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(54) **Title**: IN-SITU CROSS-LINKABLE POLYMERIC COMPOSITIONS AND METHODS THEREOF

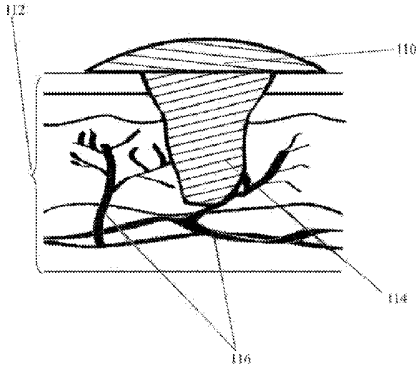

FIG. 1

(57) **Abstract**: A biocompatible polymeric composition for cross-linking in-situ in a wound is disclosed comprising 1) one or more polyanionic polymers such as alginates or hyaluronates, able to be cross-linked the surface of the wound and 2) one or more polycationic polymers such as chitosan or DEAE-Dextran, that assists in the solidification process as well as speeds up hemostasis without the need for applying pressure. The biocompatible polymeric composition may further comprise a cross-linking agent such as aqueous calcium chloride. The invention encompasses an initial polymeric composition, the solidified matrix cross-linked and integrated at the wound site, including the methods of using, applying, and cross-linking the composition.

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IN-SITU CROSS-LINKABLE POLYMERIC COMPOSITIONS AND METHODS THEREOF

This application claims the benefit of provisional patent application Ser. No. 61/559,110, filed 13 November 2011, the entire disclosure of which is incorporated herein by reference.

FIELD OF THE INVENTION

The present invention relates generally to a composition using a biocompatible polymeric formulation and, in particular, to a hemophilic polymeric matrix for use in wound healing, blood coagulation, and cosmetic use.

BACKGROUND OF THE INVENTION

Wound healing is an intricate, orchestrated process involving the interactions of various cells and matrix components to first establish a provisional tissue and then remodel this while forming the mature replacement. Initially, the hemostatic platelet plug reestablishes the infection-limiting and desiccation-limiting barrier, and elicits the first wave of cellular infiltrates. This consists mainly of leukocytes that provide both innate and acquired immunity. These cells produce enzymes and biocidal molecules to eliminate microbial contamination; however, these same defense mechanisms are detrimental to the keratinocytes, fibroblasts and endothelial cells required to regenerate the lost tissue. Thus, as healing proceeds, the events and processes of the inflammatory phase need to regress.

A particular challenge is offered in the case of skin wound repair, which occurs at a contaminated surface. If a wound becomes infected, the normal healing is disrupted as the inflammatory phase becomes chronic, suppressing the regenerative phase. Further, the enzymes liberated by both the microbes and leukocytes break down the wound tissue as well as surrounding skin. Thus, it is critical to ensure proper healing to prevent infections being established by normal skin wound contaminants.

Wound healing is usually divided into three phases: the inflammatory phase, the proliferative phase, and the remodeling phase. Fibronectin has been reported to be involved in each stage of the wound healing process, particularly by creating a scaffold to which the invading cells will adhere. Initially, there is a release of many mediators to the wound site, such as fibronectin and fibrinogen. Fibronectin promotes inflammatory cell migration into the wound and debris phagocytosis by monocytes. Thereafter, angiogenesis and

reepithelialization take place. At this stage, fibronectin exerts chemotactic activity on endothelial cells, and promotes epithelial cell and fibroblast migration onto the basal membrane. Fibronectin also appears to be essential in the remodeling phase where it plays a major role in the organization of collagen fibrils. The fibrillar collagen ultimately forms fibrous bundles that enhance the tissue tensile strength, leading to would closure.

Hydrogels have typically been utilized as topical formulations for promoting the wound healing process. The gel compositions have been selected for their properties of swelling degree, biocompatibility, permeability, and swelling kinetics. Examples of such compounds have included vinyl polymers (e.g. polyacrylic acid), cellulose, and cellulose derivatives. Polyacrylic acid polymer, also referred to as carbomer, has been used because of its superiority in delivering fibronectin to skin wounds.

Naturally occurring biopolymers have applications in tissue engineering, regenerative medicine, drug delivery, medical implant, plastic surgery, and others. Such products have components including hyaluronic acid (HA), chitosan, heparin, chondroitin sulfate, alginate and other glucosamine and glycosaminoglycans, other polysaccharides, and derivatives thereof.

In combination, concentrations of fibronectin (and similar proteins) have been utilized with alginate salt to treat chronic ulcers. The dressing system has been solidified, converting the gel into fibers, by a process of freeze-drying. This procedure creates a sponge-like structure with hydrophilic properties. In the presence of fluids, the dressings can return to a gel-like state, absorbing up to 20 times their weight in wound exudate. The dressing is easily removed after the wound treatment because of its sponge-like structure and moisture retention. However, once hydrated with saline solution, the fibronectin-cellulose dressing does not provide the desired fibrous protective film on the surface of the deepithelialized human skin. Debridement is then performed upon removal of the dressing to remove any necrotic material.

Thus, problems exist in the treatment of acute and chronic wounds, including delayed healing, reduced granulation and epithelialization, and persistent wound inflammation. Compromised wound healing can result in other complications and problems, such as infection, pain, and development of chronic (non-healing) wounds.

Current needs exist in the treatment of chronic wounds which would assist healing, decrease inflammation, reduce pain, and prevent scar formation with both acute and chronic

wounds. Such acute wounds that could be treated include burns, abrasions, dry skin, post-op surgical incisions, cuts, puncture wounds, blisters, insect bites, and other severe tissue injury. Chronic wound treatment might encompass slow to heal wounds including pressure ulcers, venous ulcers, diabetic foot ulcers, decubitus ulcers, and non-healing tissue injuries.

Overall, a composition is desired that will be easily applied, forming a matrix conducive to the healing of a tissue, and having anti-microbial properties. The composition may be biocompatible or quickly reacted to avoid possibilities of cytotoxicity. Further, the composition will stimulate and maximize wound healing while providing a controlled method for providing thin and thick layers of a solidified wound dressing, as desired.

Indirect effects may include reduced need for medical procedures such as debridement, decreased hospitalization time, reduced postoperative recovery times, shortened return interval to daily functions and work, and reduced overall treatment costs. Desirably, these improvements to wound healing, including application and method of use, will be valuable in treating and repairing various tissue(s).

SUMMARY OF THE INVENTION

The following invention is a biocompatible polymeric composition that is a gelatinous wound healing and hemostatic matrix able to be formed and solidified both internally and externally.

In one embodiment of the invention, the biocompatible polymeric composition comprises 1) one or more than one polyanionic polymer and 2) one or more than one polycationic polymer. In one embodiment of the invention, the one or more than one polyanionic polymer includes at least one cross-linkable polyanionic polymer. In another embodiment of the invention, the one or more than one polyanionic polymer includes at least one cross-linkable polyanionic polymer and at least one non-cross-linkable polyanionic polymer.

In one embodiment of the invention, the biocompatible polymeric composition comprises a mixture of 1) one or more than one polyanionic polymer able to be formed on the surface of a wound and 2) one or more than one polycationic polymer that assists in the solidification process as well as speeds up blood clotting. In another embodiment of the invention, the biocompatible polymeric composition comprises a mixture of 1) one or more than one polyanionic polymer able to be formed on the surface of a wound; 2) one or more than one polycationic polymer that assists in the solidification process as well as speeds up

blood clotting; and 3) a cross-linking mist that cross-links the gel in the wound while disinfecting the surrounding area.

In one embodiment of the invention, the one or more than one polyanionic polymer comprises alginates or hyaluronates. In one embodiment of the invention, the one or more than one polycationic polymer comprises chitosan. In one embodiment of the invention, the cross-linking mist may be aqueous calcium chloride.

One or more methods of using the medical gel of the invention are also disclosed, including rapidly achieving hemostasis without the need to apply pressure, and providing a biocompatible wound healing matrix.

Various embodiments of the invention allow the formulation to be adjusted and implemented for varying the desired viscosity and pre-determined characteristic functions. In one aspect, the ratio of the polycationic polymer to the polyanionic polymer may be improved, having varying degrees of efficiency in wound healing. In another aspect, therapeutics can be added to integrate drug formulations for drug delivery options. Further, other features may encompass controlling temperature(s) and/or pressure(s) during the preparation of the medical gel, during application of the gel, and implementing a control for the elasticity or rigidity of the solidified matrix. The matrix formulation, both liquid and solidified structures, may also be dependent on anatomical and physiological measurements and conditions.

Various embodiments of the invention allow the composition to be adjusted and implemented at a first tissue site or a second tissue site, and such modification deemed obvious may be integrated and combined in varying quantities to provide for a structural matrix of any size, shape, and configuration.

DESCRIPTION OF THE DRAWINGS

FIG. 1 is a side view of an embodiment of the present invention.

FIG. 2 is a microscopic depiction of how the present invention interacts with blood and itself.

FIGS. 3A to 3I show various polymeric subunits that can be used to make up the polycationic or polyanionic polymers.

FIG. 4 shows the benefits of the present invention as compared to existing technology.

DETAILED DESCRIPTION OF THE INVENTION

In the following detailed description, for purposes of explanation and not limitation, exemplary embodiments disclosing specific details are set forth in order to provide a thorough understanding of the present invention. However, it will be apparent to one having ordinary skill in the art that the present invention may be practiced in other embodiments that depart from the specific details disclosed herein. In other instances, detailed descriptions of well-known compositions and methods may be omitted so as not to obscure the description of the present invention.

Biocompatible polymeric compositions of the present invention may be used to treat external wounds as well as internal wounds. In one embodiment of the invention, the biocompatible polymeric composition may be applied to a variety of wounds. Non-limiting examples of wounds include, but are not limited to: an external laceration, an abrasion, a burn, an ocular laceration, damage to a parenchymal organ, an internal laceration, a laceration in the gastrointestinal tract, superficial cuts and scrapes, internal bleeding, an arterial bleed, a venous bleed, dental or oral bleeds and incisions. Subjects who can benefit from such wound treatment include a variety of animals including humans, mammals such as horses, sheep, cattle, hogs, dogs, cats, and marine animals such as whales, dolphins, seals, otters, fish, and reptiles such as turtles.

An illustration of a structural matrix in accordance with one embodiment of the invention is shown in **FIG. 1**. As depicted, a damaged section of tissue, wound **(112)**, has vasculature **(116)** protruding throughout. A biocompatible polymeric composition **(114)** has been applied to the wound **(112),** which has been coated with protective coat (**110**).

FIG. 2 shows a magnified view of one embodiment of biocompatible polymeric composition (**114),** which comprises structural polymer (**226**) and hemophilic polymer (**224**). Structural polymer (**226**) comprises about 0.1% to 95% by total composition weight of a cross-linkable polyanionic polymer and 0% to 95% by total composition weight of a non-cross-linkable polyanionic polymer. Hemophilic polymer (**224**) comprises about 1% to 90% by total composition weight of a polycationic polymer. Red blood cell (**210**) is shown in relation to the cationic function groups (**212**) via a red blood cell-cationic group linkage (**216**).

FIGS. 3A to **3I** show various polymers that can be chosen as structural polymer (**226**) or hemophilic polymer (**224**). Polymers can be modified through the addition of carboxymethyl (CM) groups to gain anionic functional groups (**218**). **FIG. 3E** shows

carboxymethyl cellulose. Alginate (**3A**), sodium hyaluronate (**3F**), κ-carrageenan (**3G**), ι-carrageenan (**3H**), and sodium polyacrylate (**3I**) are examples of polymers that would function as structural polymer (**226**). Likewise, chitin (**3B**) and chitosan (**3C**) are examples of polymers that would function as hemophilic polymer (**224**). **FIG. 3D** shows how any polymer (**340**) can be modified with a diethylaminoethyl (DEAE) group to gain cationic functional groups (**212**).

Biocompatible polymeric composition (**114**) contains about 0.1% to 99.8% by total composition weight of a solvent. In one embodiment of the invention, the solvent is ethanol. Preferably the solvent is a 5% aqueous solution of ethanol in water. Non-limiting examples of solvents include water, ethanol, amyl acetate, acetone, methyl ethyl ketone, isopropanol, and tetrahydrofuran. In solution, structural polymer (**226**) and hemophilic polymer (**224**) experience intermolecular interactions which bind them together. Cationic function groups (**212**) on hemophilic polymer (**224**) attract anionic functional groups (**218**) on structural polymer (**226**) and result in ionic cross-linking (**214**). Additionally, hemophilic polymer (**224**) and structural polymer (**226**) can be covalently cross-linked (**228**), similar to a Schiff base or azomethine linkage.

Protective coat (**110**) comprises 0.1% to 30% by weight of a di- or higher valent cation (**220**), 0% to 90% by weight of a hydrophobic polymer, and 5% to 99.9% by weight of a solvent. Protective coat (**110**) cross-links composition (**114**) by diffusing divalent cation (**220**) inwards, which results in divalent cation cross-linking (**222**) of structural polymer (**226**). This increases the rigidity of composition (**114**) and allows for better stability. Protective coat (**110**) can also contain hydrophobic polymers, which limit the water loss from composition (**114**) and improve durability. The hydrophobic polymer may be a polyurethane, nitrocellulose, a cyanoacrylate, a styrene, a polytetrafluoroethane, and a silicone, and combinations thereof. The solvent may be water, amyl acetate, acetone, methyl ethyl ketone, isopropanol, and tetrahydrofuran, and combinations thereof. The di- or higher valent cation may be Ca2+, Fe2+, Fe3+, Ag2+, Ag3+, Au2+, Au3+, Mg2+, Cu2+, Cu3+, and Zn2+. In one embodiment of the invention, the cation is Ca2+.

In one embodiment of the invention, structural polymer (**226**) comprises 0.1% to 5% by weight of sodium alginate and 1% to 5% by weight of sodium hyaluronate, hemophilic polymer (**224**) comprises 2% to 25% by weight of chitosan chloride, and the solvent comprises 65% to 96.9% by weight of a 5% aqueous solution of ethanol in water. In this embodiment, the composition functions as a wound healing matrix to facilitate faster tissue regeneration.

In another embodiment, structural polymer (**226**) comprises 2% to 5% by weight of sodium alginate and 0% to 2% by weight of sodium hyaluronate, hemophilic polymer (**224**) comprises 5% to 20% by weight of chitosan chloride, and the solvent comprises 73% to 93% by weight of a 5% aqueous solution of ethanol in water. In this embodiment, the composition functions as a thick gel for rapidly achieving hemostasis without the need to apply pressure. The composition can be delivered topically to the compromised blood vessel.

In another embodiment of the invention, structural polymer (**226**) comprises 0.1% to 4% by weight of sodium alginate and 1% to 5% by weight of a lysine-rich polypeptide, hemophilic polymer (**224**) comprises 5% to 25% by weight of diethylaminoethyl-dextran (DEAE-Dextran), and the solvent comprises 65% to 93% by weight of a 5% aqueous solution of ethanol in water. The biocompatible polymeric composite (**114**) is then cross-linked in situ by applying an aerosol mist comprising 0.1% to 1% by weight of calcium chloride, 1% to 5% by weight of nitrocellulose, and 94% to 98.9% by weight of amyl acetate. In this embodiment, the composition functions as a protective covering for cuts and scrapes that is durable and limits water loss from the wound.

In one embodiment of the invention, the biocompatible polymeric composition comprises about 3.6% by weight of sodium alginate, about 7% by weight of chitosan chloride, and about 89.4% by weight of a 5% aqueous solution of ethanol in water. This embodiment may function as a composition to treat arterial bleeds.

In one embodiment of the invention, the protective coat comprises a solution comprising about 0.1% to about 30% by weight of a di- or higher valent cation; 0% to about 90% by weight of a hydrophobic polymer; and about 5% to about 99.9% by weight of a solvent. In one embodiment of the invention, the protective coat comprises a solution comprising about 0.1% to about 1% by weight of a di-valent cation; about 1 to about 5% by weight of a hydrophobic polymer; and about 94% to about 98.9% by weight of a solvent.

In one embodiment of the invention, composition (**114**) is used as a carrier for a therapeutic agent such as a drug or biologic molecule. The use of composition (**114**) as a drug delivery system improves the efficiency of the wound healing gel. In one aspect, protective coat (**110**) is prepared with a salt of silver, increasing the antimicrobial properties of the gel. In one embodiment, the therapeutic agent is selected from the group consisting of: antimicrobial agents, antibiotics, hormones, proteins (such as calreticulin, thrombin, prothrombin, Factor VIII), and iodine, and combinations thereof. In one embodiment of the invention, the therapeutic agent is preferably iodine. In another embodiment of the invention, the therapeutic agent is a protein.

In one embodiment of the invention, the cross-linkable polyanionic polymer may be a polystyrene sulfonate (such as sodium polystyrene sulfonate), a polyacrylate (such as sodium polyacrylate), a polymethacrylate (such as sodium polymethacrylate), a polyvinyl sulphate (such as sodium polyvinyl sulphate), a polyphosphate (such as sodium polyphosphate), Iota carrageenan, Kappa carrageenan, gellan gum, carboxyl methyl cellulose, carboxyl methyl agarose, carboxyl methyl dextran, carboxyl methyl chitin, carboxyl methyl chitosan, a polymer modified with a carboxyl methyl group, an alginate (such as sodium alginate), a polymer containing a plurality of carboxylate groups, a xanthan gum, and combinations thereof. Preferably, the corsslinkable polyanionic polymer is an alginate, more preferably sodium alginate.

Preferably the cross-linkable polyanionic polymer comprises about 1% to about 95% by weight of the biocompatible polymeric composition; preferably the cross-linkable polyanionic polymer comprises about 5% to about 40% by weight of the biocompatible polymeric composition; preferably the cross-linkable polyanionic polymer comprises about 10% to about 30% by weight of the biocompatible polymeric composition.

In one embodiment of the invention, the non-cross-linkable polyanionic polymer may be a hyaluronate (such as sodium hyaluronate), a polynucleotide (such as RNA), a polypeptide chain having an average residue isoelectric point below 7, a glucosaminoglycan, and a proteoglycan, and combinations thereof. Preferably the non-cross-linkable polyanionic polymer is a hyaluronate, more preferably sodium hyaluronate.

Preferably the non-cross-linkable polyanionic polymer comprises about 0 to about 95% by weight of the biocompatible polymeric composition; preferably the non-cross-linkable polyanionic polymer comprises about 5 to about 25% by weight of the biocompatible polymeric composition; preferably the non-cross-linkable polyanionic polymer comprises about 0 to about 5% by weight of the biocompatible polymeric composition; preferably the non-cross-linkable polyanionic polymer comprises about 0 to about 2% by weight of the biocompatible polymeric composition; preferably the non-cross-linkable polyanionic polymer comprises about 1 to about 5% by weight of the biocompatible polymeric composition.

In one embodiment of the invention, the polycationic polymer may be a chitosan (such as chitosan chloride), chitin, diethylaminoethyl-dextran, diethylaminoethyl-cellulose, diethylaminoethyl-agarose, diethylaminoethyl-alginate, a polymer modified with a diethylaminoethyl group, a polymer containing a plurality of protonated amino groups, and a polypeptide having an average residue isoelectric point above 7, and combinations thereof.

Preferably the polycationic polymer is a chitosan, more preferably chitosan chloride. Preferably the polycationic polymer is diethylaminoethyl-dextran (DEAE-Dextran).

Preferably the polycationic polymer comprises about 1% to about 90% by weight of the biocompatible polymeric composition; preferably the polycationic polymer comprises about 2% to about 80% by weight of the biocompatible polymeric composition; preferably the polycationic polymer comprises about 2% to about 25% by weight of the biocompatible polymeric composition.

The individual components of the biocompatible polymeric composition may be stored in a variety of different containers for a variety of different applications, including for example, packets, sachets, tubes, tubs, pumps, syringes, bottles, bags, and aerosol-based spray cans. The components may be stored in containers made of a variety of materials, including for example, plastic, metal, or glass. The components may be provided in operably connected configurations, or as separate components for a user to set up prior to use.

The compositions and systems described herein may be included in a kit or article of manufacture for forming a biocompatible polymeric composition comprising one or more of: a solution comprising a polyanionic polymer; a solution comprising a polycationic polymer; a solvent; and a solution comprising a di- or higher valent cation, a hydrophobic polymer, and solvent. The kit or article of manufacture may further contain gauze, bandages, tape, brushes, spatulas, and sponges.

A number of implementations have been described. Nevertheless, it will be understood that various modifications may be made without departing from the spirit and scope of this document. In particular, for example, various compositions of the solutions have been described, but varying similar components and elements may be integrated or utilized in substitution to achieve the same or similar effect. Moreover, varying matrices may be employed to target diverse wound locations, internal or external to the dermal layers of the skin, including organ transplantation, tissue grafting, and/or various surgical incisions and lesions at any site or location external and/or internal to the body. Accordingly, other implementations are within the scope of the following claims.

Further, the studies described may utilize one embodiment of the composition to form a rigid matrix while another composition may be designed with an increased elasticity, alone or in combination. Further, the methods of mixing and formulating the composition may be performed in any order and combination so as to achieve the same or similar effects of the embedded solidified matrix, the matrix integrating the formation of naturally restructuring tissue. In one embodiment, the one or more than one polyanionic polymer is first applied to a

wound and then the one or more than one polycationic polymer is applied to the said one or more than one polymeric polymer at the wound site. In one embodiment, the one or more than one polyanionic polymer is mixed with the one or more than one polycationic polymer and then the mixture is then applied to the wound. In one embodiment, the one or more than one polyanionic polymer is applied to a wound at the same time, or about the same time, that the one or more than one polycationic polymer is applied to a wound.

In one embodiment, a method of treating a wound comprises applying one or more than one polyanionic polymer to a wound and then applying one or more than one polycationic polymer to the said one or more than one polymeric polymer at the wound site. In one embodiment, a method of treating a wound comprises mixing one or more than one polyanionic polymer with one or more than one polycationic polymer and then applying the mixture to the wound. In one embodiment, a method of treating a wound comprises applying one or more than one polyanionic polymer to the wound at the same time, or about the same time, as one or more than one polycationic polymer is applied to a wound.

What is claimed:

1. A biocompatible polymeric composition comprising:
    a. about 0.1% to about 95% by weight of one or more than one polyanionic polymer;
    b. about 0.1% to about 90% by weight of one or more than one polycationic polymer; and
    c. 0.1% to 99.8% by weight water.
2. A biocompatible polymeric composition of Claim 1 wherein the one or more than one polyanionic polymer comprises at least one cross-linkable polyanionic polymer.
3. A biocompatible polymeric composition of Claim 2 wherein the one or more than one polyanionic polymer further comprises at least one non-cross-linkable polyanionic polymer.
4. A biocompatible polymeric composition of Claim 3, wherein at least one cross-linkable polyanionic polymer is selected from the group consisting of: a polystyrene sulfonate, a polyacrylate, a polymethacrylate, a polyvinyl sulphate, a polyphosphate, Iota carrageenan, Kappa carrageenan, gellan gum, carboxyl methyl cellulose, carboxyl methyl agarose, carboxyl methyl dextran, carboxyl methyl chitin, carboxyl methyl chitosan, a polymer modified with a carboxyl methyl group, an alginate, a polymer containing a plurality of carboxylate groups, and xanthan gum.
5. A biocompatible polymeric composition of Claim 4, wherein one or more than one cross-linkable polyanionic polymer is selected from the group consisting of: sodium polystyrene sulfonate, sodium polyacrylate, sodium polymethacrylate, sodium polyvinyl sulphate, sodium polyphosphate, and sodium alginate.
6. A biocompatible polymeric composition as in Claim 3, wherein at least one non-cross-linkable polyanionic polymer is selected from the group consisting of: a hyaluronate, a polynucleotide, a polypeptide chain having an average residue isoelectric point below 7, a glucosaminoglycan, and a proteoglycan.
7. A biocompatible polymeric composition as in Claim 6, wherein at least one non-cross-linkable polyanionic polymer is selected from the group consisting of: sodium hyaluronate or RNA.
8. A biocompatible polymeric composition as in Claim 3, wherein the one or more than one polycationic polymer is selected from the group consisting of: chitosan, chitin, diethylaminoethyl-dextran, diethylaminoethyl-cellulose, diethylaminoethyl-agarose, diethylaminoethyl-alginate, a polymer modified with a diethylaminoethyl group, a

polymer containing a plurality of protonated amino groups, and a polypeptide having an average residue isoelectric point above 7.

9. A biocompatible polymeric composition as in Claim 3, wherein at least one cross-linkable polyanionic polymer is cross-linked to at least one polycationic polymer through hydrogen bonding.

10. A biocompatible polymeric composition as in Claim 3, wherein at least one cross-linkable polyanionic polymer is cross-linked to at least one polycationic polymer through covalent linkages.

11. A biocompatible polymeric composition as in Claim 3 further comprising a therapeutic agent selected from the group consisting of: antimicrobial agents, antibiotics, hormones, proteins, and iodine.

12. A method of forming a protective coat over a polymeric composition of Claim 1 in situ, comprising the addition of a solution comprising:
    a. about 0.1% to about 30% by weight of a di- or higher valent cation;
    b. 0% to about 90% by weight of a hydrophobic polymer; and
    c. about 5% to about 99.9% by weight of a solvent

13. A method of Claim 12, wherein said hydrophobic polymer is selected from the group consisting of: a polyurethane, nitrocellulose, a cyanoacrylate, a styrene, a polytetrafluoroethane, and a silicone.

14. A method of Claim 12, wherein said solvent is selected from the group consisting of: water, amyl acetate, acetone, methyl ethyl ketone, isopropanol, and tetrahydrofuran.

15. A method of Claim 12, wherein said di- or higher valent cation is selected from the group consisting of salts of: Ca^{2+}, Fe^{2+}, Fe^{3+}, Ag^{2+}, Ag^{3+}, Au^{2+}, Au^{3+}, Mg^{2+}, Cu^{2+}, Cu^{3+}, and Zn^{2+}.

16. A method of treating a wound comprising directly applying to a wound a biocompatible polymeric composition of Claim 1.

17. A method of Claim 16, wherein said wound is selected from the group consisting of: an external laceration, an abrasion, a burn, an ocular laceration, damage to a parenchymal organ, an internal laceration, a laceration in the gastrointestinal tract, superficial cuts and scrapes, internal bleeding, an arterial bleed, a venous bleed, dental or oral bleeds and incisions.

18. A method of achieving rapid hemostasis without the need to apply pressure to a wound comprising directly applying to a wound a biocompatible polymeric composition of Claim 1.

19. A biocompatible polymeric composition comprising:
    a. about 1% to about 20% by weight of sodium alginate;
    b. about 1% to about 5% by weight of sodium hyaluronate;
    c. about 2% to about 20% by weight of chitosan chloride; and
    d. 55% to 96% by weight of a 5% aqueous solution of ethanol in water.
20. A method of forming a protective coat over a polymeric composition of Claim 19 in situ, comprising the addition of a solution comprising:
    a. about 0.1% to about 1% by weight of calcium chloride;
    b. about 1% to about 5% by weight of nitrocellulose; and
    c. about 94% to about 98.9% by weight of amyl acetate.
21. A biocompatible polymeric composition as in Claim 1, wherein said solvent is selected from the group consisting of: water, ethanol, amyl acetate, acetone, methyl ethyl ketone, isopropanol, and tetrahydrofuran.

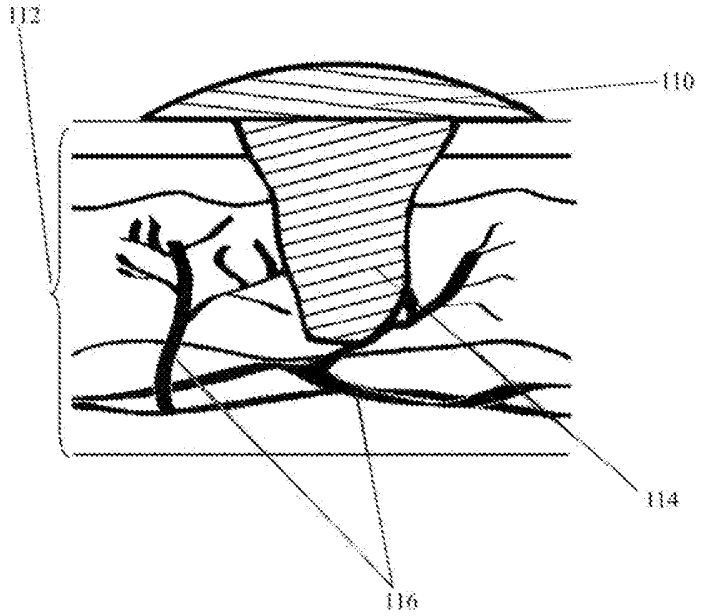


FIG.1

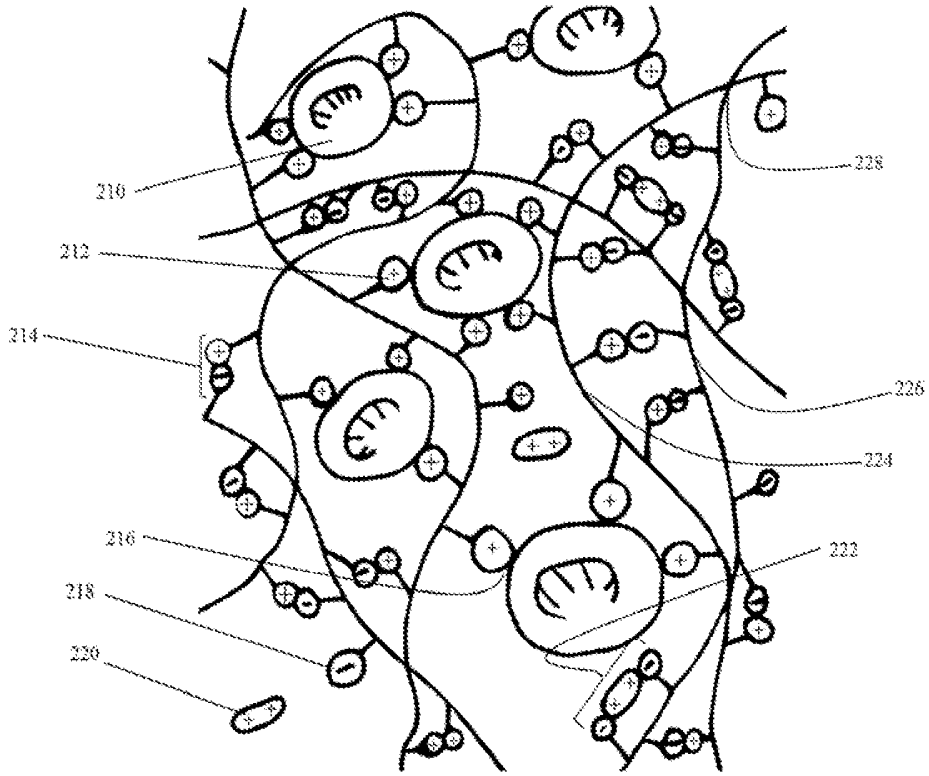


FIG.2

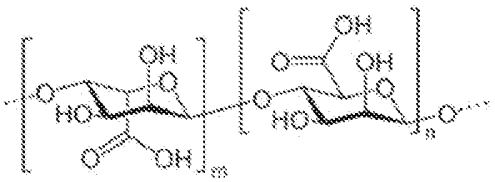


FIG.3A

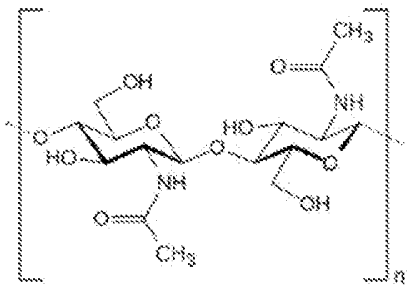


FIG.3B

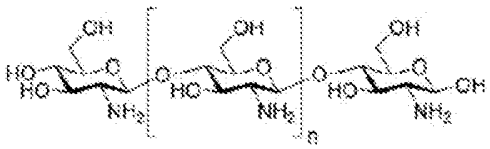


FIG.3C

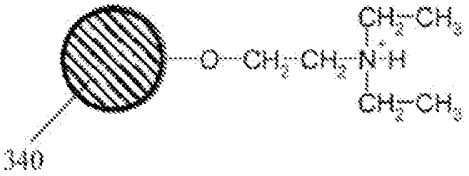
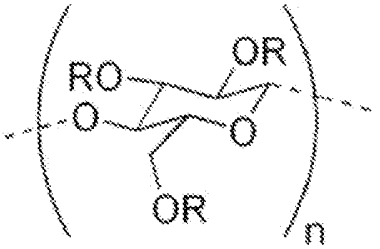


FIG.3D



R = H or CH_2CO_2H

FIG.3E

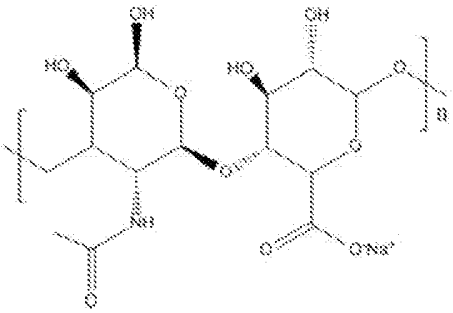


FIG.3F

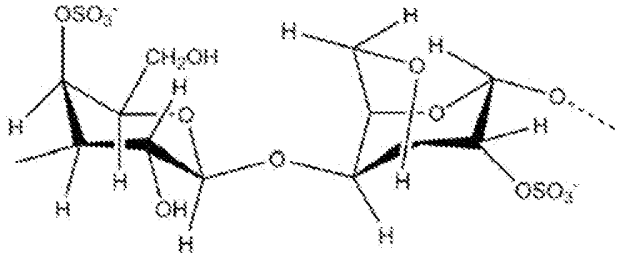


FIG.3G

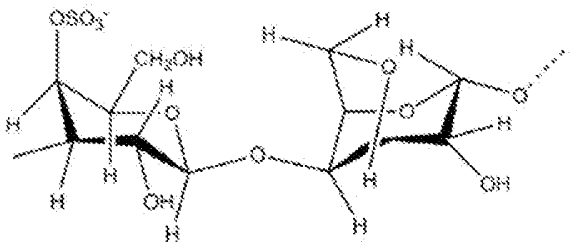


FIG.3H

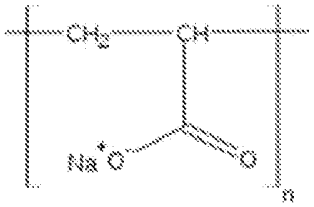


FIG.3I

	Stops Bleeding	Easily Removable	Disinfects	Faster Healing	Soothes Wound	Seals Wound	Stand-alone
Bio-compatible Polymeric Composition	✓	✓	✓	✓	✓	✓	✓
Gauze/ Bandage		✓				✓	✓
Liquid Bandage			✓			✓	✓
Clotting Agent	✓						
Alginate Dressing		✓				✓	
Hydrogel		✓		✓	✓		
Silver Anti-microbial		✓	✓	✓			

FIG.4

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/64670

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 47/30; A61K 47/36; A61L 15/22; C08F 283/00 (2013.01)
USPC - 424/447, 424/488
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8)- A61K 47/30; A61K 47/36; A61L 15/22; C08F 283/00 (2013.01);
USPC- 424/447, 424/488

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC- 424/78.08, 445, 484;
Patents and NPL (classification, keyword; search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWest (USPTO, EPO, JPO, WIPO), GoogleScholar (PL, NPL), FreePatentsOnline (USPTO, EPO, JPO, WIPO, NPL);
search terms: polyanion, polycation, crosslink, non-crosslink, hyaluronate, RNA, sodium, polystyrene, polyacrylate, polymethacrylate, polyvinyl, sulphate, sulfate, polyphosphate, alginate, cation, divalent, trivalent, in situ, wound...

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	WO 2011/075557 A1 (KOHANE et al.) 23 June 2011 (23.06.2011), para [0004], [0008], [0018], [0020], [0026], [0030], [0031], [0050], [0076], [0097], [0100], [0101], [0114], [0118], [0140], [0155], [0156], [0160], [0170], [0171]	1-16, 21 ---------- 17, 18
Y	US 2008/0139694 A1 (RATCLIFFE) 12 June 2008 (12.06.2008), para [0007], [0042], [0056], [0065]	17, 18
A, P	US 2011/0287067 A1 (STEWART) 24 November 2011 (24.11.2011), para [0009]-[0180]	1-18, 21
A	US 2011/0144229 A1 (MEYERHOFF et al.) 16 June 2011 (16.06.2011), para [0007]-[0110]	1-18, 21
A	US 2007/0166351 A1 (HOSSAINY) 19 July 2007 (19.07.2007), para [0010]-[0077]	1-18, 21

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

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 February 2013 (27.02.2013)	25 MAR 2013
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/64670

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

-- Please see extra sheet --

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-18 and 21

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/64670

Continued from Box No. III, Observatiosn where unity of invention is lacking:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, Claims 1-18 and 21, drawn to a biocompatible polymeric composition comprising:
a. about 0.1 % to about 95% by weight of one or more than one polyanionic polymer;
b. about 0.1 % to about 90% by weight of one or more than one polycationic polymer; and
c. 0.1% to 99.8% by weight water.

Group II, Claims 19-20, drawn to a biocompatible polymeric composition comprising:
a. about 1 % to about 20% by weight of sodium alginate;
b. about 1 % to about 5% by weight of sodium hyaluronate;
c. about 2% to about 20% by weight of chitosan chloride; and
d. 55% to 96% by weight of a 5% aqueous solution of ethanol in water.

The inventions listed as Groups I-II do not relate to a single general inventive concept under PCT Rule 13.1 because under PCT Rule 13.2 they lack the same or corresponding technical features for the following reasons:

Group I does not include the special technical feature of a biocompatible polymeric composition in Group II, comprising:
a. about 1 % to about 20% by weight of sodium alginate;
b. about 1 % to about 5% by weight of sodium hyaluronate;
c. about 2% to about 20% by weight of chitosan chloride; and
d. 55% to 96% by weight of a 5% aqueous solution of ethanol in water.

Group II does not include the special technical feature a biocompatible polymeric composition in Group I, comprising:
a. about 0.1 % to about 95% by weight of one or more than one polyanionic polymer;
b. about 0.1 % to about 90% by weight of one or more than one polycationic polymer; and
c. 0.1% to 99.8% by weight water.

The special technical feature common to Groups I and II, a biocompatible composition (para [0007], [0033], [0051]), is disclosed by US 2011/0144229 A1 to Meyerhoff, et al. (hereinafter 'Meyerhoff').

Meyerhoff further discloses a biocompatible polymeric composition comprising a polyanionic polymer and a polycationic polymer (para [0007], [0033], [0051]), sodium alginate (para [0035]), hyaluronic acid (para [0035]), and chitosan (para [0034]).

None of these technical features are common to the other groups, nor do they correspond to a special technical feature in the other groups. Groups I and II therefore lack unity under PCT Rule 13 because they do not share a same or corresponding special technical feature.

摘要

公開了一種用於在傷口中原位交聯的生物相容的聚合物組合物，包含：1)能夠在傷口表面交聯的一種或多種多聚陰離子聚合物例如藻酸鹽或透明質酸鹽和2)一種或多種多聚陽離子聚合物，例如殼聚醣或DEAE-葡聚醣，其輔助固化過程以及加速止血而無需加壓。所述生物相容的聚合物組合物還可包含交聯劑例如水性氯化鈣。本發明涵蓋初始聚合物組合物、在傷口部位交聯並整合的固化基質，包括使用、應用和交聯所述組合物的方法。