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(54) Title: LIQUID CARRIER MATERIALS

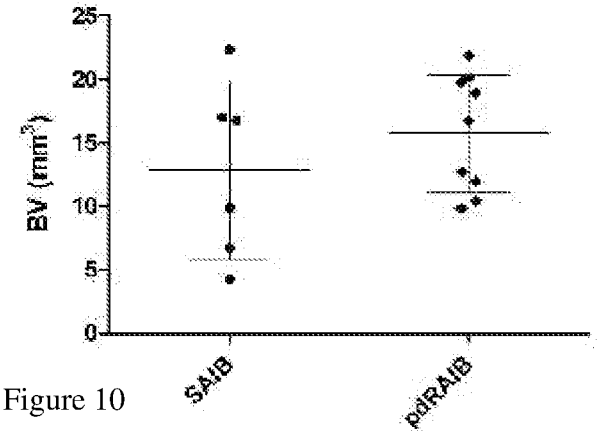


Figure 10

(57) Abstract: Abstract The invention relates to polymeric high viscosity liquid carrier materials (HVLCMs), in particular esterified polysaccharides, compositions comprising these HVLCMs, coatings for implants which are based on these HVLCMs, methods of their production and their use in delivering substances, including drugs and bioactive agents, systemically to a body as a sustained release device, or locally, as employed in bone tissue engineering and other applications.

Liquid Carrier Materials

Cross-Reference to Related Application

The present application claims priority from Australian Provisional Patent Application 2014900566 filed on 21 February 2014, the content of which is incorporated herein by reference.

Technical Field

The disclosure relates to polymeric high viscosity liquid carrier materials (HVLCMs), their method of production and use in delivering substances, including drugs and bioactive agents, systemically to a body as a sustained release device, or locally, as employed in bone tissue engineering and other applications.

Background of the Invention

Biomaterials engineering is an emerging biomedical field that involves the design and manufacture of new systems for delivering bioactive agents to various parts of the body. In bone tissue engineering the main class of bioactive agents currently used are the recombinant human bone morphogenetic proteins (rhBMPs), which are capable of inducing the formation of large amounts of new bone. Historically, the primary approach has been to deliver rhBMPs in porous solid scaffolds. Disadvantages with this method include a requirement for surgical implantation and a general inefficiency in the production of new bone.

Some delivery systems can be delivered via injection. The majority of current generation injectable materials are hydrogels. Chitosan/ -glycerophosphate, hyaluronic acid and PEG/fibrinogen hydrogels have shown a capacity to deliver rhBMP-2. Materials such as these hydrogels have several significant limitations. A critical constraint is the requirement for an implantable containment device or scaffold to prevent unwanted dispersal of the delivery system *in vivo*.

Alternative injectable systems can be phase transitioned by UV curing, but this method again requires surgery and presents an infection risk. Injectable poly(-hydroxy acid) polymers and foaming polymers have been developed, but bulk degradation with large polymer implants can create an acidic microenvironment that impairs osteoconduction. Micro-and nanoparticle encapsulation are also methods for injectable systems.

Ceramics which phase transition from liquid to solid have also been utilised for delivery. However, while some promising experimental results have been put forward,

these have not proven effective for tissue engineering and bone repair, and are not currently available.

Alternative delivery systems involve the use of non-polymeric high viscosity liquid carrier materials (HVLCM), such as sucrose acetate isobutyrate (SAIB). SAIB is a monomeric sugar-based ester of sucrose and acetic and isobutyric acids. It is highly viscous and demonstrates properties of a semi-solid material. SAIB is an injectable medium that has been used as a carrier for specific bioactive agents including systemic pharmaceuticals, local anaesthetics and delivering actives to promote bone repair *in vivo*. SAIB advantageously is able to stay at the site where it is administered and provides a reduced risk of infection associated with open implantation. However, its application is somewhat limited by its hydrophobicity which can retard solubility of actives and promote precipitation and denaturing of some actives.

There is a need for new carrier and delivery systems that are able to deliver a range of substances and are diverse in their application to a patient or subject.

Any discussion of documents, acts, materials, devices, articles or the like which has been included in the present specification is not to be taken as an admission that any or all of these matters form part of the prior art base or were common general knowledge in the field relevant to the present disclosure as it existed before the priority date of each claim of this application.

Summary of the Invention

Polymeric high viscosity liquid carrier materials (HVLCMs) have been developed and disclosed herein as alternative delivery systems for delivering agents including pharmaceutical drugs and bioactive agents. The HVLCMs disclosed herein are suitable for delivering substances locally or systemically.

In a first aspect, the invention provides an esterified polysaccharide which is a homopolymer or copolymer comprising esterified sugar monomer units, wherein the sugar monomer units are esterified ketose or aldose sugars.

In a second aspect, the invention provides an esterified polysaccharide which is a homopolymer or copolymer comprising esterified sugar monomer units, where the sugar monomer units are selected from: esterified 2-deoxyribose, esterified 2-deoxy-D-ribose, esterified fructose, esterified galactose, esterified glucose, esterified 2-deoxy-glucose, esterified 2-deoxy-D-glucose, esterified arabinose, esterified lyxose, esterified, esterified ribose, esterified xylose, esterified ribulose, esterified xyulose, esterified allose, esterified altrose, esterified mannose, esterified gulose esterified, esterified

idose, esterified talose, esterified psicose, esterified fructose, esterified sorbose, esterified tagatose, or a mixture thereof.

In a third aspect, the invention provides an esterified polysaccharide which is a homopolymer comprising esterified sugar monomer units, wherein the sugar monomer units are esterified 2-deoxyribose monomer units.

In a fourth aspect, the invention provides an esterified polysaccharide which is a homopolymer comprising esterified sugar monomer units, wherein the sugar monomer units are esterified fructose monomer units.

In a fifth aspect, the invention provides an esterified polysaccharide which is a homopolymer comprising esterified sugar monomer units, wherein the sugar monomer units are esterified galactose monomer units.

In a sixth aspect, the invention provides an esterified polysaccharide which is a homopolymer comprising esterified sugar monomer units, wherein the sugar monomer units are esterified glucose monomer units.

In a seventh aspect, the invention provides a pharmaceutical composition comprising the esterified polysaccharide according to any one of the first to sixth aspects, together with one or more pharmaceutically acceptable carriers and/or excipients.

In an eighth aspect, the invention provides a method to promote bone growth, the method comprising providing a composition according to the seventh aspect to a site in a subject to promote bone growth at the site.

In a ninth aspect, the invention provides a method to heal wounds in or on a subject, the method comprising a step of providing a composition according to the seventh aspect, to a wound site in or on the subject to promote healing of the wound.

In a tenth aspect, the invention provides a method to deliver an agent on or in a subject, the method comprising a step of providing a composition according to the seventh aspect, to a site on or in the subject.

In an eleventh aspect, the invention provides use of a composition according to the seventh aspect in the preparation of the medicament for promoting bone growth in a subject.

In a twelfth aspect, the invention provides use of a composition according to the seventh aspect in the preparation of the medicament for healing wounds in or on a subject.

In a thirteenth aspect, the invention provides use of a composition according to the seventh aspect in the preparation of the medicament for delivering an agent to a subject.

In a fourteenth aspect, the invention provides use of a composition according to the seventh aspect for promoting bone growth in a subject.

In a fifteenth aspect, the invention provides use of a composition according to the seventh aspect for healing wounds in or on a subject.

In a sixteenth aspect, the invention provides use of a composition according to the seventh aspect to deliver an agent to a subject.

In a seventeenth aspect, the invention provides a composition according to the seventh aspect for the controlled release of an agent.

In an eighteenth aspect, the invention provides an esterified polysaccharide according to any one of the first to sixth aspect for the controlled release of an agent.

In a nineteenth aspect, the invention provides an esterified polysaccharide according to any one of the first to sixth aspect for the local release of an agent.

In a twentieth aspect, the invention provides an esterified polysaccharide used as a high viscosity liquid carrier material.

In a twenty first aspect, the invention provides a composition for the controlled release of an agent comprising:

- a polymeric high viscosity liquid carrier material; and
- an agent.

In a twenty second aspect, the invention provides a composition for the local release of an agent comprising:

- a polymeric high viscosity liquid carrier material; and
- an agent.

In a twenty third aspect, the invention provides a coating for an implant comprising an esterified polysaccharide as defined in any one of the first to sixth aspects.

In a twenty fourth aspect, the invention provides a coating for an implant comprising a composition as defined in the seventh aspect.

In a twenty fifth aspect, the invention provides a use of an esterified polysaccharide as defined in any one of any one of the first to sixth aspects, for coating an implant.

In a twenty sixth aspect, the invention provides a use of a composition as defined in the seventh aspect, for coating an implant.

Brief Description of the Drawings

Figure 1 shows an exemplified condensation polymerisation mechanism utilising pendent hydroxyl moieties on sugar monomers to yield a polymer and results in the progressive loss of water molecules.

Figure 2 shows exemplified esterification reactions which may be utilised in the present invention: a) Fischer esterification; b) Steglich esterification; and c) an esterification reactions using an anhydride, alcohol and a base.

Figure 3 shows the FTIR spectra for: a) an esterified polymer of deoxyribose comprising acetate and isobutyrate esters (pdRAIB); and b) deoxyribose.

Figure 4 shows the FTIR spectra for: a) fructose; and b) an esterified polymer of fructose comprising acetate and isobutyrate esters (pdFAIB).

Figure 5 shows the ^{1}H NMR spectrum for an esterified polymer of deoxyribose comprising acetate and isobutyrate esters (pdRAIB).

Figure 6 shows the ^{13}C NMR spectrum for an esterified polymer of deoxyribose comprising acetate and isobutyrate esters (pdRAIB).

Figure 7 shows the dynamic viscosity for three systems with 20% ethanol at 37 °C, recorded at increasing shear rates, using a Physica MCR 301 (Anton Paar), with a gap of 50 µm. The three systems are:

a) an esterified polymer of deoxyribose comprising acetate and isobutyrate esters (pdRAIB), diluted with ethanol to give a pdRAIB:ethanol ratio of 80:20 (w/w);

b) an esterified polymer of fructose comprising acetate and isobutyrate esters (pFAIB), diluted with ethanol to give a pFAIB:ethanol ratio of 80:20 (w/w); and

c) sucrose acetate isobutyrate (SAIB) diluted with ethanol to give a SAIB:ethanol ratio of 80:20 (v/v).

Figure 8 shows histological sections from the three systems of Figure 7 with 5µg rhBMP-2 after 1 week intramuscular implantation in a mouse. Key: H&E refers to haematoxylin and eosin; Saf O refers to safranin O staining.

Figure 9 shows X-rays at 3 weeks post implantation of 5 µg rhBMP-2 in 20 µL of the SAIB and pdRAIB into bilateral quadriceps of C57BL6 mice.

Figure 10 shows: (A) representative X-ray images of bone formed by SAIB (control) and pdRAIB (test) at 3 weeks after implantation in mice; and (B) quantification of bone formed in multiple tests (multiple mice) by X-ray microtomography (microCT).

Figure 11 shows representative histological images of bone created by SAIB and pdRAIB used as carriers for rhBMP-2, wherein: (A) shows an ectopic bone nodule showing a cortical shell and pseudo marrow space made with SAIB; (B) shows a comparable cortical shell and pseudo marrow space which was observed with pdRAIB; (C) shows an example of a vessel surrounded by new bone with the ectopic bone nodule of a pdRAIB specimen; and (D) shows an enlargement of the bone/vessel from panel C with the red blood cells inside the vessel more clearly visible.

Figure 12 shows an esterified polymer of deoxyribose comprising acetate and isobutyrate esters (pdRAIB) dripped onto a porous bone graft substitute ("Vitoss") and bone graft ("Metaphyseal bone") and examined using fluorescent microscopy. The figure shows the "Background" autofluorescence of the Vitoss and bone graft overlaid with the fluorescent images of the Alexa 555 impregnated pdRAIB.

Detailed Description of the Invention

Herein, the phrase "pharmaceutically acceptable" is directed to compounds (including esterified or non-esterified polysaccharides, and solvents) or compositions and materials utilised to produce these compounds or compositions, which are not deleterious to a recipient, for example a human or animal patient receiving a treatment.

The esterified polysaccharides compounds disclosed herein are a new class of HVLCM (high viscosity liquid carrier material). Any reference throughout the specification to the "HVLCMs disclosed herein" relates specifically to the "esterified polysaccharide compounds" disclosed and claimed herein.

Herein, the term "polymer" may be used interchangeably with "polysaccharide" and "polymer ester" may be used interchangeably with "esterified polysaccharide".

Herein, in one embodiment a polysaccharide or an esterified polysaccharide can be, or be synthesised as, a "homopolymer", wherein only a single sugar monomer is present in the polysaccharide or the esterified polysaccharide.

Herein, in another embodiment a polysaccharide or an esterified polysaccharide can be, or be synthesised as, a "copolymer", wherein two or more different sugar monomers, for example two different sugar monomers, are present in the polysaccharide or the esterified polysaccharide.

In one embodiment the polysaccharide used for the production of an HVLCM disclosed herein is a homopolymer.

In another embodiment the polysaccharide used for the production of an HVLCM disclosed herein is a copolymer.

In another embodiment the esterified polysaccharide used for the production of an HVLCM disclosed herein is a homopolymer.

In yet another embodiment the esterified polysaccharide used for the production of an HVLCM disclosed herein is a copolymer.

Formation of Esterified Polysaccharides

Condensation Polymerisation

The formation of the esterified polysaccharides disclosed herein involves a condensation reaction to form polysaccharides followed by esterification. Herein the polysaccharides are primarily formed via a condensation polymerisation - an example is shown in Figure 1 - prior to any esterification reaction. Herein, the condensation polymerisation reaction is based on progressive, step-dehydration of two hydroxyl groups from adjacent sugar molecules resulting in the formation of ether bond between the individual sugar monomers and the release of one molecule of water. Formation of branched polymeric structures is anticipated together with the generation of random ether bonds, due to the high number of pendant hydroxyl moieties typically present on sugar molecules. For instance the polysaccharides are anticipated to comprise, for example, 1-4, 1-6, 2-4 etc. bonds between individual monomer units.

The synthesis of esterified polysaccharides based on simple sugar molecules consists of three separate steps:

1) condensation polymerisation (polycondensation) of sugars to form what is hereinafter referred to as the "polysaccharide";
2) esterification of the resulting polysaccharide to form what is hereinafter referred to as the "esterified polysaccharide"; and
3) purification of the final product.

It is possible to conduct the synthesis sequentially (steps 1 to 3) without stopping the process; alternatively the process can be interrupted between the three discrete stages of the production.

The process is applicable to a wide range of simple sugars, however adjustments of the operating conditions may be necessary for a person skilled in the art, in order to ensure optimal yield and decrease the undesired degradation products taking in to account the physical and/or chemical properties of individual sugar molecules.

The operating parameters can also be altered in order to fine tune specific properties of the final product, for instance: the desired molecular weight of the synthesised polysaccharide; and/or the hydrophilic/lipophilic balance of the final esterified polysaccharide.

The synthesis of the polymers and esterified polymers can be conducted in a laboratory suitable for general organic chemistry operations. Products on the scale of 5 to 100 g can be conveniently obtained using standard laboratory glassware. However, precise control of reaction temperature is necessary in order to obtain products with reproducible characteristics. Exothermic condensation and esterification reactions must be controlled to avoid overheating. Reactors with separate heating jackets, cooling coils and systems for programmed, precise dosing of the reagents may become necessary. To avoid oxidation and formation of degradation products steps 1) and 2) may need to be conducted under vacuum.

In a preferred embodiment the polysaccharide and/or esterified polysaccharide are pharmaceutically acceptable.

Traditional condensation polymerisation methodologies of sugar moieties, known to those skilled in the art, for example using a melt, can be used to produce the sugar based polymers. These approaches involve heating a sugar in the presence of a catalyst, such as phosphoric acid, resulting in the formation of polymers coupled with the expulsion of water molecules.

Herein polymers can be produced in solutions comprising short chain aliphatic organic acids, such as formic acid or acetic acid, rather than organic solvents.

A polysaccharide used for the production of the HVLCM disclosed herein can be synthesised as a homopolymer, wherein only a single sugar monomer is used in a condensation polymerisation; or synthesised as a copolymer wherein two or more different sugar monomers, for example two different sugar monomers, are used in a condensation polymerisation.

In one embodiment the polysaccharide used for the production of an HVLCM disclosed herein is a homopolymer.

In another embodiment the polysaccharide used for the production of an HVLCM disclosed herein is a copolymer.

Sugars

Sugars used as monomers for the production of the polysaccharides disclosed herein include any ketose or aldose sugars. In addition, polysaccharide starting materials can also be utilised as "macro-monomers" for the production of the polysaccharides disclosed herein.

One example of a sugar monomer utilised herein is deoxyribose. Deoxyribose is an endogenous sugar that fulfils multiple biological roles in mammals and is an important precursor to DNA, but the naturally occurring D-deoxyribose also has

important angiogenic properties. The angiogenic effects of deoxyribose are regulated by its secretion as deoxyribose-1-phosphate (D1P), which is dephosphorylated by the enzyme thymidine phosphorylase (TP) to regulate availability of the unphosphorylated pro-angiogenic deoxyribose sugar. Deoxyribose has been shown to increase vessel formation in a chick chorioallantoic membrane (CAM) assay and D1P promotes neoangiogenesis when implanted into mice on Matrigel plugs. Deoxyribose has also been found to act as a chemo-attractant in endothelial cell migration assays.

In one embodiment example sugar monomers used for the synthesis of polysaccharides disclosed herein include: deoxyribose (including D-deoxyribose and L-deoxyribose), arabinose (including D-arabinose and L-arabinose), lyxose (including D-lyxose and L-lyxose), ribose (including D-ribose and L-ribose), xylose (including D-xylose and L-xylose), ribulose (including D-ribulose and L-ribulose), xyulose (including D-xyulose and L-xyulose), allose (including D-allose and L-allose), altrose (including D-altrose and L-altrose), glucose (including D-glucose and L-glucose), 2-deoxy-glucose (including 2-deoxy-D-glucose and 2-deoxy-L-glucose), mannose (including D-mannose and L-mannose), gulose (including D-gulose and L-gulose), idose (including D-idose and L-idose), galactose (including D-galactose and L-galactose), talose (including D-talose and L-talose), psicose (including D-psicose and L-psicose), fructose (including D-fructose and L-fructose), sorbose (including D-sorbose and L-sorbose), tagatose (including D-tagatose and L-tagatose), inulin, starch, or a combination thereof.

In one embodiment sugar monomers used for the synthesis of polysaccharides disclosed herein include: deoxyribose, fructose, glucose, 2-deoxy-D-glucose or galactose.

In one particular embodiment deoxyribose is used as a sugar monomer in the production of a polysaccharide disclosed herein.

In one particular embodiment fructose is used as a sugar monomer in the production of a polysaccharide disclosed herein.

In one particular embodiment glucose is used as a sugar monomer in the production of a polysaccharide disclosed herein.

In one particular embodiment galactose is used as a sugar monomer in the production of a polysaccharide disclosed herein.

In one particular embodiment 2-deoxy-D-glucose is used as a sugar monomer in the production of a polysaccharide disclosed herein.

In one embodiment a sugar monomer disclosed herein promotes angiogenesis.

In one embodiment an esterified sugar monomer disclosed herein promotes angiogenesis.

In another embodiment a sugar monomer disclosed herein provides anti-angiogenic properties.

In another embodiment an esterified sugar monomer disclosed herein provides anti-angiogenic properties and is utilised in the treatment of tumours.

In another embodiment a sugar monomer disclosed herein provides anti-angiogenic properties.

In another embodiment an esterified sugar monomer disclosed herein provides anti-angiogenic properties and is utilised in the treatment of tumours.

Esterification

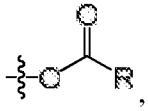
In order to produce the esterified polysaccharides disclosed herein (the HVLCMs), the polysaccharides disclosed herein are esterified. Free hydroxyl moieties on the sugar monomers are converted in to esters. These esters can be formed via a reaction with aliphatic organic acid anhydrides. Various esterification methods known to a person skilled in the art can be used to convert pendent alcohol groups on the sugar units to ester groups. Examples of methods that can used in the synthesis of esters are shown in Figure 2.

Esterifications methods can include: Steglich esterifications utilising a carboxylic acid and dicyclohexylcarbodiimide and 4-*N*,*N*-dimethylaminopyridine; Fischer esterifications utilising a carboxylic acid and a Lewis or Brønsted acid catalyst, for example hydrochloric acid or sulphuric acid; or esterifications utilising an acid anhydride and a base, such as pyridine or dicyclohexylcarbodiimide.

In one embodiment anhydrides are preferred for esterification reactions over the corresponding acids because esterification with acids results in the release of water which may hydrolyse the polysaccharide and decrease its molecular weight. Esterification with anhydrides results in the release of free acid which can be removed or lead to secondary esterification if the free acid is left in the system. Esterification can also be conducted with free fatty acids or fatty acid esters by the process of cross-esterification.

In one embodiment an esterified polysaccharide disclosed herein comprises one or more types of ester groups selected from: acetate, propanoate, butanoate, isobutanoate, pentanoate, isopentanoate, neopentanoate groups, or a mixture thereof. For example in one embodiment an esterified polysaccharide disclosed herein comprises a mixture of isobutanoate and acetate groups.

In one embodiment an esterified polysaccharide disclosed herein comprises esterified sugar monomer units that comprise ester groups of the formula:



wherein R can be an alkyl group, for example an alkyl group comprising 1 to 25 carbon atoms (C_{1-25} alkyl), for example 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24 or 25 carbon atoms. Example alkyl moieties include: methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, *tert*-butyl, *n*-pentyl, *tert*-pentyl, neopentyl, isopentyl, 1-methylbutyl and 1-ethylpropyl, *n*-hexyl, *n*-heptyl, or a mixture thereof.

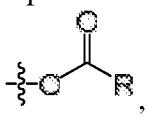
In one embodiment the esterified polysaccharide disclosed herein comprises only one ester group.

In one embodiment the esterified polysaccharide disclosed herein comprise two different ester groups.

In one embodiment the esterified polysaccharide disclosed herein comprises more than two different ester groups, for example 3, different ester groups.

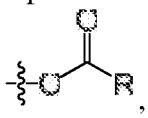
The hydrophilic/lipophilic balance of the esterified polymer can be varied based upon the choice of ester group "R" and the degree of esterification on the polysaccharide polymer.

In one embodiment the esterified polysaccharide disclosed herein comprises esterified sugar monomer units that comprise ester groups of the formula:



wherein R is methyl, ethyl or isopropyl, or a mixture thereof.

In one preferred embodiment the polysaccharide disclosed herein comprises esterified sugar monomer units that comprise two ester groups of the formula:



wherein one ester group possesses an R group which is methyl and one ester group possesses an R group which is isopropyl.

In a preferred embodiment the esterified polysaccharide disclosed herein is a HVLCM that has phase-transitioning properties and can be delivered by injection. In addition it is preferred that the esterified polysaccharide is able to transport bioactive agents. For example the esterified polysaccharide can be incorporated into a composition, such as a composition to promote bone growth, at a site in a subject,

wherein the composition functions as an injectable delivery system for other bioactive agents contained within the composition.

Water Loading

In some cases the HVLCMs disclosed herein may need to be used in conjunction with a solvent, for example ethanol, to aid in administration, for example administration by syringe, to a relevant site on or in a patient. Some solvents do not allow for the efficient transfer of biological material due to a lack of solubility, or the solvent inducing detrimental issues into the biological material, for example the denaturing of proteins.

A suitable carrier for biological material, such as proteins is water, hence the ability of the polysaccharides disclosed herein (both esterified and non-esterified) to retain water is important. A polymer that can hold water is able to transport biological material such as cells and/or proteins can reduce or negate any detrimental effects on the biological material.

In one embodiment the HVCLMs disclosed herein advantageously have a high water loading ability, particularly when compared to known HVCLMs including SAIB.

In one embodiment the HVLCMs disclosed herein are able to be loaded with water to a value of at least 10% v/v, preferably at least 20% v/v, more preferably at least 30, most preferably at least 40% v/v. For example at least 15, 20, 25, 30, or 35% v/v.

In one embodiment the HVLCMs disclosed herein are able to be loaded with water to a value in a range of about 10% v/v to about 40% v/v, for example about 15, 20, 25, 30, or 35% v/v.

High Viscosity Liquid Carrier Material (HVLCM)

The esterified polysaccharides disclosed herein are high viscosity liquid carrier materials (HVLCMs). Accordingly, the HVLCMs disclosed herein are polymers.

In one embodiment the HVLCMs disclosed herein are phase-transitioning, wherein they form semi-solid depots at physiological conditions, i.e. *in vivo*.

In another embodiment the HVLCMs are biodegradable.

In another embodiment the rate of release of an agent from an HVLCM carrier can be controlled via the choice of sugar monomer in the HVLCM, the type and quantity of ester groups on the HVLCM and the molecular weight of the HVLCM.

In one embodiment, the HVLCMs disclosed herein do not crystallise neat under ambient or physiological conditions.

In one particular embodiment a HVLCM disclosed herein is an esterified polysaccharides with a viscosity of at least 5000 mPa.s at 37 °C (for example at least 6000, 7000, 8000, 9000, 10000, 11000, 12000, 13000, 14000, 15000, 16000, 17000, 18000, 19000, 20000, 21000, 22000, 23000, 24000, 25000 or even about 50000 mPa.s at 37 °C). For example a HVLCM disclosed herein is an esterified polysaccharides with a viscosity in a range of: 5000 to 50000 mPa.s at 37 °C; 5000 to 45000 mPa.s at 37 °C; 5000 to 40000 mPa.s at 37 °C; 5000 to 35000 mPa.s at 37 °C; 5000 to 30000 mPa.s at 37 °C; 5000 to 25000 mPa.s at 37 °C; 5000 to 20000 mPa.s at 37 °C; 5000 to 15000 mPa.s at 37 °C; 5000 to 10000 mPa.s at 37 °C; 10000 to 50000 mPa.s at 37 °C; 15000 to 50000 mPa.s at 37 °C; 20000 to 50000 mPa.s at 37 °C; 25000 to 50000 mPa.s at 37 °C; 30000 to 50000 mPa.s at 37 °C; 35000 to 50000 mPa.s at 37 °C; 40000 to 50000 mPa.s at 37 °C; or 45000 to 50000 mPa.s at 37 °C. The viscosity can be measured, for example, at 37 °C on a Physica MCR 301 (Anton Paar) with 20% solvent (w/v), with increasing shear rates, and with a gap of 50 μm.

In order to administer an HVLCM disclosed herein or allow the HVLCM to release an agent contained therein, for example a drug encapsulated therein, the HVLCM can be mixed with a solvent in order to reduce the viscosity. The reduction in viscosity makes it easier to administer or apply the HVLCM on or on to a subject. A composition comprising an HVLCM disclosed herein and a solvent can have any desired viscosity. For *in vivo* applications, to allow ease of administration and application, typically a composition comprising an HVLCM disclosed herein and a solvent possess a viscosity that is less than about 1000 mPa.s at 37 °C, for example less than about 900, 800, 700, 600, 500, 400, 300, 200, or 100 mPa.s at 37 °C. In one embodiment, the viscosity is less than about 200 mPa.s at 37 °C. For example the HVLCM disclosed herein and a solvent possess may possess a viscosity in a range of 50 to 1000 mPa.s at 37 °C; 100 to 1000 mPa.s at 37 °C; 150 to 1000 mPa.s at 37 °C; 200 to 1000 mPa.s at 37 °C; 250 to 1000 mPa.s at 37 °C; 300 to 1000 mPa.s at 37 °C; 400 to 1000 mPa.s at 37 °C; 450 to 1000 mPa.s at 37 °C; 500 to 1000 mPa.s at 37 °C; 550 to 1000 mPa.s at 37 °C; 600 to 1000 mPa.s at 37 °C; 650 to 1000 mPa.s at 37 °C; 700 to 1000 mPa.s at 37 °C; 750 to 1000 mPa.s at 37 °C; 800 to 1000 mPa.s at 37 °C; 850 to 1000 mPa.s at 37 °C; 900 to 1000 mPa.s at 37 °C; 950 to 1000 mPa.s at 37 °C; 50 to 950 mPa.s at 37 °C; 50 to 900 mPa.s at 37 °C; 50 to 850 mPa.s at 37 °C; 50 to 800 mPa.s at 37 °C; 50 to 750 mPa.s at 37 °C; 50 to 700 mPa.s at 37 °C; 50 to 650 mPa.s at 37 °C; 50 to 600 mPa.s at 37 °C; 50 to 550 mPa.s at 37 °C; 50 to 500 mPa.s at 37 °C; 50 to 450 mPa.s at 37 °C; 50 to 400 mPa.s at 37 °C; 50 to 350 mPa.s at 37 °C; 50 to 300 mPa.s at 37 °C; 50 to 250 mPa.s at 37 °C; 50 to 200 mPa.s at 37 °C; 50 to

150 mPa.s at 37 °C; or 50 to 100 mPa.s at 37 °C. The viscosity can be measured, for example, at 37 °C on a Physica MCR 301 (Anton Paar) with 20% solvent (w/v), with increasing shear rates, and with a gap of 50 µm.

When an HVLCM disclosed herein is diluted in a solvent there is a reduction in viscosity. One advantage of the present system is the phase-transition properties, wherein semi-solid depots of the HVLCMs are formed *in vivo* following dissipation of the solvent.

Advantageously the HVLCMs disclosed herein remain at a site of delivery or application. It is highly preferred that once delivered/applied to a site on or in a subject, the HVLCM does not spread from the site at which it is delivered. This is advantageous with, for example, wound healing as delivered bioactive agents can remain at the wound to promote healing. When used for promoting bone growth, the esterified polysaccharide is able to remain at a delivery site and reduce that chance of irregular or ectopic bone formation.

In one embodiment the HVLCM is an esterified polysaccharide and has a viscosity of at least 5000 mPa.s at 37 °C.

In another embodiment the HVLCM is an esterified polysaccharide and has a viscosity of less than about 1000 mPa.s at 37 °C, when diluted with a volume of solvent.

In yet another embodiment the HVLCM is an esterified polysaccharide and has a viscosity of less than about 1000 mPa.s at 37 °C when measured on using a Physica MCR 301 (Anton Paar) with 20% solvent (w/v), with increasing shear rates, and with a gap of 50 µm.

Preferably the HVLCM disclosed herein is an esterified polysaccharide that is biodegradable and possesses phase transitioning properties so that it is capable of being delivered via, for example an injection, but forms a solid or semi-solid mass after deposition or introduction to a physiological environment. In one embodiment the site requires the promotion of bone growth and in another embodiment wound healing.

Advantageously, the phase transitioning properties allow the HVLCM disclosed herein to remain at a site at which it is delivered. This favourably allows for both surgical and non-surgical delivery, optimises release kinetics for any biologically active material carrier by the HVLCM. With bone delivery it also minimises risks of irregular shaped or ectopic bone formation.

In another embodiment a polysaccharide disclosed herein promotes angiogenesis.

In another embodiment an esterified polysaccharide disclosed herein promotes angiogenesis.

In another embodiment a HVLCM disclosed herein promotes angiogenesis.

In one embodiment a polysaccharide disclosed herein provides anti-angiogenic properties.

In another embodiment an esterified polysaccharide disclosed herein provides anti-angiogenic properties.

In another embodiment a HVLCM disclosed herein provides anti-angiogenic properties.

In one embodiment a polysaccharide disclosed herein provides anti-angiogenic properties and is utilised in the treatment of tumours.

In another embodiment an esterified polysaccharide disclosed herein provides anti-angiogenic properties and is utilised in the treatment of tumours.

In another embodiment a HVLCM disclosed herein provides anti-angiogenic properties and is utilised in the treatment of tumours.

Pharmaceutical Compositions of the Invention

Also disclosed herein are pharmaceutical compositions comprising the esterified polysaccharide disclosed herein as a HVLCM, and one or more pharmaceutically acceptable ingredients that are known to those skilled in the art. In a preferred embodiment the composition is pharmaceutically acceptable.

The esterified polysaccharide disclosed herein is present in a composition of the invention, preferably a pharmaceutically acceptable composition in any amount that achieves a desired effect. Example amounts include an amount in the range from about 99.5 percent to about 5 percent by weight relative to the total weight of the composition; in an amount in the range from about 99.5 percent to about 10 percent by weight relative to the total weight of the composition; in an amount in the range from about 95 to about 25 percent by weight relative to the total weight of the composition; and in an amount in the range from about 85 to about 45 percent by weight relative to the total weight of the composition.

The pharmaceutically acceptable ingredients include: pharmaceutically acceptable carriers, diluents, excipients, adjuvants, fillers, buffers, preservatives, anti-oxidants, lubricants, stabilisers, solubilisers, surfactants (e.g., wetting agents), chelators, adjuvants, penetration enhancers or a mixture thereof.

In one embodiment the composition disclosed herein further includes an agent and an esterified polysaccharide as a HVLCM and optionally a solvent, preferably a pharmaceutically acceptable solvent.

In one particular embodiment the pharmaceutical composition comprises an esterified polysaccharide as disclosed herein as a HVLCM.

In another preferred embodiment the pharmaceutical composition comprises an esterified polysaccharide as disclosed herein as a HVLCM and one or more of the following:

- a solvent, preferably a pharmaceutically acceptable solvent; and/or
- one or more agents (including: bioactive agents such as: an anti-resorptive agent; an angiogenic compound; an osteoconductive agent; and/or an angiogenic agent).

The agents, in particular the bioactive agents, disclosed herein, are present in an amount sufficient to deliver to a host subject an effective amount of the agent required to achieve a desired effect. The amount of agent, in particular bioactive agent, incorporated into the composition disclosed herein depends upon a desired release profile, the concentration of agent required for an effect such as a biological effect, and the desired period of release of the agent. Concentrations will be dependent on factors such as: absorption, inactivation, and excretion rates of the agent. Dosages will be adjusted by a person skilled in the art to take into consideration factors such as the severity of a particular condition in a subject.

The composition disclosed herein may be administered in a single dose or divided to be administered in more than one dose administered over a desired/required period of time.

In one embodiment a composition, preferably a pharmaceutically acceptable composition, disclosed herein promotes angiogenesis.

Solvent

In one embodiment, a composition or carrier disclosed herein comprises a solvent, preferably a pharmaceutically acceptable solvent.

In one embodiment the esterified polysaccharide of the invention is a HVLCM that can be diluted in a suitable solvent to form a liquid suitable for administration, e.g. by injection. Here is preferred that once administered, e.g. by injection, the solvent dissipates away leaving the HVLCM at the site of administration.

In order to facilitate administration, for example via injection, of an esterified polysaccharide of the invention, the esterified polymer can be diluted with a solvent. In

a preferred embodiment the solvent is a pharmaceutically acceptable solvent. Suitable solvents include: alcohols, such as ethanol, propanol, and benzyl alcohol; tetraglycol (glycofurol/tetrahydrofurfuryl ether polyethyleneglycol); dimethyl sulfoxide, triacetin, Solketal (isopropylideneglycerol); N-methyl-2-pyrrolidone (NMP) and 2-pyrrolidone (2-pyrol); esters of carbonic acid and alkyl alcohols such as propylene carbonate, ethylene carbonate and dimethyl carbonate; fatty acids such as acetic acid, lactic acid and heptanoic acid; alkyl esters of mono-, di-, and tri-carboxylic acids such as 2-ethyoxyethyl acetate, ethyl acetate, methyl acetate, ethyl lactate, ethyl butyrate, diethyl malonate, diethyl glutonate, tributyl citrate, diethyl succinate, tributyrin, isopropyl myristate, dimethyl adipate, dimethyl succinate, dimethyl oxalate, dimethyl citrate, triethyl citrate, acetyl tributyl citrate, glyceryl triacetate; alkyl ketones such as acetone and methyl ethyl ketone; ether alcohols such as 2-ethoxyethanol, ethylene glycol dimethyl ether, glycerol formal; polyhydroxy alcohols such as propylene glycol, polyethylene glycol (PEG), glycerin (glycerol), 1,3-butyleneglycol, and isopropylidene glycol (2,2-dimethyl-1,3-dioxolone-4-methanol), dialkylamides such as dimethylformamide, dimethylacetamide; dimethylsulfoxide (DMSO) and dimethylsulfone; tetrahydrofuran; lactones such as -caprolactone and butyrolactone; cyclic alkyl amides such as caprolactam; aromatic amides such as N,N-dimethyl-m-toluamide, and 1-dodecylazacycloheptan-2-one, or mixtures and combinations thereof. In one embodiment the solvents are: ethanol, ethyl acetate, DMSO, tetraglycol (glycofurol), benzyl alcohol, dimethyl sulfoxide, ethyl lactate, ethyl acetate, triacetin, N-methylpyrrolidone, propylene carbonate, glycerol formal, Solketal (isopropylideneglycerol), or a mixture thereof.

In one embodiment the solvent is ethanol, benzyl alcohol or tetraglycol.

In another embodiment the solvent is ethanol.

In another embodiment the solvent is benzyl alcohol.

In yet another embodiment the solvent is tetraglycol.

In one embodiment the esterified polysaccharide of the invention is an HVLCM that is dissolved in a solvent, wherein the solvent is present in an amount of about 10 to about 40%v/v, or in an amount of about 10 to about 30%v/v. Example amounts include: about 10, about 11, about 12, about 13, about 14, about 15, about 16, about 17, about 18, about 19, about 20, about 21, about 22, about 23, about 24, about 25, about 26, about 27, about 28, about 29, about 30, about 31, about 32, about 33, about 34, about 35, about 36, about 37, about 38, about 39, or about 40 % v/v.

In one embodiment the esterified polysaccharide of the invention is an HVLCM that is dissolved in ethanol, wherein ethanol is present in an amount of about 10 to

about 40%v/v, or in an amount of about 10 to about 30%v/v. Example amounts include: about 10, about 11, about 12, about 13, about 14, about 15, about 16, about 17, about 18, about 19, about 20, about 21, about 22, about 23, about 24, about 25, about 26, about 27, about 28, about 29, about 30, about 31, about 32, about 33, about 34, about 35, about 36, about 37, about 38, about 39, or about 40 % v/v.

In one embodiment the esterified polysaccharide of the invention is an HVLCM that is dissolved in benzyl alcohol, wherein benzyl alcohol is present in an amount of about 10 to about 40%v/v, or in an amount of about 10 to about 30%v/v. Example amounts include: about 10, about 11, about 12, about 13, about 14, about 15, about 16, about 17, about 18, about 19, about 20, about 21, about 22, about 23, about 24, about 25, about 26, about 27, about 28, about 29, about 30, about 31, about 32, about 33, about 34, about 35, about 36, about 37, about 38, about 39, or about 40 % v/v.

In one embodiment the esterified polysaccharide of the invention is an HVLCM that is dissolved in tetraglycol, wherein tetraglycol in an amount of about 10 to about 40%v/v, or in an amount of about 10 to about 30%v/v. Example amounts include: about 10, about 11, about 12, about 13, about 14, about 15, about 16, about 17, about 18, about 19, about 20, about 21, about 22, about 23, about 24, about 25, about 26, about 27, about 28, about 29, about 30, about 31, about 32, about 33, about 34, about 35, about 36, about 37, about 38, about 39, or about 40 % v/v.

In a preferred embodiment any solvent introduced with an esterified polysaccharide of the invention rapidly dissipates *in vivo* leading to a semisolid or highly viscous depot of the esterified polysaccharide of the invention.

Agents

Herein the term agent refers to any substance to be delivered to the subject and includes bioactive agents. Bioactive agents as used herein refers to an organic molecule including a drug, peptide, protein, carbohydrate (including monosaccharides, oligosaccharides, and polysaccharides), nucleoprotein, mucoprotein, lipoprotein, synthetic polypeptide or protein, or a small molecule linked to a protein, glycoprotein, steroid, nucleic acid (any form of DNA, including CDNA, or RNA, or a fragment thereof), nucleotide, nucleoside, oligonucleotides (including antisense oligonucleotides), gene, lipid, hormone, vitamin, including vitamin C and vitamin E; inorganic compound, anti-cancer drug, or combination thereof, that causes a biological effect when administered *in vivo* to a subject, for example a human being or an animal, or on a subject, for example where the bioactive agent is delivered topically.

The term drug, as used herein, refers to any substance used internally or externally as a medicine for the treatment, cure, or prevention of a disease or disorder, and includes: immunosuppressants, antioxidants, anaesthetics, chemotherapeutic agents, steroids (including retinoids), hormones, antibiotics, antivirals, antifungals, antiproliferatives, antihistamines, anticoagulants, antiphotoaging agents, melanotropie peptides, nonsteroidal and steroidal anti-inflammatory compounds, antipsychotics, and radiation absorbers, including UV-absorbers.

Biodegradable Polymer

In one embodiment, a composition or carrier disclosed herein further comprises an additional biodegradable polymer. Examples of additional biodegradable polymers include: poly(lactic acid) (PLA), including poly(D-lactic acid) (PDLA), poly(lactic-co-glycolic acid) (PLGA), poly(glycolic acid) (PGA), poly(-caprolactone) (PCL), or a mixture thereof.

In one embodiment a solvent is added in addition to a biodegradable polymer. Example solvents include: ethyl acetate, alcohols, such as ethanol, propanol, and benzyl alcohol; tetraglycol (glycofurol/tetrahydrofurfuryl ether polyethyleneglycol); dimethyl sulfoxide, triacetin, Solketal (isopropylideneglycerol); N-methyl-2-pyrrolidone (NMP) and 2-pyrrolidone (2-pyrol); esters of carbonic acid and alkyl alcohols such as propylene carbonate, ethylene carbonate and dimethyl carbonate; fatty acids such as acetic acid, lactic acid and heptanoic acid; alkyl esters of mono-, di-, and tri-carboxylic acids such as 2-ethyoxyethyl acetate, methyl acetate, ethyl lactate, ethyl butyrate, diethyl malonate, diethyl glutonate, tributyl citrate, diethyl succinate, tributyrin, isopropyl myristate, dimethyl adipate, dimethyl succinate, dimethyl oxalate, dimethyl citrate, triethyl citrate, acetyl tributyl citrate, glyceryl triacetate; alkyl ketones such as acetone and methyl ethyl ketone; ether alcohols such as 2-ethoxyethanol, ethylene glycol dimethyl ether, glycerol formal; polyhydroxy alcohols such as propylene glycol, polyethylene glycol (PEG), glycerin (glycerol), 1,3-butyleneglycol, and isopropylidene glycol (2,2-dimethyl-1,3-dioxolone-4-methanol), dialkylamides such as dimethylformamide, dimethylacetamide; dimethylsulfoxide (DMSO) and dimethylsulfone; tetrahydrofuran; lactones such as -caprolactone and butyrolactone; cyclic alkyl amides such as caprolactam; aromatic amides such as N,N-dimethyl-m-toluamide, and 1-dodecylazacycloheptan-2-one, or mixtures and combinations thereof. Preferred solvents are ethanol, ethyl acetate, DMSO, tetraglycol (glycofurol), benzyl alcohol, dimethyl sulfoxide, ethyl lactate, ethyl acetate, triacetin, N-methylpyrrolidone,

propylene carbonate, glycerol formal, Solketal (isopropylideneglycerol), or a mixture thereof.

In one embodiment the biodegradable polymer is present in an amount of about 0.1% to about 60% (w/w), for example: about 0.1% to about 50% (w/w), about 0.1% to about 40% (w/w), about 0.1% to about 30% (w/w), about 0.1% to about 20% (w/w), about 0.1% to about 10% (w/w), or about 0.1% to about 5% (w/w).

Osteoinductive Agent

In one embodiment the composition or carrier disclosed herein, comprises a bioactive agent that is an osteoinductive agent.

In one embodiment, the osteoinductive agent may be selected from a group that comprises: an osteogenic protein, or a growth factor, or a member or the TGF-beta superfamily, or a mixture thereof.

In a preferred embodiment, the osteoinductive agent is an osteogenic protein.

In a further preferred embodiment, the osteogenic protein is a bone morphogenetic protein (BMP), including human bone morphogenetic proteins (rhBMPs). Examples of BMPs include: BMP-2, BMP-4, BMP-6, BMP-7 (OP-1), and BMP-9, rhBMP-1, rhBMP-2, rhBMP-3, rhBMP-4, rhBMP-5, rhBMP-6, rhBMP-7, rhBMP-8a, rhBMP-8b, rfiBMP-9, rhBMP-10, rhBMP-15, noggin resistant BMPs, or a combination thereof.

In yet a further preferred embodiment, the osteoinductive agent is a BMP approved for human use which is rhBMP-2, or rhBMP-7.

In one embodiment the osteoinductive agent is rhBMP-2 is present in an amount of about 0.1 to about 40 mg, preferably about 1 to about 12 mg. For example, the osteinductive agent is rhBMP-2 and is present in a dose of about 0.1 to about 5 mg per mL; or is present in a dose of about 1 to about 2 mg per mL.

In one embodiment the osteoinductive agent is rhBMP-7 is present in an amount of about 0.1 to about 40 mg, preferably about 1 to about 12 mg. For example, the osteinductive agent is rhBMP-7 and is present in a dose of about 0.1 to about 5 mg per mL; or is present in a dose of about 1 to about 2 mg per mL.

In another embodiment the osteoinductive agent is a growth factor. Examples of growth factors include: platelets/platelet derived growth factor (PDGF), vascular endothelial growth factor (VEGF), Myostatin (GDF-8), insulin-like growth factor (IGF), and/or a member of the TGF-beta superfamily such as TGF-betal, TGF-beta2, TGF-beta3, growth and differentiation factors (GDFs), fibroblast growth factor-1 (FGF-1), fibroblast growth factor-2 (FGF-2), other fibroblasts growth factors,

Growth/differentiation factor 5 (GDF-5) hepatocyte growth factor (HGF), epidermal growth factor (EGF) activins, inhibins, follistatin or other specific activators of these pathways.

In another embodiment a mix of growth factors has been derived from human bone or other tissue, or from the products of cultured cells.

Anti-resorptive Agent

In one embodiment compositions of the invention, preferably pharmaceutically acceptable compositions, comprise a bioactive agent that is an anti-resorptive agent. Preferably the anti-resorptive agent has synergy with any osteoconductive agents present in the composition. Examples of anti-resorptive agents include: bisphosphonates including: zoledronic acid, pamidronic acid, ibandronic acid, etidronic acid, alendronic acid, risedronic acid, and tilurondic acid; IKK inhibitors; Osteoprotegerin (OPG); inhibitors of Cathepsin K, chloride ion channel blockers; antibodies directed against RANKL, SOST, and DKK1; and proton pump inhibitors, or a mixture thereof.

In a preferred embodiment the anti-resorptive agent is selected from: zoledronic acid, OPG, and inhibitors of both IKK and Cathepsin K, anti-RANKL Ab, anti-SOST Ab, and anti DKK1 Ab.

In one embodiment the anti-resorptive agent is Zoledronic acid and is present in an amount of about 10 to about 1000 µg, preferably about 20 to about 500 µg. For other bisphosphonates, example amounts include in the order of about 1 to about 50 mg for Pamindronate, about 100 µg to about 1 mg for Aledronate, and about 40 µg to about 1 mg for Ibandronate, and about 50 µg to about 1 mg for Risedronate.

Osteoconductive Agent

In one embodiment compositions of the invention, preferably pharmaceutically acceptable compositions, comprise a bioactive agent that is an osteoconductive agent.

In one embodiment the osteoconductive agent is a ceramic particle. Examples of ceramic particles includes: ceramic particles derived from calcium phosphate including: hydroxyapatite, tricalcium phosphate (and), tetracalcium phosphate, anhydrous dicalcium phosophate, monocalcium phosphate monohydrate, dicalcium phosphate dehydrate, heptacalcium phosphate, octocalcium phosphate, calcium pyrophosphate, oxyapatite, calcium metaphosphate, dahlite, carbonatoapatite, monocalcium phosphate anhydrous, amorphous calcium phosphate, calcium deficient hydroxyapatite, fluorapatite; a calcium silicate ceramic that includes: calcium

orthosilicate, wollastonite, dicalcium silicate, diopside, and bioglass (any composition); or a calcium salt such as calcium sulfate (-calcium sulfate hemihydrates, -calcium sulfate hemihydrates, calcium sulfate dehydrate and mixtures thereof), plaster of paris; or a mixture thereof.

In another embodiment a portion of the calcium content in the ceramic is replaced by another divalent cation such as magnesium or strontium.

In a preferred embodiment the osteoconductive agent is hydroxyapatite.

In one embodiment the osteoconductive agent is present in an amount of about 0.1 to about 10 % (w/v), preferably about 1 to about 5 % (w/v).

In one embodiment the osteoconductive agent is present in an amount of about 1 to about 5 % (w/v).

In one embodiment the osteoconductive agent is hydroxyapatite, wherein the hydroxyapatite is present in an amount of about 0.1 to about 10 % (w/v).

In one embodiment the osteoconductive agent is hydroxyapatite, wherein the hydroxyapatite is present in an amount of about 1 to about 5 % (w/v).

In one embodiment an anti-resorptive agent, for example a bisphosphonate is adsorbed on to a ceramic particle, for example a ceramic particle of hydroxyapatite.

Angiogenic Agent

In another embodiment a composition, preferably a pharmaceutically acceptable composition, disclosed herein comprises a bioactive agent that is an angiogenic agent. Examples of angiogenic compounds include: VEGF, angiopoietin, erythropoietin (EPO), nicotinic acid and desferoxamine (DFO).

Additional Bioactive Agents

In one embodiment, the compositions disclosed herein, preferably pharmaceutically acceptable compositions, comprise a bioactive agent that is known to be associated with bone and affect the delivery and presentation of growth factors to cells included or added. Examples include: heparin and other glycosaminoglycans and their components, as well as specific binding proteins such as TGF- binding protein.

In another embodiment, the composition disclosed herein, preferably a pharmaceutically acceptable composition, can comprise additional agents that are cells. Examples of cells include: bone forming cells such as progenitor cells, stem cells, derived from marrow, adipose or another tissue, and/or osteoblasts. The cells may also be derived from the blood of the patient, either monocytes or platelets. The cells may

be from a subject who requires bone growth in their body; alternatively the cells may be from a cell line or from a suitable donor.

In yet another embodiment, the compositions disclosed herein, preferably pharmaceutically acceptable compositions, can be used to deliver antibodies, neutralizing antibodies, antibody Fcs, or antibody-based therapeutics that affect bone formation, resorption or repair. These include anti-sclerostin and anti-RANKL treatments that can promote bone formation and/or inhibit resorption. In one embodiment compositions of the invention, preferably pharmaceutically acceptable compositions, comprise antibodies, neutralizing antibodies, antibody Fcs, or antibody-based therapeutics that affect bone formation, resorption or repair.

In yet another embodiment, the compositions disclosed herein can include a bioactive agent that is a growth factor that promotes wound healing, mitogenesis or angiogenesis. These include IGFs (e.g. IGF-1), PDGF or platelets, APC (activated protein C) or related factors.

In yet another embodiment, the compositions disclosed herein, preferably pharmaceutically acceptable compositions, can include a bioactive agent that is an antibiotic for infection prophylaxis or treatment, antibiotics include those that interfere with the bacterial cell wall, cell membrane, essential bacterial enzymes, or are bacteriocidal or bacteriostatic. These include: cationic steroid antibiotics, cyclic lipopeptides, glycylcyclines, oxazolidinones and lipiarmycins. Other antimicrobials include ceragenins.

Methods of Treatment

Herein recipients of compounds, including esterified polysaccharides, or the compositions disclosed herein, or subjects of methods of treatment using compounds, including esterified polysaccharides, or compositions of the invention, can be animals. “Animals” or "animal" comprises: warm blooded animals, including mammals (comprising but not limited to dogs, cats, cattle, pigs, sheep, goats, rats, guinea pigs, horses, or other bovine, ovine, equine, canine, feline, rodent or murine species), birds, reptiles, fish and amphibians.

Alternatively, or in addition to the above, recipients of compounds, including esterified polysaccharides, or compositions of the invention, or subjects of methods of treatment using compounds, including esterified polysaccharides, or compositions of the invention, can be human beings, male or female.

Herein a “subject” or “subjects” refers to either:

a) an animal selected from the group comprising, but not limited to: warm blooded animals, including mammals (comprising but not limited to: dogs, cats, cattle, pigs, sheep, goats, rats, guinea pigs, horses, or other bovine, ovine, equine, canine, feline, rodent or murine species), birds, reptiles, fish and amphibians (male or female); or

b) a human being, male or female.

Herein a "patient" or "patients" refers to either:

a) an animal selected from the group comprising, but not limited to: warm blooded animals, including mammals (comprising but not limited to: dogs, cats, cattle, pigs, sheep, goats, rats, guinea pigs, horses, or other bovine, ovine, equine, canine, feline, rodent or murine species), birds, reptiles, fish and amphibians (male or female); or

b) a human being, male or female.

Compounds, including polymers, or compositions disclosed herein, may be used in conjunction with other methods of treatment that a patient or subject may require.

Delivery of compositions disclosed herein to a subject may take any form and may be directed by the condition being treated in the subject. Administration routes include: topically (for example to skin directly or on a bandage); systematically (for example, mucosally (orally, rectally, vaginally, or nasally), parenterally (intravenously, subcutaneously, intramuscularly, or intraperitoneally), or through the pulmonary system, in an appropriate carrier. Other delivery administration methods include application by injection, pouring, spray dip, aerosol, or coating applicator.

In a preferred embodiment, a compound, including polymers, or compositions disclosed herein, is provided to a patient as an injection. In one preferred embodiment the injection comprises a HVLCM of the invention and a pharmaceutically acceptable, water-soluble solvent. Here the solvent leaches into the aqueous fluid of the host, forming a highly viscous depot. Any bioactive agents carried in the HVLCM can then be released as the HVLCM is hydrolysed or resorbed.

HVLCMs disclosed herein can be injected using a standard or modified syringe, which can include features such as a luer lock or mechanisms for mixing with a growth factor or other additives in a sterile environment. Following injection, any solvent present will ideally disperse *in vivo* from the HLVCM carrier to leave a semi-solid depot. This can allow for prolonged drug release as well as creation of a potential space.

In another embodiment HVLCMs can coat an implant. The implant could constitute organic material such as autograft, allograft, xenograft or collagen or

glycosaminoglycans, proteoglycans, hyaluronic acid or heparin sulphate. It could also coat synthetic devices such as bone substitutes made from ceramic, resorbable or non-resorbable polymers, or metal coatings including porous metal coatings of titanium, tantalum, cobalt chrome or stainless steel or their alloys.

In another embodiment the HVLCMs can be delivered dermally, wherein HVLCMs can be applied to skin or an open wound. The HVLCMs can be applied as a diluted or applied as a gel. In another embodiment HVLCMs could be diluted with solvent and then applied as an aerosol.

Solvent may also be present when a composition of the invention is in the form of an aerosol. When used in an aerosol the solvent in a solution evaporates upon application leaving the HVLCM.

Compounds, including polymers, or compositions disclosed herein, can be delivered/administered to a site in a subject where bone growth is required, for fixing cartilage defects, producing intramuscular depots, and peridontic treatment is required. The site of administration can be a bone fracture, bone graft, bone wound, bone defect, bone non-union or pseudarthrosis, the spine via a posterior or anterior approach, surface of a bone implant.

Applications of HVLCMs of the Invention

Angiogenesis has a key role in a range of processes including bone formation and regeneration with wound healing. In the formation of new bone angiogenesis has been found to temporally precede osteogenesis. When treating and healing bone defects the development of a microvasculature and microcirculation is critical to promote homeostasis and regenerate living bone.

On the other hand angiogenesis can promote tumour growth. HVLCMs manufactured with anti-antiogenic sugars such as 2-deoxy-D-glucose could be of used as anti-angiogenic agents.

In one embodiment HVLCMs disclosed herein act as anti-angiogenic agents.

In another embodiment HVLCMs disclosed herein act as anti-angiogenic agents in the treatment of tumours.

HVLCMs and compositions disclosed herein can be used to form protective tissue coatings, including preventing the formation of surgical adhesions. A HVLCM can adhere to surrounding tissue or bone, and can thus be injected subdermally like collagen to build up tissue or to fill in defects. A HVLCM of the invention can be incorporated into a composition and be injected into wounds, including burn wounds, to prevent the formation of deep scars.

In one embodiment HVLCMs and compositions disclosed herein are used in applications including, but not limited to: blocking surgical adhesions, void filling, guided tissue regeneration, inducing hemostasis, tissue adhesive, scaffolding, and wound dressing.

In another embodiment HVLCMs and compositions disclosed herein can be utilised in wound healing, this includes the treatment of diabetic wounds. The HVLCMs can be used with or without growth factors for the promotion of wound repair. This can include skin injuries (including burns), cuts and abrasions, or cuts or puncture wounds. HVLCMs can be applied topically or injected into a deeper wound. HVLCMs based on angiogenic sugars can improve healing by promoting revascularisation, or act as a dressing. Surgical patients can also have HVLCMs applied during surgery to improve wound healing. Antibiotics can also be included in compositions comprising HVLCMs of the invention to help promote wound healing. With wound healing, in order to prevent infections, HVLCMs can be delivered with antibiotics including those that interfere with the bacterial cell wall, cell membrane, essential bacterial enzymes, or are bacteriocidal or bacteriostatic. These include cationic steroid antibiotics, cyclic lipopeptides, glycylcyclines, oxazolidinones, lipiarmycins and ceragenins

In one embodiment HVLCMs and compositions disclosed herein are used to deliver drugs systemically for prolonged release. These can include anti-hypertensive agents (including statins and other cholesterol lowering drugs), anti-cancer agents, bone agents, hormone replacement therapy (for example for inducing ovulation in mares by delivering hormones), anaesthetics or analgesics or other drugs for pain relief, contraceptives, and drugs for chronic diseases and/or inherited diseases. HVLCMs can be dosed by subcutaneous/subdermal injection, intramuscular injection, or other injection or device implantation.

In one embodiment HVLCMs and compositions disclosed herein are used for local drug delivery, herein HVLCMs are used to deliver drugs locally, including local anaesthetics including but not limited to drugs such as bupivacaine, lignocaine, or ropivicaine or opioid analgesics such as morphine and related molecules. This can. HVLCMs can also be used for rectal drug delivery.

In one embodiment HVLCMs and compositions disclosed herein can be used as carriers for bioactive agents, including drugs. Antibiotics can be co-delivered with other bioactive agents contained within an HVLCM, and be provided adjunctively alongside treatments for wound healing or orthopaedic repair.

In one embodiment HVLCMs and compositions disclosed herein can be used for bone repair and bone tissue engineering. For example the HVLCMs can be used for: fracture healing (particularly with open fractures), spinal fusion, correction of bone defects, promoting the osteointegration of bone implants including plates, screws, frames, and joint replacement implants, restoration of osteonecrotic bone (including Perthes disease of the hip), and restoration of osteoporotic bone. For bone applications these could include closed fractures, open fractures, small bone defects, critical sized bone defects, stress fractures, scoliosis/spine fusion, osteonecrosis (including osteonecrosis of the hip). In addition, osteochondral defects and defects of the cartilage could also be treated, including injuries to joints and joint replacement.

In one embodiment HVLCMs disclosed herein have angiogenic properties and are used in the treatment of tumours.

Other applications for the HVLCMS with the treatment of bone related conditions include:

a) Treatment of delayed or non-union of fractures or fractures at risk of delayed or non-union. In this application injectable delivery can be used into or adjacent to the fracture site that would not require as invasive an operation as open surgery.

b) Treatment of osteonecrosis of the hip where rhBMPs and/or bisphosphonates are injected into the necrotic bone.

c) Spine fusion, where the HVLCM containing osteoinductive growth factors are injected adjacent to the spine. This can be used for single level or multi-level fusions.

d) For implants used for fixation or joint replacement, the presence of HVLCMs can improve osseointegration, reduce implant loosening, and improve repair. Co-delivery of antibiotics for this application would also be of specific benefit. For critical defects, an implant containing HVLCMs and osteoinductive growth factors can be applied to a defect that is also stabilized by surgery.

e) HVLCMs can also be used to co-deliver cells including stem cells, bone progenitor cells, or bone marrow cells harvested surgically. Cells can be allogenic or autogenic. In a preferred embodiment, cells would be delivered in HVLCMs diluted in solvents that are biocompatible or cytoprotective.

f) Metabolic bone disease can be treated by injected depots of HVLCMs containing agents that act upon bone in a systemic fashion. These include bisphosphonates, other small molecule drugs that affect bone formation or resorption, and antibodies that affect bone formation or resorption. Preferred

agents include Zoledronic acid, Pamidronate, OPG, Anti-Sclerostin antibody, and Anti-RANKL antibody.

Other applications for the HVLCMS include:

a) Patients that can gain specific benefits include those with compromised angiogenesis or vasculogenesis including: smokers, diabetics and the elderly; and

b) Fibrosis treatment and prevention: HVLCMs can be used *in vivo* for the prevention of fibrosis or after the removal of fibrous tissue to promote the growth of new non-fibrotic tissue. HVLCMs can contain non-fibrotic agents including, but not limited to TGFb-inhibitors and JNK-inhibitors.

Throughout this specification the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated element, integer or step, or group of elements, integers or steps, but not the exclusion of any other element, integer or step, or group of elements, integers or steps.

It will be appreciated by persons skilled in the art that numerous variations and/or modifications may be made to the invention as shown in the specific embodiments without departing from the scope of the invention as broadly described. The present embodiments are, therefore, to be considered in all respects as illustrative and not restrictive.

Example Embodiments

1. An esterified polysaccharide which is a homopolymer or copolymer comprising esterified sugar monomer units, where the sugar monomer units are esterified ketose or aldose sugars.

2. An esterified polysaccharide which is a homopolymer or copolymer comprising esterified sugar monomer units, where the sugar monomer units are selected from: esterified deoxyribose (including esterified D-deoxyribose and esterified L-deoxyribose), esterified arabinose (including esterified D-arabinose and esterified L-arabinose), esterified lyxose (including esterified D-lyxose and esterified L-lyxose), esterified ribose (including esterified D-ribose and esterified L-ribose), esterified xylose (including esterified D-xylose and esterified L-xylose), esterified ribulose (including esterified D-ribulose and esterified L-ribulose), esterified xyulose including esterified D-xyulose and esterified L-xyulose), esterified allose (including esterified D-allose and esterified L-allose), esterified altrose (including esterified D-altrose and esterified L-altrose), esterified glucose (including esterified D-glucose and esterified L-glucose), esterified 2-deoxy-glucose (including esterified 2-deoxy-D-glucose and esterified 2-deoxy-L-glucose), esterified mannose (including esterified D-mannose and esterified L-mannose), esterified gulose (including esterified D-gulose and esterified L-gulose), esterified idose (including esterified D-idose and esterified L-idose), esterified galactose (including esterified D-galactose and esterified L-galactose), esterified talose (including esterified D-talose and esterified L-talose), esterified psicose (including esterified D-psicose and esterified L-psicose), esterified fructose (including esterified D-fructose and esterified L-fructose), esterified sorbose (including esterified D-sorbose and esterified L-sorbose), tagatose (including esterified D-tagatose and esterified L-tagatose), or a combination thereof.

3. The esterified polysaccharide according to example embodiment 2, which is a homopolymer or copolymer comprising esterified sugar monomer units, where the sugar monomer units are selected from: esterified 2-deoxyribose, esterified 2-deoxy-D-ribose esterified fructose, esterified galactose, esterified glucose, esterified 2-deoxy-glucose, esterified 2-deoxy-D-glucose, or a mixture thereof.

4. An esterified polysaccharide which is a homopolymer comprising esterified sugar monomer units, wherein the sugar monomer units are esterified 2-deoxyribose monomer units (including esterified D-deoxyribose and esterified L-deoxyribose).

5. An esterified polysaccharide which is a homopolymer comprising esterified sugar monomer units, wherein the sugar monomer units are esterified fructose (including esterified D-fructose and esterified L-fructose).

6. An esterified polysaccharide which is a homopolymer comprising esterified sugar monomer units, wherein the sugar monomer units are esterified galactose (including esterified D-galactose and esterified L-galactose).

7. An esterified polysaccharide which is a homopolymer comprising esterified sugar monomer units, wherein the sugar monomer units are esterified glucose (including esterified D-glucose and esterified L-glucose).

8. The esterified polysaccharide according to any one of example embodiments 1 to 7, wherein the esterified sugar monomer prior to esterification promotes angiogenesis.

9. The esterified polysaccharide according to any one of example embodiments 1 to 7, wherein the esterified sugar monomer promotes angiogenesis.

10. The esterified polysaccharide according to any one of example embodiments 1 to 7, wherein the esterified sugar monomer prior to esterification provides anti-angiogenic properties.

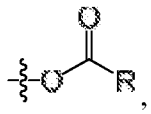
11. The esterified polysaccharide according to any one of example embodiments 1 to 7, wherein the esterified sugar monomer provides anti-angiogenic properties.

12. The esterified polysaccharide according to any one of example embodiments 1 to 11, wherein the esterified polysaccharide comprises one type of ester group, for example an ester group comprising 1 to 25 carbon atoms such as an acetate, propanoate, butanoate, isobutanoate, pentanoate, isopentanoate, or a neopentanoate group.

13. The esterified polysaccharide according to any one of example embodiments 1 to 12, wherein the esterified polysaccharide comprises more than one type of ester group, for example a mixture of an acetate, propanoate, butanoate, isobutanoate,

pentanoate, isopentanoate, neopentanoate group, including a mixture of isobutanoate and acetate groups.

14. The esterified polysaccharide according to any one of example embodiments 1 to 13, wherein the esterified sugar monomer units comprise ester groups of the formula:



wherein R is an alkyl group comprising 1 to 25 carbon atoms.

15. The esterified polysaccharide according to example embodiment 14, wherein the polysaccharide comprises one type of R group.

16. The esterified polysaccharide according to example embodiment 14, wherein the polysaccharide includes more than one type of R group.

17. The esterified polysaccharide according to any one of example embodiments 14 to 16, wherein R is selected from: methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, *tert*-butyl, *n*-pentyl, *tert*-pentyl, neopentyl, isopentyl, 1-methylbutyl and 1-ethylpropyl, *n*-hexyl, *n*-heptyl, or a mixture thereof.

18. The esterified polysaccharide according to any one of example embodiments 14 to 17, wherein R is methyl, ethyl, isopropyl, or a mixture thereof.

19. The esterified polysaccharide according to any one of example embodiments 14 to 18, wherein R is a mixture of methyl and isopropyl.

20. The esterified polysaccharide according to any one of example embodiments 1 to 19, wherein the polysaccharide is a high viscosity liquid carrier material.

21. The esterified polysaccharide according to any one of example embodiments 1 to 20 wherein the polysaccharide has a viscosity of at least 5000 mPa.s at 37 °C, for example at least 6000, 7000, 8000, 9000, 10000, 11000, 12000, 13000, 14000, 15000, 16000, 17000, 18000, 19000, 20000, 21000, 22000, 23000, 24000, 25000 or even about 50000 mPa.s at 37 °C, or for example a viscosity in a range of: 5000 to 50000 mPa.s at 37 °C; 5000 to 45000 mPa.s at 37 °C; 5000 to 40000 mPa.s at 37 °C; 5000 to 35000 mPa.s at 37 °C; 5000 to 30000 mPa.s at 37 °C; 5000 to 25000 mPa.s at 37 °C; 5000 to

20000 mPa.s at 37 °C; 5000 to 15000 mPa.s at 37 °C; 5000 to 10000 mPa.s at 37 °C; 10000 to 50000 mPa.s at 37 °C; 15000 to 50000 mPa.s at 37 °C; 20000 to 50000 mPa.s at 37 °C; 25000 to 50000 mPa.s at 37 °C; 30000 to 50000 mPa.s at 37 °C; 35000 to 50000 mPa.s at 37 °C; 40000 to 50000 mPa.s at 37 °C; or 45000 to 50000 mPa.s at 37 °C, wherein the viscosity can be measured, for example, at 37 °C on a Physica MCR 301 (Anton Paar) with 20% solvent (w/v), with increasing shear rates, and with a gap of 50 μm.

22. The esterified polysaccharide according to any one of example embodiments 1 to 21, wherein a mixture of the polysaccharide and a solvent has a viscosity of at less than about 1000 mPa.s at 37 °C, for example less than about 900, 800, 700, 600, 500, 400, 300, 200, or 100 mPa.s at 37 °C, for example a viscosity in a range of 50 to 1000 mPa.s at 37 °C; 100 to 1000 mPa.s at 37 °C; 150 to 1000 mPa.s at 37 °C; 200 to 1000 mPa.s at 37 °C; 250 to 1000 mPa.s at 37 °C; 300 to 1000 mPa.s at 37 °C; 400 to 1000 mPa.s at 37 °C; 450 to 1000 mPa.s at 37 °C; 500 to 1000 mPa.s at 37 °C; 550 to 1000 mPa.s at 37 °C; 600 to 1000 mPa.s at 37 °C; 650 to 1000 mPa.s at 37 °C; 700 to 1000 mPa.s at 37 °C; 750 to 1000 mPa.s at 37 °C; 800 to 1000 mPa.s at 37 °C; 850 to 1000 mPa.s at 37 °C; 900 to 1000 mPa.s at 37 °C; 950 to 1000 mPa.s at 37 °C; 50 to 950 mPa.s at 37 °C; 50 to 900 mPa.s at 37 °C; 50 to 850 mPa.s at 37 °C; 50 to 800 mPa.s at 37 °C; 50 to 750 mPa.s at 37 °C; 50 to 700 mPa.s at 37 °C; 50 to 650 mPa.s at 37 °C; 50 to 600 mPa.s at 37 °C; 50 to 550 mPa.s at 37 °C; 50 to 500 mPa.s at 37 °C; 50 to 450 mPa.s at 37 °C; 50 to 400 mPa.s at 37 °C; 50 to 350 mPa.s at 37 °C; 50 to 300 mPa.s at 37 °C; 50 to 250 mPa.s at 37 °C; 50 to 200 mPa.s at 37 °C; 50 to 150 mPa.s at 37 °C; or 50 to 100 mPa.s at 37 °C, wherein the viscosity can be measured, for example, at 37 °C on a Physica MCR 301 (Anton Paar) with 20% solvent (w/v), with increasing shear rates, and with a gap of 50 μm.

23. The esterified polysaccharide according to example embodiment 22, wherein the viscosity is less than about 200 mPa.s at 37 °C.

24. The esterified polysaccharide according to example embodiment 22 or example embodiment 23, wherein the solvent is selected from: alcohols including ethanol, propanol, and benzyl alcohol; tetraglycol; dimethyl sulfoxide, triacetin, Solketal; N-methyl-2-pyrrolidone, 2-pyrrolidone; esters of carbonic acid and alkyl alcohols including propylene carbonate, ethylene carbonate and dimethyl carbonate; fatty acids including acetic acid, lactic acid and heptanoic acid; alkyl esters of mono-, di-, and tri-

carboxylic acids including 2-ethyoxyethyl acetate, ethyl acetate, methyl acetate, ethyl lactate, ethyl butyrate, diethyl malonate, diethyl glutonate, tributyl citrate, diethyl succinate, tributyrin, isopropyl myristate, dimethyl adipate, dimethyl succinate, dimethyl oxalate, dimethyl citrate, triethyl citrate, acetyl tributyl citrate, glyceryl triacetate; alkyl ketones including acetone and methyl ethyl ketone; ether alcohols including 2-ethoxyethanol, ethylene glycol dimethyl ether, glycerol formal; polyhydroxy alcohols including propylene glycol, polyethylene glycol, glycerin, 1,3-butyleneglycol, and isopropylidene glycol (2,2-dimethyl-1,3-dioxolone-4-methanol); dialkylamides including dimethylformamide, dimethylacetamide; dimethylsulfoxide and dimethylsulfone; tetrahydrofuran; lactones including -caprolactone and butyrolactone; cyclic alkyl amides including caprolactam; aromatic amides including N,N-dimethyl-m-toluamide, and 1-dodecylazacycloheptan-2-one, or mixtures thereof.

25. The esterified polysaccharide according to any one of example embodiments 21 to 24, wherein the viscosity is measured at 37 °C, recorded at increasing shear rates, using a Physica MCR 301 (Anton Paar) with a gap of 50 µm.

26. The esterified polysaccharide according to any one of example embodiments 1 to 25, wherein the polysaccharide does not crystallise neat under ambient or physiological conditions.

27. The esterified polysaccharide according to any one of example embodiments 1 to 26, wherein the polysaccharide is phase-transitioning producing a semi-solid depot *in vivo*.

28. The esterified polysaccharide according to any one of example embodiments 1 to 27, wherein the polysaccharide is biodegradable.

29. The esterified polysaccharide according to any one of example embodiments 1 to 28, wherein the polysaccharide promotes angiogenesis.

30. The esterified polysaccharide according to any one of example embodiments 1 to 28, wherein the polysaccharide provides anti-angiogenic properties.

31. The esterified polysaccharide according to any one of example embodiments 1 to 30 wherein the homopolymer or copolymer is produced through a condensation polymerisation followed by an esterification reaction.

32. The esterified polysaccharide according to any one of example embodiments 1 to 31 for healing a wound in a subject.

33. The esterified polysaccharide according to any one of example embodiments 1 to 31 for delivering an agent to a site in or on a subject.

34. The esterified polysaccharide according to example embodiment 33, wherein the subject is an animal.

35. The esterified polysaccharide according to example embodiment 33, wherein the subject is a human being.

36. The esterified polysaccharide according to any one of example embodiments 1 to 31 for promoting bone growth in a subject.

37. A pharmaceutical composition comprising the polysaccharide according to any one of example embodiments 1 to 31, together with one or more pharmaceutically acceptable carriers and/or excipients.

38. The composition according to example embodiment 37, wherein the pharmaceutical composition comprises one or more of the following:

- a solvent; and/or
- one or more agents.

39. The composition according to example embodiment 38, wherein the composition comprises a solvent selected from: alcohols including ethanol, propanol, and benzyl alcohol; tetraglycol; dimethyl sulfoxide, triacetin, Solketal; N-methyl-2-pyrrolidone, 2-pyrrolidone; esters of carbonic acid and alkyl alcohols including propylene carbonate, ethylene carbonate and dimethyl carbonate; fatty acids including acetic acid, lactic acid and heptanoic acid; alkyl esters of mono-, di-, and tri-carboxylic acids including 2-ethyoxyethyl acetate, ethyl acetate, methyl acetate, ethyl lactate, ethyl butyrate, diethyl malonate, diethyl glutonate, tributyl citrate, diethyl succinate,

tributyrin, isopropyl myristate, dimethyl adipate, dimethyl succinate, dimethyl oxalate, dimethyl citrate, triethyl citrate, acetyl tributyl citrate, glyceryl triacetate; alkyl ketones including acetone and methyl ethyl ketone; ether alcohols including 2-ethoxyethanol, ethylene glycol dimethyl ether, glycerol formal; polyhydroxy alcohols including propylene glycol, polyethylene glycol, glycerin, 1,3-butyleneglycol, and isopropylidene glycol (2,2-dimethyl-1,3-dioxolone-4-methanol); dialkylamides including dimethylformamide, dimethylacetamide; dimethylsulfoxide and dimethylsulfone; tetrahydrofuran; lactones including -caprolactone and butyrolactone; cyclic alkyl amides including caprolactam; aromatic amides including N,N-dimethyl-m-toluamide, and 1-dodecylazacycloheptan-2-one, or mixtures thereof.

40. The composition according to example embodiment 38 or example embodiment 39, wherein the composition comprises a solvent selected from ethanol, benzyl alcohol, tetraglycol, or a mixture thereof.

41. The composition according to any one of example embodiments 38 to 40, wherein the solvent is present in an amount of about 10 to about 40% (v/v) relative to the composition as a whole.

42. The composition according to any one of example embodiments 38 to 41, wherein the solvent is present in an amount of about 10 to about 30% (v/v) relative to the composition as a whole.

43. The composition according to any one of example embodiments 33 or 38 to 42, wherein the agent is a bioactive agent selected from: an organic molecule that is a: drug, peptide, protein, carbohydrate, nucleoprotein, mucoprotein, lipoprotein, synthetic polypeptide or protein, small molecule linked to a protein, glycoprotein, steroid, nucleic acid, nucleotide, nucleoside, oligonucleotide, gene, lipid, hormone, vitamin, inorganic compound, anti-cancer agent, or combination thereof.

44. The composition according to example embodiment 43, wherein the bioactive agent causes a biological effect when administered *in vivo* to a subject.

45. The composition according to any one of example embodiments 38 to example embodiment 44, wherein the composition comprises an agent that is an osteoinductive agent.

46. The composition according to example embodiment 45, wherein the osteoinductive agent is an osteogenic protein, or a growth factor, or a member or the TGF-beta superfamily, or a mixture thereof.

47. The composition according to example embodiment 46, wherein the osteogenic protein is a bone morphogenetic protein (BMP).

48. The composition according to example embodiment 47, wherein the BMP is selected from: BMP-2, BMP-4, BMP-6, BMP-7 (OP-1), and BMP-9, rhBMP-1, rhBMP-2, rhBMP-3, rhBMP-4, rhBMP-5, rhBMP-6, rhBMP-7, rhBMP-8a, rhBMP-8b, rfiBMP-9, rhBMP-10, rhBMP-15, noggin resistant BMPs, or a combination thereof.

49. The composition according to example embodiment 47 or example embodiment 48, wherein the BMP is rhBMP-2 or rhBMP-7.

50. The composition according to any one of example embodiments 45 to 49 wherein the osteoinductive agent is present in an amount of 0.1 to about 40 mg.

51. The composition according to any one of example embodiments 45 to 50 wherein the osteoinductive agent is present in an amount of 0.1 to about 5 mg.

52. The composition according to any one of example embodiments 38 to example embodiment 51, wherein the composition comprises an agent that is an anti-resorptive agent.

53. The composition according to example embodiment 49, wherein the anti-resorptive agent is selected from: a bisphosphonate; IKK inhibitors; osteoprotegerin (OPG); inhibitors of Cathepsin K, chloride ion channel blockers; antibodies directed against RANKL, SOST, and DKK1; proton pump inhibitors, or a mixture thereof.

54. The composition according to example embodiment 53, wherein the bisphosphonate is selected from: zoledronic acid, pamidronic acid, ibandronic acid, etidronic acid, alendronic acid, risedronic acid, and tilurondic acid.

55. The composition according to any one of example embodiment 47 to 49, wherein the anti-resorptive agent is selected from: zoledronic acid, OPG, inhibitors of both IKK and Cathepsin K, anti-RANKL Ab, anti-SOST Ab, and anti DKK1 Ab.

56. The composition according to any one of example embodiments 38 to 55, wherein the composition comprises an agent that is an osteoconductive agent.

57. The composition according to example embodiment 56, wherein the osteoconductive agent is a ceramic particle.

58. The composition according to example embodiment 56 or 57, wherein the osteoconductive agent is selected from the group comprising: hydroxyapatite, bioglass, silicon substituted hydroxyapatite, porous tri-calcium phosphate, or combinations, composites, or other derivatives of calcium phosphate, or a mixture thereof.

59. The composition according to any one of example embodiments 56 to 58, wherein the osteoconductive agent is hydroxyapatite.

60. The composition according to any one of example embodiments 56 to 59, wherein the osteoconductive agent is present in an amount of about 0.1 to about 10% (w/v).

61. The composition according to any one of example embodiments 56 to 60, wherein the osteoconductive agent is present in an amount of about 1 to about 5% (w/v).

62. The composition according to any one of example embodiments 37 to 61, wherein the composition promotes angiogenesis.

63. The composition according to any one of example embodiments 37 to 61, wherein the composition provides anti-angiogenesis properties.

64. The composition according to any one of example embodiments 37 to 62, wherein the composition comprises an agent that is an angiogenic compound.

65. The composition according to example embodiment 64, wherein the angiogenic compound is selected from: VEGF, nicotinic acid, angiopoietin, erythropoietin (EPO), nicotinic acid and desferoxamine (DFO).

66. The composition according to any one of example embodiments 37 to 65, further comprising a biodegradable polymer.

67. The composition according to example embodiment 66, wherein the biodegradable polymer is selected from: poly(lactic acid) (PLA), including poly(D-lactic acid) (PDLA), poly(lactic -co-glycolic acid) (PLGA), poly(glycolic acid) (PGA), poly(-caprolactone) (PCL), or a mixture thereof.

68. The composition according to any one of example embodiments 37 to 67 for healing a wound in a subject.

69. The composition according to any one of example embodiments 37 to 67 for delivering an agent to a site in or on a subject.

70. The composition according to example embodiment 69, wherein the subject is an animal.

71. The composition according to example embodiment 69, wherein the subject is a human being.

72. The composition according to any one of example embodiments 37 to 67 for promoting bone growth in a subject.

73. A method to promote bone growth, the method comprising providing a composition according to any one of example embodiments 37 to 67 to a site in a subject to promote bone growth at the site.

74. A method to heal wounds in or on a subject, the method comprising providing a composition according to any one of example embodiments 37 to 67, to a wound site in or on the subject to promote healing of the wound.

75. A method to deliver an agent on or in a subject, the method comprising providing a composition according to any one of example embodiments 37 to 67, to a site on or in the subject.

76. The method according to example embodiment 75, wherein the agent is a bioactive agent selected from: an organic molecule that is a: drug, peptide, protein, carbohydrate, nucleoprotein, mucoprotein, lipoprotein, synthetic polypeptide or protein, small molecule linked to a protein, glycoprotein, steroid, nucleic acid, nucleotide, nucleoside, oligonucleotide, gene, lipid, hormone, vitamin, inorganic compound, anti-cancer drug, or combination thereof.

77. The method according to any one of example embodiments 73 to 76, wherein the composition is provided to the site by injection.

78. The method according to example embodiment 73, wherein the site is selected from bone fracture, bone graft, bone wound, bone defect, bone non-union or pseudarthrosis, the spine, surface of a bone implant, or injected within a bone implant, porous scaffold, cage, balloon, membrane, or other containment device.

79. The method according to any one of example embodiments 73 to 78, wherein the subject is an animal.

80. The method according to example embodiment 79, wherein the animal is selected from: warm blooded animals, including mammals, wherein mammals comprises dogs, cats, cattle, pigs, sheep, goats, rats, guinea pigs, horses, or other bovine, ovine, equine, canine, feline, rodent or murine species; birds; reptiles; fish and amphibians.

81. The method according to any one of example embodiments 73 to 78, wherein the subject is a human being.

82. Use of a composition according to any one of example embodiments 37 to 67 in the preparation of the medicament for promoting bone growth in a subject.

83. Use of a composition according to any one of example embodiments 37 to 67 in the preparation of the medicament for healing wounds in or on a subject.

84. Use of a composition according to any one of example embodiments 37 to 67 in the preparation of the medicament for delivering an agent to a subject.

85. The use according to example embodiment 84, wherein the agent is a bioactive agent selected from: an organic molecule that is a: drug, peptide, protein, carbohydrate, nucleoprotein, mucoprotein, lipoprotein, synthetic polypeptide or protein, small molecule linked to a protein, glycoprotein, steroid, nucleic acid, nucleotide, nucleoside, oligonucleotide, gene, lipid, hormone, vitamin, inorganic compound, or combination thereof.

86. Use of a composition according to any one of example embodiments 37 to 67 for promoting bone growth in a subject.

87. Use of a composition according to any one of example embodiments 37 to 67 for healing wounds in or on a subject.

88. Use of a composition according to any one of example embodiments 37 to 67 to deliver an agent to a subject.

89. The use according to example embodiment 88, wherein the agent is a bioactive agent selected from: an organic molecule that is a: drug, peptide, protein, carbohydrate, nucleoprotein, mucoprotein, lipoprotein, synthetic polypeptide or protein, small molecule linked to a protein, glycoprotein, steroid, nucleic acid, nucleotide, nucleoside, oligonucleotide, gene, lipid, hormone, vitamin, inorganic compound, anti-cancer drug or combination thereof.

90. The use according to any one of example embodiments 82 to 89, wherein the subject is an animal.

91. The use according to example embodiment 90, wherein the animal is selected from: warm blooded animals, including mammals, wherein mammals comprises dogs, cats, cattle, pigs, sheep, goats, rats, guinea pigs, horses, or other bovine, ovine, equine, canine, feline, rodent or murine species; birds; reptiles; fish and amphibians.

92. The use according to any one of example embodiments 82 to 89, wherein the subject is a human being.

93. A composition according to example embodiment 37 for the controlled release of an agent.

94. An esterified polysaccharide according to any one of example embodiments 1 to 31 for the controlled release of an agent.

95. An esterified polysaccharide according to any one of example embodiments 1 to 31 for the local release of an agent.

96. An esterified polysaccharide used as a high viscosity liquid carrier material.

97. The esterified polysaccharide according to example embodiment 96, wherein the esterified polysaccharide is defined according to any one of example embodiments 1 to 31.

98. The esterified polysaccharide according to example embodiment 96 or example embodiment 97 for the controlled release of an agent.

99. The esterified polysaccharide according to example embodiment 96 or example embodiment 97 for the local release of an agent.

100. A composition for the controlled release of an agent comprising:

- a polymeric high viscosity liquid carrier material; and
- an agent.

101. A composition for the local release of an agent comprising:

- a polymeric high viscosity liquid carrier material; and
- an agent.

102. A composition according to example embodiment 96 or 97 wherein the polymeric high viscosity liquid carrier material is an esterified polysaccharide as defined in any one of example embodiments 1 to 31.

103. The composition according to any one of example embodiments 100 to 102, wherein the agent is a bioactive agent selected from: an organic molecule that is a: drug, peptide, protein, carbohydrate, nucleoprotein, mucoprotein, lipoprotein, synthetic polypeptide or protein, small molecule linked to a protein, glycoprotein, steroid, nucleic acid, nucleotide, nucleoside, oligonucleotide, gene, lipid, hormone, vitamin, inorganic compound, anti-cancer compound, or combination thereof.

104. A coating for an implant comprising an esterified polysaccharide as defined in any one of example embodiments 1 to 31.

105. A coating for an implant comprising a composition as defined in any one of example embodiments 37 to 72.

106. The coating for an implant according to example embodiment 104 or example embodiment 105, wherein the implant is an organic material and includes: an autograft, allograft, xenograft or collagen or glycosaminoglycans, proteoglycans, hyaluronic acid or heparin sulphate.

107. The coating for an implant according to example embodiment 104 or example embodiment 105, wherein the implant is a synthetic device including: a bone substitute, such as a bone substitute made from ceramic, resorbable or non-resorbable polymers, or metal coatings including porous metal coatings of titanium, tantalum, cobalt chrome or stainless steel or their alloys.

108. Use of an esterified polysaccharide as defined in any one of example embodiments 1 to 31 for coating an implant.

109. Use of a composition as defined in any one of example embodiments 37 to 72 for coating an implant.

110. The use according to example embodiment 108 or example embodiment 109, wherein the implant is an organic material and includes: an autograft, allograft, xenograft or collagen or glycosaminoglycans, proteoglycans, hyaluronic acid or heparin sulphate.

111. The use according to example embodiment 108 or example embodiment 109, wherein the implant is a synthetic device including: a bone substitute, such as a bone substitute made from ceramic, resorbable or non-resorbable polymers, or metal coatings including porous metal coatings of titanium, tantalum, cobalt chrome or stainless steel or their alloys.

Examples

In order to better understand the nature of this invention, a number of illustrative examples will now be described.

Exemplified Synthetic Procedures

A) Condensation Polymerisation

An example condensation polymerisation synthesis for the present invention is described below.

1) To a three neck, round bottom flask of sufficient capacity (for example 250 to 500 ml) 50 to 100 mM of a sugar (for example deoxyribose), is added followed by the addition of 50 mM acetic acid as the solvent, and 25 to 50 mM of citric acid as catalyst. Other suitable non-toxic solvents which may be used include: N-methyl pyrolidone, short chain aliphatic acids such as formic, acetic and propionic acid, and glycerol.
2) A condenser is mounted on the flask, a magnetic stirring bar is placed inside and the reaction mixture is heated to a temperature of about 90 to about 140 °C.
3) When the sugar has fully dissolved in the acetic acid a mild vacuum is applied to the flask. Stirring rate and vacuum are adjusted to prevent excessive foaming and splashing of liquid on side walls of the flask.
4) The reaction is allowed to proceed for between about 10 and about 120 min. The progress of the condensation polymerisation reaction can be estimated by the visual increase in viscosity of the solution, or by precisely measuring by the amount of released water during the reaction.

B) Esterification of the Sugar Polymers (Polysaccharides)

An example esterification reaction for the present invention is described below. The example esterification reaction utilises the reaction product in step A) above, however the esterification can be performed on a polysaccharide produced in an independent condensation polymerisation if required.

1) The temperature of the reaction mixture of part A) above is increased to about 120 to about 150 °C.
2) If the synthesis aims to produce a mixed ester, for example a mixture of acetate and isobutyrate esters, or isobutyrate and propanoate esters, two anhydrides, for example isobutyric anhydride and acetic anhydride, are mixed in advance. A hydride or mixture of anhydrides is then preheated to about 60 to about 80 °C in a suitable glass bottle.

3) The preheated anhydride or anhydrides are transferred to a separatory funnel or other suitable vessel equipped with a Schliff valve to allow fine control of the introduction into the reactor.
4) The vacuum is broken, about 25 mM of sodium acetate added to the solution, the funnel connected to the reaction vessel and vacuum is applied.
5) The stirring rate is increased to allow the mixing of the catalyst and the addition of the anhydride or the anhydride
6) The anhydride or anhydrides are added to the reaction mixture and the esterification proceeds for about 15 to about 60 min.

C) Purification of Polysaccharide Ester

An example purification of the esterified polysaccharide is described below. The example purification esterification reaction utilises the reaction product in step B) above, however the purification can be performed on an esterified polysaccharide produced in an independent condensation polymerisation and/or esterification if required. In the example below, the residual anhydrides are high boiling point compounds and are difficult to remove by vacuum distillation. To overcome this obstacle they are converted to their corresponding ethanoate esters by esterification with ethyl alcohol. The polysaccharide esters are hydrophobic and are precipitated by the addition of water. The residual ethanoate esters are partially soluble in water and removed by a series of washes with water. The removal of trace ethanol and ethanoate esters from the final product is achieved by drying under deep under vacuum.

1) After the complete esterification of the polysaccharide in part B), 0.4-0.8 M of ethanol is added to the reaction mixture. The temperature is lowered to 90 °C and the reaction lead for about 30 to 60 min. The residual anhydrides are converted to their ethanoate esters.
2) The reactor is lifted from a heating apparatus, for example an oil bath, to cool down.
3) After several minutes the reaction mixture is poured into about 40 to about 80 M of iced cooled water.
4) Precipitation of the esterified polysaccharides occurs gradually. The remaining ethanoate esters, unreacted or incompletely esterified hydrophilic polysaccharide fractions remain in the supernatant and are discarded.
5) The final product is dissolved in a small volume of ethanol (approximately 0.1 M) and precipitated by the addition of ice cold water and isolated by centrifugation.

6) The above procedure is repeated three times.
7) The final product is split in to several containers and vacuum dried at 40 °C for several days.

D) Characterisation of Esterified Polysaccharides

FTIR

Using the approaches of A) to C) an esterified polymer of deoxyribose comprising acetate and isobutyrate esters (pdRAIB) and an esterified polymer of fructose comprising acetate and isobutyrate esters (pdRAIB) were synthesised. Figure 3 and Figure 4 display the FTIR spectra of polydeoxyribose acetate isobutyrate (pdRAIB) and polyfructose acetate isobutyrate (pFAIB), respectively. The main peaks that appear around 1730 cm^{-1} belongs to the ester C=O stretch and can be used to quantitate esterification of the polymers. This is in conjunction with the disappearance of the broad peaks around 3000 cm^{-1} belonging to free OH groups in the sugar molecules. The appearance of the peaks around 1150 cm^{-1} is attributed to the formation C-O ether bond during the condensation polymerisation of the simple sugars. The ratio of the peaks 1150/1730 cm^{-1} can be used to estimate the hydrophilic-lipophilic balance (HLB) of the resulting polymer.

Gel Permeation Chromatography

Samples of polycondensed deoxyribose acetate isobutyrate (pdRAIB) and polycondensed fructose acetate isobutyrate (pFAIB) were examined via gel permeation chromatography (GPC), and compared to sucrose acetate isobutyrate (SAIB) purchased from a commercial source (Sigma-Aldrich, three separate batches purchased independently).

To define the size ranges of the materials, GPC was performed on multiple synthesis batches (Table 1). The M_n, M_w, M_z, and M_{z+1}, and polydispersity index (PDI) were measured. It is known in the art that PDI values are an indicator of the range of molecular weights seen, with a value of 1 relating to 100% homogenous material. Values of ~1.1 for SAIB and FAIB indicate an extremely high consistency of molecule size. Values <2 for pdRAIB still show a high degree of consistency of molecule size. One batch showed a lower average molecular weight and lower polydispersity and this corresponded with a new and independent batch of 2-deoxyribose purchased from Carbosynth (Berkshire, United Kingdom).

The Inventors have found that as the polycondensation of sugars is an exothermic reaction, it is difficult to maintain consistent temperature with the common

oil bath heater. It would be expected that technical elaborations that improve the consistency of temperature regulation during the reaction and control of the applied vacuum would further reduce the polydispersity. Such improvements could be achieved using computer controlled heating/cooling system consisting of reactor with separate heating coil and cooling jacket. Incorporation of additional system for capture and volumetric determination of removed water is believed to greatly improve the consistency of the final product.

Table 1

Sample Reference	**M_n**	**M_w**	**M_z**	**M_{z+1}**	**PDI**	**T (^oC)**	**t (min)**	**Vacuum / N_2**
pdRAIB 20131209	1524	2167	3044	4008	1.42	105	5	N_2
pdRAIB 20140311	1459	2769	4715	6744	1.90	110	15	500 mmHg
pdRAIB 20140318	1318	2249	3537	4886	1.71	95	15	500 mmHg
pdRAIB Sweden 80%	2083	4048	7040	9885	1.94	95	15	500 mmHg
pdRAIB 20140702*	792	1054	1383	1743	1.33	94	15	500 mmHg
pFAIB 20131129	770	861	985	1158	1.12	110	25	N_2
pFAIB 20131203	738	831	955	1122	1.13	110	60	N_2
pFAIB Surgery	730	827	950	1104	1.13	110	60	N_2
SAIB1	992	1111	1253	1411	1.12			
SAIB2	981	1089	1217	1361	1.11			
SAIB3	969	1081	1217	1374	1.11			

Nuclear Magnetic Resonance (NMR)

Nuclear magnetic resonance (NMR) was performed on exemplified pdRAIB samples to describe the branching of the molecules made by polycondensation.

^1H NMR

Figure 5 shows the ^1H NMR spectrum of the exemplified pdRAIB samples. Figure 5 shows a prominent multiplet peak with a chemical shift of 1.1 and 2 ppm corresponding to the protons of the two -CH_3 groups and the –CH- proton from the isobutyric residue. The acetic CH_3 protons are more deshielded being closer to the electronegative C=O group and give a peak at 2.5 ppm.

The assignments of the protons from the deoxyribose backbone given below:

C1-**H** multiplet at 6.3 ppm

C5-**H** multipet at 5.1 ppm

C4-**H** multiplet at 4.1 ppm

C3-**H** multiplet at 3.9 ppm

C2-**H** multiplet at 3.7 ppm

All of these peaks are much broader in the ^{1}H NMR spectrum of pdRAIB compared to assays performed on SAIB due to the slower tumbling in the polymer backbone and provide a direct evidence of increased molecular weight.

^{13}C NMR

Figure 6 shows the ^{13}C NMR spectrum of the exemplified pdRAIB sample. Here the ^{13}C NMR spectrum of pdRAIB is dominated by three close peaks with chemical shifts of 77.4, 77 and 76.6 ppm corresponding to -**C**-O- atoms which suggests the deoxyribopyranose conformation rather than deoxyribofuranose or open ring structure. It may be speculated that all of the three –OH groups have participated in the polycondensation reaction to an equal extent, giving rise to a highly branched structure.

Example Compositions

Given the disclosure herein, a person skilled in the art will be able to prepare and use a wide variety of HVLCM compositions. The following examples, for ease of illustration, describe the preparation and use of an esterified polymer of deoxyribose comprising acetate and isobutyrate esters (pdRAIB). Other HVLCMS, additives, substrates and solvents can be used in a similar manner.

The following general procedure can be used to prepare the desired formulations in the Examples. Formulations can be made in 20 mL scintillation vials and shaken, stirred, and/or heated to dissolve the a biologically active substance in the pdRAIB /solvent system. Where a biologically active substance does not dissolve, the formulations can be refrigerated and stirred to get the best distribution of biologically active substance.

The *in vitro* release of the biologically active compound can be determined best using a dissolution apparatus. If such equipment is not available the following general procedure could be used instead. Phosphate-buffered saline ("PBS") (10 mL) of either pH 7.4 or pH 6.8 can be added to a 16x125 mm test tube. The pH of the PBS, for example 7.4 or 6.8, is determined based upon the application and solubility of the biologically active substance. The PBS can include 0.2% sodium azide to prevent the

growth of microorganisms. From 0.03 to 0.09 g of a pdRAIB/solvent/biologically active substance formulation would be expelled from a disposable plastic pipette into the test tube, and the weight will be recorded. The test tubes are capped and placed in a shaker bath set at 37 °C with constant shaking.

The test tubes can then be periodically removed from the shaker bath at various time points. At that time, the PBS can be removed from the test tube containing the formulation and placed in a clean, dry test tube. These samples can then be UV analysed to determine the amount of biologically active material in the PBS solution.

Fresh PBS can then be placed in the test tube containing the formulation, which can then returned to shaker bath. This procedure can be repeated at the various time points to obtain sufficient data to plot a release profile. The concentration of the biologically active material in the release solutions can be used to construct release profiles, based on the original amount of biologically active material in the formulation. This amount can be determined using UV-visible spectrophotometry or HPLC.

A variety of solvents can be used, these include: ethanol (EtOH), dimethylsulfoxide (DMSO), ethyl lactate (EtLac), ethyl acetate (EtOAc), benzyl alcohol (FCH2OH) , triacetin, N-methylpyrrolidone (NMP), propylene carbonate (PC), and glycofurol (GF).

Larger percentages of solvent can generally provide a greater concentration of biologically active substance in the formulation. The amount and type of the solvent are also directly related to viscosity of the solution.

Effect of the Biologically Active Substance

As known in the art, methylene blue and bovine serum albumin (BSA) can be used to demonstrate drug release. As known in the art, biologically active compounds that can be released from a pdRAIB/solvent system include chlorhexidine, diclofenac, doxycycline, flurbiprofen, naproxen, and theophylline.

Example 1

Ethanol (2 g) can be combined with pdRAIB (8 g). After gentle mixing, the resulting solution can be expelled from a glass pipette into water to test whether a spherical matrix is formed and how long this matrix is able to hold its form.

Example 2

Ethanol (3 g) can be combined with pdRAIB (7 g). A resulting solution, can then be mixed with water in order to form a thin film. The film can be assessed to determine how long the film can retain its shape.

Example 3

Solutions can be prepared with varying amounts of ethanol and pdRAIB according to the process of Example 1. To this solution 0.07% methylene blue can be added. Spherical drops can then be prepared, in phosphate buffered saline (PBS), as described in Example 1. The PBS samples can then be maintained at 37 °C and at regular intervals PBS can be removed and analysed for methylene blue content by ultraviolet-visible spectrophotometry.

Example 4

A series of formulations can be prepared according to the process of Example 3, using bovine serum albumin (BSA) instead of methylene blue. Various percentages of BSA, solvents and pdRAIB can be used in these formulations. Example solutions are disclosed in Table 2, Table 3 and Table 4.

Table 2

% BSA (w/v)	% EtOH (v/v)	% PVP (w/v)	50%/50% glycerol/DMSO (v/v)
27	37	0	4.4
4.6	36	0	5.6
5.5	36	0	5.8
5.0	33	5.9	6.9
5.5	31	8.2	8.3
4.9	27	18.8	9.8

Table 3

% BSA (w/v)	Solvent	% Solvent (v/v)	Additive	% Additive (v/v)
1.1	PC	31.3	diH_2O	9.8
9.2	no solvent was used (a paste of BSA/ pdRAIB			
9.6	glycerol	9.2	-	-
1.9	EtOH	30	-	-
1.9	EtOH	20	-	-
1.9	EtOH	10	-	-
10	EtOH	10	-	-

Table 4

% BSA (w/v)	Solvent	% Solvent (v/v)	Additive	% Additive
1	EtOH	9.6	-	-
1	EtOH	19	-	-
1	EtOH	29	-	-
1	EtOH	50	-	-
1	EtOH	89	-	-

Example 5

The procedure of Example 3 can be repeated using a series of formulations containing chlorhexidine as the biologically active agent. Formulations containing various amounts of solvent, pdRAIB and additives can be prepared. Formulations to which chlorhexidine can be added as the biologically active substance are set forth below in Table 5.

Table 5

% Chlorhexidine (w/v)	Solvent	% Solvent (v/v)	Additive	% Additive
5	EtLac	50	-	-
5	EtLac	30	-	-
5	EtLac	10	-	-
5	NMP	50	-	-
5	NMP	30	-	-
5	NMP	10	-	-
5	PC	31	-	-
5	PC	20	-	-
5	PC	10	-	-
5	EtOH	50	-	-
5	EtOH	30	-	-
5	EtOH	10	-	-
5	EtOH	45	CAB	5
5	EtOH	40	CAB	5
5	EtOH	35	CAB	5
2.6	EtOH	23	PVP	5.1
2.5	EtOH	23	CAB	5

% Chlorhexidine (w/v)	Solvent	% Solvent (v/v)	Additive	% Additive
2.5	EtOH	23	CAP	5
2.75	EtOH	23	PEG(10K)	5.2
2.4	EtOH	23	PEG(1K)	5.5

The release profile for chlorhexidine in various solvents can be optimised by a person skilled in the art by varying the ratio and type of components, including additives.

Example 6

The procedure of Example 3 can be repeated using a series of formulations containing diclofenac sodium as the biologically active agent. Formulations containing various amounts of solvent, pdRAIB and additives including sucrose, cellulose acetate butyrate (CAB), cellulose acetate phthalate (CAP), polyethylene glycol (PEG), and/or polyvinylpyrrolidone (PVP) can be prepared. Formulations to which diclofenac sodium can be added as the biologically active substance are set forth below in Table 6.

Table 6

% Diclofenac sodium (w/v)	Solvent	% Solvent (v/v)	Additive	% Additive (w/v) or (v/v)
2.68	EtOH	19.1	-	-
2.48	EtOH	15.6	-	-
2.40	EtOH	9.6	-	-
2.68	EtOH	7	-	-
2.43	EtOH	7.1	sucrose	2.6
2.56	EtOH	3.6	sucrose	5.1
2.39	EtOH	28.7	CAB	4.8
2.44	EtOH	28.6	PEG(1K)	4.8
2.89	EtOH	28.7	PVP(25)	4.8
2.38	EtOH	28.3	PEG(10K)	5.3
2.35	EtOH	36.3	CAP	5.2
2.57	Triacetin	50	-	-
2.89	Triacetin	30	-	-
2.43	Triacetin	11.5	-	-
2.58	DMSO	50	-	-

% Diclofenac sodium (w/v)	Solvent	% Solvent (v/v)	Additive	% Additive (w/v) or (v/v)
2.45	DMSO	30.5	-	-
2.36	DMSO	10.2	-	-

The release profile for diclofenac sodium in various solvents can be optimised by a person skilled in the art by varying the ratio and type of components, including additives.

Example 7

The procedure of Example 3 can be repeated using a series of formulations containing doxocyline as the biologically active agent. Formulations containing various amounts of solvent, pdRAIB and additives can be prepared. Formulations to which doxocyline can be added as the biologically active substance are set forth below in Table 7.

Table 7

% Doxocyline (w/v)	Solvent	% Solvent (v/v)	Additive	% Additive
5	EtOH	15	-	-
2.56	EtOH	15	-	-
4.97	EtOAc	30	-	-
5.5	EtLac	30	-	-
5.45	PC	30	-	-
2.5	GF	30	-	-
2.5	DMSO	30	-	-

The release profile for doxocyline in various solvents can be optimised by a person skilled in the art by varying the ratio and type of components, including additives.

Example 8

The procedure of Example 3 can be repeated using a series of formulations containing flurbiprofen as the biologically active agent. Formulations containing various amounts of solvent, pdRAIB and additives can be prepared. Formulations to which flurbiprofen can be added as the biologically active substance are set forth below in Table 8.

Table 8

% Flurbiprofen	Solvent	% Solvent	Additive	% Additive
2.48	EtOH	15	-	-
4.98	EtOH	15	-	-
9.98	EtOH	15	-	-
4.99	EtOH	45	CAB	5.0
9.92	EtOH	45	CAB	5.5

The release profile for flurbiprofen in various solvents can be optimised by a person skilled in the art by varying the ratio and type of components, including additives.

Example 9

The procedure of Example 3 can be repeated using a series of formulations containing naproxen (free acid) as the biologically active agent. Formulations containing various amounts of solvent, pdRAIB and additives can be prepared. Formulations to which naproxen (free acid) can be added as the biologically active substance are set forth below in Table 9.

Table 9

% Naproxen	Solvent	% Solvent	Additive	% Additive
5.2	GF	21	-	-
3.6	GF	37	-	-
4.1	GF	44	-	-

The release profile for naproxen (free acid) in various solvents can be optimised by a person skilled in the art by varying the ratio and type of components, including additives.

Example 10

The procedure of Example 3 can be repeated using a series of formulations containing carbamazapine or phenytoin as the biologically active agent. Formulations containing various amounts of solvent, pdRAIB and additives can be prepared. Formulations to which carbamazapine or phenytoin can be added as the biologically active substance are set forth below in Table 10 and Table 11.

Table 10

Drug	% Drug (w/v)	Solvent	% Solvent (v/v)	Additive	% Additive (w/v)
Carbamazapine	0.5	EtOH	15	-	-
Carbamazapine	1	EtOH	15	-	-
Carbamazapine	2.5	EtOH	15	-	-
Carbamazapine	5	EtOH	15	-	-
Carbamazapine	10	EtOH	15	CAB	5
Carbamazapine	2.5	EtOH	53	CAB	10
Carbamazapine	2.5	EtOH	47	CAB	15
Carbamazapine	2.5	EtOH	43	CAB	6
Carbamazapine	2.5	EtOH	53	CAB	10
Carbamazapine	2.6	EtOH	48	CAB	15
Carbamazapine	2.5	EtOH	43	-	-
Carbamazapine	5.2	EtOAc	48	-	-
Carbamazapine	4.8	EtOAc	29	-	-
Carbamazapine	5.0	EtOAc	9.5	-	-
Carbamazapine	5.0	FCH_2OH	48	-	-
Carbamazapine	5.2	FCH_2OH	29	-	-
Carbamazapine	5.0	FCH_2OH	11	-	-
Carbamazapine	5.4	EtOH	10	-	-
Carbamazapine	6.5	EtOH	20	-	-
Carbamazapine	5.5	EtOH	30	-	-
Carbamazapine	5.5	EtOH	25	CAB	5.5
Carbamazapine	7.2	EtOH	34	CAB	5.4
Carbamazapine	5.4	EtOH	45	CAB	5.9
Carbamazapine	5.1	PC	11	-	-
Carbamazapine	5.5	PC	20	-	-
Carbamazapine	5.5	PC	31	-	-

Table 11

Drug	% Drug (w/v)	Solvent	% Solvent (v/v)	Additive	% Additive (w/v)
Phenytoin	0.5	EtOH	15	-	-
Phenytoin	1	EtOH	15	-	-
Phenytoin	2.5	EtOH	15	-	-
Phenytoin	5	EtOH	15	-	-

Drug	% Drug (w/v)	Solvent	% Solvent (v/v)	Additive	% Additive (w/v)
Phenytoin	10	EtOH	15	CAB	5
Phenytoin	2.5	EtOH	53	CAB	10
Phenytoin	2.5	EtOH	47	CAB	15
Phenytoin	2.5	EtOH	43	CAB	6
Phenytoin	2.5	EtOH	53	CAB	10
Phenytoin	2.6	EtOH	48	CAB	15
Phenytoin	2.5	EtOH	43	-	-
Phenytoin	5.2	EtOAc	48	-	-
Phenytoin	4.8	EtOAc	29	-	-
Phenytoin	5.0	EtOAc	9.5	-	-
Phenytoin	5.0	FCH_2OH	48	-	-
Phenytoin	5.2	FCH_2OH	29	-	-
Phenytoin	5.0	FCH_2OH	11	-	-
Phenytoin	5.4	EtOH	10	-	-
Phenytoin	6.5	EtOH	20	-	-
Phenytoin	5.5	EtOH	30	-	-
Phenytoin	5.5	EtOH	25	CAB	5.5
Phenytoin	7.2	EtOH	34	CAB	5.4
Phenytoin	5.4	EtOH	45	CAB	5.9
Phenytoin	5.1	PC	11	-	-
Phenytoin	5.5	PC	20	-	-
Phenytoin	5.5	PC	31	-	-

The release profile carbamazapine or phenytoin in various solvents can be optimised by a person skilled in the art by varying the ratio and type of components, including additives.

Example 11

A formulation can be prepared comprising 80% pdRAIB and 20% EtOH, the resulting solution can be loaded into an aerosol container, using procedures known to a person skilled in the art. The solution can then be sprayed onto agar plates to form an-adhesive continuous film.

Example 12

Wound dressing

A solution of pdRAIB in Dymel® 134a/P Pharmaceutical Grade HFC-134a Propellant (a trademark of DuPont) can be prepared by cooling the Dymel® in a dry ice bath and adding controlled amounts to a pressure bottle preloaded with pdRAIB. Upon raising the temperature to room temperature a clear solution can be obtained. This solution can be sprayed onto a full thickness wound on a pig, where a clear coherent film results. This preparation can be inspected for lower rates of infection and faster healing, compared to controls of gauze or non-treatment. Other wound dressings can include 5% by weight amikacin or 0.02% basic fibroblast growth factor.

Standard cotton gauze can be pre-treated with an aerosol of pdRAIB in ethanol, or dipped into pdRAIB in ethanol. The ethanol can be allowed to evaporate from the gauze. The treated and untreated gauze can be placed onto dermal wounds on the back of pigs.

The preparation can be inspected for wound closure to check whether it is faster for the gauze treated with pdRAIB rather than the untreated gauze.

Example 13

In Vivo and I*n Vitro* Testing of Sugar Based Polymers

In the following tests three different carrier were used. For the studies the carriers were diluted using ethanol. There carriers were:

- sucrose acetate isobutyrate (SAIB) diluted with ethanol to give a SAIB:ethanol ratio of 80:20 (v/v);
- an esterified polymer of fructose comprising acetate and isobutyrate esters (pFAIB), diluted with ethanol to give a pFAIB:ethanol ratio of 80:20 (w/w); and
- an esterified polymer of deoxyribose comprising acetate and isobutyrate esters (pdRAIB), diluted with ethanol to give a pdRAIB:ethanol ratio of 80:20 (w/w).

In Vitro Viscosity Testing

The viscosities of the three carriers were tested at 37° using a Physica MCR 301, with a gap of 50µm. Dynamic viscosity was recorded at increasing shear rates. The results are shown in Figure 7. This testing shows that the pFAIB and pdRAIB samples are both more viscous than SAIB.

The viscosity characterisation reaction demonstrates that it is possible to make HVLCMs from by polymerising (via a condensation polymerisation) and esterification of simple sugars like deoxyribose and fructose. In addition it shows that dilution with solvent lowers the viscosity such that they can be injected. With 0% solvent and at room temperature these compounds are semi-solid and cannot be measured by a viscometer.

In Vivo Toxicity Testing

Eight week old female C57BL6 mice were anaesthetised by inhaled isoflourane gas. The surgical site, the quadriceps, was wiped with 70% ethanol prior to bilateral injections. The three carriers were all dissolved in ethanol at concentrations of 80:20 (v/v) SAIB, and at 80:20 (w/w) pFAIB and pdRAIB, as stated above. Prior to implantation, rhBMP-2 was mixed in, and then this mixture was injected into the mouse. Each leg received 20 µL containing 5 µg of rhBMP-2. These animals were then closely monitored for 1 week, at which point they were culled.

The main outcome in the study was that all mice survived. The pFAIB mouse was seen to have significant local swelling in the first 36 hours. This can also be seen histologically in Figure 8 with increased cell infiltration around the implantation site. The pdDRAIB is well tolerated by the mice and show no adverse effects or inflammation, even when co-delivered with rhBMP-2.

In Vivo Bone Formation Assay

Eight week old female C57BL6 mice were anaesthetised by inhaled isoflourane gas. The surgical site, the quadriceps, was wiped with 70% ethanol prior to bilateral injections. The three carriers were dissolved in ethanol at concentrations of 80:20 (v/v) SAIB, and at 80:20 (w/w) pdRAIB, as stated above. Prior to implantation, rhBMP-2 was mixed in, and then this mixture was injected into the mouse. Each leg received 20 µL containing 5 µg of rhBMP-2. These mice were followed out to three weeks, and at this point, bone formation was assessed. Figure 9 shows X-rays at 3 weeks post implantation of 5µg rhBMP-2 in 20 µL of the carrier into bilateral quadriceps of C57BL6 mice.

Results reveal that for BMP-2 carrier efficacy pdRAIB is equivalent to or superior to SAIB as a bone delivery agent. It has been shown previously (Cheng *et al.*, *Eur. Cell Mater.*, **26**, 208-221, 2013) that SAIB is equivalent or superior to the clinical standard for BMP-2 delivery, which is a porous collagen scaffold (Medtronic).

Bone volume was measured by X-ray mircotomography (microCT) (Skyscan 1174) (Figure 10) and representative histology performed by sectioning of decalcified samples and staining with haematoxylin and eosin (Figure 11)

Figure 10 shows (A) representative X-ray images of bone formed by SAIB (control) and pdRAIB (test) at 3 weeks after implantation; and (B) quantification of bone formed in multiple tests (multiple mice) by microCT. Thresholds for calculating bone volume were set at 0.3 g/cm^3 of calcium hydroxyapatite.

The data in Figure 10 shows evidence that the use of pdRAIB as a delivery system for rhBMP-2 has been reduced to practice in a pre-clinical model. Notably the bone volumes achieved showed less variation than the SAIB samples, which would be expected to be advantageous in a clinical setting. The bone volumes formed were comparable to SAIB, which itself has been found to be 3-fold more effective than the current clinical standard of porous collagen matrix ((Cheng *et al.*, *Eur. Cell Mater.*, **26**, 208-221, 2013). This indirectly indicates that pdRAIB could also be superior to current clinical methods.

Figure 11 shows representative histological images of bone created by SAIB and pdRAIB used as carriers for rhBMP-2. (A) shows an ectopic bone nodule showing a cortical shell and pseudo marrow space made with SAIB; (B) shows a comparable cortical shell and pseudo marrow space which was observed with pdRAIB; (C) shows an example of a vessel surrounded by new bone with the ectopic bone nodule of a pdRAIB specimen; and (D) shows an enlargement of the bone/vessel from panel C with the red blood cells inside the vessel more clearly visible.

The data in Figure 11 indicates that the calcified tissue measured by microCT in Figure 10 shows the histological features of normal bone. There is also evidence of vessel formation in the bone (Figure 11 panel C and Figure 11 panel D), which would be consistent with the principle that pdRAIB may have additional benefits for bone formation by having a pro-angiogenic effect.

Example 14

Use of the HVLCMs as Coatings

A sample of pdRAIB was used as a coating. Alexa 555, a fluorescent dye was incorporated into pdRAIB 50:50 with ethanol. The coating was dripped onto a porous bone graft substitute ("Vitoss") and bone graft ("Metaphyseal bone"), air dried for 2 minutes, and then examined using fluorescent microscopy. The results are shown in Figure 12, where the "Background" autofluorescence of the Vitoss and bone graft overlaid with the fluorescent images of the Alexa 555 impregnated pdRAIB. Figure 12

demonstrates the efficiency in coating interstices of complex scaffolds with an HVLCM of the invention, for the delivery of bioactive agents.

CLAIMS

1. An esterified polysaccharide which is a homopolymer or copolymer comprising esterified sugar monomer units, where the sugar monomer units are esterified ketose or aldose sugars.

2. An esterified polysaccharide which is a homopolymer or copolymer comprising esterified sugar monomer units, where the sugar monomer units are selected from: esterified deoxyribose, esterified arabinose, esterified lyxose, esterified ribose, esterified xylose, esterified ribulose, esterified xyulose, esterified allose, esterified altrose, esterified glucose, esterified 2-deoxy-glucose, esterified mannose, esterified gulose, esterified idose, esterified galactose, esterified talose, esterified psicose, esterified fructose, esterified sorbose, tagatose, or a combination thereof.

3. The esterified polysaccharide according to claim 2, which is a homopolymer or copolymer comprising esterified sugar monomer units, where the sugar monomer units are selected from: esterified 2-deoxyribose, esterified 2-deoxy-D-ribose esterified fructose, esterified galactose, esterified glucose, esterified 2-deoxy-glucose, esterified 2-deoxy-D-glucose, or a mixture thereof.

4. An esterified polysaccharide which is a homopolymer comprising esterified sugar monomer units, wherein the sugar monomer units are esterified 2-deoxyribose monomer units.

5. An esterified polysaccharide which is a homopolymer comprising esterified sugar monomer units, wherein the sugar monomer units are esterified fructose.

6. An esterified polysaccharide which is a homopolymer comprising esterified sugar monomer units, wherein the sugar monomer units are esterified galactose.

7. An esterified polysaccharide which is a homopolymer comprising esterified sugar monomer units, wherein the sugar monomer units are esterified glucose.

8. The esterified polysaccharide according to any one of claims 1 to 7, wherein the esterified sugar monomer prior to esterification promotes angiogenesis.

9. The esterified polysaccharide according to any one of claims 1 to 7, wherein the esterified sugar monomer promotes angiogenesis.

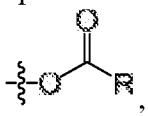
10. The esterified polysaccharide according to any one of claims 1 to 7, wherein the esterified sugar monomer prior to esterification provides anti-angiogenic properties.

11. The esterified polysaccharide according to any one of claims 1 to 7, wherein the esterified sugar monomer provides anti-angiogenic properties.

12. The esterified polysaccharide according to any one of claims 1 to 11, wherein the esterified polysaccharide comprises one type of ester group.

13. The esterified polysaccharide according to any one of claims 1 to 12, wherein the esterified polysaccharide comprises more than one type of ester group.

14. The esterified polysaccharide according to any one of claims 1 to 13, wherein the esterified sugar monomer units comprise ester groups of the formula:



wherein R is an alkyl group comprising 1 to 25 carbon atoms.

15. The esterified polysaccharide according to claim 14, wherein the polysaccharide comprises one type of R group.

16. The esterified polysaccharide according to claim 14, wherein the polysaccharide includes more than one type of R group.

17. The esterified polysaccharide according to any one of claims 14 to 16, wherein R is selected from: methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, *tert*-butyl, *n*-pentyl, *tert*-pentyl, neopentyl, isopentyl, 1-methylbutyl and 1-ethylpropyl, *n*-hexyl, *n*-heptyl, or a mixture thereof.

18. The esterified polysaccharide according to any one of claims 14 to 17, wherein R is methyl, ethyl, isopropyl, or a mixture thereof.

19. The esterified polysaccharide according to any one of claims 14 to 18, wherein R is a mixture of methyl and isopropyl.

20. The esterified polysaccharide according to any one of claims 1 to 19, wherein the polysaccharide is a high viscosity liquid carrier material.

21. The esterified polysaccharide according to any one of claims 1 to 20 wherein the polysaccharide has a viscosity of at least 5000 mPa.s at 37 °C.

22. The esterified polysaccharide according to any one of claims 1 to 21, wherein a mixture of the polysaccharide and a solvent has a viscosity of at less than about 1000 mPa.s at 37 °C.

23. The esterified polysaccharide according to claim 22, wherein the viscosity is less than about 200 mPa.s at 37 °C.

24. The esterified polysaccharide according to claim 22 or claim 23, wherein the solvent is selected from: alcohols including ethanol, propanol, and benzyl alcohol; tetraglycol; dimethyl sulfoxide, triacetin, Solketal; N-methyl-2-pyrrolidone, 2-pyrrolidone; esters of carbonic acid and alkyl alcohols including propylene carbonate, ethylene carbonate and dimethyl carbonate; fatty acids including acetic acid, lactic acid and heptanoic acid; alkyl esters of mono-, di-, and tri-carboxylic acids including 2-ethyoxyethyl acetate, ethyl acetate, methyl acetate, ethyl lactate, ethyl butyrate, diethyl malonate, diethyl glutonate, tributyl citrate, diethyl succinate, tributyrin, isopropyl myristate, dimethyl adipate, dimethyl succinate, dimethyl oxalate, dimethyl citrate, triethyl citrate, acetyl tributyl citrate, glyceryl triacetate; alkyl ketones including acetone and methyl ethyl ketone; ether alcohols including 2-ethoxyethanol, ethylene glycol dimethyl ether, glycerol formal; polyhydroxy alcohols including propylene glycol, polyethylene glycol, glycerin, 1,3-butyleneglycol, and isopropylidene glycol (2,2-dimethyl-1,3-dioxolone-4-methanol); dialkylamides including dimethylformamide, dimethylacetamide; dimethylsulfoxide and dimethylsulfone; tetrahydrofuran; lactones including -caprolactone and butyrolactone; cyclic alkyl amides including caprolactam; aromatic amides including N,N-dimethyl-m-toluamide, and 1-dodecylazacycloheptan-2-one, or mixtures thereof.

25. The esterified polysaccharide according to any one of claims 21 to 24, wherein the viscosity is measured at 37 °C, recorded at increasing shear rates, using a Physica MCR 301 (Anton Paar) with a gap of 50 μm.

26. The esterified polysaccharide according to any one of claims 1 to 25, wherein the polysaccharide does not crystallise neat under ambient or physiological conditions.

27. The esterified polysaccharide according to any one of claims 1 to 26, wherein the polysaccharide is phase-transitioning producing a semi-solid depot *in vivo*.

28. The esterified polysaccharide according to any one of claims 1 to 27, wherein the polysaccharide is biodegradable.

29. The esterified polysaccharide according to any one of claims 1 to 28, wherein the polysaccharide promotes angiogenesis.

30. The esterified polysaccharide according to any one of claims 1 to 28, wherein the polysaccharide provides anti-angiogenic properties.

31. The esterified polysaccharide according to any one of claims 1 to 30 wherein the homopolymer or copolymer is produced through a condensation polymerisation followed by an esterification reaction.

32. The esterified polysaccharide according to any one of claims 1 to 31 for healing a wound in a subject.

33. The esterified polysaccharide according to any one of claims 1 to 31 for delivering an agent to a site in or on a subject.

34. The esterified polysaccharide according to claim 33, wherein the subject is an animal.

35. The esterified polysaccharide according to claim 33, wherein the subject is a human being.

36. The esterified polysaccharide according to any one of claims 1 to 31 for promoting bone growth in a subject.

37. A pharmaceutical composition comprising the polysaccharide according to any one of claims 1 to 31, together with one or more pharmaceutically acceptable carriers and/or excipients.

38. The composition according to claim 37, wherein the pharmaceutical composition comprises one or more of the following:

- a solvent; and/or
- one or more agents.

39. The composition according to claim 38, wherein the composition comprises a solvent selected from: alcohols including ethanol, propanol, and benzyl alcohol; tetraglycol; dimethyl sulfoxide, triacetin, Solketal; N-methyl-2-pyrrolidone, 2-pyrrolidone; esters of carbonic acid and alkyl alcohols including propylene carbonate, ethylene carbonate and dimethyl carbonate; fatty acids including acetic acid, lactic acid and heptanoic acid; alkyl esters of mono-, di-, and tri-carboxylic acids including 2-ethyoxyethyl acetate, ethyl acetate, methyl acetate, ethyl lactate, ethyl butyrate, diethyl malonate, diethyl glutonate, tributyl citrate, diethyl succinate, tributyrin, isopropyl myristate, dimethyl adipate, dimethyl succinate, dimethyl oxalate, dimethyl citrate, triethyl citrate, acetyl tributyl citrate, glyceryl triacetate; alkyl ketones including acetone and methyl ethyl ketone; ether alcohols including 2-ethoxyethanol, ethylene glycol dimethyl ether, glycerol formal; polyhydroxy alcohols including propylene glycol, polyethylene glycol, glycerin, 1,3-butyleneglycol, and isopropylidene glycol (2,2-dimethyl-1,3-dioxolone-4-methanol); dialkylamides including dimethylformamide, dimethylacetamide; dimethylsulfoxide and dimethylsulfone; tetrahydrofuran; lactones including -caprolactone and butyrolactone; cyclic alkyl amides including caprolactam; aromatic amides including N,N-dimethyl-m-toluamide, and 1-dodecylazacycloheptan-2-one, or mixtures thereof.

40. The composition according to claim 38 or claim 39, wherein the composition comprises a solvent selected from ethanol, benzyl alcohol, tetraglycol, or a mixture thereof.

41. The composition according to any one of claims 38 to 40, wherein the solvent is present in an amount of about 10 to about 40% (v/v) relative to the composition as a whole.

42. The composition according to any one of claims 38 to 41, wherein the solvent is present in an amount of about 10 to about 30% (v/v) relative to the composition as a whole.

43. The composition according to any one of claims 33 or 38 to 42, wherein the agent is a bioactive agent selected from: an organic molecule that is a: drug, peptide, protein, carbohydrate, nucleoprotein, mucoprotein, lipoprotein, synthetic polypeptide or protein, small molecule linked to a protein, glycoprotein, steroid, nucleic acid, nucleotide, nucleoside, oligonucleotide, gene, lipid, hormone, vitamin, inorganic compound, or combination thereof.

44. The composition according to claim 43, wherein the bioactive agent causes a biological effect when administered *in vivo* to a subject.

45. The composition according to any one of claims 38 to claim 44, wherein the composition comprises an agent that is an osteoinductive agent.

46. The composition according to claim 45, wherein the osteoinductive agent is an osteogenic protein, or a growth factor, or a member or the TGF-beta superfamily, or a mixture thereof.

47. The composition according to claim 46, wherein the osteogenic protein is a bone morphogenetic protein (BMP).

48. The composition according to claim 47, wherein the BMP is selected from: BMP-2, BMP-4, BMP-6, BMP-7 (OP-1), and BMP-9, rhBMP-1, rhBMP-2, rhBMP-3, rhBMP-4, rhBMP-5, rhBMP-6, rhBMP-7, rhBMP-8a, rhBMP-8b, rfiBMP-9, rhBMP-10, rhBMP-15, noggin resistant BMPs, or a combination thereof.

49. The composition according to claim 47 or claim 48, wherein the BMP is rhBMP-2 or rhBMP-7.

50. The composition according to any one of claims 45 to 49 wherein the osteoinductive agent is present in an amount of 0.1 to about 40 mg.

51. The composition according to any one of claims 45 to 50 wherein the osteoinductive agent is present in an amount of 0.1 to about 5 mg.

52. The composition according to any one of claims 38 to claim 51, wherein the composition comprises an agent that is an anti-resorptive agent.

53. The composition according to claim 49, wherein the anti-resorptive agent is selected from: a bisphosphonate; IKK inhibitors; osteoprotegerin (OPG); inhibitors of Cathepsin K, chloride ion channel blockers; antibodies directed against RANKL, SOST, and DKK1; proton pump inhibitors, or a mixture thereof.

54. The composition according to claim 53, wherein the bisphosphonate is selected from: zoledronic acid, pamidronic acid, ibandronic acid, etidronic acid, alendronic acid, risedronic acid, and tilurondic acid.

55. The composition according to any one of claims 47 to 49, wherein the anti-resorptive agent is selected from: zoledronic acid, OPG, inhibitors of both IKK and Cathepsin K, anti-RANKL Ab, anti-SOST Ab, and anti DKK1 Ab.

56. The composition according to any one of claims 38 to 55, wherein the composition comprises an agent that is an osteoconductive agent.

57. The composition according to claim 56, wherein the osteoconductive agent is a ceramic particle.

58. The composition according to claim 56 or 57, wherein the osteoconductive agent is selected from: hydroxyapatite, bioglass, silicon substituted hydroxyapatite, porous tri-calcium phosphate, or combinations, composites, or other derivatives of calcium phosphate, or a mixture thereof.

59. The composition according to any one of claims 56 to 58, wherein the osteoconductive agent is hydroxyapatite.

60. The composition according to any one of claims 56 to 59, wherein the osteoconductive agent is present in an amount of about 0.1 to about 10% (w/v).

61. The composition according to any one of claims 56 to 60, wherein the osteoconductive agent is present in an amount of about 1 to about 5% (w/v).

62. The composition according to any one of claims 37 to 61, wherein the composition promotes angiogenesis.

63. The composition according to any one of claims 37 to 61, wherein the composition provides anti-angiogenesis properties.

64. The composition according to any one of claims 37 to 62, wherein the composition comprises an agent that is an angiogenic compound.

65. The composition according to claim 64, wherein the angiogenic compound is selected from: VEGF, nicotinic acid, angiopoietin, erythropoietin (EPO), nicotinic acid and desferoxamine (DFO).

66. The composition according to any one of claims 37 to 65, further comprising a biodegradable polymer.

67. The composition according to claim 66, wherein the biodegradable polymer is selected from: poly(lactic acid) (PLA), including poly(D-lactic acid) (PDLA), poly(lactic -co-glycolic acid) (PLGA), poly(glycolic acid) (PGA), poly(-caprolactone) (PCL), or a mixture thereof.

68. The composition according to any one of claims 37 to 67 for healing a wound in a subject.

69. The composition according to any one of claims 37 to 67 for delivering an agent to a site in or on a subject.

70. The composition according to claim 69, wherein the subject is an animal.

71. The composition according to claim 69, wherein the subject is a human being.

72. The composition according to any one of claims 37 to 67 for promoting bone growth in a subject.

73. A method to promote bone growth, the method comprising providing a composition according to any one of claims 37 to 67 to a site in a subject to promote bone growth at the site.

74. A method to heal wounds in or on a subject, the method comprising providing a composition according to any one of claims 37 to 67, to a wound site in or on the subject to promote healing of the wound.

75. A method to deliver an agent on or in a subject, the method comprising providing a composition according to any one of claims 37 to 67, to a site on or in the subject.

76. The method according to claim 75, wherein the agent is a bioactive agent selected from: an organic molecule that is a: drug, peptide, protein, carbohydrate, nucleoprotein, mucoprotein, lipoprotein, synthetic polypeptide or protein, small molecule linked to a protein, glycoprotein, steroid, nucleic acid, nucleotide, nucleoside, oligonucleotide, gene, lipid, hormone, vitamin, inorganic compound, or combination thereof.

77. The method according to any one of claims 73 to 76, wherein the composition is provided to the site by injection.

78. The method according to claim 73, wherein the site is selected from bone fracture, bone graft, bone wound, bone defect, bone non-union or pseudarthrosis, the spine, surface of a bone implant, or injected within a bone implant, porous scaffold, cage, balloon, membrane, or other containment device.

79. The method according to any one of claims 73 to 78, wherein the subject is an animal.

80. The method according to claim 79, wherein the animal is selected from: warm blooded animals, including mammals, wherein mammals comprises dogs, cats, cattle,

pigs, sheep, goats, rats, guinea pigs, horses, or other bovine, ovine, equine, canine, feline, rodent or murine species; birds; reptiles; fish and amphibians.

81. The method according to any one of claims 73 to 78, wherein the subject is a human being.

82. Use of a composition according to any one of claims 37 to 67 in the preparation of the medicament for promoting bone growth in a subject.

83. Use of a composition according to any one of claims 37 to 67 in the preparation of the medicament for healing wounds in or on a subject.

84. Use of a composition according to any one of claims 37 to 67 in the preparation of the medicament for delivering an agent to a subject.

85. The use according to claim 84, wherein the agent is a bioactive agent selected from: an organic molecule that is a: drug, peptide, protein, carbohydrate, nucleoprotein, mucoprotein, lipoprotein, synthetic polypeptide or protein, small molecule linked to a protein, glycoprotein, steroid, nucleic acid, nucleotide, nucleoside, oligonucleotide, gene, lipid, hormone, vitamin, inorganic compound, or combination thereof.

86. Use of a composition according to any one of claims 37 to 67 for promoting bone growth in a subject.

87. Use of a composition according to any one of claims 37 to 67 for healing wounds in or on a subject.

88. Use of a composition according to any one of claims 37 to 67 to deliver an agent to a subject.

89. The use according to claim 88, wherein the agent is a bioactive agent selected from: an organic molecule that is a: drug, peptide, protein, carbohydrate, nucleoprotein, mucoprotein, lipoprotein, synthetic polypeptide or protein, small molecule linked to a protein, glycoprotein, steroid, nucleic acid, nucleotide, nucleoside, oligonucleotide, gene, lipid, hormone, vitamin, inorganic compound, or combination thereof.

90. The use according to any one of claims 82 to 89, wherein the subject is an animal.

91. The use according to claim 90, wherein the animal is selected from: warm blooded animals, including mammals, wherein mammals comprises dogs, cats, cattle, pigs, sheep, goats, rats, guinea pigs, horses, or other bovine, ovine, equine, canine, feline, rodent or murine species; birds; reptiles; fish and amphibians.

92. The use according to any one of claims 82 to 89, wherein the subject is a human being.

93. A composition according to claim 37 for the controlled release of an agent.

94. An esterified polysaccharide according to any one of claims 1 to 31 for the controlled release of an agent.

95. An esterified polysaccharide according to any one of claims 1 to 31 for the local release of an agent.

96. An esterified polysaccharide used as a high viscosity liquid carrier material.

97. The esterified polysaccharide according to claim 96, wherein the esterified polysaccharide is defined according to any one of claims 1 to 31.

98. The esterified polysaccharide according to claim 96 or claim 97 for the controlled release of an agent.

99. The esterified polysaccharide according to claim 96 or claim 97 for the local release of an agent.

100. A composition for the controlled release of an agent comprising:
- a polymeric high viscosity liquid carrier material; and
- an agent.

101. A composition for the local release of an agent comprising:
- a polymeric high viscosity liquid carrier material; and

- an agent.

102. A composition according to claim 96 or 97 wherein the polymeric high viscosity liquid carrier material is an esterified polysaccharide as defined in any one of claims 1 to 31.

103. The composition according to any one of claims 100 to 102, wherein the agent is a bioactive agent selected from: an organic molecule that is a: drug, peptide, protein, carbohydrate, nucleoprotein, mucoprotein, lipoprotein, synthetic polypeptide or protein, small molecule linked to a protein, glycoprotein, steroid, nucleic acid, nucleotide, nucleoside, oligonucleotide, gene, lipid, hormone, vitamin, inorganic compound, or combination thereof.

104. A coating for an implant comprising an esterified polysaccharide as defined in any one of claims 1 to 31.

105. A coating for an implant comprising a composition as defined in any one of claims 37 to 72.

106. The coating for an implant according to claim 104 or claim 105, wherein the implant is an organic material selected from: an autograft, allograft, xenograft or collagen or glycosaminoglycans, proteoglycans, hyaluronic acid or heparin sulphate.

107. The coating for an implant according to claim 104 or claim 105, wherein the implant is a synthetic device selected from: a bone substitute, including a bone substitute made from ceramic, resorbable or non-resorbable polymers, or metal coatings including porous metal coatings of titanium, tantalum, cobalt chrome or stainless steel or their alloys.

108. Use of an esterified polysaccharide as defined in any one of claims 1 to 31 for coating an implant.

109. Use of a composition as defined in any one of claims 37 to 72 for coating an implant.

110. The use according to claim 108 or claim 109, wherein the implant is an organic material selected from: an autograft, allograft, xenograft or collagen or glycosaminoglycans, proteoglycans, hyaluronic acid or heparin sulphate.

111. The use according to claim 108 or claim 109, wherein the implant is a synthetic device selected from: a bone substitute, including a bone substitute made from ceramic, resorbable or non-resorbable polymers, or metal coatings including porous metal coatings of titanium, tantalum, cobalt chrome or stainless steel or their alloys.

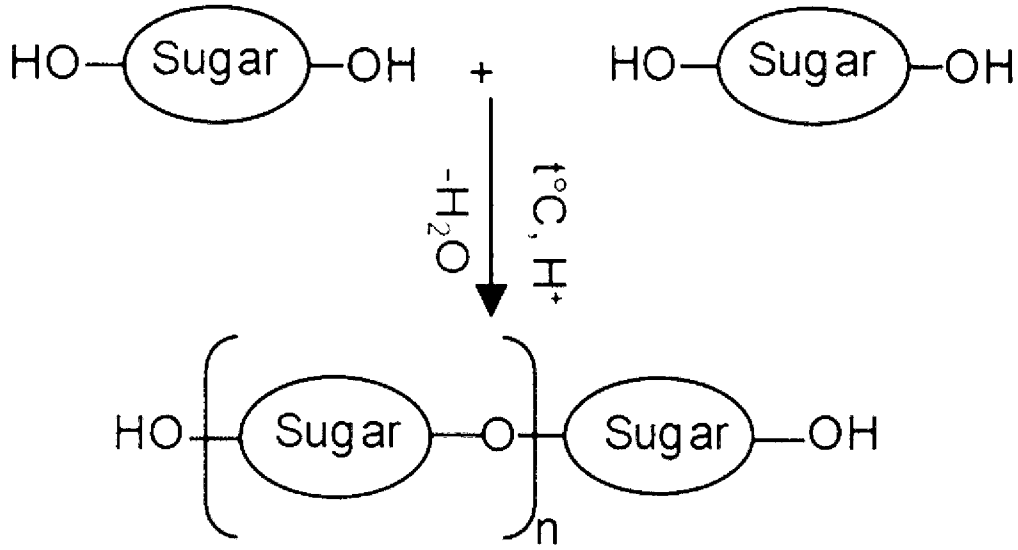


Figure 1

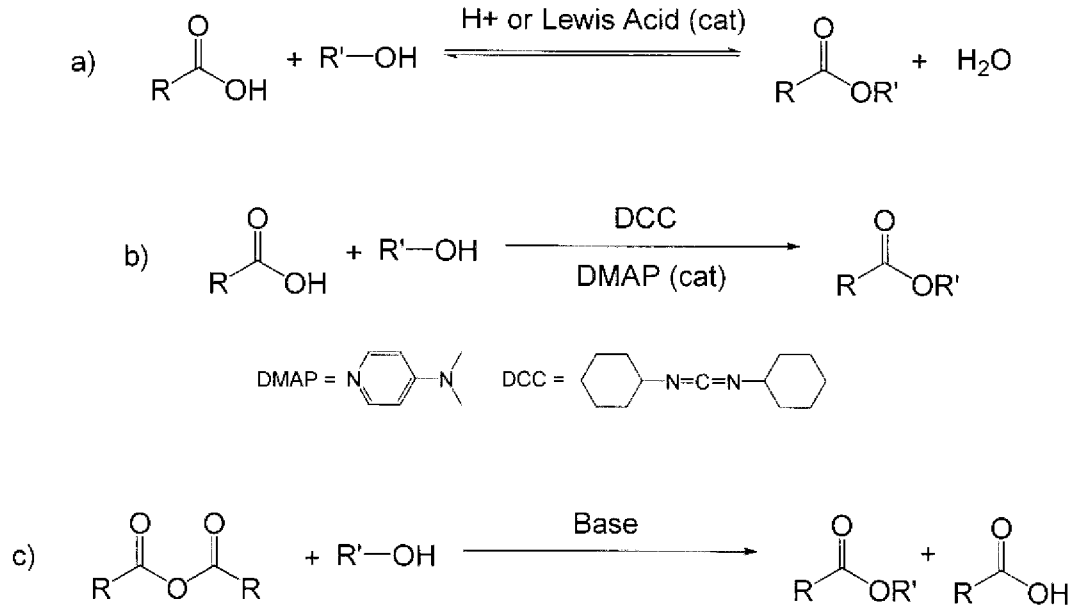

a)
+ R'—OH
H+ or Lewis Acid (cat)
+ H_2O
b)
+ R'—OH
DCC
DMAP (cat)
DMAP =
DCC =
N=C=N
c)
+ R'—OH
Base

Figure 2

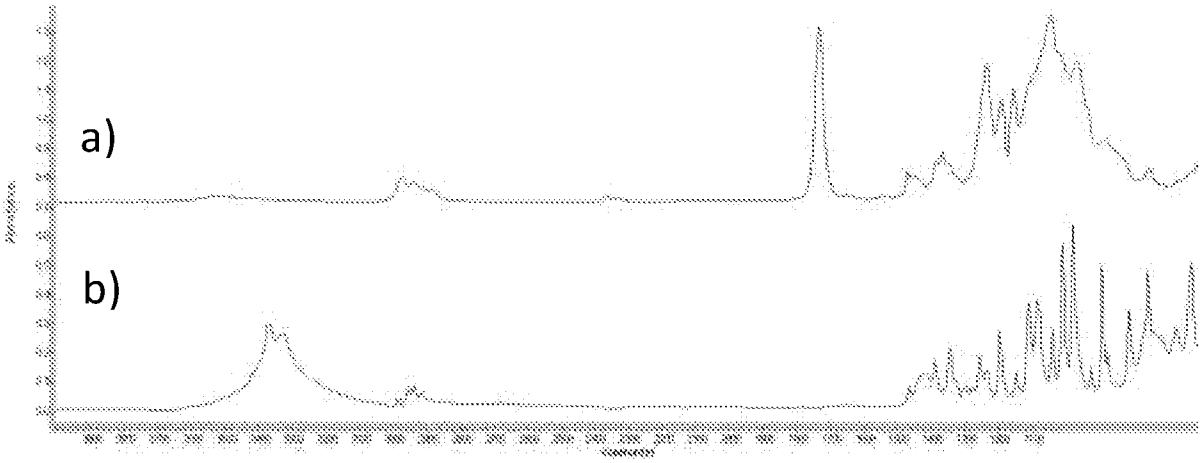


Figure 3

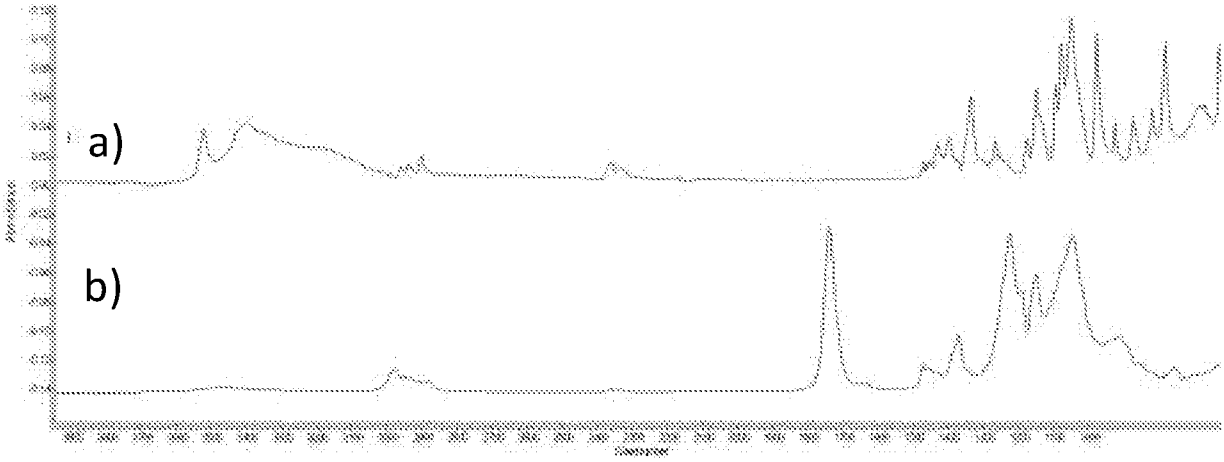


Figure 4

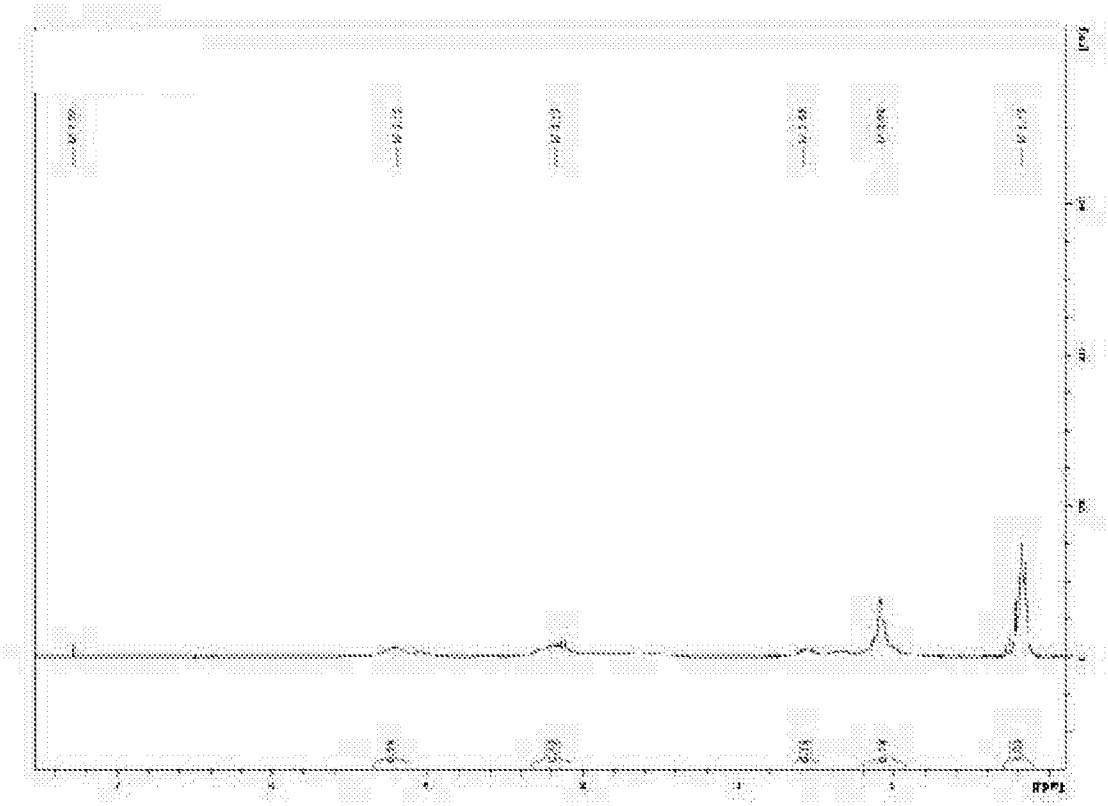


Figure 5

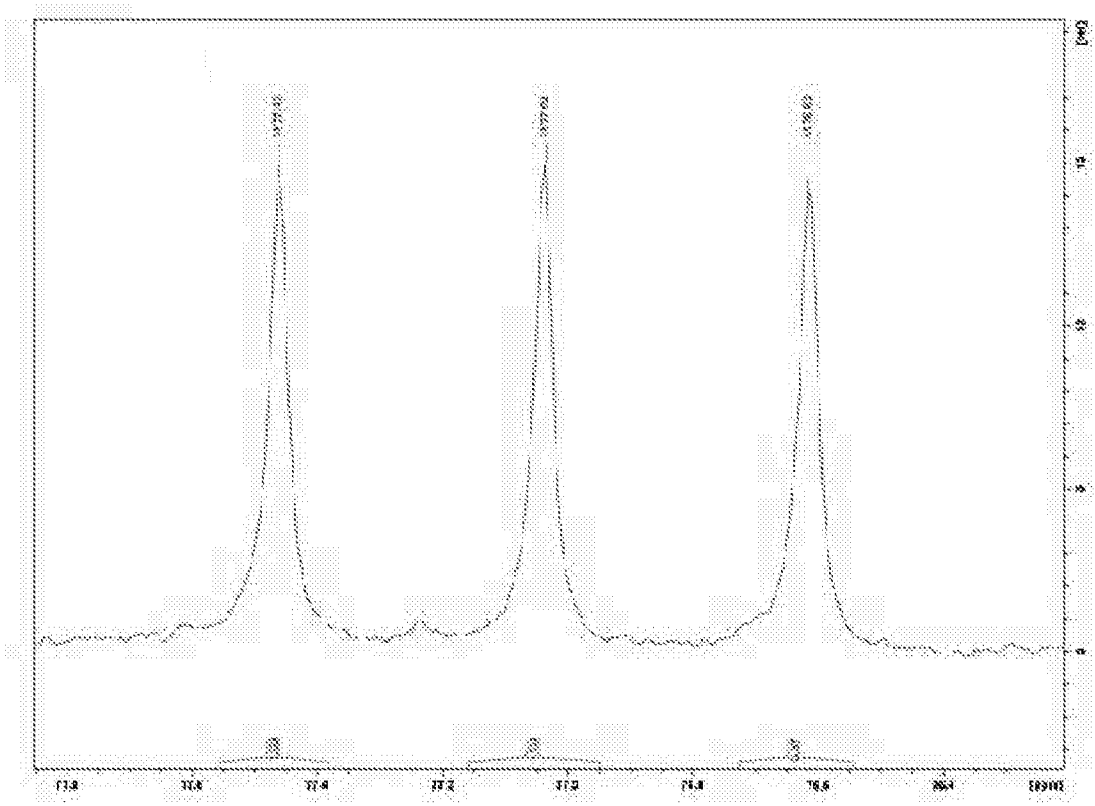


Figure 6

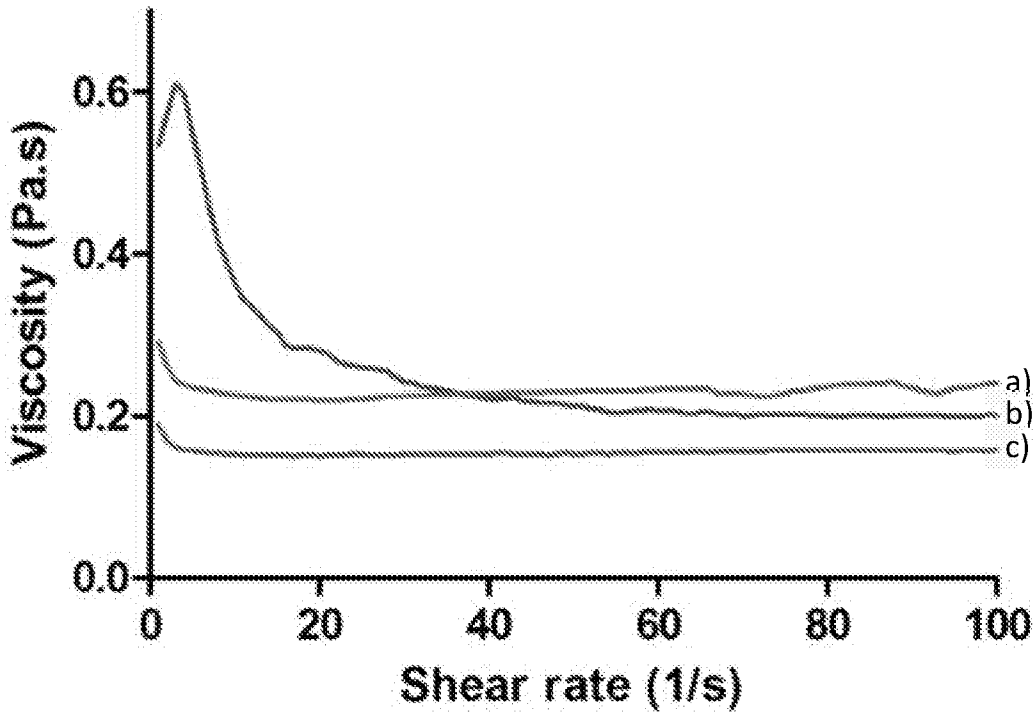


Figure 7

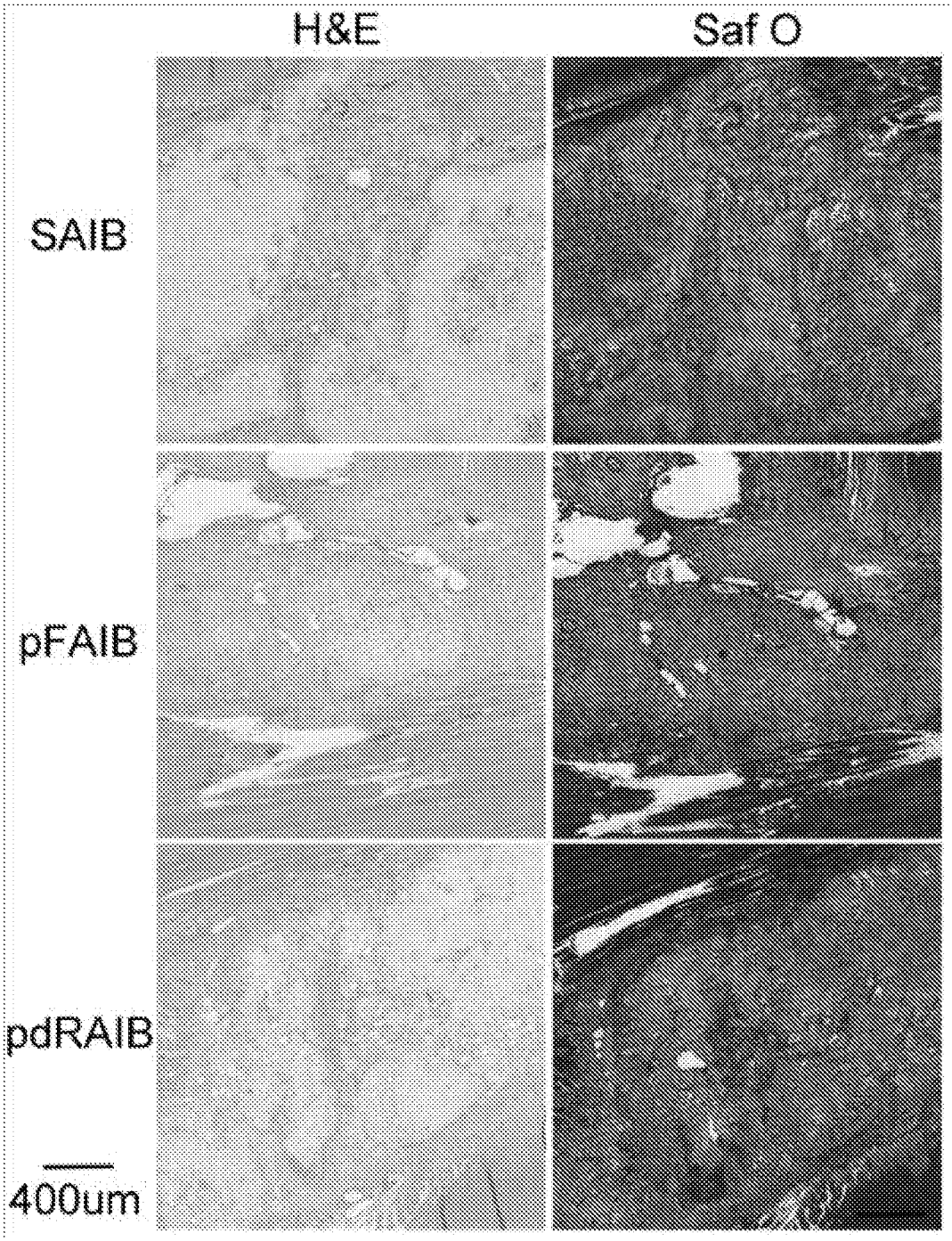


Figure 8

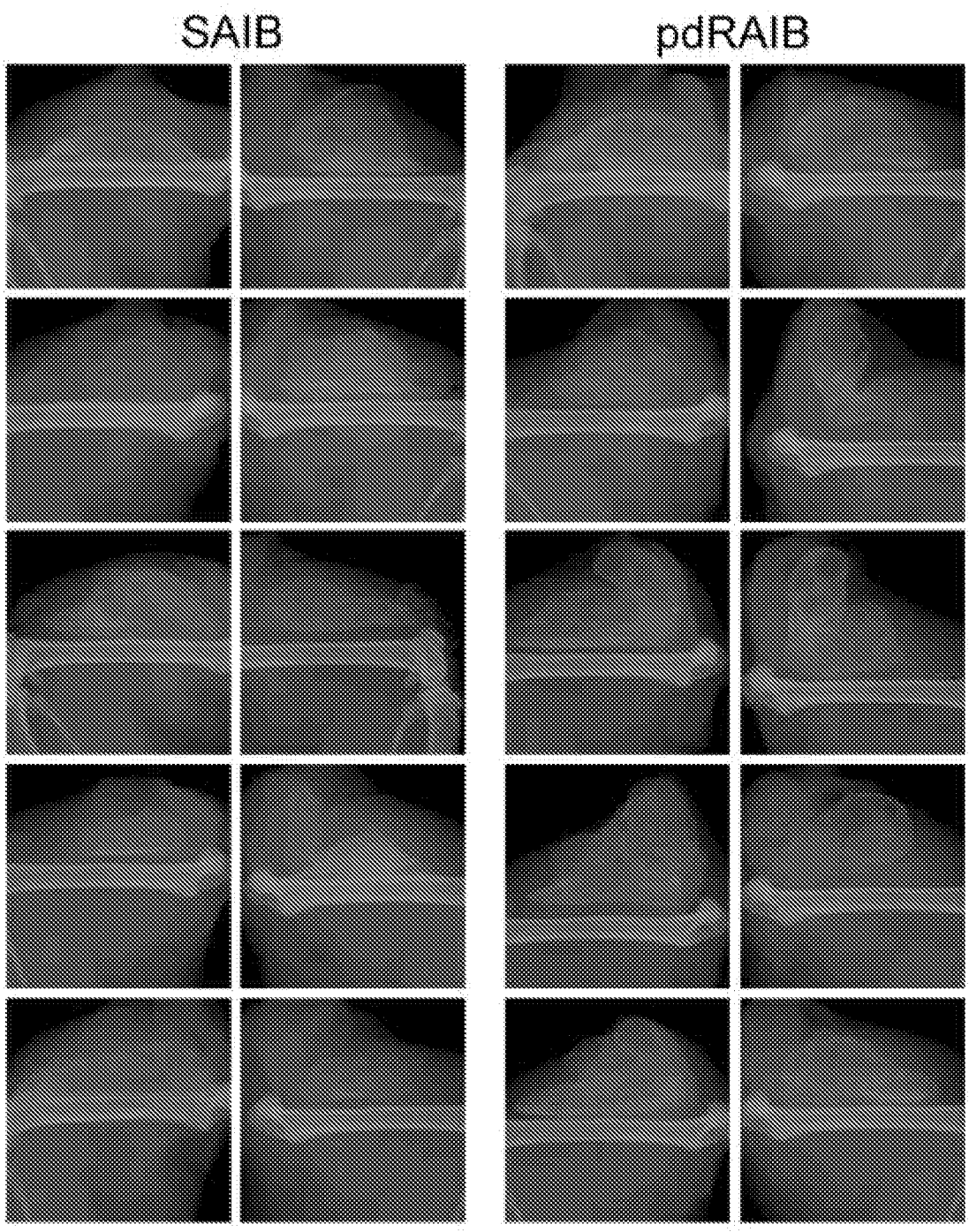


Figure 9

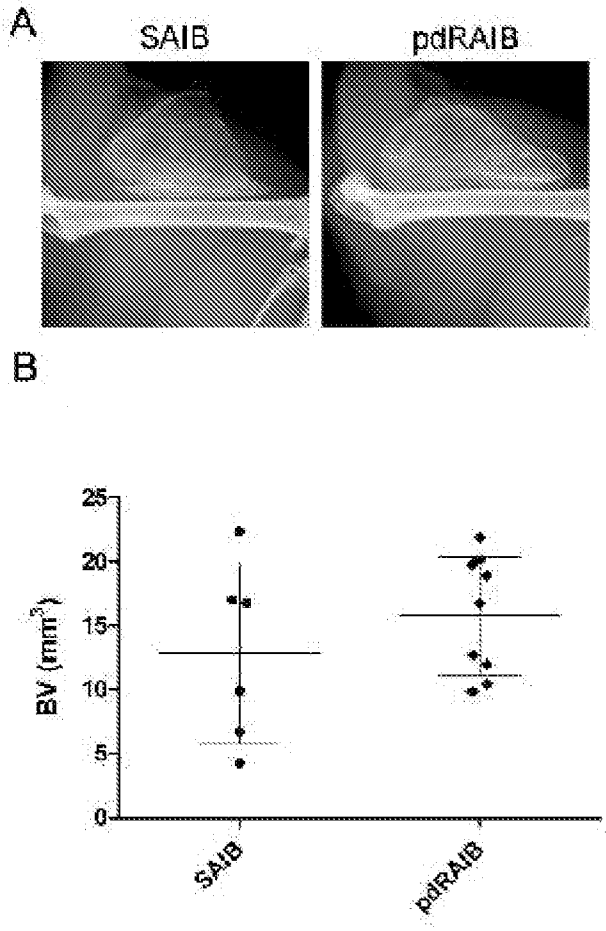


Figure 10

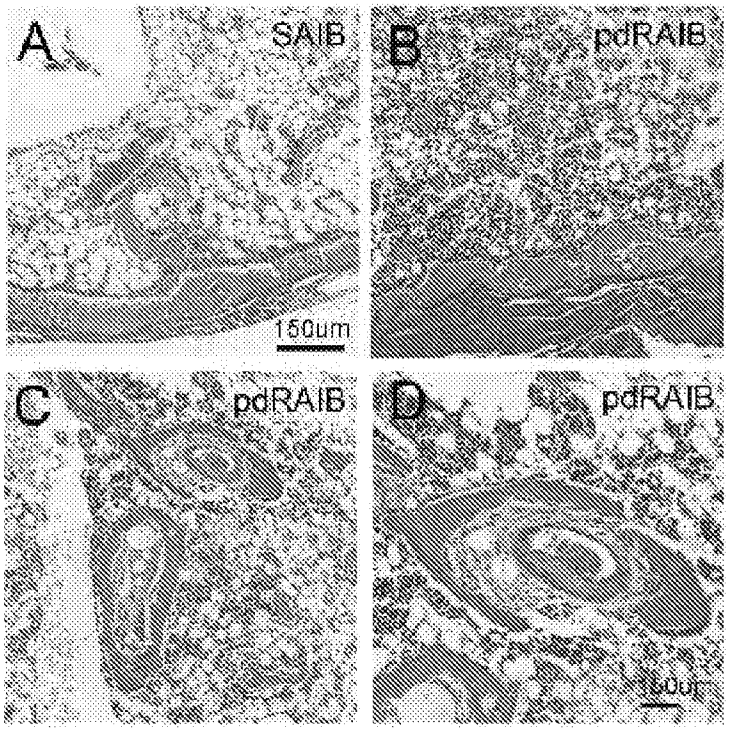


Figure 11

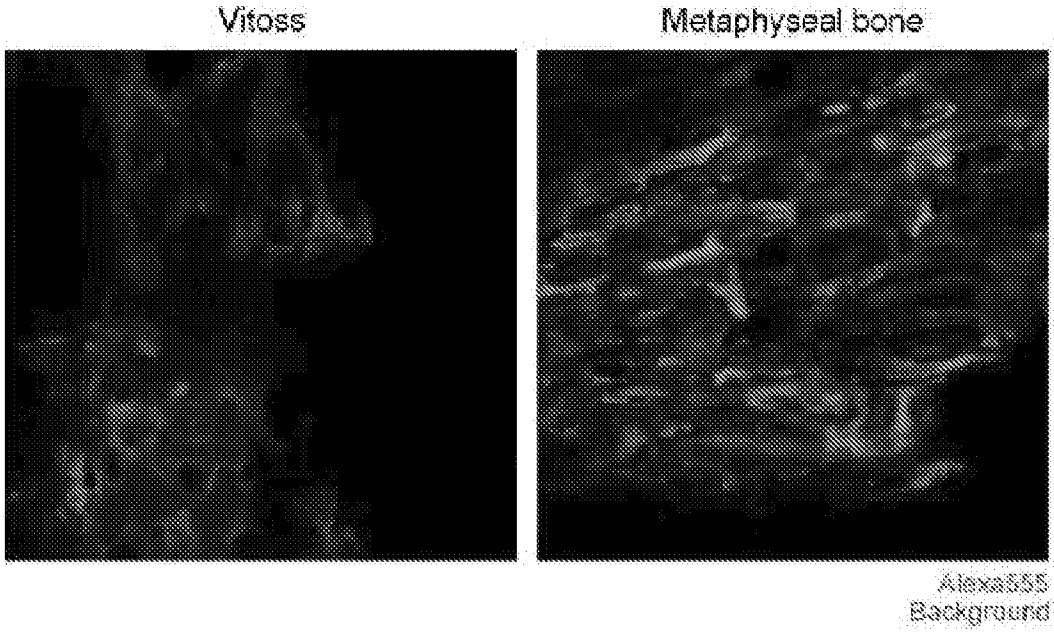


Figure 12

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2015/050069

A. CLASSIFICATION OF SUBJECT MATTER

C08B 3/02 (2006.01) C07H 13/04 (2006.01) C07H 13/06 (2006.01) A61K 9/14 (2006.01)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

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

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

EPODOC, WPIAP MEDLINE, HCAPLUS, WPIDS, BIOSIS: Keyword search (HIGH VISCOSITY, LIQUID, HVLC, HVLCM, POLYMER, POLYSACCHARIDE, CARBOHYDRATE, CELLULOSE, STARCH, GLYCOGEN, GALACTAN, DRUG, SUBSTANCE, ACTIVE, AGENT, BIOLOGICAL, PHARMACEUTICAL, DELIVER, DEOXYRIBOSE, ARABINOSE, LYXOSE, RIBOSE, XYLOSE, RIBULOSE, XYULOSE, ALLOSE, ALTROSE, GLUCOSE, MANNOSE, GULOSE, IDOSE, GALACTOSE, TALOSE, PSICOSE, FRUCTOSE, SORBOSE, TAGATOSE, ESTER and like terms).

ESPACENET, AUSPAT: Additional applicant and inventor search.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	Documents are listed in the continuation of Box C	

[X] Further documents are listed in the continuation of Box C [X] See patent family annex

* Special categories of cited documents:

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

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

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

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

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

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

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

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 June 2015	02 June 2015
Name and mailing address of the ISA/AU	**Authorised officer**
AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA Email address: pct@ipaustralia.gov.au	Marc Kloth AUSTRALIAN PATENT OFFICE (ISO 9001 Quality Certified Service) Telephone No. +61 3 9935 9609

INTERNATIONAL SEARCH REPORT C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		International application No. **PCT/AU2015/050069**
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2007/056125 A2 (EASTMAN CHEMICAL COMPANY) 18 May 2007 abstract & claim 1	1-111
X	WO 2009/075782 A1 (DURECT CORPORATION) 18 June 2009 abstract; page 2, lines 12-17 & examples	1-111
A	US 6,413,536 B1 (GIBSON et al) 02 July 2002 whole document	1-111
A	US 2013/0289069 A1 (DURECT CORPORATION) 31 October 2013 whole document	1-111

INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/AU2015/050069**

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

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Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/AU2015/050069**

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INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/AU2015/050069**

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Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/AU2015/050069**

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