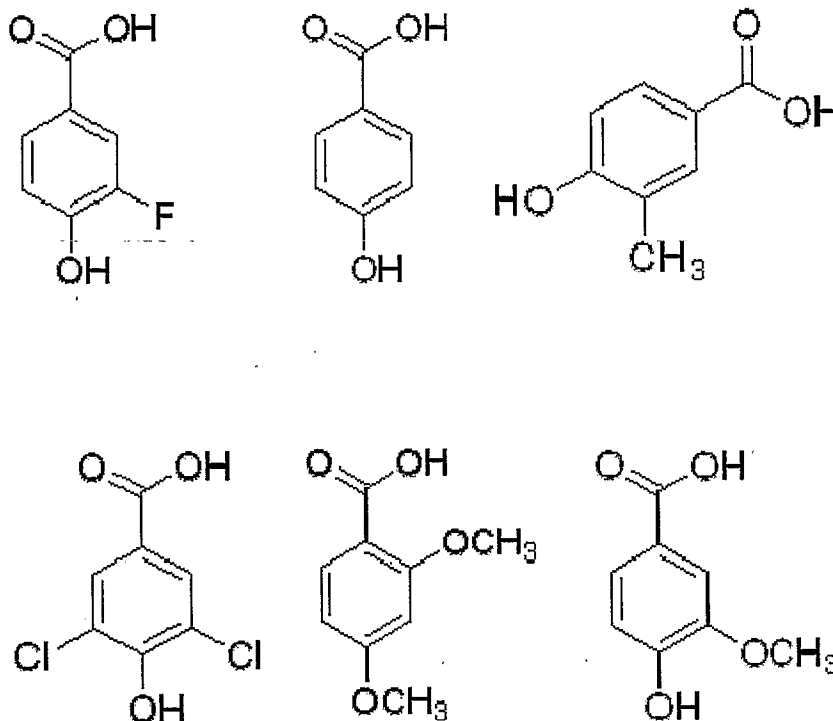


14. A polymeric material as claimed in any one of claims 1 to 13 wherein said first and second hydroxybenzoic acid derivatives are derivatives of 4-hydroxybenzoic acid.
15. A polymeric material as claimed in claim 14 wherein said first and second hydroxybenzoic acid derivatives are different hydroxybenzoic acid derivatives.
16. A polymeric material as claimed in claim 14 wherein said first and second hydroxybenzoic acid derivatives are the same hydroxybenzoic acid derivatives.
17. A polymeric material as claimed in claim 14, 15 or 16 wherein said first and second hydroxybenzoic acid derivatives have the general formula (II):



- wherein x, y and z represent optional substituents which may be present at any vacant position on the aromatic ring and are selected from straight or branched chain alkyl groups, straight or branched chain alkoxy groups, and halogen groups.

18. A polymeric material as claimed in claim 17 wherein said hydroxybenzoic acid derivatives comprises a compound of the formula:



5

19. A polymeric material as claimed in any preceding claim wherein said first hydroxybenzoic acid derivative (b) comprises 4-hydroxybenzoic acid.

10

20. A polymeric material as claimed in any preceding claim wherein said second hydroxybenzoic acid derivative (d) comprises a derivative of 4-hydroxybenzoic acid wherein one of the substituents x, y and z represents a methoxy group.

15

21. A polymeric material as claimed in claim 20 wherein said second hydroxybenzoic acid derivative (d) comprises 4-hydroxy-3-methoxybenzoic acid.

22. A polymeric material as claimed in any preceding claim wherein the diol comprises at least two phenyl rings.

20

23. A polymeric material as claimed in claim 22 wherein said phenyl rings are linked together by means of a direct bond or a linking group.

24. A polymeric material as claimed in claim 23 wherein said linking group comprises an alkyl, ether or sulphone group.

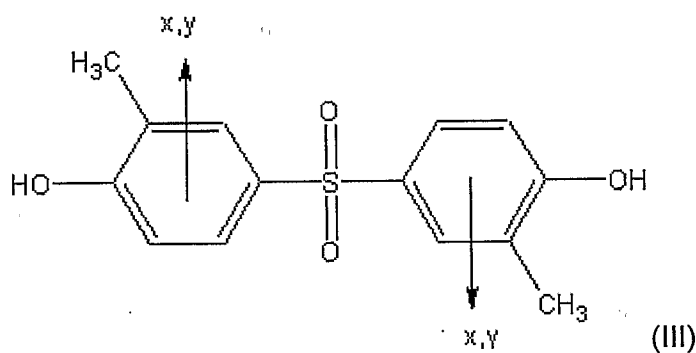
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25. A polymeric material as claimed in claim 22 wherein said phenyl rings are directly fused together into a polycyclic ring system.

26. A polymeric material as claimed in 22, 23 or 24 wherein said diol comprises a diphenyl derivative.

27. A polymeric material as claimed in claim 25 wherein said diol comprises a naphthalene derivative.

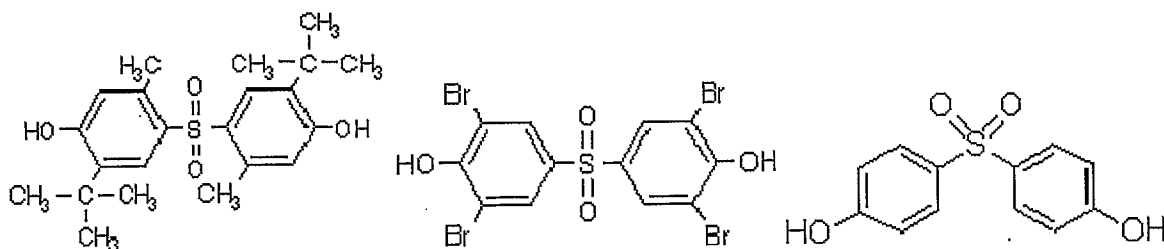
28. A polymeric material as claimed in claim 24 wherein said linking group comprises a sulphone group, and said diol component has the general formula (III):



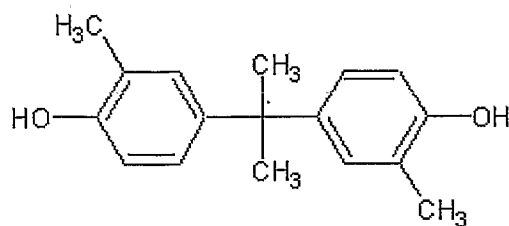
wherein x, y and z represent optional substituents which may be present at any vacant position on the aromatic ring and may be selected from straight or branched chain alkyl groups, straight or branched chain alkoxy groups, and halogen groups.

29. A polymeric material as claimed in claim 28 wherein said one or both of the depicted methyl groups is absent.

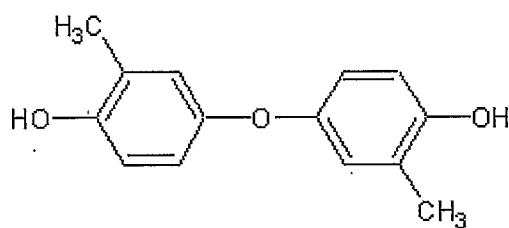
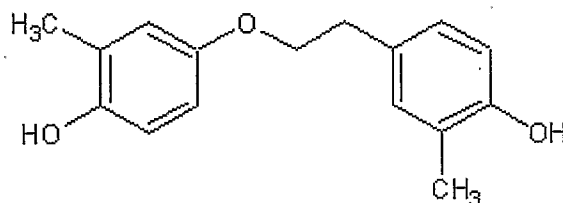
30. A polymeric material as claimed in claim 29 wherein said diol component comprises a compound of the formula:



31. A polymeric material as claimed in claim 23 wherein said diol component comprises a compound of the formula:

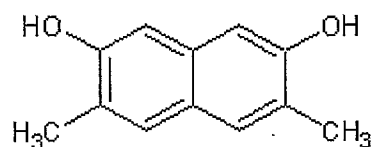
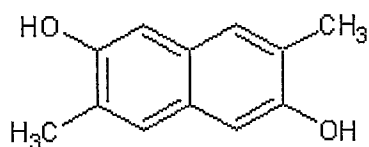


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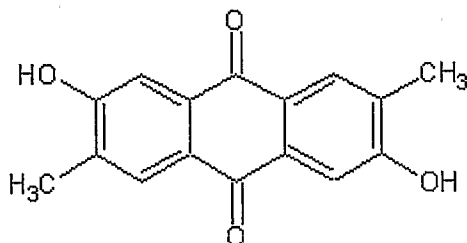
32. A polymeric material as claimed in claim 27 wherein said diol component comprises a compound of the formula:



15

33. A polymeric material as claimed in claim 23 wherein two phenyl rings are linked by two linking groups.

34. A polymeric material as claimed in claim 33 wherein said diol component comprises an anthraquinone compound of the formula:

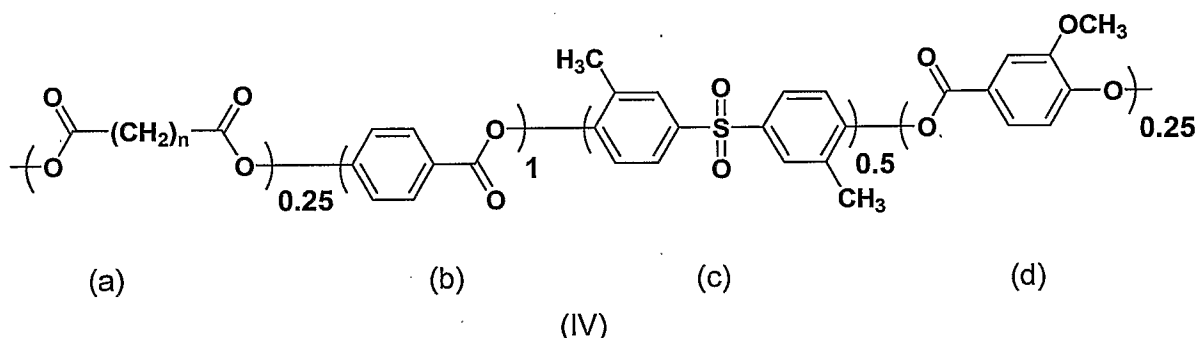


35. A polymeric material as claimed in claim 1 which comprises monomer units derived from (a) an aliphatic dicarboxylic acid, (b) 4-hydroxybenzoic acid, (c) 4,4-sulphonylbis(2-methylphenol) and (d) 4-hydroxy-3-methylbenzoic acid.

36. A polymeric material as claimed in claim 35 wherein said monomers are combined in the ratio of 0.25:1.0:0.25:0.5 ((a):(b):(c):(d)) and the polymer is of the formula (IV):

10

15



wherein n is a positive integer which is preferably in the range of from 1 to 10.

20

25

37. A polymeric material as claimed in claim 35 wherein the dicarboxylic acid comprises adipic acid, and the polymer comprises units of (a) adipic acid, (b) 4-hydroxybenzoic acid, (c) 4,4-sulphonylbis(2-methylphenol) and (d) 4-hydroxy-3-methylbenzoic acid (vanillic acid) in the ratio of Y:X:Y:X/2 ((a):(b):(c):(d)), wherein $3X/2 + 2Y = 100\%$.

30

38. A degradable polymeric material comprising monomer units derived from (a) a dicarboxylic acid, (b) a first hydroxybenzoic acid derivative, (c) a diol comprising at least two phenyl rings and (d) a second hydroxybenzoic acid derivative which has been processed into a fibre, wherein the combined content of units of the first and second hydroxybenzoic acid derivatives (b) and (d) in the polymer is greater than 55%, expressed as a mole fraction.

39. A polymeric material as claimed in claim 38 wherein the combined content of units of the first and second hydroxybenzoic acid derivatives (b) and (d) is greater than 57%, expressed as a mole fraction.
- 5 40. A polymeric material as claimed in claim 38 or 39 wherein the combined content of units of the first and second hydroxybenzoic acid derivatives (b) and (d) is greater than 59%, expressed as a mole fraction.
- 10 41. A polymeric material as claimed in claim 38, 39 or 40 wherein the combined content of units of the first and second hydroxybenzoic acid derivatives (b) and (d) is greater than 61%, expressed as a mole fraction.
- 15 42. A polymeric material as claimed in any one of claims 38 to 41 wherein the combined content of units of the first and second hydroxybenzoic acid derivatives (b) and (d) is greater than 63%, expressed as a mole fraction.
- 20 43. A polymeric material as claimed in any one of claims 38 to 42 wherein the combined content of units of the first and second hydroxybenzoic acid derivatives (b) and (d) is greater than 65%, expressed as a mole fraction.
44. A polymeric material as claimed in any one of claims 38 to 43 wherein said fibres have a tensile strength of at least 200 MPa.
- 25 45. A polymeric material as claimed in any one of claims 38 to 44 wherein said fibres have a tensile modulus of at least 7 GPa.
46. A polymeric material as claimed in any one of claims 1 to 45 for use in medical devices suitable for use in the human body.
- 30 47. A polymeric material as claimed in claim 46 wherein said device is selected from plates, rods, screws, pins, anchors, staples, arrows, medical device coatings and composite devices.
- 35 48. A polymeric material as claimed in claim 46 or 47 wherein said device is made by injection moulding.

49. A polymeric material as claimed in any one of claims 1 to 48 wherein the combined content of units of the first and second hydroxybenzoic acid derivatives (b) and (d) is 65%, expressed as a mole fraction and wherein said polymeric material degrades at a rate such that it loses around 90% of its molecular weight in about 6 weeks at a temperature of 70°C.
50. A polymeric material as claimed in any one of claims 1 to 48 wherein the combined content of units of the first and second hydroxybenzoic acid derivatives (b) and (d) is 75%, expressed as a mole fraction, and wherein said polymeric material degrades at a rate such that it loses around 80% of its molecular weight in about 6 weeks at a temperature of 70°C.
51. A polymeric material as claimed in any one of claims 1 to 50 wherein MC3T3 E1 viable cells are growing on the polymer after 7 days.
52. A polymeric material as claimed in any preceding claim which is biodegradable.
53. A polymeric material as claimed in any preceding claim which is bioresorbable.
54. A fibre formed from a polymeric material as claimed in any one of claims 1 to 53.
55. A composite device comprising (i) a degradable polymer comprising monomer units derived from (a) a dicarboxylic acid, (b) a first hydroxybenzoic acid derivative, (c) a diol comprising at least two phenyl rings and (d) a second hydroxybenzoic acid derivative, and (ii) a polymer matrix, wherein the combined content of units of the first and second hydroxybenzoic acid derivatives (b) and (d) in the polymer is greater than 55%, expressed as a mole fraction.
56. A composite device as claimed in claim 55 wherein the combined content of units of the first and second hydroxybenzoic acid derivatives (b) and (d) in the polymeric material is greater than 57%, expressed as a mole fraction.
57. A composite device as claimed in claim 55 or 56 wherein the combined content of units of the first and second hydroxybenzoic acid derivatives (b) and (d) in the polymeric material is greater than 59%, expressed as a mole fraction.

58. A composite device as claimed in claim 55, 56 or 57 wherein the combined content of units of the first and second hydroxybenzoic acid derivatives (b) and (d) in the polymeric material is greater than 61%, expressed as a mole fraction.
- 5 59. A composite device as claimed in any one of claims 55 to 58 wherein the combined content of units of the first and second hydroxybenzoic acid derivatives (b) and (d) in the polymeric material is greater than 63%, expressed as a mole fraction.
- 10 60. A composite device as claimed in any one of claims 55 to 59 wherein the combined content of units of the first and second hydroxybenzoic acid derivatives (b) and (d) in the polymeric material is greater than 65%, expressed as a mole fraction.
61. A composite device as claimed in any one of claims 55 to 60 wherein said polymer matrix material comprises poly(ϵ -caprolactone).
- 15 62. A medical device whenever obtained from a polymeric material as claimed in any one of claims 1 to 53.
- 20 63. A method of manufacturing a degradable polymer, said method comprising the steps of mixing (a) a dicarboxylic acid, (b) a first hydroxybenzoic acid derivative, (c) a diol comprising at least two phenyl rings and (d) a second hydroxybenzoic acid derivative in a solvent, heating the mixture to approximately 80°C, adding Vilsmeier reagent, and precipitating the resultant polymer out of the solution, wherein the combined content of units of the first and second hydroxybenzoic acid derivatives (b) and (d) is greater than 25 55%, expressed as a mole fraction.
64. A method as claimed in claim 63 wherein the combined content of units of the first and second hydroxybenzoic acid derivatives (b) and (d) is greater than 57%, expressed as a mole fraction.
- 30 65. A method as claimed in claim 63 or 64 wherein the combined content of units of the first and second hydroxybenzoic acid derivatives (b) and (d) is greater than 59%, expressed as a mole fraction.
- 35 66. A method as claimed in claim 63, 64 or 65 wherein the combined content of units of the first and second hydroxybenzoic acid derivatives (b) and (d) is greater than 61%, expressed as a mole fraction.

67. A method as claimed in any one of claims 63 to 66 wherein the combined content of units of the first and second hydroxybenzoic acid derivatives (b) and (d) is greater than 63%, expressed as a mole fraction.
- 5 68. A method as claimed in any one of claims 63 to 67 wherein the combined content of units of the first and second hydroxybenzoic acid derivatives (b) and (d) is greater than 65%, expressed as a mole fraction.
- 10 69. A method as claimed in any one of claims 63 to 68 wherein said solvent comprises a mixture of pyridine and dimethylformamide.
70. A plate whenever obtained from a polymeric material as claimed in any one of claims 1 to 53.
- 15 71. A rod whenever obtained from a polymeric material as claimed in any one of claims 1 to 53.
72. A screw whenever obtained from a polymeric material as claimed in any one of claims 1 to 53.
- 20 73. A pin whenever obtained from a polymeric material as claimed in any one of claims 1 to 53.
74. An anchor whenever obtained from a polymeric material as claimed in any one of claims 1 to 53.
- 25 75. A staple whenever obtained from a polymeric material as claimed in any one of claims 1 to 53.
- 30 76. An arrow whenever obtained from a polymeric material as claimed in any one of claims 1 to 53.
77. A medical device coating whenever obtained from a polymeric material as claimed in any one of claims 1 to 53.
- 35 78. A composite device whenever obtained from a polymeric material as claimed in any one of claims 1 to 53.

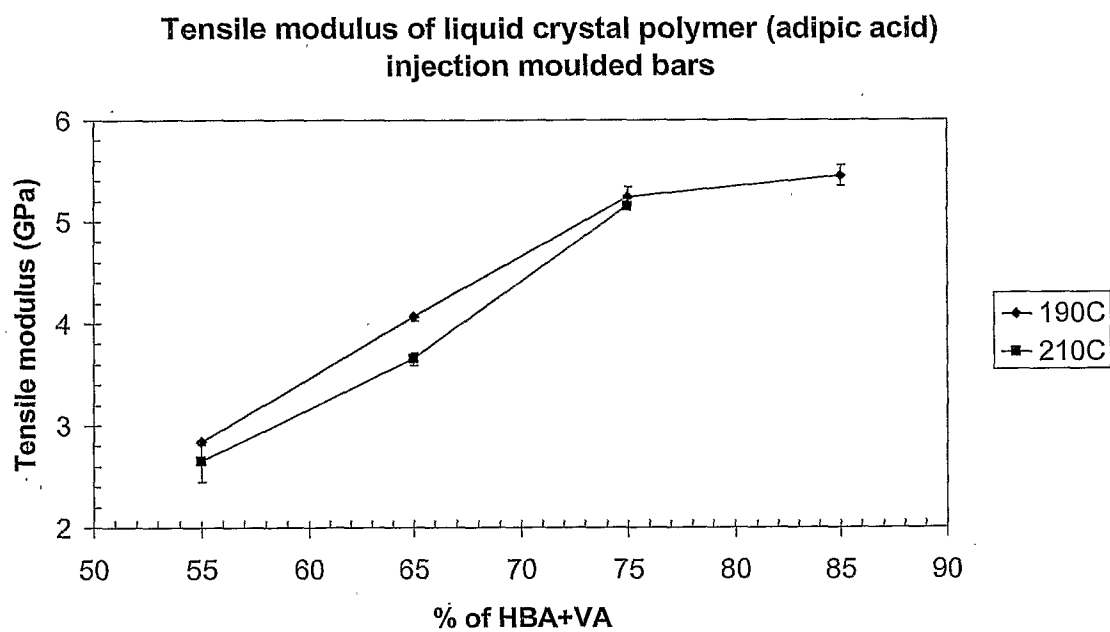
79. A degradable polymeric material as hereinbefore defined and with reference to the accompanying description and drawings.

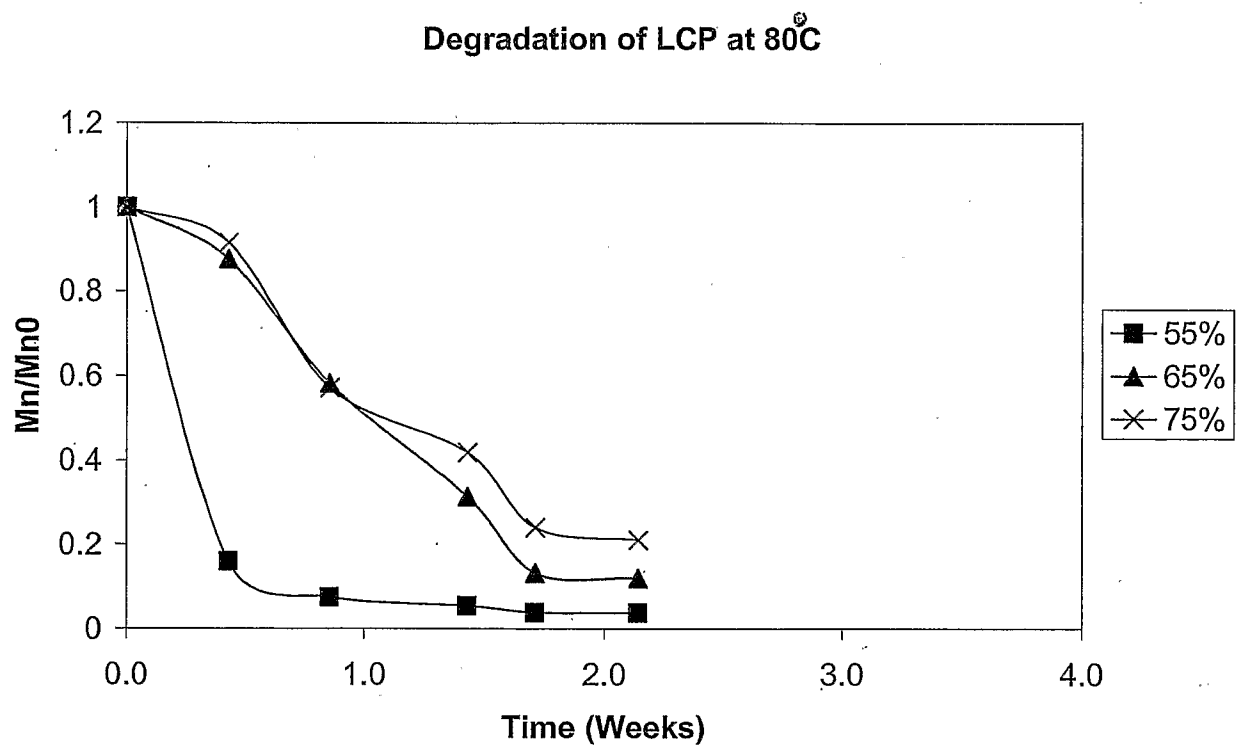
5 80. A method of manufacturing a degradable polymer as hereinbefore defined and with reference to the accompanying description and drawings.

81. A degradable polymeric material which has been processed into a fibre as hereinbefore defined and with reference to the accompanying description and drawings.

10 82. A composite device as hereinbefore defined and with reference to the accompanying description and drawings.

15

**FIGURE 1**

**FIGURE 2**

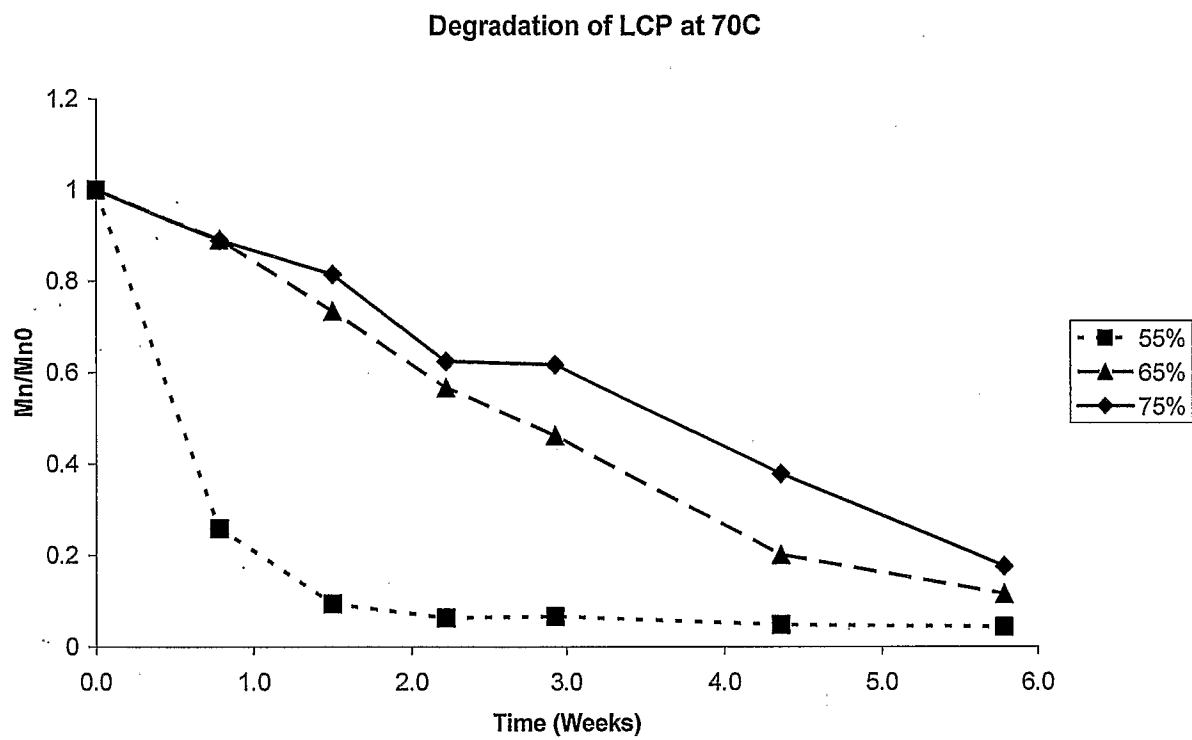


FIGURE 3

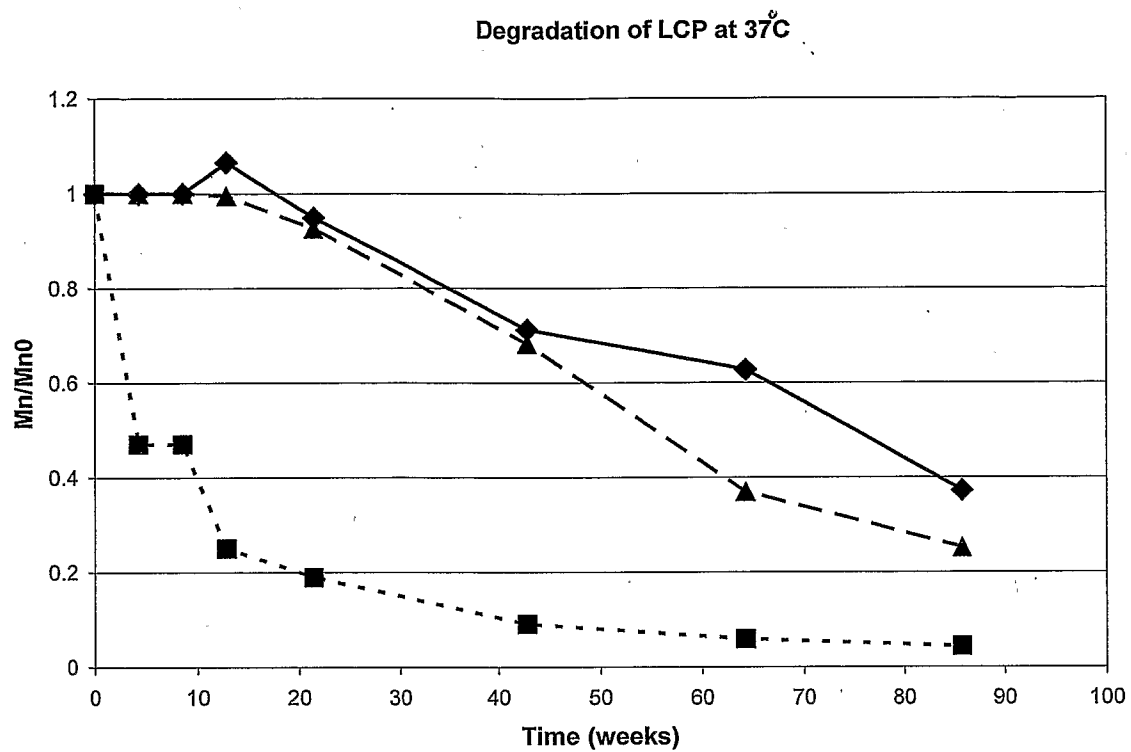


FIG 4

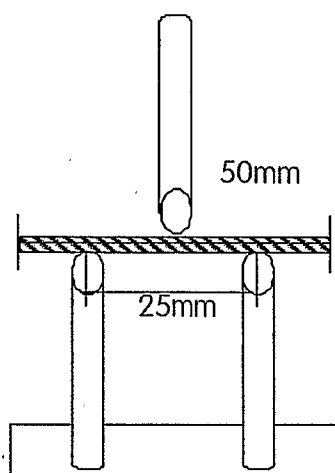


Figure 5

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2009/002646

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61L31/06 A61L31/14 C08G63/60

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)

A61L C08G

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, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2007/110609 A1 (SMITH & NEPHEW [GB]; DAGGER ANTHONY [GB]; MONTES DE OCA HORACIO [GB]) 4 October 2007 (2007-10-04) page 4, paragraph 0011 - page 4, paragraph 0012; claims 1, 5-8, 11, 14-18, 20-22, 24-26, 28-42; example 1	1-82
X	EP 0 347 963 A2 (ENIRICERCH SPA [IT]) 27 December 1989 (1989-12-27) claims 2-4; example 4	1-37

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

☒ See patent family annex.

* Special categories of cited documents:

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

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step 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

3 February 2010

Date of mailing of the international search report

09/02/2010

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Fax: (+31-70) 340-3016

Authorized officer

Enescu, Cristina

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/GB2009/002646

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2007110609	A1	04-10-2007	
		AU 2007231211 A1	04-10-2007
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