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(54) **PROTEIN-BASED POLYMER TISSUE ADHESIVES FOR MEDICAL USE**

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See application file for complete search history.

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(57) **ABSTRACT**

Tissue adhesives formed by crosslinking albumin and/or gelatin with certain polyamines and/or polycarboxylates using a water-soluble carbodiimide are disclosed. The use of the tissue adhesives for medical and veterinary applications such as topical wound closure; and surgical procedures, such as intestinal anastomosis, vascular anastomosis, tissue repair, and ophthalmic procedures; drug delivery; anti-adhesive applications; and as a bulking agent to treat urinary incontinence are described.

11 Claims, No Drawings

PROTEIN-BASED POLYMER TISSUE ADHESIVES FOR MEDICAL USE

CROSS-REFERENCE TO RELATED APPLICATION

This application claims priority under 35 U.S.C. §119 from U.S. Provisional Application Ser. No. 60/632,272, filed Dec. 1, 2004.

FIELD OF THE INVENTION

The invention relates to the field of medical adhesives. More specifically, the invention relates to protein-based tissue adhesives formed by crosslinking albumin and/or gelatin with certain polyamines and/or certain polycarboxylates using a water-soluble carbodiimide.

BACKGROUND OF THE INVENTION

Tissue adhesives have many potential medical applications, including topical wound closure, supplementing or replacing sutures or staples in internal surgical procedures, adhesion of synthetic onlays or inlays to the cornea, drug delivery devices, and as anti-adhesion barriers to prevent post-surgical adhesions. Conventional tissue adhesives are generally not suitable for a wide range of adhesive applications. For example, cyanoacrylate-based adhesives have been used for topical wound closure, but the release of toxic degradation products limits their use for internal applications. Fibrin-based adhesives are slow curing, have poor mechanical strength, and pose a risk of viral infection. Additionally, the Fibrin-based adhesives do not covalently bind to the underlying tissue.

Protein-based tissue adhesives using albumin or gelatin are known. For example, Wilkie et al. (U.S. Patent Application Publication No. 2002/0022588) and Tammishetti et al. (WO 99/66964) describe tissue adhesives formed by crosslinking albumin with a carbodiimide. The addition of a polyamine, specifically, poly(lysine) or chitosan, or a polycarboxylate, specifically, citric acid or poly(acrylic acid), to increase the rate of crosslinking is also described in those disclosures. However, for use as a tissue adhesive for in vivo applications, such as intestinal anastomosis, adhesives with lower toxicity and enhanced adhesive strength are needed. The use of carbodiimides in the adhesive composition causes some toxicity problems. The toxicity problem is exacerbated by the use of a toxic polyamine such as poly(lysine). Chitosan is not soluble enough to be effective in increasing the adhesive properties of the adhesive.

Otani et al. (*J. Biomed. Mater. Res.* 31:157-166 (1996); and *Biomaterials* 17:1387-1391 (1996)) describe a tissue adhesive prepared by crosslinking gelatin and poly(L-glutamic acid) with a water-soluble carbodiimide. Although the adhesive is less toxic than the albumin-poly(lysine) adhesive described above, it lacks adhesive strength.

Therefore in the continuing search for new tissue adhesives for in vivo applications, such as intestinal anastomosis, the problem to be solved is to provide a protein-based tissue adhesive with lower toxicity and higher adhesive strength than those currently available.

Applicants have addressed the stated problem by discovering a tissue adhesive formed by crosslinking albumin and/or gelatin with certain polyamines and/or certain polycarboxylates using a water-soluble carbodiimide. The polyamines and polycarboxylates of the invention have low toxicity and provide a tissue adhesive with improved adhesive strength. Additionally, the polyamines and polycarboxylates of the invention permit the use of a lower carbodiimide concentration than can be used in the absence of the polyamines or polycarboxylates or in the presence of the polyamines or polycarboxylates known in the art, thereby further reducing the toxicity of the adhesive.

SUMMARY OF THE INVENTION

The invention provides a kit comprising:

A) a first vessel containing an aqueous solution comprising albumin, gelatin or a mixture thereof;

B) a second vessel containing an undissolved water-soluble carbodiimide; and

C) a third vessel, the contents of which comprise water;

provided that:

(i) the contents of at least one of the first or third vessels further comprise at least one of:

(a) at least one polyamine selected from the group consisting of a water-dispersible multi-arm polyether amine, a water-dispersible aminoalkylated polysaccharide, and a water-dispersible aminoalkylated poly (vinyl alcohol), the total polyamine concentration being in the range of about 0.5% to about 20% by weight; or

(b) at least one polycarboxylate selected from the group consisting of carboxymethyl cellulose, carboxymethyl dextran, and carboxymethyl starch, the total polycarboxylate concentration being in the range of about 0.5% to about 5% by weight; or

(c) a mixture of said polyamine of (i)(a) having a total polyamine concentration in the range of about 0.5% to about 20% by weight and said polycarboxylate of (i)(b) having a total polycarboxylate concentration in the range of about 0.5% to about 5% by weight;

or

(ii) the kit further comprises a fourth vessel containing at least one of:

(a) at least one polyamine selected from the group consisting of a water-dispersible multi-arm polyether amine, a water-dispersible aminoalkylated polysaccharide, and a water-dispersible aminoalkylated poly (vinyl alcohol) as a neat liquid; or

(b) an aqueous polyamine solution comprising at least one polyamine selected from the group consisting of a water-dispersible multi-arm polyether amine, a water-dispersible aminoalkylated polysaccharide, and a water-dispersible aminoalkylated poly(vinyl alcohol), the total polyamine concentration being in the range of about 0.5% to about 20% by weight; or

(c) an aqueous polycarboxylate solution comprising at least one polycarboxylate selected from the group consisting of carboxymethyl cellulose, carboxymethyl dextran, and carboxymethyl starch, the total polycarboxylate concentration being in the range of about 0.5% to about 5% by weight; or

(d) an aqueous mixed polyamine/polycarboxylate solution comprising said at least one polyamine of (ii)(b) having a total polyamine concentration of about 0.5% to about 20% by weight, and said at least one polycarboxylate of (ii)(c) having a total polycarboxylate concentration of about 0.5% to about 5% by weight;

or

(iii) a combination of (i) and (ii);

provided further that:

(iv) if the aqueous solution in the first vessel of (A) comprises albumin, but not gelatin, then the concentration of albumin in the aqueous solution is about 25% to about 40% by weight;

(v) if the aqueous solution in the first vessel of (A) comprises gelatin, but not albumin, then the concentration of gelatin in the aqueous solution is about 15% to about 35% by weight; and

(vi) if the aqueous solution in the first vessel of (A) comprises a mixture of albumin and gelatin, then the total concentration of albumin and gelatin combined is about 15% to about 40% by weight.

In another embodiment, the invention provides a method for forming a coating on an anatomical site on tissue of a living organism comprising:

(A) forming on said site an aqueous mixture comprising:

(i) at least one of albumin or gelatin;

(ii) a water-soluble carbodiimide; and

(iii) at least one of:

(a) at least one polyamine selected from the group consisting of a water-dispersible multi-arm polyether amine, a water-dispersible aminoalkylated polysaccharide, and a water-dispersible aminoalkylated poly (vinyl alcohol); or

(b) at least one polycarboxylate selected from the group consisting of carboxymethyl cellulose, carboxymethyl dextran, and carboxymethyl starch; and

allowing said aqueous mixture to cure, thereby forming said coating; or

(B) forming an aqueous mixture comprising:

(i) at least one of albumin or gelatin;

(ii) a water-soluble carbodiimide; and

(iii) at least one of:

(a) at least one polyamine selected from the group consisting of a water-dispersible multi-arm polyether amine, a water-dispersible aminoalkylated polysaccharide, and a water-dispersible aminoalkylated poly (vinyl alcohol); or

(b) at least one polycarboxylate selected from the group consisting of carboxymethyl cellulose, carboxymethyl dextran, and carboxymethyl starch; and

applying said mixture to the site before the mixture completely cures, and allowing said aqueous mixture to cure completely, thereby forming said coating;

provided that:

(i) if the aqueous mixture comprises albumin, but not gelatin, then the concentration of albumin in the aqueous mixture is about 20% to about 36% by weight;

(ii) if the aqueous mixture comprises gelatin, but not albumin, then the concentration of gelatin in the aqueous mixture is about 12% to about 32% by weight;

(iii) if the aqueous mixture comprises a mixture of albumin and gelatin, then the total concentration of albumin and gelatin combined is about 12% to about 36% by weight;

(iv) the concentration of the water-soluble carbodiimide in the aqueous mixture is about 1% to about 10% by weight;

(v) if the aqueous mixture comprises the polyamine, but not the polycarboxylate, then the concentration of the polyamine in the aqueous mixture is about 0.4% to about 20% by weight;

(vi) if the aqueous mixture comprises the polycarboxylate, but not the polyamine, then the concentration of the polycarboxylate in the aqueous mixture is about 0.4% to about 5% by weight; and

(vii) if the aqueous mixture comprises both the polyamine and the polycarboxylate, then the concentration of the polyamine in the aqueous mixture is about 0.4% to about 20% by weight and the concentration of the polycarboxylate is about 0.4% to about 5% by weight.

In another embodiment, the invention provides a method for bonding at least two anatomical sites together comprising:

A) forming an aqueous mixture in contact with at least two anatomical sites comprising:

(i) at least one of albumin or gelatin;

(ii) a water-soluble carbodiimide; and

(iii) at least one of:

(a) at least one polyamine selected from the group consisting of a water-dispersible multi-arm polyether amine, a water-dispersible aminoalkylated polysaccharide, and a water-dispersible aminoalkylated poly (vinyl alcohol); or

(b) at least one polycarboxylate selected from the group consisting of carboxymethyl cellulose, carboxymethyl dextran, and carboxymethyl starch; and

B) allowing said aqueous mixture to cure;

provided that:

(i) if the aqueous mixture comprises albumin, but not gelatin, then the concentration of albumin in the aqueous mixture is about 20% to about 36% by weight;

(ii) if the aqueous mixture comprises gelatin, but not albumin, then the concentration of gelatin in the aqueous mixture is about 12% to about 32% by weight;

(iii) if the aqueous mixture comprises a mixture of albumin and gelatin, then the total concentration of albumin and gelatin combined is about 12% to about 36% by weight;

(iv) the concentration of the water-soluble carbodiimide in the aqueous mixture is about 1% to about 10% by weight;

(v) if the aqueous mixture comprises the polyamine, but not the polycarboxylate, then the concentration of the polyamine in the aqueous mixture is about 0.4% to about 20% by weight;

(vi) if the aqueous mixture comprises the polycarboxylate, but not the polyamine, then the concentration of the polycarboxylate in the aqueous mixture is about 0.4% to about 5% by weight; and

(vii) if the aqueous mixture comprises both the polyamine and the polycarboxylate, then the concentration of the polyamine in the aqueous mixture is about 0.4% to about 20% by weight and the concentration of the polycarboxylate is about 0.4% to about 5% by weight.

In another embodiment, the invention provides a composition resulting from forming an aqueous mixture comprising:

(a) at least one of albumin or gelatin;

(b) a water-soluble carbodiimide; and

(c) at least one of:

(i) at least one polyamine selected from the group consisting of a water-dispersible multi-arm polyether amine, a water-dispersible aminoalkylated polysaccharide, and a water-dispersible aminoalkylated poly (vinyl alcohol); or

(ii) at least one polycarboxylate selected from the group consisting of carboxymethyl cellulose, carboxymethyl dextran, and carboxymethyl starch; and

allowing the aqueous mixture to cure:

provided that:

(i) if the aqueous mixture comprises albumin, but not gelatin, then the concentration of albumin in the aqueous mixture is about 20% to about 36% by weight;

(ii) if the aqueous mixture comprises gelatin, but not albumin, then the concentration of gelatin in the aqueous mixture is about 12% to about 32% by weight;

(iii) if the aqueous mixture comprises a mixture of albumin and gelatin, then the total concentration of albumin and gelatin combined is about 12% to about 36% by weight;

(iv) the concentration of the water-soluble carbodiimide in the aqueous mixture is about 1% to about 10% by weight;

(v) if the aqueous mixture comprises the polyamine, but not the polycarboxylate, then the concentration of the polyamine in the aqueous mixture is about 0.4% to about 20% by weight;

(vi) if the aqueous mixture comprises the polycarboxylate, but not the polyamine, then the concentration of the polycarboxylate in the aqueous mixture is about 0.4% to about 5% by weight; and

(vii) if the aqueous mixture comprises both the polyamine and the polycarboxylate, then the concentration of the polyamine in the aqueous mixture is about 0.4% to about 20% by weight and the concentration of the polycarboxylate is about 0.4% to about 5% by weight.

Methods for using the protein-based polymer tissue adhesive of the invention for topical wound closure, intestinal and vascular anastomoses, sealing corneal incisions, preventing adhesions, and drug delivery are also provided.

DETAILED DESCRIPTION OF THE INVENTION

The invention relates to a protein-based tissue adhesive formed by crosslinking albumin and/or gelatin with certain polyamines and/or certain polycarboxylates using a water-soluble carbodiimide. The tissue adhesive of the invention is useful as an adhesive for medical and veterinary applications including, but not limited to, topical wound closure, and surgical procedures, such as intestinal anastomosis, vascular anastomosis, tissue repair, and ophthalmic procedures. Additionally, the tissue adhesive may have utility in drug delivery, anti-adhesive applications, and as a bulking agent to treat urinary incontinence.

The following definitions are used herein and should be referred to for interpretation of the claims and the specification.

The term "polyamine" refers to a compound having at least two primary amine groups.

The term "polycarboxylate" refers to a compound having at least two carboxylic acid groups.

The term "water-dispersible, multi-arm polyether amine" refers to a branched polyether, wherein at least three of the branches ("arms") are terminated by a primary amine group, which is water soluble or able to be dispersed in water to form a colloidal suspension capable of reacting with a second reactant in aqueous solution.

The term "polyether" refers to a polymer having the repeat unit [—O—R]—, wherein R is a hydrocarbylene group having 2 to 5 carbon atoms.

The term "hydrocarbylene group" refers to a divalent group formed by removing two hydrogen atoms, one from each of two different carbon atoms, from a hydrocarbon.

The term "branched polyether" refers to a polyether having one or more branch points ("arms"), including star, dendritic, comb, and hyperbranched polyethers.

The term "dendritic polyether" refers to a highly branched polyether having a tree-like structure.

The term "comb polyether" refers to a polyether having a main chain with multiple trifunctional branch points from each of which a linear arm emanates.

The term "star polyether" refers to a polyether having a single branch point from which linear arms emanate.

The term "hyperbranched polyether" refers to a highly branched polyether having fewer branches and less regular branching than a dendritic polyether.

The term "water-dispersible aminoalkylated polysaccharide" refers to a polysaccharide which has at least two of its hydroxyl hydrogens replaced by hydrocarbyl groups bearing at least one primary amino group, wherein the hydrocarbyl groups are optionally substituted or optionally contain heteroatoms, and wherein the aminoalkylated polysaccharide is water soluble or able to be dispersed in water to form a colloidal suspension capable of reacting with a second reactant in aqueous solution.

The term "water-dispersible aminoalkylated poly(vinyl alcohol) refers to a poly(vinyl alcohol) which has at least two of its hydroxyl hydrogens replaced by hydrocarbyl groups bearing at least one primary amino group, wherein the hydrocarbyl groups are optionally substituted or optionally contain heteroatoms, and wherein the aminoalkylated poly(vinyl alcohol) is water soluble or able to be dispersed in water to form a colloidal suspension capable of reacting with a second reactant in aqueous solution.

The term "hydrocarbyl group" refers to a univalent group formed by removing a hydrogen atom from a hydrocarbon.

The term "% by weight" as used herein refers to the weight percent relative to the total weight of the solution, unless otherwise specified.

The term "anatomical site" refers to any external or internal part of the body of humans or animals.

The term "tissue" refers to any tissue, both living and dead, in humans or animals.

The term "hydrogel" refers to a water-swellable polymeric matrix, consisting of a three-dimensional network of macromolecules held together by covalent or non-covalent crosslinks that can absorb a substantial amount of water to form an elastic gel.

The term "gene" refers to a nucleic acid fragment that effects the production of a specific protein, including regulatory sequences preceding (5' non-coding sequences) and following (3' non-coding sequences) the coding sequence.

The term "recombinant host cell", as used herein, refers to a cell that has been transformed using genetic engineering techniques to produce albumin or gelatin.

By medical application is meant medical applications as related to humans and for veterinary purposes.

The invention provides a tissue adhesive formed by crosslinking albumin and/or gelatin with certain polyamines and/or certain polycarboxylates using a water-soluble carbodiimide. Because these proteins contain both amine and carboxylic acid groups, they can be crosslinked with polyamines and/or polycarboxylates using carbodiimide crosslinking. The polyamines and polycarboxylates of the invention have low toxicity and provide a tissue adhesive with improved adhesive strength. Additionally, the polyamines and polycarboxylates of the invention permit the use of a lower carbodiimide concentration than can be used in the absence of the polyamines or polycarboxylates or in the presence of the polyamines or polycarboxylates known in the art, thereby further reducing the toxicity of the adhesive. The crosslinking reaction forms a hydrogel, which has many desirable characteristics as a tissue adhesive, including, but not limited to,

improved adhesion and cohesion properties, crosslinks readily at body temperature, maintains dimensional stability initially, does not degrade rapidly, and has a lower toxicity to cells than other tissue adhesives that use carbodiimides.

Albumin:

Albumins are water-soluble proteins that are found in many animal tissues and fluids, such as milk, blood serum, and eggs. Most albumins are believed to be suitable for use in the invention. Of particular use are mammalian serum albumins and egg albumins (ovalbumins). Suitable mammalian serum albumins include, but are not limited to, bovine serum albumin, ovine (sheep) serum albumin, porcine (pig) serum albumin, human serum albumin, equine (horse) serum albumin, lapine (rabbit) serum albumin, rat serum albumin, and murine (mouse) serum albumin. Suitable egg albumins include, but are not limited to, chicken egg albumin. Mixtures of these albumins may also be used.

Albumin may be purified directly from tissues or fluids using methods known in the art, for example organic solvent precipitation or chromatographic methods, such as ion exchange or affinity chromatography. Additionally, albumin from many sources is available commercially from companies such as Sigma-Aldrich (St. Louis, Mo.).

The albumin may also be a recombinant albumin produced by a suitable recombinant host cell that expresses an albumin gene using standard recombinant DNA and molecular cloning techniques (Sambrook, J., Fritsch, E. F. and Maniatis, T., *Molecular Cloning: A Laboratory Manual*, Second Edition, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (1989); Silhavy, T. J., Bennan, M. L. and Enquist, L. W., *Experiments with Gene Fusions*, Cold Spring Harbor Laboratory Cold Press Spring Harbor, NY (1984); and Ausubel, F. M. et al., *Current Protocols in Molecular Biology*, published by Greene Publishing Assoc. and Wiley-Interscience (1987)). For example, the nucleotide sequences of the genes that encode bovine serum albumin (GenBank Accession. No. AF542068 and M73993), human serum albumin (Lawn et al. (*Nucleic Acids Res.* 9:6103-6114 (1981)), and ovalbumin (Woo et al. *Biochemistry* 20:6437-6446 (1981)) are known. These gene sequences may be expressed in a suitable host cell to produce the desired recombinant albumin. For example, recombinant human serum albumin may be expressed in *Escherichia coli*, as described by Lawn et al. (*Nucleic Acids Res.* 9:6103-6114 (1981)), in *Saccharomyces cerevisiae*, as described by Kalman et al. (*Nucleic Acids Res.* 18:6075-6081 (1990)), or in transgenic mice, as described by Shani et al. (*Trangenic Research* 1:195-208 (1992)). Additionally, recombinant human serum albumin is available commercially from companies such as GTC Biotherapeutics (Framingham, Mass.) and Delta Biotechnology Limited (Nottingham, UK).

Additionally, a recombinant albumin variant may be used, in which one or more amino acid residues are inserted, deleted, or substituted using standard techniques, such as site-directed mutagenesis. Suitable albumin variants have an amino acid sequence that has a percent identity of at least about 70%, or at least about 80%, or at least about 85%, or at least about 90%, or at least about 95% relative to the native albumin sequence. The "percent identity", which is a relationship between two or more polypeptide sequences, can be readily calculated by known methods, including but not limited to, those described in: *Computational Molecular Biology* (Lesk, A. M., ed.) Oxford University Press, NY (1988); *Biocomputing: Informatics and Genome Projects* (Smith, D. W., ed.) Academic Press, NY (1993); *Computer Analysis of Sequence Data, Part I* (Griffin, A. M., and Griffin, H. G., eds.) Humana Press, N.J. (1994); *Sequence Analysis in Molecular Biology* (von Heinje, G., ed.) Academic Press (1987); and *Sequence Analysis Primer* (Gribskov, M. and Devereux, J., eds.) Stockton Press, NY (1991). Preferred methods to determine identity are designed to give the best match between the sequences tested. Methods to determine identity are codified in publicly available computer programs. Sequence alignments and percent identity calculations may be performed using the Megalign program of the LASERGENE bioinformatics computing suite (DNASTAR Inc., Madison, Wis.). Multiple alignment of the sequences may be performed using the Clustal method of alignment (Higgins and Sharp (1989) *CABIOS.* 5:151-153) with the default parameters (GAP PENALTY=10, GAP LENGTH PENALTY=10). Default parameters for pairwise alignments using the Clustal method are KTUPLE 1, GAP PENALTY=3, WINDOW=5 and DIAGONALS SAVED=5.

In the invention, the albumin is used in the form of an aqueous solution. The albumin is added to water to give a concentration of about 25% to about 40% by weight relative to the total weight of the solution. The optimal concentration to be used depends on the application and on the concentrations of the water-soluble carbodiimide and the polyamine and/or polycarboxylate used, as described below, and can be readily determined by one skilled in the art using routine experimentation.

For use on living tissue, it is preferred that the aqueous solution comprising the albumin be sterilized to prevent infection. Any suitable sterilization method known in the art that does not degrade the protein may be used, including, but not limited to, gamma irradiation, ethylene oxide sterilization, or ultra-filtration through a 0.2 μm pore membrane.

The aqueous solution comprising the albumin may further comprise various additives depending on the intended application. For example, the solution may optionally include at least one pH modifier to adjust the pH of the solution. Suitable pH modifiers are well known in the art. The pH modifier may be an acidic or basic compound. Examples of acidic pH modifiers include, but are not limited to, carboxylic acids, inorganic acids, and sulfonic acids. Examples of basic pH modifiers include, but are not limited to, hydroxides, alkoxides, nitrogen-containing compounds other than primary and secondary amines, and basic carbonates and phosphates.

The aqueous solution comprising the albumin may optionally include at least one viscosity modifier. The viscosity modifier may be selected from among known viscosity modifiers, including, but not limited to, polysaccharides and derivatives thereof, such as starch or hydroxyethyl cellulose.

The aqueous solution comprising the albumin may optionally include at least one antimicrobial agent. Suitable antimicrobial agents are well known in the art. Examples of suitable antimicrobials include, but are not limited to, antibiotics such as tetracycline, ampicillin, vancomycin, polymyxin B, ciprofloxacin, teicoplanin, cefoxitin, gentamicin, and tobramycin.

The aqueous solution comprising the albumin may also optionally include at least one colorant to enhance the visibility of the solution. Suitable colorants include dyes, pigments, and natural coloring agents. Examples of suitable colorants include, but are not limited to, FD&C dyes and FD&C lakes, such as FD&C Violet No. 2, FD&C Yellow No. 6, FD&C Red No. 3, FD&C Blue No. 2; beetroot red; canthaxanthin, chlorophyll; eosin; saffron; and carmine.

The aqueous solution comprising the albumin may also optionally include at least one surfactant. Surfactant, as used herein, refers to a compound that lowers the surface tension of water. The surfactant may be an ionic surfactant, such as sodium lauryl sulfate, and octanoic acid; or a neutral surfac-

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