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(54) Title: NITRIC OXIDE-RELEASING DIAZENIUMDIOLATED POLYMERS, COMPOSITIONS, MEDICAL DEVICES, AND USES THEREOF

(57) Abstract: The invention described herein provides novel nitric oxide-releasing polyurethanes, polyureas, and copolymers thereof. The polymers of the invention comprise at least two polyurethane/polyurea repeat units and contain at least one nitrogen-bound diazeniumdiolate. The diazeniumdiolated polyurethane/polyurea-based polymers can be used in medical devices, such as wound dressings. The invention also provides compositions and medical devices comprising such diazeniumdiolated polymers and methods of preparing and using such compounds.

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NITRIC OXIDE-RELEASING DIAZENIUMDIOLATED POLYMERS, COMPOSITIONS, MEDICAL DEVICES, AND USES THEREOF

CROSS-REFERENCE TO A RELATED APPLICATION

[0001] This patent application claims the benefit of U.S. Provisional Patent Application No. 60/987,537, filed November 13, 2007, which is incorporated by reference.

BACKGROUND OF THE INVENTION

[0002] The management of chronic wounds that are recalcitrant to treatment is a major public health problem. It is estimated that nearly 6 million people in the United States suffer from this condition. Of these, roughly 2 million people have venous leg ulcers, 500,000 have diabetic ulcers, and 3 million individuals have pressure ulcers (Singer et al., *New Engl. J. Med.*, 341(10): 738-746 (1999)). Over the past decade, millions of dollars have been spent on new treatments for chronic wounds, including growth factors and skin replacements (Kunimoto, *Ostomy Wound Management*, 45(8): 56-64 (1999); Flour et al., *Semin. Cutan. Med. Surg.*, 17(4): 260-265 (1998); Mandracchia et al., *Clin. Podiatr. Med. Surg.*, 18(1): 189-209, viii (2001); and Harding et al., *British Medical Journal*, 324(7345): 160-163 (2002)).

[0003] Wound healing is a multi-stage process involving many different cell types such as platelets, fibroblasts, and epithelial cells. The wound healing response initially involves an inflammatory phase as the wound is populated by platelets and erythrocytes, followed by an influx of polymorphonuclear cells, macrophages, and lymphocytes. Proliferation, differentiation, and apoptosis of several cell types occur, including keratinocytes, fibroblasts, and endothelial cells. Angiogenesis, the growth of new blood vessels, is another key component of wound repair. Collagen synthesis, deposition, and remodeling complete the wound healing process. Included among the many agents produced by the various cells involved in wound healing is nitric oxide (NO).

[0004] A number of studies suggest that elevated NO production is associated with and necessary for the wound healing response (Schwentker et al., *Nitric Oxide*, 7: 1-10 (2002) and Efron et al., *Curr. Opin. Nutr. Metab. Care*, 3: 197-204 (2000)). NO production is

upregulated following tissue injury, and most evidence shows that increased NO production is beneficial to normal healing (Schaffer et al., *J. Surg. Res.*, 63: 237-240 (1996)). For example, topical NO administration has been found to promote healing of chronic leg ulcerations in diabetic subjects and patients with peripheral vascular disease (Shabani et al., *Wound Repair Regener.*, 4: 353-362 (1996)).

[0005] Nitric oxide is believed to play a particularly key role in the initial inflammatory phase of wound healing. Many of the effects of NO, such as vasodilation, antimicrobial activity, antiplatelet effects, and induction of vascular permeability, are especially important in the inflammatory phase. NO is believed to achieve its effect by modulating inflammation-associated cytokines, such as IL-8, IL-1, IL-6, TGF-pl, and TNF-a. NO also affects the process of cellular proliferation during wound healing. NO has been shown to modulate the differentiation, proliferation, and apoptosis of keratinocytes (Yamaoka et al., *Free Radic. Res.*, 38(9): 943-950 (2004)), fibroblasts (Vernet et al., *Nitric Oxide*, 7(4): 262-276 (2002)), and endothelial cells (Picard et al., *J. Cardiovasc. Pharmacol.*, 31(Supp 1): S323-327 (1998)). For example, NO donors have been shown to promote re-endothelialization in models of arterial injury (Picard et al., *J. Cardiovasc. Pharmacol.*, 31(Supp 1): S323-327 (1998)). Nitric oxide also appears to play a key role in the third phase of wound repair: angiogenesis, the formation of new blood vessels. In ischemic murine tissues, NO has been shown to increase angiogenesis (Murohara et al., *J. Clin. Invest.*, 101(11): 2567-2568 (1998)). Conversely, NO inhibitors impair angiogenesis in gastric ulcer healing (Brzozowski et al., *Digestion*, 56(6): 463-471 (1995)). Finally, the role of NO in the last phases of collagen synthesis, deposition, and remodeling has been well-described in *in vitro* and *in vivo* studies. Many studies have found a link between increased NO levels and enhanced collagen content in experimental wounds, whether by treatment with NO donors, dietary L-arginine, or iNOS over-expression via gene therapy (Witte et al., *British Journal of Surgery*, 89(12): 1594-1601 (2002); Chen et al., *Chin. Med. J. (Engl.)*, 112(9): 828-831 (1999); and Thornton et al., *Biochem. Biophys. Res. Commun.*, 246(3): 654-659 (1998)).

[0006] Experimental therapeutic approaches to modulate NO levels in wound healing have included dietary supplementation with L-arginine, chemical NO donors, and gene therapy involving NOS isoforms. One of the critical challenges with nitric oxide therapy is

the instability of NO. Therapeutic potential of NO in wound repair has not been realized due to the inability to develop a suitable delivery vehicle.

[0007] Wound dressings have long been used to minimize tissue loss in chronic wounds by preventing the loss of body fluids and proteins from the body, reducing bacterial infection rates, and improving the healing process by providing a supportive network for proliferating cells. A wide range of synthetic polymers have been used for wound dressings. Polyurethane foams in particular offer a number of advantages including absorptive capacity, mechanical strength, and mass transport and flow-through, and the ability to incorporate bioactive agents. Polyurethane foam dressing products are commercially available, including Hydrasorb (Kendall), Allevyn (Smith & Nephew), Lyofoam (BMS Convatec), and Polymem (Ferris).

[0008] One approach to develop clinically relevant, diazeniumdiolated polyurethane composites has been investigated by Mowery et al., who developed NO-releasing diazeniumdiolated polyurethane films (Mowery et al., *Biomaterials*, 21(1): 9-21 (2000)). Multiple approaches for preparing the NO-releasing polymer films were reported, including dispersion of diazeniumdiolated molecules within the polyurethane matrix and covalent attachment of the diazeniumdiolates to the polyurethane backbone.

[0009] Diazeniumdiolated compounds have been incorporated into the backbone or pendant side-branches of polyurethanes via reaction with specific moieties of the pre-formed polymer (see, e.g., U.S. Patent 5,405,919). In these examples, the incorporation of an NO-releasing group into a polymer was carried out by grafting into the main backbone, attaching to the main backbone as a pendant group, or onto a side chain of the substrate polymer by reaction of nitric oxide gas and an active hydrogen (e.g., N-H).

[0010] Thus, despite the literature available on NO and nitric oxide-releasing compounds, there is a desire for stable nitric oxide-releasing polymers, especially polyurethanes and polyureas, that exhibit sustained release of nitric oxide.

BRIEF SUMMARY OF THE INVENTION

[0011] The invention provides novel nitric oxide-releasing polymers, such as those based on polyurethane, polyurea, and a combination thereof. The polymers of the invention comprise at least two polyurethane or polyurea repeat units and contain at least one nitrogen-bound diazeniumdiolate. The invention also provides compositions and medical devices, such as wound dressings, comprising such diazeniumdiolated polymers and methods of preparing and using such polymers.

BRIEF DESCRIPTION OF THE DRAWING

[0012] Figure 1 is a graph of time (minutes) versus moles of nitric oxide released from a diazeniumdiolated polyurethane film in accordance with an embodiment of the invention.

DETAILED DESCRIPTION OF THE INVENTION

[0013] Provided are novel polyurethane-based polymers, polyurethane-urea-based polymers, polyurea-based polymers, and copolymers thereof. The novel polymers of the invention comprise at least two polyurethane or polyurea repeat units and have at least one ~~covalently-bound diazeniumdiolate group.~~ The diazeniumdiolated polyurethane, polyurea, and polyurethane-urea polymers of the invention are stable, that is they do not release nitric oxide until used, but when used, are capable of releasing nitric oxide. The incorporation of the diazeniumdiolated moiety occurs during the polymerization of the polyurethane, the polyurea, or the copolymer. Because the $-N_2O_2^-$ group is directly attached to a nitrogen atom of the polyurethane or polyurea backbone, there is no need for a linking group. Preferably, the polyurethane or polyurea is prepared with prepolymers that have terminal isocyanate groups. The terminal isocyanate groups can react with at least one diazeniumdiolated polyamine and create one or more linkages that typically constitute at least part of the hard segments of polyurethane/polyurea compositions or are incorporated as a part of the hard segments of polyurethane/polyurea compositions. Surprisingly, the diazeniumdiolated functional group ($-N_2O_2^-$) remains unreacted during the polymerization step(s), thereby

allowing the resulting polyurethane/polyurea to retain the NO-donating ability of the parent polyamine.

[0014] It is envisioned that the incorporation of the diazeniumdiolated functional group as a part of the hard segments of a polyurethane/polyurea composition provides the ability to control the rate of release of nitric oxide over an extended period of time as the chemical composition or structure of both the hard and soft segments can be engineered in various ways. In another aspect of this invention, being able to incorporate a diazeniumdiolate functional group into the hard segments of a polyurethane/polyurea composition provides increased flexibility or options in the structural positioning and controlling the amount of diazeniumdiolate functional group that can be incorporated into the polymer backbone. As a result, additional control of the rate of nitric oxide release becomes possible.

[0015] In one embodiment, the present invention provides a nitric oxide-releasing polyurethane prepared from a composition comprising

(a) at least one polyol selected from the group consisting of an alkyl polyol, a cycloalkyl polyol, an aryl polyol, a polyether polyol, a polyester polyol, a polycarbonate polyol, a polycaprolactone polyol, a polyester polycarbonate polyol, silicone polyol, acrylic polyol, and a combination thereof;

(b) at least one polyisocyanate selected from the group consisting of an optionally substituted aromatic di- or polyisocyanate, an aralkyl di- or polyisocyanate, an aliphatic di- or polyisocyanate, and an alicyclic di- or polyisocyanate;

(c) optionally at least one polymer modifier selected from the group consisting of a chain extender, a cross-linker, and a mixture thereof; and

(d) at least one -$N_2O_2^-$-containing polyamine;

wherein the $N_2O_2^-$ group is attached to the hard segment of the polyurethane backbone. In particular, the $N_2O_2^-$ group is attached to and is an integral part of the hard segment of the

polyurethane backbone or is incorporated into the hard segment of the polyurethane backbone. Thus, the $-N_2O_2^-$-containing polyamine residue, after reaction, is incorporated into the hard segment.

[0016] In another embodiment, the present invention also provides nitric oxide-releasing polyurea prepared from

(a) at least one polyisocyanate selected from the group consisting of an optionally substituted aromatic di- or polyisocyanate, an aralkyl di- or polyisocyanate, an aliphatic di- or polyisocyanate, and an alicyclic di- or polyisocyanate;

(b) at least one amine-functionalized flexible segment, optionally at least one amine-functionalized chain extender, and;

(c) at least one $-N_2O_2^-$-containing polyamine;

wherein the $-N_2O_2^-$ group is attached to the hard segment of the polyurea backbone. In particular, the $N_2O_2^-$ group is attached to and is an integral part of the hard segment of the polyurethane backbone or is incorporated into the hard segment of the polyurea backbone.

[0017] The polyol is any suitable polyol used for polyurethane chemistry, such as an alkyl polyol, a cycloalkyl polyol, an aryl polyol, a polyether polyol, a polyester polyol, a polycarbonate polyol, a polycaprolactone polyol, a polyester polycarbonate polyol, silicone polyol, and acrylic polyol. The silicone polyol is selected from a specific structural type of silicone nonionic surfactant polymers, having multiple polyoxyalkylene sidechains, such as dimethicone copolyol. In an embodiment, the polyol can be a polyester that is biodegradable (e.g., glycolide, L-lactide, D-L lactate, caprolactone, copolymers of lactide and glycolide, copolymers of D-L lactide and glycolide, copolymers of L-lactide and caprolactone, copolymers of L-lactide and glycolide, poly paradioxanone, or combinations thereof). The polyol can have any desired molecular weight, ranging from several hundred to several thousand Daltons (e.g., about 200-10,000 g/mol, about 500-8,000 g/mol, about 500-5,000 g/mol, about 1,000-5,000 g/mol).

[0018] Polyether polyols (e.g., poly(tetramethylene ether) glycol) and polyester polyols (e.g., polyethylene adipate) are especially preferred polyols. Suitable polyether polyols usually are manufactured from propylene oxide (PO) and ethylene oxide (EO) and have a relatively low molecular weight (e.g., about 200-8,000 g/mol, about 500-5,000 g/mol, about 500-3,000 g/mol). The functionality of the polyether polyol (i.e., the number of active hydroxyl groups per molecule) can be varied depending on the desired properties of the resulting polyurethane. For example, a functionality of 2 typically provides a more elastomeric matrix suitable for elastomers, a functionality of 3 provides a base for flexible matrix or a soft segment cross-linked, and 3 to 6 or more provides a base for rigid matrix. Polyester polyols are typically produced by the condensation reaction of a diol such as ethylene glycol with a dicarboxylic acid.

[0019] The polyisocyanate is any suitable optionally substituted aromatic di- or polyisocyanate, an aralkyl di- or polyisocyanate, an aliphatic di- or polyisocyanate, or an alicyclic di- or polyisocyanate. Preferably, the polyisocyanate is selected from the group consisting of methylene-4,4′-diphenyldiisocyanate (MDI), methylene-2,4′-diphenyldiisocyanate, methylene-2,2′-diphenyldiisocyanate, polymeric MDI (PMDI), naphthalene-1,5-diisocyanate (NDI), carbodiimide-modified MDI, tolylene diisocyanate (TDI), paraphenylene diisocyanate (PPDI), 4,4′-methylene bis(cyclohexyl isocyanate) (H12MDI), isophorone diisocyanate (IPDI), 1,4-cyclohexyl diisocyanate (CHDI), 1,6-hexamethylene diisocyanate (HMDI), isocyanate-terminated biuret adduct of HDI, isocyanate terminated trimerization products based on HDI and IPDI, and any combination thereof. In an embodiment, the isocyanate can be biodegradable (e.g., lysine diisocyanate, 1,6-hexamethylene diisocyanate, 1,4-butane diisocyanate).

[0020] In an embodiment, the polymer backbone can be prepared with components that provide a biodegradable backbone. Thus, it is envisioned to prepare biodegradable NO-releasing polyurethanes, polyureas, and polyurethane/ureas. A biodegradable polyol and/or polyisocyanate can be used. For example, the polyol component can be a polyester that is biodegradable (e.g., glycolide, L-lactide, D-L lactate, caprolactone, copolymers of lactide and glycolide, copolymers of D-L lactide and glycolide, copolymers of L-lactide and caprolactone, copolymers of L-lactide and glycolide, poly paradioxanone, or combinations

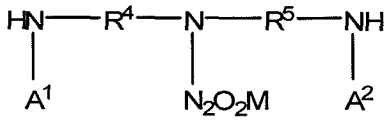
thereof). The isocyanate component also can be biodegradable (e.g., lysine diisocyanate, 1,6-hexamethylene diisocyanate, 1,4-butane diisocyanate, or combinations thereof).

[0021] The chain extender can be any suitable hydroxyl- or amine-functionalized chain extender known in polyurethane or polyurea chemistry. In an embodiment, the hydroxyl-functionalized chain extender is selected from the group consisting of 1,3-propanediol, 1,4-butanediol, 1,6-hexanediol, 1,12-dodecanediol, dimethylcyclohexyldiol, 1,4-bis-hydroxydiethyl hydroquinone (HQEE), diethylene glycol, dipropylene glycol, neopentyl glycol, diethanolamine, dipropanolamine, bis(hydroxyethyl)biphenol, and bis(hydroxypropyl)biphenol. In another embodiment, the amine-functionalized chain extender is selected from the group consisting of 1,3-propanediamine, 1,4-butanediamine, 1,6-hexanediamine, isophoronediamine, and 1,4-cyclohexanediamine.

[0022] Optionally included is a cross-linker to react with and cross-link the residual isocyanate groups present on the (pre)polymer used. The cross-linker is preferably multi-functional with two or more groups that are reactive with isocyanate. In another embodiment, the cross-linker is preferably multi-functional with at least three groups that are reactive with isocyanate. Cross-linkers with terminal hydroxyl, amine, and carbonyl groups are typically suitable. For example, the cross-linker can be selected from the group consisting of glycerol, trimethylolpropane, pentaerythritol, sorbitol, sucrose, triethanolamine, a low molecular weight poly(oxyalkylene) glycerol adduct, a low molecular weight poly(oxyalkylene) trimethylolpropane adduct, a low molecular weight polycaprolactone triol, and an oxyalkylene derivative of ethylenediamine. Particularly useful are a silicone polyethylene oxide copolymer with terminal hydroxyl groups, (e.g., Surfactant 193, Dow Corning), an ethylene glycol/propylene glycol copolymer (e.g., Pluronic L-64, BASF), other alkylene oxide surfactants (e.g., Pluronic 17R1 and 25R2, BASF; and BRIJ, ICI Americas).

[0023] The diazeniumdiolated polyamine is any suitable polyamine, such as those disclosed in, for example, U.S. Patents 5,155,137 and 5,250,550. Thus, there is more than one free amino group in the diazeniumdiolated polyamine. The polyamine preferably has at least three amino groups, at least one of which is bonded to a diazenimdiolate ($-N_2O_2^-$) group.

In an embodiment, the polyamine comprises three or four amino groups. For example, the diazeniumdiolated polyamine can have the structure of formula (I)



(I),

wherein

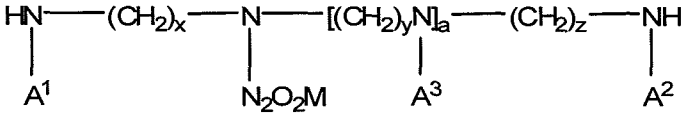
A^1 and A^2 are the same or different and each is hydrogen, an optionally substituted C_{1-12} alkyl, optionally substituted C_{3-30} cycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

R^4 and R^5 are the same or different and each is an optionally substituted C_{1-12} alkyl, an optionally substituted C_{2-12} alkenyl, optionally substituted C_{3-30} cycloalkyl, or optionally substituted aryl, and

M is a counterion as described herein.

[0024] In general, the diazeniumdiolated polyamine may or may not contain peptide bonds or amino acid residues.

[0025] A preferred embodiment of the polyamine of formula (I) is a compound of formula (Ia),



(Ia),

wherein

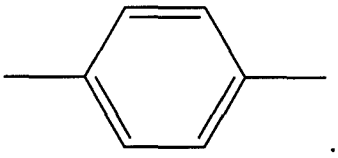
A^1 and A^2 are the same or different and each is hydrogen, an optionally substituted C_{1-12} alkyl, optionally substituted C_{3-30} cycloalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, or optionally substituted heteroarylalkyl;

A^3 is $-N_2O_2M$, hydrogen, an optionally substituted C_{1-12} alkyl, optionally substituted C_{3-30} cycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

x, y, and z are independently 2-12 (i.e., 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12);

a is 0 or 1; and

M is a counterion as described herein.

[0026] In any of the embodiments of the invention, A^1 and A^2 are preferably hydrogen. A^3 is preferably or $-N_2O_2M$ or an optionally substituted C_{1-12} alkyl. R^4 and/or R^5 are preferably a C_{2-12} alkylene (i.e., $-(CH_2)_{2-12}-$) or  .

[0027] Specific polyamines suitable for the present invention include diazeniumdiolated diethylene triamine, 3,3'-iminobispropylamine, and triethylenetetraamine. A preferred diazeniumdiolated polyamine is diethylenetriamine NONOate ("DETA/NO").

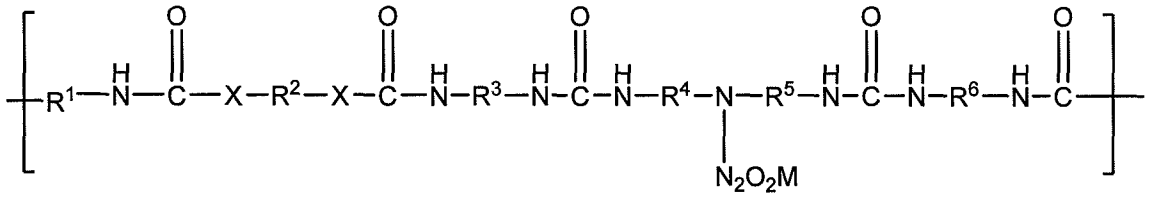
[0028] The concentration of the $-N_2O_2^-$ functional groups bound to the polyurethane/polyurea can be controlled, e.g., by the equivalent weight of the starting components. In keeping with the invention, the polyurethane or polyurea backbone can contain numerous $-N_2O_2^-$ groups.

[0029] Typically each $-N_2O_2^-$ group on the polymer also comprises a suitable counterion to balance the charge. Within a single polymer chain, the counterions can be the same or different, but preferably they are the same. Preferably, the counterion is a pharmaceutically acceptable counterion which could be a metal or non-metal counterion, e.g., alkali metal counterions such as sodium ion, potassium ion, lithium ion, and the like; alkaline earth metal counterions such as magnesium ion, calcium ion, and the like; Group III metal counterions such as aluminum ion; Group IV metal counterions such as tin ion; and transition metals, including iron ion, copper ion, manganese ion, zinc ion, cobalt ion, vanadium ion,

molybdenum ion, platinum ion, and the like. Non-metal counterions include quaternary ammonium ions. The only requirement for the pharmaceutically acceptable counterion is biological compatibility in a mammal, such as a human.

[0030] The amine-functionalized flexible segment and chain extenders include amine-terminated polyethers, C_{1-10} alkyl, C_{2-10} alkenyl, and C_{3-12} cycloalkyl mono- and diamines such as methylamine, ethylamine, diethylamide, ethylmethylamine, n-propylamine, allylamine, isopropylamine, *n*-butylamine, *n*-butylmethylamine, *n*-amylamine, *n*-hexylamine, 2-ethylhexylamine, cyclohexylamine, ethylenediamine, polyethyleneamine, 1,4-butanediamine, 1,6-hexanediamine, N-methylcyclohexylamine and alkylene amines such as ethyleneimine.

[0031] In connection with the foregoing, the present invention provides a nitric oxide-releasing polyurethane or polyurea comprising at least one repeat unit of the structure:



wherein

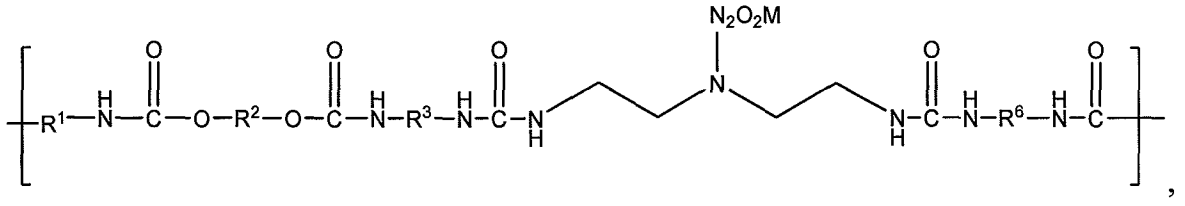
X is O or NH;

R^1, R^2, R^3, R^4, R^5, and R^6 are the same or different and each is an optionally substituted C_{1-12} alkyl, optionally substituted C_{3-30} cycloalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted alkoxyalkyl, optionally substituted polyether, optionally substituted polyester, optionally substituted polycarbonate, optionally substituted polycaprolactone, optionally substituted polyester polycarbonate, or optionally substituted heteroaryl; and

M is a counterion as described herein.

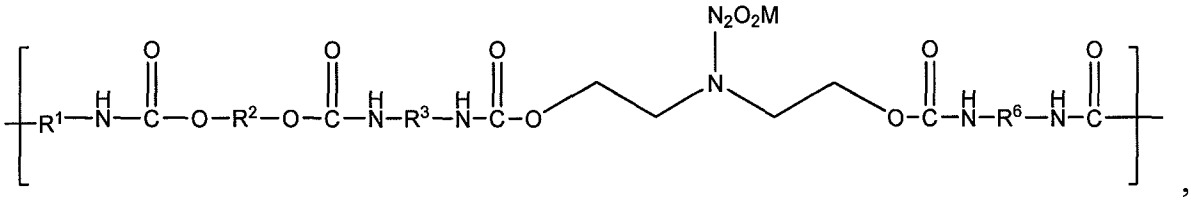
[0032] Any one or more of the C_{1-12} alkyl, C_{3-30} cycloalkyl, aryl, aralkyl, alkoxyalkyl, polyester, polycarbonate, polycaprolactone, polyester polycarbonate, or heteroaryl described above can be substituted. Generally each of these moieties can have 1 to 10 substituents (e.g., 1 to 8, 1 to 6, 1 to 4, 1 to 3 substituents) that are independently selected from the group consisting of halo, C_{1-12} alkyl, C_{6-30} aryl, heteroaryl, C_{1-12} alkoxy, C_{1-12} aryloxy, acyloxy, acetyl, and carboxyl.

[0033] In an embodiment, a polymer of the invention has at least one repeat unit with the following structure:



wherein R^2 is the flexible segment made from, e.g., optionally substituted polyether, optionally substituted polyester, optionally substituted polycarbonate, and optionally substituted polycaprolactone. In some embodiments, R^3 is optionally substituted C_{1-12} alkyl, optionally substituted C_{3-30} cycloalkyl, or optionally substituted aryl.

[0034] In another embodiment, a polymer of the invention has at least one repeat unit with the following structure:



wherein R^2 is the flexible segment made from, e.g., optionally substituted polyether, optionally substituted polyester, optionally substituted polycarbonate, and optionally substituted polycaprolactone. In some embodiments, R^3 is optionally substituted C_{1-12} alkyl, optionally substituted C_{3-30} cycloalkyl, or optionally substituted aryl.

[0035] It is understood that the invention encompasses embodiments in which a diazeniumdiolated polyurethane can optionally comprise a small amount of polyurea. Similarly, a diazeniumdiolated polyurea of the invention can optionally comprise a small amount of polyurethane.

[0036] The term "prepolymer," as used herein, means a reactive relatively low-molecular weight macromolecule or oligomer that has at least one functional group capable of further polymerization. For example, the polyol can be pre-reacted with part or all of the polyisocyanate to form a prepolymer. The reactive terminal isocyanate group on the prepolymer can then be reacted with the at least one diazeniumdiolated polyamine.

[0037] Suitable polyurethane polymers or prepolymers can be synthetically prepared using standard techniques. For example, a polymer comprising at least two polyurethane or polyurea repeat units can be prepared using condensation polymerization and free radical polymerization. Suitable catalysts in these reactions are amine or organometallic catalysts including di- and tributyltin dilaureate and stannous octoate. Typically, the desired form of the polymer or prepolymer and/or the desired molecular weight will dictate the polymerization conditions to be used.

[0038] Diazeniumdiolated polyamines that contain at least one, preferably two or more, -NH- or NH_2 terminal groups can react directly with isocyanate (or an isocyanate prepolymer) in solution to form a polyurethane solution. Preferably, the diazeniumdiolated polyamine is covalently bound to the polyurethane by prepolymer-based reactions between an amino group and an isocyanate or a hydroxyl group and an isocyanate. In one embodiment, an NO-releasing segmented poly(urethane-urea) is prepared by reacting NCO-prepolymer (or quasi-prepolymer) with amine-containing diazeniumdiolate compounds. In another embodiment, NO-releasing segmented polyurethane is prepared by reacting NCO-prepolymers or quasi-prepolymers with hydroxyl-containing diazeniumdiolate compounds. In all cases, the diazeniumdiolated compound is an integral part of the hard segment of the polyurethane backbone. The synthesis is designed such that incorporation of the diazeniumdiolated polyamines occurs via a mechanism similar to the incorporation of chain extenders or cross-linkers in a typical polyurethane/urea reaction. Typically, the

polymerization reaction occurs over several hours at room temperature. Preferably an inert atmosphere (e.g., nitrogen blanket) is used to prevent any premature loss of nitric oxide or undesirable side reactions. The resulting NO-releasing material can be in any suitable form, such as a film (including a biostable film), powder, tube, extruded fiber or an extruded and annealed fiber, an injection molded part, an injection molded device, a matrix or reinforcement components of composites, coating, foam, and reticulated foam. Other suitable forms include a fiber, a yarn, a fabric, a membrane, a gel, a plastic, or a matrix. The desired form usually is dictated by the desired end use.

[0039] In an embodiment, the polyurethane based device is a composite with a polyurethane substrate comprising open-celled hydrophobic polyurethane foam with a hydrophilic polyurethane foam (microporous) coating. In another embodiment, the polyurethane based device is a composite with a polyurethane substrate comprising reticulated hydrophobic polyurethane matrices containing inter-connected and inter-communicating pores with a hydrophilic polyurethane foam (microporous) coating. The coatings on the open-celled hydrophobic polyurethane foam or on the reticulated hydrophobic polyurethane matrices can be a film. In addition, the film or foam coating can be at least partially hydrophilic. The resulting composite combines the strength, durability, surface area, and mass transport characteristics of hydrophobic polyurethane, with the biocompatibility, reservoir capacity, and chemical binding properties of hydrophilic coating both in form or foam and film. The polyurethane based composite is hemo-compatible, non-immunogenic, and has a large internal surface area. In one embodiment, A range of pore sizes is available in the device or in the composite including about 20-1,000 μm (e.g., about 50-800 μm, 100-600 μm, and 150-500 μm). The polyurethane foam composite has the unique ability to incorporate bioactive agents (e.g., enzymes) within the hydrophilic layer of the polymer system. The composite is designed to have elevated enzymatic activity levels per volume due to greater surface area, enhanced flow-through, and reduced deactivation of the enzymes due to thermal degradation during the polymerization step. Both catalase and lipase have been immobilized successfully within the foam composite and demonstrated hydrolytic and synthetic activity levels in *in vitro* assay systems. In addition, the foam composite can be used as an antimicrobial swab that can be impregnated with a broad

spectrum of enzymes and/or non-ionic detergents to remove biocontaminants from endoscope biopsy channels.

[0040] In order to prepare a diazeniumdiolated polyurethane of the present invention, typically the following methods can be used: a prepolymer method or one-shot reaction.

[0041] The prepolymer (or quasi-prepolymer) method involves a two-step process. Typically, in the first step, an NCO-prepolymer is prepared by reacting the polyisocyanate and polyol at an NCO/OH equivalent ratio of about 2/1. If the NCO/OH equivalent ratio is greater than about 2/1, a quasi-prepolymer is formed that contains prepolymer adduct and free monomeric isocyanate. In the second chain-extension step, the prepolymer (or quasi-prepolymer) is reacted with at least one $-N_2O_2^-$-containing polyamine forming a poly(urethane-urea) linkage. Alternatively, prepolymer (or quasi-prepolymer) is reacted with a mixture of at least one $-N_2O_2^-$-containing polyamine and chain extender/crosslinker to form a poly(urethane-urea) linkage. In other embodiment, a diazeniumdiolated polyurethane is prepared by reacting NCO-prepolymers (or quasi-prepolymers) with hydroxyl group containing diazeniumdiolate compounds and chain extenders/crosslinkers to form polyurethane linkages. Linear poly(urethane-urea) or polyurethane is formed if the functionality of reactive components is two. In an embodiment, a linear polymer is formed with di-functional isocyanate and di-functional isocyanate chain-extenders. Crosslinked poly(urethane-urea) or polyurethane is formed if the functionality of reactive components is higher than two. In one embodiment, a crosslinked polymer is formed with isocyanate and cross-linkers having functionality greater than 2. In some embodiments, hydrogen bonding exists in both linear and cross-linked isocyanate chain-extenders.

[0042] The prepolymers or quasi-prepolymers can be prepared by bulk or solution polymerization. Preferably, the chain extension reaction is solution polymerization that minimizes the reaction heat exotherm and thus provides the stability of the NO-releasing poly(urethane-urea). Theoretically, chain extension is carried out by a slow bulk polymerization method as well.

[0043] Accordingly, the present invention provides method of preparing a nitric oxide-releasing polyurethane comprising

(a) combining

(i) at least one polyol selected from the group consisting of an alkyl polyol, a cycloalkyl polyol, an aryl polyol, a polyether polyol, a polyester polyol, a polycarbonate polyol, a polycaprolactone polyol, a polyester polycarbonate polyol, silicone polyol, acrylic polyol, or a combination thereof with

(ii) at least one polyisocyanate selected from the group consisting of an optionally substituted aromatic di- or polyisocyanate, an aralkyl di- or polyisocyanate, an aliphatic di- or polyisocyanate, or an alicyclic di- or polyisocyanate to form a prepolymer; and

(b) combining the prepolymer with an $N_2O_2^-$-containing polyamine or a hydroxyl group containing diazeniumdiolate to form the nitric oxide-releasing polymer, wherein the $N_2O_2^-$ group is attached to the hard segment of the polymer backbone. Alternatively, the mixture of $N_2O_2^-$-containing polyamine and at least one polymer modifier selected from the group consisting of a chain extender, a cross-linker, and a mixture thereof can be combined with the prepolymer.

[0044] In the one-shot reaction method, the NO-releasing polyurethane/urea polymers can be prepared by combining and reacting all the components (i.e., polyols, polyisocyanates, chain extenders/crosslinkers, and at least one -$N_2O_2^-$-containing polyamine) together. The resulting NO-releasing polymer has randomly distributed hard and soft segments.

[0045] Thus, in an embodiment, the present invention further provides a method of preparing a nitric oxide-releasing polyurethane comprising combining

(i) at least one polyol selected from the group consisting of an alkyl polyol, a cycloalkyl polyol, an aryl polyol, a polyether polyol, a polyester polyol, a polycarbonate

polyol, a polycaprolactone polyol, a polyester polycarbonate polyol, silicone polyol, acrylic polyol, or a combination thereof;

(ii) at least one polyisocyanate selected from the group consisting of an optionally substituted aromatic di- or polyisocyanate, an aralkyl di- or polyisocyanate, an aliphatic di- or polyisocyanate, or an alicyclic di- or polyisocyanate;

(iii) optionally at least one polymer modifier selected from the group consisting of a chain extender, a cross-linker, and a mixture thereof; and

(iv) at least one $N_2O_2^-$-containing polyamine or a hydroxyl group containing diazeniumdiolate to form the nitric oxide-releasing polymer, wherein the $N_2O_2^-$ group is attached to the hard segment of the polymer backbone.

[0046] Similar prepolymer or one-shot reaction methods can be used to prepare a diazeniumdiolated polyurea of the present invention. Thus, the present invention includes a method of preparing a nitric oxide-releasing polyurea comprising combining

(i) at least one polyisocyanate selected from the group consisting of an optionally substituted aromatic di- or polyisocyanate, an aralkyl di- or polyisocyanate, an aliphatic di- or polyisocyanate, or an alicyclic di- or polyisocyanate;

(ii) at least one amine-functionalized flexible segment; and

(iii) at least one $N_2O_2^-$-containing polyamine to form the nitric oxide-releasing polyurea. The method can further comprise the addition of an amino-functionalized chain extender.

[0047] In any of the polymerization methods described herein, the solvent should not react with any of the starting materials. The solvent preferably is free of reactive amine, hydroxyl, and/or carboxyl groups. Suitable solvents include, but are not limited to, methylene chloride, tetrahydrofuran (THF), dimethylacetamide (DMAC), acetonitrile,

chloroform, dichloroethane, dimethyl sulfoxide (DMSO), dichloroethylene, dimethylformamide, N-methylpyrrolidone (NMP), and methylene bromide.

[0048] The polymers of the invention can have any desired molecular weight based on the choice of starting materials. Typical average molecular weights are up to about 100,000 g/mol but can be as high as about 200,000 g/mol. The polyurethane, polyurea, or copolymer thereof, either before or after incorporation of the $-N_2O_2^-$ functional group, can be characterized quantitatively using known methods. For example, molecular weight determinations can be made using gel permeation chromatography (also known as size exclusion chromatography and gel filtration chromatography), matrix-assisted laser desorption/ionization mass spectroscopy (MALDI), light scattering (e.g., low angle and multi angle), small angle neutron scattering (SANS), sedimentation velocity, end group analysis, osmometry, cryoscopy/ebulliometry, and viscometry.

[0049] Also, further structural characterization of the polymer can be accomplished using, for example, both solution and solid state nuclear magnetic resonance spectroscopy (NMR), infrared spectroscopy (IR), ultraviolet spectroscopy (UV-vis), differential thermal analysis (DTA), thermal gravimetric analysis (TGA), differential scanning calorimetry (DSC), and mass spectrometry. For example, the diazeniumdiolated polymers of the invention can be assessed for free isocyanate content to evaluate the efficiency in consuming or decreasing free isocyanate groups. In addition, for example, IR can be used to assess a diazeniumdiolated polyurethane or polyurea for polyurea-NONOate linkages.

[0050] Nitric oxide detection can be determined using known techniques such as those described in U.S. Patent Nos. 6,511,991 and 6,379,660; Keefer, et al., "NONOates(1-Substituted Diazen-1-ium-1, 2 diolates) as Nitric Oxide Donors: Convenient Nitric Oxide Dosage Forms," *Methods in Enzymology*, 28: 281-293 (1996); Horstmann et al., "Release of nitric oxide from novel diazeniumdiolates monitored by laser magnetic resonance spectroscopy," *Nitric Oxide*, 6(2): 135-41 (2002); and Kitamura et al., "In vivo nitric oxide measurements using a microcoaxial electrode," *Methods Mol. Biol.*, 279: 35-44 (2004), which are incorporated herein by reference. In general, the amount of NO produced can be detected

by chemiluminescence, electrochemically, or by absorbance. In addition, nitric oxide assay kits are commercially available.

[0051] The diazeniumdiolated polyurethane/polyurea is capable of releasing nitric oxide over an extended period of time. The release of nitric oxide can be either *in vivo* or *ex vivo*, depending on the ultimate use of the polymer. It is possible that carriers, solvents, and/or excipients (e.g., water, glycerol) can impact the rate of NO release. Preferably, the polymer releases nitric oxide at its intended site for treatment of a biological disorder (e.g., to enhance wound healing and/or promote angiogenesis). Accordingly, the present invention provides a method of releasing nitric oxide from a nitric oxide-releasing polyurethane/polyurea of the invention. Preferably, the release of NO is under physiological conditions. In one example, the release of NO can occur *in vivo* or *ex vivo* at about 37 °C and pH about 7. Also, preferably a polymer of the present invention releases NO over a period of at least one day (i.e., at least about 24 hours), at least three days (i.e., at least about 72 hours), at least 5 days (i.e., at least about 120 hours), at least 7 days (i.e., at least about 168 hours), at least 10 days (i.e., at least about 240 hours), and at least 14 days (i.e., at least about 336 hours).

[0052] It is envisioned that the incorporation of the diazeniumdiolated functional group as a part of the hard segments of a polyurethane/polyurea composition provides the ability to control the rate of release of nitric oxide. In one aspect of the invention, the rate of release of nitric oxide over an extended period of time from diazeniumdiolated polyurethane/polyurea or polyurethane can be controlled in several ways. For example, the release of NO can be controlled through alterations in chemistry, structure or morphology, or the molecular weights of both the hard and soft segments. In one embodiment, the type of polyols, molecular weight of the polyols, the crystallinity of the polyols, or a combination of polyols can be altered to control the rate and amount of nitric oxide release. Other methods of controlling the rate and amount of NO release include: varying the amount of the hard segment, varying the amount of urea-based hard segments, varying the amount of chain extenders, varying the amount of cross-linking in the hard segment, varying the amount of cross-linking in the soft segment, varying the amount of hydrogen bonding between components, and combinations thereof. Properties such as flexibility, hydrophilicity, and polarity also can be varied to control the rate and amount of nitric oxide release.

[0053] In another aspect, the invention provides a pharmaceutical composition comprising at least one diazeniumdiolated polyurethane of the invention. Any suitable pharmaceutically acceptable carrier can be used within the context of the invention, and such carriers are well known in the art. For example, the carrier comprises aqueous and non-aqueous solutions, a liquid that contains a buffer and a salt, sterile powders, granules, and tablets, a semipermeable matrix, a parenteral vehicle, or an intravenous vehicle. The choice of carrier will be determined, in part, by the particular site to which the pharmaceutical composition is to be administered and the particular method used to administer the pharmaceutical composition.

[0054] One skilled in the art will appreciate that suitable methods of administering a composition comprising at least one diazeniumdiolated polyurethane of the invention to a mammal, e.g., a mammal such as a human, are known, and, although more than one route can be used to administer a particular composition, a particular route can provide a more immediate and more effective reaction than another route. Formulations suitable for topical, oral, or parenteral administration preferably comprise at least one diazeniumdiolated polyurethane/polyurea. Suitable carriers and their formulations are further described in A.R. Gennaro, ed., *Remington: The Science and Practice of Pharmacy* (19th ed.), Mack Publishing Company, Easton, PA (1995).

[0055] In some embodiments, a diazeniumdiolated polyurethane/polyurea of the invention can be bound to a substrate. The diazeniumdiolated polyurethane can be contacted with a substrate, in which, preferably, the substrate has moieties that allow for chemical bonding of the diazeniumdiolated polyurethane. In addition, the diazeniumdiolated polyurethane/polyurea can be recovered from solution and coated onto a substrate. The coating can have any degree of hydrophobicity or hydrophilicity. See, for example, U.S. Patents 6,703,046, 6,528,107, and 6,270,779, which are incorporated herein in their entirety.

[0056] In an embodiment, the composition used to prepare the diazeniumdiolated polyurethane/polyurea of the invention does not comprise an isocyanatosilane.

[0057] The substrate can be of any suitable biocompatible material, such as metal, glass, ceramic, plastic, or rubber. Preferably, the substrate is metal. The substrate used in the preparation of the medical device can be derived from any suitable form of a biocompatible material, such as, for example, a sheet, a fiber, a tube, a fabric, an amorphous solid, an aggregate, dust, or the like.

[0058] Metal substrates suitable for use in the invention include, for example, stainless steel, nickel, titanium, tantalum, aluminum, copper, gold, silver, platinum, zinc, Nitinol, inconel, iridium, tungsten, silicon, magnesium, tin, alloys, coatings containing any of the above, and combinations of any of the above. Also included are such metal substrates as galvanized steel, hot dipped galvanized steel, electrogalvanized steel, annealed hot dipped galvanized steel, and the like. Preferably, the metal substrate is stainless steel.

[0059] Glass substrates suitable for use in the invention include, for example, soda lime glass, strontium glass, borosilicate glass, barium glass, glass-ceramics containing lanthanum as well as combinations thereof.

[0060] Ceramic substrates suitable for use in the invention include, for example, boron nitrides, silicon nitrides, aluminas, silicas, combinations thereof, and the like.

[0061] Plastic substrates suitable for use in the invention include, for example, acrylic, acrylonitrile-butadiene-styrene, acetals, polyphenylene oxides, polyimides, polystyrene, polypropylene, polyethylene, polytetrafluoroethylene, polyvinylidene, polyethylenimine, polyesters, polyethers, polyamide, polyorthoester, polyanhydride, polyether sulfone, polycaprolactone, polyhydroxy-butyrate valerate, polylactones, polyurethanes, polycarbonates, polyethylene terephthalate, as well as copolymers and combinations thereof. Typical rubber substrates suitable for use in the invention include, for example, silicone, fluorosilicone, nitrile rubbers, silicone rubbers, fluorosilicone rubbers, polyisoprenes, sulfur-cured rubbers, butadiene-acrylonitrile rubbers, isoprene-acrylonitrile rubbers, and the like. The substrate could also be a protein, an extracellular matrix component, collagen, fibrin or another biologic agent or a mixture thereof. Silicone, fluorosilicone, polyurethanes, polycarbonates, polylactones, and mixtures or copolymers thereof are preferred plastic or

rubber substrates because of their proven bio- and hemocompatability when in direct contact with tissue, blood, blood components, or bodily fluids.

[0062] Other suitable substrates include those described in WO 00/63462 and U.S. Patent 6,096,070, and incorporated herein by reference.

[0063] Polyurethanes and polyureas can be tailored to produce a range of products from soft and flexible to hard and rigid. They can be, for example, extruded, injection molded, compression molded, and solution spun. Thus, polyurethanes and polyureas, are important biomedical polymers, and are used in medical devices, including implantable devices. Thus, the invention provides medical devices which are capable of releasing nitric oxide when in use, but which are otherwise inert to nitric oxide release. In particular, the inventive NO-releasing polyurethane/polyurea is coated on a substrate, which is subsequently used as medical device. Alternatively, the diazeniumdiolated polyurethane/polyurea can form the medical device itself.

[0064] A "medical device" includes any device having surfaces that contact tissue (e.g., skin), blood, or other bodily fluids in the course of their use or operation, which are found on or are subsequently used within a mammal. Medical devices include, for example, extracorporeal devices for use in surgery, such as blood oxygenators, blood pumps, blood storage bags, blood collection tubes, blood filters including filtration media, dialysis membranes, tubing used to carry blood and the like which contact blood which is then returned to the patient or mammal. Medical devices also include endoprostheses implanted in a mammal (e.g., a human), such as vascular grafts (e.g., a vascular occlusion device), stents, a spinal fixation device, a pacemaker, a pacemaker lead, a surgical prosthetic conduit, a heart valve, and the like, that are implanted in blood vessels or the heart. Medical devices also include devices for temporary intravascular use such as a catheter (e.g., a central venous catheter), a guidewire, an amniocentesis and/or biopsy needle, a cannula, a drainage tube, a shunt, a sensing device, a transducer, a probe and the like which are placed into the blood vessels, the heart, organs or tissues for purposes of monitoring or repair or treatment. Medical devices also include prostheses such as artificial joints such as hips or knees as well as artificial hearts. In addition, medical devices include penile implants, condoms, tampons,

sanitary napkins, ocular lenses, sling materials, sutures, hemostats used in surgery, antimicrobial materials, surgical mesh, tissue patches, transdermal patches, and wound dressings/bandages.

[0065] In a preferred embodiment, the medical device is a vascular graft, which can be used to embolize a blood vessel with the intent to block blood flow. It is often desirable to block blood flow in a section of vasculature for purposes such as controlling internal bleeding, stopping a blood supply to a tumor and/or fibroid, and relieving vessel-wall pressure in a region of a vessel aneurysm. For example, a vascular graft can be useful to treat an abdominal aortic aneurysm, aortopulmonary collateral vessels, hemorrhage, renal arteriovenous fistula or carcinoma, coronary artery fistula, or intracranial aneurysm occlusion.

[0066] In a preferred embodiment, the medical device is a wound dressing. The wound dressings can include various combinations of other ingredients without departing from the scope of the present invention, including, for example, medicaments, soaps, disinfecting and sterilizing agents, odor management agents, hemostatic agents, proteins, enzymes, and nucleic acids. Preferably these agents can also be incorporated directly and dispersed throughout the prepolymerization mixture and are thereby incorporated into the resulting product (e.g., foam matrix). Alternatively these other ingredients can be incorporated into the dressing by absorbing them into the formed product (e.g., foam cover layer) following the polymerization reaction by affixing to the formed wound dressing, by any suitable means, an additional layer incorporating such other ingredients, as will be understood by those skilled in the art.

[0067] Suitable medicaments, soaps, disinfecting and sterilizing agents, proteins, and enzymes are commercially available and include those which aid recovery of wounds. Preferably, the medicaments include antifungal agents, antibacterial agents, and angiogenesis promoting agents. More preferred medicaments include antifungal agents such as metronidazole and antibacterial agents such as chlorhexidine. Any suitable soap, disinfecting and sterilizing agent can be used (e.g., hydrogen peroxide). Suitable proteins and enzymes

include those which aid in wound recovery such as fibrin sealants and angiotensins, as described in U.S. Patents 5,962,420 and 5,955,430, hereby incorporated by reference herein.

[0068] The wound dressings of the present invention can be formed to have any desired thickness or shape. In an embodiment, an NO-releasing polyurethane foam is provided as a thin layer (e.g., a thickness of about 1 mm to about 10 mm, and preferably about 1 mm to about 6 mm).

[0069] A particularly advantageous presentation for the dressing of the invention is as an NO-releasing polyurethane foam layer on a backing layer, wherein at least the marginal portions of the backing layer are coated with adhesive. Any medically acceptable, skin friendly adhesive is suitable, including acrylic-, hydrocolloid-, polyurethane- and silicone-based adhesives. The adhesive can be applied either continuously or discontinuously over the marginal portions of the backing layer. Preferably, however, the adhesive is applied continuously over the whole of the backing layer if the backing layer is not itself impermeable to bacteria, so as to ensure that the backing layer/adhesive combination is impermeable to bacteria.

[0070] Nitric oxide-releasing polymers of the invention are useful for the treatment of many biological disorders, and accordingly, the present invention provides methods of using a nitric oxide-releasing polyurethane/polyurea. In one embodiment, a method of treating a mammal, e.g., a human, with a wound is provided. The method comprises applying to the wound an effective amount of a diazeniumdiolated polyurethane/polyurea of the invention, a composition thereof, or a medical device thereof in an amount sufficient to treat the wound. Preferably, the method for treating a wound comprises administering to a specific location on or within the mammal a medical device comprising a nitric oxide-releasing polyurethane/polyurea. The treatment can be prophylactic or therapeutic. By "prophylactic" is meant any degree in inhibition of the onset of the biological disorder, including complete inhibition. By "therapeutic" is meant any degree in inhibition of the progression of the biological disorder in the mammal (e.g., human). In these embodiments, a "wound" can be any wound, as long as the wound is treatable with nitric oxide. Suitable wounds can be of any type, including a surgical wound, a pressure sore, a diabetic ulcer, and a venous ulcer, or

can result from any condition, such as an infection, including a viral or parasitic infection, a bacterial infection, or a fungal infection. The term "mammal" used herein includes humans, sheep, horses, cattle, pigs, dogs, cats, rats, and mice.

[0071] A validated three-dimensional organotypic human skin model can be used to assess the ability of a diazeniumdiolated polyurethane/polyurea of the invention to enhance wound healing. By growing human keratinocytes at an air-liquid interface on a de-epidermalized dermis placed on a contracted collagen gel, it is possible to generate a fully differentiated stratified epithelium with normal tissue architecture. These organotypic cultures mimic the essential features of the *in vivo* tissue and demonstrate normalized growth, differentiation, and basement membrane assembly. In particular, these models respond to wounding in a way that mimics the re-epithelialization seen *in vivo*. Transplant of these organotypic tissues into nude mice result in the appearance of stable surface grafts with the clinical appearance of normal skin and all histologic features of normal epithelial and dermal compartments. Wound dressings prepared with at least one diazeniumdiolated polyurethane/polyurea of the invention are designed to decrease the time course of re-epithelialization in both the *ex vivo* and transplanted wound models.

[0072] In addition, diazeniumdiolated polymers of the present invention can be used to promote the growth of new blood vessels and capillaries in a process known as angiogenesis. The NO-releasing polyurethanes/polyureas of the present invention can also be used to reduce inflammation and enhance healing when used as a coating or substrate for medical devices. Accordingly, the present invention provides a method for promoting angiogenesis in a tissue of a mammal in need thereof. The method comprises either applying or administering to the mammal a medical device comprising a diazeniumdiolated polyurethane/polyurea of the invention to a specific location on or within the mammal in an amount effective to promote angiogenesis in the tissue.

[0073] Biological disorders that can be treated in accordance with a method for promoting angiogenesis are characterized by insufficient vascularization (or predisposition thereto) of the affected tissue, i.e., conditions in which neovascularization is needed to achieve sufficient vascularization in the affected tissue. Such biological disorders include,

for example, pressure sores, diabetic ulcers, venous ulcer, gangrene, surgical or other wounds requiring neovascularization to facilitate healing, Buerger's syndrome, hypertension, ischemic diseases (e.g., cerebrovascular ischemia, renal ischemia, pulmonary ischemia, limb ischemia, ischemic cardiomyopathy, and myocardial ischemia), ischemia of tissues (e.g., muscle, brain, kidney and lung), and other conditions characterized by a reduction in microvasculature. Exemplary tissues in which angiogenesis can be promoted include: ulcers (e.g., diabetic ulcers), surgical wounds, and ischemic tissue (i.e., a tissue having a deficiency in blood as the result of an ischemic disease).

[0074] An "effective amount" means an amount sufficient to show a meaningful benefit in an individual, e.g., enhancing wound healing or promoting angiogenesis. Effective amounts can vary depending upon the biological effect desired in the individual, the condition to be treated, and/or the specific characteristics of the diazeniumdiolated polyurethane of the invention (taking into consideration, at least, the rate of NO evolution, the extent of NO evolution, and the bioactivity of any decomposition products derived from the diazeniumdiolates), the condition of the mammal (e.g., human), and the body weight of the mammal (e.g., human) to be treated. The size of the dose also will be determined by the existence, nature, and extent of any adverse side effects that might accompany the administration of a particular composition. In this respect, any suitable dose of the diazeniumdiolated polyurethane/polyurea of the invention can be administered to the mammal, according to the type of wound or tissue to be treated. Various general considerations taken into account in determining the "effective amount" are known to those of skill in the art and are described, e.g., in Gilman et al., eds., Goodman And Gilman's: *The Pharmacological Bases of Therapeutics*, 8th ed., Pergamon Press, 1990; and Remington's Pharmaceutical Sciences, 17th Ed., Mack Publishing Co., Easton, Pa., 1990, each of which is herein incorporated by reference. The dose of the diazeniumdiolated polyurethane/polyurea of the invention desirably comprises about 0.1 mg per kilogram (kg) of the body weight of the mammal (mg/kg) to about 400 mg/kg (e.g., about 0.75 mg/kg, about 5 mg/kg, about 30 mg/kg, about 75 mg/kg, about 100 mg/kg, about 200 mg/kg, or about 300 mg/kg). In another embodiment, the dose of the diazeniumdiolated polyurethane/polyurea comprises about 0.5 mg/kg to about 300 mg/kg (e.g., about 0.75 mg/kg, about 5 mg/kg, about 50 mg/kg, about 100 mg/kg, or about 200 mg/kg), about 10 mg/kg to about 200 mg/kg (e.g., about 25 mg/kg,

about 75 mg/kg, or about 150 mg/kg), or about 50 mg/kg to about 100 mg/kg (e.g., about 60 mg/kg, about 70 mg/kg, or about 90 mg/kg). A suitable concentration in pharmaceutical compositions for topical administration is 0.05 to 15% (by weight). A preferred concentration is from 0.02 to 5%. A more preferred concentration is from 0.1 to 3%.

[0075] In another aspect of the invention, an NO-releasing polyurethane-containing matrix can be used to augment torn or weakened muscle tissue (e.g., neck, back, leg, arm, rotator cuff). Preferably the matrix is porous with an open structure that is characterized by interconnected and intercommunicating pores. Also preferably, the matrix is elastomeric and can demonstrate resilient recovery after being deformed under compression and/or tension. For surgical implantation, the matrix is sized and shaped appropriately from a block of polyurethane-based foam and can be sterilized by any suitable method (e.g., alpha-, beta-, or gamma-radiation, electron radiation). Ideally, a matrix patch used for tissue extension will integrate, at least to some degree, with the surrounding area (e.g., tendon, bone, etc.). The preparation and deployment of an NO-releasing polyurethane-containing matrix can follow techniques known in the art, e.g., Cole et al., *Knee Surgery, Sports Traumatology, Arthroscopy*, 15(5): 632-637 (published online September 9, 2006).

[0076] Accordingly, the present invention is directed to a method of augmenting muscle tissue in a mammal in need thereof. The method comprises either applying or administering to the mammal a matrix (e.g., a t issue patch) comprising a diazeniumdiolated polyurethane (including a copolymer of polyurethane) of the invention to a specific location on or within the mammal in an amount effective to augment the tissue. The term "augmenting" means any degree of reinforcing or reducing subsequent tearing or deterioration of the muscle tissue. With augmentation, the matrix will preferably, but not necessarily, integrate with surrounding tissue (e.g., tendon and/or bone).

[0077] Referring now to terminology used generically herein, the term "alkyl" implies a straight-chain or branched alkyl substituent containing from, for example, about 1 to about 12 carbon atoms, preferably from about 1 to about 8 carbon atoms, more preferably from about 1 to about 6 carbon atoms. Examples of such substituents include methyl, ethyl, propyl,

isopropyl, *n*-butyl, *sec*-butyl, isobutyl, *tert*-butyl, pentyl, isoamyl, hexyl, octyl, dodecanyl, and the like.

[0078] The term "alkenyl," as used herein, means a linear alkenyl substituent containing from, for example, about 2 to about 10 carbon atoms (branched alkenyls are about 3 to about 10 carbons atoms), preferably from about 2 to about 8 carbon atoms (branched alkenyls are preferably from about 3 to about 8 carbon atoms), more preferably from about 3 to about 6 carbon atoms. Examples of such substituents include propenyl, isopropenyl, *n*-butenyl, *sec*-butenyl, isobutenyl, *tert*-butenyl, pentenyl, isopentenyl, hexenyl, octenyl, dodecenyl, and the like.

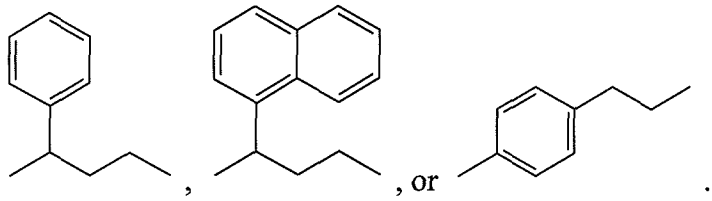
[0079] The term "cycloalkyl," as used herein, means a cyclic alkyl substituent containing from, for example, about 3 to about 30 carbon atoms, preferably about 3 to about 8 carbon atoms, preferably from about 5 to about 8 carbon atoms, more preferably from about 5 to about 6 carbon atoms. Examples of such substituents include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like.

[0080] The term "aryl" refers to an unsubstituted or substituted aromatic carbocyclic substituent, as commonly understood in the art, and includes monocyclic and polycyclic aromatics such as, for example, phenyl, biphenyl, naphthyl, anthracenyl and the like. The aryl substituent can be optionally substituted as described herein (e.g., tolyl, anisolyl). An aryl substituent generally contains from, for example, about 3 to about 30 carbon atoms, preferably from about 6 to about 18 carbon atoms, more preferably from about 6 to about 14 carbon atoms and most preferably from about 6 to about 10 carbon atoms. It is understood that the term aryl applies to cyclic substituents that are planar and comprise $4n+2$ π electrons, according to Hückel's Rule.

[0081] The term "heteroaryl" refers to aromatic 5 or 6 membered monocyclic groups, 9 or 10 membered bicyclic groups, and 11 to 14 membered tricyclic groups which have at least one heteroatom (O, S or N) in at least one of the rings. Each ring of the heteroaryl group containing a heteroatom can contain one or two oxygen or sulfur atoms and/or from one to four nitrogen atoms provided that the total number of heteroatoms in each ring is four or less

and each ring has at least one carbon atom. The fused rings completing the bicyclic and tricyclic groups may contain only carbon atoms and may be saturated, partially saturated, or unsaturated. The nitrogen and sulfur atoms may optionally be oxidized, and the nitrogen atoms may optionally be quaternized. Heteroaryl groups which are bicyclic or tricyclic must include at least one fully aromatic ring but the other fused ring or rings may be aromatic or non-aromatic. The heteroaryl group may be attached at any available nitrogen or carbon atom of any ring. Illustrative examples of heteroaryl groups are pyridinyl, pyridazinyl, pyrimidyl, pyrazinyl, benzimidazolyl, triazinyl, pyrrolyl, pyrazolyl, imidazolyl, (1,2,3,)- and (1,2,4)-triazolyl, pyrazinyl, pyrimidinyl, tetrazolyl, furyl, thienyl, isothiazolyl, thiazolyl, furyl, phienyl, isoxazolyl, oxadiazolyl, and oxazolyl.

[0082] The term "aralkyl" as utilized herein means alkyl as defined herein, wherein at least one hydrogen atom is replaced with an aryl substituent as defined herein. Aralkyls include, for example, benzyl, phenethyl, and substituents of the formula:



[0083] The following examples further illustrate the invention but, of course, should not be construed as in any way limiting its scope.

EXAMPLE 1

[0084] This example illustrates the preparation of an NO-releasing polyurethane-urea by using a DETA/NO chain extender in accordance with an embodiment of the invention.

[0085] An NCO-urethane prepolymer was prepared by reacting isocyanate H12MDI (Bayer AG) and polycarbonate diol PC 1122 (Stahl Chemical) at an NCO/OH equivalent ratio 2.05/1, by using the following procedure: H12MDI (54.12 g) was placed in a 0.5 L glass reaction kettle, which was equipped with a mechanical stirrer, thermometer, heating mantle, and a gas inlet outlet for continuous flow of nitrogen. When the temperature of the

isocyanate reached 70 °C, the polycarbonate polyol (200 g) was added in several portions to the reactor under constant mixing. The reaction temperature was maintained at 70-80 °C, and samples were periodically withdrawn to determine the isocyanate content. After the percentage of isocyanate (NCO%) reached 4.36%, the reaction was stopped by cooling to room temperature, and the prepolymer (P-1) was stored in a sealed glass bottle under nitrogen. The NCO% of the prepolymer checked after 3 days was 3.9%.

[0086] In the reaction kettle, 30 g (0.028 equivalents) of the prepolymer P-1 and 70 ml of N-methylpyrrolidone (NMP) at room temperature were mixed to homogenize. Subsequently, 0.028 equivalents (2.28 g) of DETA/NO were dissolved in 90 ml of NMP forming a hazy emulsion, and added through a funnel to the solution of the prepolymer under continuous mixing and nitrogen flow. The polymerization was carried out at room temperature. The NCO% in the reaction solution after one hour was 0.036%, as determined by titration method, which relates to about 95% completed polymerization. After two hours reaction time, the polymerization was completed. The resulting viscous solution was a hazy emulsion.

EXAMPLE 2

[0087] This example illustrates the preparation of a polyurethane-urea film in accordance with an embodiment of the invention.

[0088] The NO-donor containing polyurethane-urea (2 g) prepared in Example 1 was placed in solution and put in a metal tray approximately 5.5 cm in diameter. The film was placed in a vacuum oven and degassed at room temperature to remove air bubbles and remaining solvent. Isopropyl alcohol (IPA) was poured over the resin, and a film was formed by replacing NMP with IPA (phase inversion process). The film was washed several times by immersing it (together with the metal tray) into IPA. Afterwards, the film was dried in a vacuum oven at room temperature for at least 24 hours. Dried films were stored in a freezer in the closed container filled with zeolites.

EXAMPLE 3

[0089] This example illustrates the release of NO from the diazeniumdiolated polyurethane-urea film prepared in Example 2.

[0090] A film sample weighing 85 mg as immersed in 0.1 M phosphate buffer (pH 7.4, 37 C). The NO release was measured by a Thermal Energy Analyzer following an inert gas sweep. NO release was biphasic, with half lives of 1.84 h and 12.93 h. See Figure 1. There was detectable NO release for 10 days. A total of 9.6 nmol of NO was released per mg of the polymer film. NO-release from these compounds was measured under in vitro conditions (0.1 M phosphate buffer pH 7.4 at 37°C) and the NO-release monitored by a Thermal Energy Analyzer. The films demonstrated controlled NO release, which appeared to be biphasic, and detectable NO-release occurred for three days (Fig. 1).

EXAMPLE 4

[0091] This example illustrates the preparation of implantable devices carrying nitric oxide releasing polyurethane utilizing $-N_2O_2^-$-containing polyamine-containing polyurethane solution/dispersion.

[0092] A piece of porous foam (e.g., polycarbonate PU foam) of selected size and shape can be first dipped in the $-N_2O_2^-$-containing polyamine-containing polyurethane solution and then immersed into IPA several times to create a fine coating on the foam surface. The foam can be vacuum dried at room temperature.

[0093] A nitric oxide-releasing flexible tube can be created as well by dipping a wire into $-N_2O_2^-$-containing polyamine-containing polyurethane solution/dispersion and then immersed in IPA to precipitate polyurethane around the wire. The NO-containing polyurethane tube can be recovered upon drying.

[0094] All references, including publications, patent applications, and patents, cited herein are hereby incorporated by reference to the same extent as if each reference were individually and specifically indicated to be incorporated by reference and were set forth in its entirety herein.

[0095] The use of the terms "a" and "an" and "the" and similar referents in the context of describing the invention (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. The terms "comprising," "having," "including," and "containing" are to be construed as open-ended terms (i.e., meaning "including, but not limited to,") unless otherwise noted. Recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such as") provided herein, is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention unless otherwise claimed. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the invention.

[0096] Preferred embodiments of this invention are described herein, including the best mode known to the inventors for carrying out the invention. Variations of those preferred embodiments may become apparent to those of ordinary skill in the art upon reading the foregoing description. The inventors expect skilled artisans to employ such variations as appropriate, and the inventors intend for the invention to be practiced otherwise than as specifically described herein. Accordingly, this invention includes all modifications and equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is encompassed by the invention unless otherwise indicated herein or otherwise clearly contradicted by context.

CLAIM(S):

1. A nitric oxide-releasing polyurethane prepared from a composition comprising

(a) at least one polyol selected from the group consisting of an alkyl polyol, a cycloalkyl polyol, an aryl polyol, a polyether polyol, a polyester polyol, a polycarbonate polyol, a polycaprolactone polyol, a polyester polycarbonate polyol, silicone polyol, and acrylic polyol;

(b) at least one polyisocyanate selected from the group consisting of an optionally substituted aromatic di- or polyisocyanate, an aralkyl di- or polyisocyanate, an aliphatic di- or polyisocyanate, and an alicyclic di- or polyisocyanate;

(c) optionally at least one polymer modifier selected from the group consisting of a chain extender, a cross-linker, and a mixture thereof; and

(d) at least one $N_2O_2^-$-containing polyamine;

wherein the $N_2O_2^-$ group is attached to the hard segment of the polymer backbone.

2. A nitric oxide-releasing polyurea prepared from a composition comprising

(a) at least one polyisocyanate selected from the group consisting of an optionally substituted aromatic di- or polyisocyanate, an aralkyl di- or polyisocyanate, an aliphatic di- or polyisocyanate, and an alicyclic di- or polyisocyanate;

(b) at least one amine-functionalized flexible segment, optionally at least one amine-functionalized chain extender; and

(c) at least one $N_2O_2^-$-containing polyamine;

wherein the $-N_2O_2^-$ group is attached to the hard segment of the polyurea backbone.

3. The nitric oxide-releasing polyurethane or polyurea of claim 1 or 2, wherein the polyisocyanate is selected from the group consisting of methylene-4,4′-diphenyldiisocyanate (MDI), methylene-2,4′-diphenyldiisocyanate, methylene-2,2′-diphenyldiisocyanate, polymeric MDI (PMDI), naphthalene-1,5-diisocyanate (NDI), carbodiimide-modified MDI, tolylene diisocyanate (TDI), paraphenylene diisocyanate (PPDI), polymeric isocyanates of functionality between 2 and 3, 4,4′-methylene bis(cyclohexyl isocyanate) (H12MDI), isophorone diisocyanate (IPDI), 1,4-cyclohexyl diisocyanate (CHDI), 1,6-hexamethylene diisocyanate (HDI), isocyanate-terminated biuret

adduct of HDI, isocyanate terminated trimerization products based on HDI and IPDI, lysine diisocyanate, 1,4-butane diisocyanate, and combinations thereof.

4. The nitric oxide-releasing polyurethane of claim 1 or 3, wherein the polymer modifier is at least one chain extender, and the chain extender is hydroxyl-functionalized.

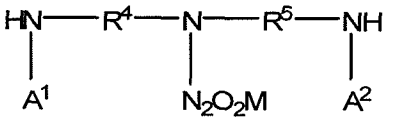
5. The nitric oxide-releasing polyurethane of claim 4, wherein the hydroxyl-functionalized chain extender is selected from the group consisting of 1,3-propanediol, 1,4-butanediol, 1,6-hexanediol, 1,12-dodecanediol, cyclohexane-1,4-dimethanol, 1,4-bis-hydroxydiethyl hydroquinone (HQEE), diethylene glycol, dipropylene glycol, neopentyl glycol, diethanolamine, dipropanolamine, bis(hydroxyethyl)biphenol, and bis(hydroxypropyl)biphenol.

6. The nitric oxide-releasing polyurethane of claim 1 or 3, wherein the polymer modifier is at least one chain extender, and the chain extender is amine-functionalized.

7. The nitric oxide-releasing polyurethane of claim 2 or 6, wherein the amine-functionalized chain extender is selected from the group consisting of 1,3-propanediamine, 1,4-butanediamine, 1,6-hexanediamine, isophoronediamine, and 1,4-cyclohexanediamine.

8. The nitric oxide-releasing polyurethane or polyurea of any one of claims 1, 4, and 5, wherein the at least one cross-linker is selected from the group consisting of glycerol, trimethylolpropane, pentaerythritol, sorbitol, sucrose, triethanolamine, a low molecular weight poly(oxyalkylene) glycerol adduct, a low molecular weight poly(oxyalkylene) trimethylolpropane adduct, a low molecular weight polycaprolactone triol, and an oxyalkylene derivative of ethylenediamine.

9. The nitric oxide-releasing polyurethane or polyurea of any of claims 1-8, wherein the at least one $N_2O_2^-$-containing polyamine is a compound of formula (I)



(I),

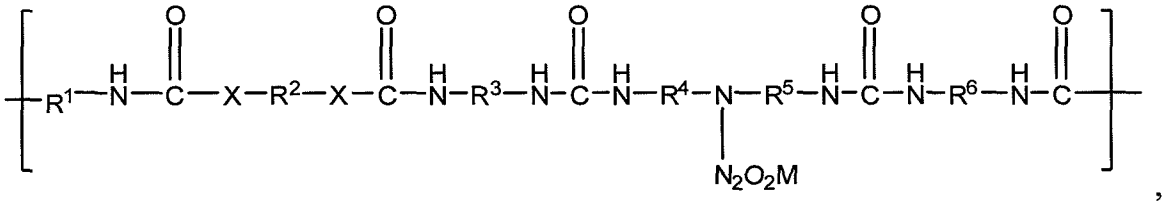
wherein

A^1 and A^2 are the same or different and each is hydrogen, an optionally substituted C_{1-12} alkyl, optionally substituted C_{3-30} cycloalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, or optionally substituted heteroarylalkyl;

R^4 and R^5 are the same or different and each is an optionally substituted C_{1-12} alkyl, an optionally substituted C_{2-12} alkenyl, optionally substituted C_{3-30} cycloalkyl, or optionally substituted aryl, and

M is a counterion.

10. A nitric oxide-releasing polymer comprising at least one repeat unit of the structure:



,

wherein

X is O or NH;

R^1, R^2, R^3, R^4, R^5, and R^6 are the same or different and each is an optionally substituted C_{1-12} alkyl, optionally substituted C_{3-30} cycloalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted alkoxyalkyl, optionally substituted polyether, optionally substituted polyester, optionally substituted polycarbonate, optionally substituted polycaprolactone, optionally substituted polyester polycarbonate, or optionally substituted heteroaryl; and

M is a counterion.

11. The nitric oxide-releasing polyurethane or polyurea of any of claims 1-10, wherein the polymer is bound to a substrate.

12. The nitric oxide-releasing polyurethane or polyurea of claim 11, wherein the substrate comprises metal, glass, ceramic, plastic, or rubber.

13. A medical device comprising the nitric oxide-releasing polyurethane or polyurea of any of claims 1-12.

14. The medical device of claim 13, wherein the device is selected from the group consisting of a wound dressing/bandage, surgical mesh, tissue patch, transdermal patch, tubing, a vascular graft, a vascular stent, drainage tube, shunt, an artificial joint, an artificial heart, a penile implant, condom, tampon, sanitary napkin, ocular lens, sling material, suture, hemostat, and antimicrobial material.

15. The medical device of claim 14, wherein the device is a vascular graft.

16. A method for treating a wound in a mammal, comprising applying to the wound the medical device of claim 13 or 14, wherein the medical device will release a therapeutically effective amount of nitric oxide.

17. A method for promoting angiogenesis in a tissue of a mammal in need thereof, comprising administering to the mammal, the medical device of claim 13 or 14 to a specific location on or within the mammal in an amount effective to promote angiogenesis in the tissue.

18. A method for augmenting tissue in a mammal in need thereof, comprising administering to the mammal, the medical device of claim 13 or 14 to a specific location on or within the mammal in an amount effective to augment the tissue.

19. A method of preparing a nitric oxide-releasing polyurethane comprising

(a) combining

(i) at least one polyol selected from the group consisting of an alkyl polyol, a cycloalkyl polyol, an aryl polyol, a polyether polyol, a polyester polyol, a polycarbonate polyol, a polycaprolactone polyol, a polyester polycarbonate polyol, silicone polyol, and acrylic polyol with

(ii) at least one polyisocyanate selected from the group consisting of an optionally substituted aromatic di- or polyisocyanate, an aralkyl di- or polyisocyanate, an aliphatic di- or polyisocyanate, or an alicyclic di- or polyisocyanate to form a prepolymer; and

(b) combining the prepolymer with an $N_2O_2^-$-containing polyamine to form the nitric oxide-releasing polymer, wherein the $N_2O_2^-$ group is attached to the hard segment of the polymer backbone.

20. A method of preparing a nitric oxide-releasing polyurethane comprising combining

(i) at least one polyol selected from the group consisting of an alkyl polyol, a cycloalkyl polyol, an aryl polyol, a polyether polyol, a polyester polyol, a polycarbonate polyol, a polycaprolactone polyol, a polyester polycarbonate polyol, silicone polyol, and acrylic polyol;

(ii) at least one polyisocyanate selected from the group consisting of an optionally substituted aromatic di- or polyisocyanate, an aralkyl di- or polyisocyanate, an aliphatic di- or polyisocyanate, or an alicyclic di- or polyisocyanate;

(iii) optionally at least one polymer modifier selected from the group consisting of a chain extender, a cross-linker, and a mixture thereof; and

(iv) at least one $-N_2O_2^-$-containing polyamine to form the nitric oxide-releasing polyurethane, wherein the $-N_2O_2^-$ group is attached to the hard segment of the polyurethane backbone.

21. A method of preparing a nitric oxide-releasing polyurea comprising combining

(i) at least one polyisocyanate selected from the group consisting of an optionally substituted aromatic di- or polyisocyanate, an aralkyl di- or polyisocyanate, an aliphatic di- or polyisocyanate, or an alicyclic di- or polyisocyanate;

(ii) at least one amine-functionalized flexible segment ; and

(iii) at least one $-N_2O_2^-$-containing polyamine to form the nitric oxide-releasing polyurea, wherein the $-N_2O_2^-$ group is attached to the hard segment of the polyurea backbone.

22. The method of claim 21, further comprising the addition of an amine-functionalized chain extender.

23. The method of any of claims 19-22, wherein the polyisocyanate is selected from the group consisting of methylene-4,4′-diphenyldiisocyanate (MDI), methylene-2,4′-diphenyldiisocyanate, methylene-2,2′-diphenyldiisocyanate, polymeric MDI (PMDI), carbodiimide-modified MDI, tolylene diisocyanate (TDI), paraphenylene diisocyanate (PPDI), polymeric isocyanates of functionality between 2 and 3, 4,4'-methylene bis(cyclohexyl isocyanate) (H12MDI), isophorone diisocyanate (IPDI), 1,4-cyclohexyl diisocyanate (CHDI), 1,6-hexamethylene diisocyanate (HDI), isocyanate-terminated biuret adduct of HDI, isocyanate terminated trimerization products based on HDI and IPDI, and combinations thereof.

24. The method of claim 20, wherein the polymer modifier is at least one chain extender, and the chain extender is hydroxyl-functionalized.

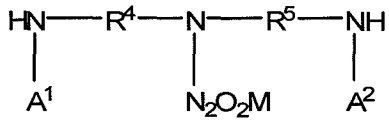
25. The method of any of claim 24, wherein the hydroxyl-functionalized chain extender is selected from the group consisting of 1,3-propanediol, 1,4-butanediol, 1,6-hexanediol, 1,12-dodecanediol, cyclohexane-1,4-dimethanol, 1,4-bis-hydroxydiethyl hydroquinone (HQEE), diethylene glycol, dipropylene glycol, neopentyl glycol, diethanolamine, dipropanolamine, bis(hydroxyethyl)biphenol, and bis(hydroxypropyl)biphenol.

26. The method of claim 20, wherein the polymer modifier is at least one chain extender, and the chain extender is amine-functionalized.

27. The method of claim 22 or 26, wherein the amine-functionalized chain extender is selected from the group consisting of 1,3-propanediamine, 1,4-butanediamine, 1,6-hexanediamine, isophoronediamine, and 1,4-cyclohexanediamine.

28. The method of claim 20, wherein the polymer modifier is at least one cross-linker selected from the group consisting of glycerol, trimethylolpropane, pentaerythritol, sorbitol, sucrose, triethanolamine, a low molecular weight poly(oxyalkylene) glycerol adduct, a low molecular weight poly(oxyalkylene) trimethylolpropane adduct, a low molecular weight polycaprolactone triol, and an oxyalkylene derivative of ethylenediamine.

29. The method of any of claims 19-28, wherein the at least one $N_2O_2^-$-containing polyamine is a compound of formula (I)



(I),

wherein

A^1 and A^2 are the same or different and each is hydrogen, an optionally substituted C_{1-12} alkyl, optionally substituted C_{3-30} cycloalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, or optionally substituted heteroarylalkyl;

R^4 and R^5 are the same or different and each is an optionally substituted C_{1-12} alkyl, an optionally substituted C_{2-12} alkenyl, optionally substituted C_{3-30} cycloalkyl, or optionally substituted aryl, and

M is a counterion.

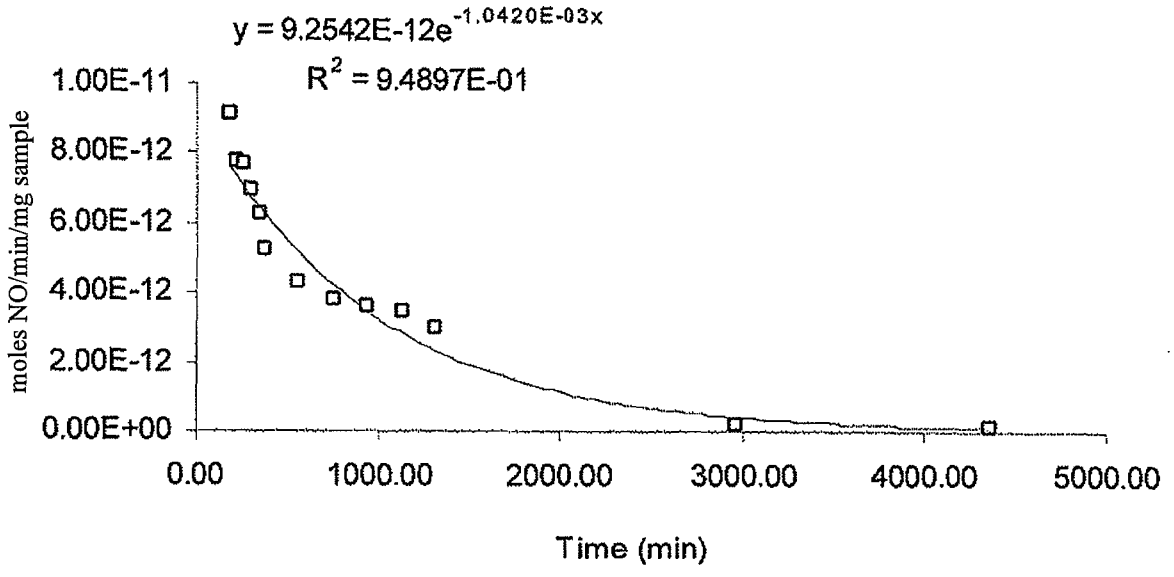

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R2 = 9.4897E-01
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8.00E-12
6.00E-12
4.00E-12
2.00E-12
0.00E+00
moles NO/min/mg sample
0.00
1000.00
2000.00
3000.00
4000.00
5000.00
Time (min)

FIG. 1