A BIOLOGICALLY DERIVED MEDICAL ADHESIVE AND ITS USES

An adhesive composition suited for surgical applications which consists essentially of an aqueous solution of natural collagen or gelatin which has a melt index temperature within the range of 35 °C to 45 °C.
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A BIOLOGICALLY DERIVED MEDICAL ADHESIVE AND ITS USES

BACKGROUND OF THE INVENTION

This application is a Continuation-in-Part of S.N. 549,797 filed July 9, 1990 by applicants Barry L. Bowyer and Jeffrey Robin.

Adhesives which can be used in surgical applications have been taught since the late 1940's. The first report of a surgical adhesive was published in 1949 concerning Tassman's use of fibrin coagulum to fix keratoplasty wounds, to hold cataract surgery incisions and to repair corneal lacerations. This adhesive did not enjoy success due to its susceptibility of enzyme degradation in in vitro surgical applications. Fibrin as a surgical adhesive was almost completely abandoned in the early 1950's.

In the early 1960's the National Health Institute and Battelle Memorial developed a adhesive based upon resorcinol crosslinked gelatin (specifically a mixture of gelatin, resorcinol and formaldehyde, sometimes referred to as "GRF"). While gelatin can be considered biocompatible with many tissues, the other additives of this mixture pose serious cytotoxicity concerns.

Furthermore, the adhesives employing this chemistry proved complex to prepare and subject to inconsistent adhesive characteristics. While the adhesive capacity required for applications in the heart could be achieved, it was not achieved in all instances.

Concurrent with the GRF research cyanoacrylates became available and their application in surgical applications was investigated. The adhesive characteristics of these materials are excellent. However, the materials are generally quite rigid, they
are impermeable to nutrients essential to tissue healing and their byproducts, formaldehyde and cyanide, are toxic to tissue cells. Furthermore, the materials do not bioerode so they may have to be removed at some later date. While the materials are used in a small number of surgical applications, such as closing small perforations, the United States Federal Food and Drug Administration has not approved of their use. Furthermore, due to their basic plastic like characteristics they cannot be used to close incisions.

In the 1970's investigators in Europe developed an adhesive composed of human fibrinogen and bovine thrombin which is commercially available in Europe as TisseelR (from Immuno Ag, Vienna, Austria). Since the commercial product is made from pooled human serum the possibility of viral infection is present and limits the desirability of the adhesive. This adhesive is a multi-component system which is difficult to prepare in order to provide consistent results and one of its components, fibrinogen, degrades rapidly when used to bond living tissues together.

Recently, a polyphenolic proteinaceous adhesive derived from molluscs has been developed. This adhesive is a two component system which is difficult to prepare consistently and produces widely varying adhesive characteristics.

Other surgical or medical adhesives have been reported in the patent literature. For instance, U.S. Patent No. 4,035,334 describes a medical adhesive comprised of two epoxy ethyl-alpha-cyanoacrylate, poly-N-vinyl ether and 1-4, bis (p-toluidino)-anthraquinone. While this medical adhesive is an improvement over prior cyanoacrylates, it does still require the use of diisocyanate chemistry to polymerize and thus still
presents potentially toxic chemistry to the tissue being joined. Furthermore, the polymerized material is not erodible and must be removed at some point in time. Furthermore, the materials which comprise this adhesive chemically bond to tissue which can damage the tissue.

Collagen materials have been widely considered useful in medical applications. For instance, U. S. Patent No. 4,760,131 describes a wound healing composition comprising fibrillar collagen, heparin and granulated platelets or platelet releaseate. However, this composition is meant to act as a wound dressing; it has no adhesive properties and cannot be considered a wound or incision closing agent. Reported medical adhesives include a chemically crosslinked gelatin which had been researched extensively in the mid to late 1960's. See, for instance, the October 1966 issue of Surgery, pages 857-861 entitled "The use of Cross-Linked Gelatins - a Tissue Adhesive to Control Hemorrhage from Liver and Kidney". It should be noted that this material was not intended close wounds.

Furthermore, the procedures reported use a gelatin-resorcinol mixture crosslinked with formaldehyde as the adhesive. The use of a medical material that includes or produces formaldehyde is unfeasible.

It is an object of the invention to provide a medical adhesive which allows for the closure of wounds or surgical incisions and allows for the augmentation or replacement of sutures. Furthermore, it is an object of this invention to provide an adhesive which will promote healing of the wound and will not cause localized stresses on the incision or wound. Further objects are to provide an adhesive which does not rapidly degrade in its adhesive strength, and does not set so rapidly that the tissues being joined cannot be
manipulated into their desired configuration and which does not require complex preparation just prior to its use. Furthermore, it is an object of the present invention to provide an adhesive which is permeable to nutrients essential to healing of the wound or incision.

**BRIEF DESCRIPTION OF THE FIGURES**

10. Figure 1 is a scanning electron microscope photograph of the cross-section of a rabbit cornea tissue sample bonded together with adhesive of the present invention.

15. Figure 2 is a scanning electron microscope photograph of the cross-section of a rabbit cornea tissue sample which had been bonded with a 12.5 weight percent collagen adhesive of the present invention after being pulled apart.

20. Figure 3 is the scanning electron microscope photograph of a cross section of a rabbit cornea tissue sample glued together with a 20 weight percent collagen solution.

**SUMMARY OF THE INVENTION**

25. The present invention relates to a medical adhesive which can be used as a material useful in closing wounds and/or surgical incisions. The composition consists essentially of an aqueous solution of collagen or gelatin that has: 1) a melt index in the range of 33°C to 60°C, and 2) a viscosity which allows the material, when heated above its melt index temperature to flow readily and be easily handled, and 3) adheres to tissues.
In general, one way these characteristics can be achieved is by controlling the crosslink density of the collagen/gelatin. The viscosity can be controlled to some degree by varying the concentration of the total amount of collagen or gelatin in the aqueous solution. Generally, this concentration is within the 5 to 30 weight percent range.

The present invention allows one to provide an adhesive composition with a set of characteristics which may uniquely be suited to a specific medical procedure since by blending crosslinked and noncrosslinked collagen or gelatin one can provide a material with a given viscosity, adhesiveness, melt index temperature, setting temperature and transparency.

**DETAILED DESCRIPTION OF THE INVENTION**

The invention is a medical adhesive useful in closing wounds or surgical incisions which consists essentially of an aqueous solution of naturally occurring collagen or purified gelatin wherein said solution has the following characteristics: 1) a melt index temperature within the range of 33°C to 60°C, preferably in the range of 35 to 45°C and most preferably 40 to 45°C, 2) a viscosity which allows the material when heated above its melt index temperature to flow readily, and 3) an ability to adhere to tissues. These characteristics are obtained by crosslinking natural collagen to a specified degree at a given concentration. Control of the degree of crosslinking can best be achieved by mixing a solution of crosslinked collagen or gelatin with a solution of a relatively noncrosslinked natural collagen or gelatin.
(collagen which has been extracted and purified but not undergone any processes which increased the crosslink density of the material) or gelatin.

Increasing the crosslink density of the collagen or gelatin can be achieved by a number of means. For instance, collagen or gelatin can have their crosslink densities increased by exposure to ultraviolet irradiation. They can also be crosslinked by thermal means. For instance, a collagen solution can be dried and then heated above 100°C to a defined temperature for a controlled length of time which will result in a specific crosslinked density. After this step, the crosslinked collagen is then put into solution where it exhibits the same characteristics as the non-crosslinked natural collagen solution with the exception that its melt index is higher than a non-crosslinked collagen and its viscosity above its melt index temperature is slightly higher.

Melt index temperature is defined for the purpose of this application to be the temperature mid-point at which a collagen or gelatin solution changes from being relatively nonflowable to flowable. In practical terms, one sees the solution go from a very thick nonflowable material to a liquid which flows quite readily (typically the viscosity of the solution goes from being immeasurable to less than 50,000 centipoise when the solution is heated ten degrees above its melt index temperature). This transition occurs over a relatively narrow temperature band (typically less than about 8 to 10 degrees Centigrade).

It is thought that this phenomenon with collagen solution occurs because as the solution temperature increases the internal hydrogen bonding of the triple helix of the collagen decreases and the molecule
unwinds. Thus, the collagen molecule loses much of its secondary structural characteristics and becomes more flowable. By increasing the covalent crosslinked density across the strands one can increase the triple helices integrity and raise its melt index.

The collagen material used in the present invention can be purified from any number of sources. However, it is preferred that the collagen material be Type I collagen. The preferred source of the collagen is porcine sclera. Gelatin likewise can be obtained from a number of sources.

A typical means of obtaining such materials is by treatment of the sclera of an animal eye. The eye is thoroughly cleaned of its internal coatings, the residual tissue is removed and the sclera is cleaned and isolated. The isolated sclera is then cut into small pieces, then rinsed with distilled water and transferred to a solution of alkaline hydroxide in a saturated sodium sulfate solution which digests the sclera typically for an extended period (typically 48 hours). The solution is then decanted, the tissues are washed with water and neutralized to within a range of 6.0 to 7.0 (typically with boric acid). The scleral tissue is then washed with diluted with water to remove the acid counter ion. The tissue is then put into a 0.5 to 1.0 molar solution of an organic acid and allowed to stand, under refrigeration, for up to 3 days. The solution is homogenized, centrifuged, allowed to stand for 1 further day at low temperature and then filtered to remove residual particulate matter. The sample is then dialyzed against a buffer system bringing the solution to a pH of 4.5 to 7.5.

The properties of the adhesive, i.e. its adhesiveness, viscosity, melt index temperature and
transparency can be controlled by means of controlling the crosslink density, concentration, and the tissue source of the adhesive. Thus one can according to the invention provide an adhesive with a specific set of characteristics for a given medical procedure.

One method for controlling the crosslink density of the adhesive is to blend solutions of densely crosslinked collagen or gelatin with a solution of noncrosslinked collagen or gelatin. Typically, the total collagen or gelatin content of the medical adhesive will be in the range of 5 to 35 weight percent of the solution total. The ratio of densely crosslinked material to relatively noncrosslinked material can vary from 10 to 1 to 1 to 1. Of course, it should be recognized as well that this ratio may rely upon the degree of crosslinked density in the densely crosslinked material.

The starting purified collagen solution material may be used as the relatively noncrosslinked collagen solution, although it may be crosslinked to a degree. The essential concept is to have two solutions with different crosslink densities in order to blend the two to produce the precise solution characteristics with respect to viscosity and melt index temperature.

It is also possible to obtain a medical adhesive of the present invention by controlling the degree of crosslinking of only one collagen or gelatin solution and using this solution as the medical adhesive. Presently, the most convenient approach is to blend collagen or gelatin solutions. In either case, it is critical to homogenize the final adhesive composition in order to insure that the melt index temperature will be consistent from one sample to the next.
The present invention is useful as a medical adhesive in a wide range of surgical procedures including many ophthalmic procedures such as cataract surgeries, epikeratophakia, corneal perforations, corneal transplants and other ophthalmic surgical procedures.

Specifically, it is believed the adhesive will be useful in cataract extraction. Recent trends in cataract surgery especially the trend to smaller and posterior incisions being used more posterior than previous practices appear to make the use of adhesive more advantageous. Such techniques provide incisions which are flap-like in form and require less compressive force to close. The adhesive could also be used intraocularly in complicated extracapsular cataract extractions where there has been a rent or rupture in the posterior capsule.

The adhesive will also be useful in corneal transplants. The standard method presently used employs up to sixteen individual sutures. The adhesive may reduce the degree of postoperative astigmatism and allow for more rapid visual rehabilitation by reducing the number of sutures.

Lamellar keratoplasty, which is a partial thickness corneal transplant performed for the treatment of specific eye diseases where a full thickness transplant is not indicated, can benefit from the use of the adhesive. Layering of the adhesive along the lamellar resection may allow for better wound closure than can be presently accomplished. The benefits of the adhesive outlined above will also be available in other surgical procedures such as retinopexy and ophthalmic plastic surgery.
The adhesive is used by first heating it to its melt index temperature so that it will readily flow. The material is then placed on the surface of the tissue planes to be adhered, and then the tissue is appropriately positioned. As the adhesive cools to body temperature it thickens into an effective adhesive.

In addition to acting as an adhesive, the material may also be employed to deliver pharmacological agents. Pharmacological agents may be incorporated into the formulation in order to help control the rate of healing at the wound site. For instance, growth factors could be added to the adhesive to accelerate healing. Alternately, factors such as cortistearoids or antimetabolites could be added to slow wound healing. Antibiotics may be added to the adhesive as well. The use the adhesive in conjunction with pharmacological agents allows one to deliver to the precise wound site the pharmacologic agent. One can thus use a smaller amount of pharmacologic.

The adhesives of the present invention may also contain other biological polymers in small amounts. Such biological polymers may include glycosaminoglycans such as chondroitins, hyaluronic acid and keratin sulfate, or synthetic analogs such as dextrans.

The following examples illustrate the invention in certain aspects but do not fully delineate the scope of the invention.

30 Example 1

A 10 weight percent solution was prepared from a porcine scleral collagen. A portion of the solution was dried and heated to 145°C for 60 minutes to produce
densely crosslinked material. A second portion was similarly treated for 15 minutes at 145°C, and served as a relatively non-crosslinked sample.

A mixture comprising 5 weight percent of the 5 relatively non-crosslinked material and 95 weight percent of the densely crosslinked material was made and diluted to various total solids concentrations (12.5 weight percent, 15 weight percent, 20 weight percent and 30 weight percent collagen).

Freshly harvested rabbit corneal tissue was cut into standard size samples (about 5mm x 10mm) which were then bonded using the adhesive compositions which had been heated to more than about 38°C to 45°C and then allowed to cool. The bonding strength of the samples, in grams, was measured at specified periods after the tissue samples were initially joined with the adhesive. The following results were achieved as shown in Table I. The results are reported in grams per standard area of sample.

**TABLE I**

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<th>wt% solids</th>
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**Example 2**

The 12.5 wt% total solids medical adhesive as described in Example 1 was used to adhere rabbit
corneal tissue samples together. Scanning electron microscopy was used to take pictures of the samples in various stages of testing the adhesive capacity of the glue. Figure 1 shows the tissue samples 1, 3 glued together with the adhesive of the present invention, 2.

The samples glued together with 15 wt% collagen adhesive showed little disruption of the tissues being bonded, indicating that the strength of the tissues exceeded the strength of the adhesive bond. Samples adhered with the 20 wt% collagen adhesive displayed significant damage to the tissue upon adhesive failure of the sample.

Figures 2 and 3 show the SEM of the failed samples using 12.5 wt% and 20 wt% collagen, respectively. Figure 2 shows that the point of adhesive failure was in the adhesive layer 4 and that the tissue 5 showed very little disruption. The degree of magnification in Figures 2 and 3 is greater than that used to generate Figure 1.

Figure 3 shows that when a 20 weight percent collagen adhesive was used the point of adhesive failure 8 was within the tissue sample, 4, 6. These results indicate that with the 20 wt% collagen adhesive the strength of the adhesive bond was greater than the strength of the tissue.

From these results, it is clear that the strength of the adhesive can be designed for a particular medical application.

Example 3

A dried collagen film fabricated from a 1% weight solution of porcine scleral collagen as described in Example 1 was cut into small pieces and used to prepare
a 10% collagen weight solution in distilled water by heating at 60°C for 60 minutes with stirring. The solution was cast and dried, and the resulting film was heated at 145°C for 80 minutes to induce crosslinking. The crosslinked film was then ground to a coarse powder and used to prepare a 27% dry weight solution by heating to 65°C and homogenizing with a tissue grinder. The molten solution was then deaerated by centrifugation and loaded into 1 cc syringes while being maintained above its melt temperature. Once in the syringes, the adhesive cools to form a solid which may be reheated and used as a surgical adhesive.

Example 4

The adhesive loaded syringe prepared in Example 3 is heated to 50°C for 30 minutes in a water bath. The adhesive is then used to seal a posterior incision from a cataract extraction which was made under a flap of scleral tissue. The molten adhesive is extruded onto the incision site and the flap is brought over to cover the adhesive and incision. The flap placement is further manipulated with forceps until the adhesive cools to its solidification or set temperature below its melt index temperature.

Example 5

Commercial 300 bloom gelatin derived from pigskin is added to distilled water in the amount of 10% based on total weight of water and gelatin. It is heated 60°C with stirring to produce a solution which is then cast and dried. The resulting film is then heated to 145°C for 80 minutes to induce crosslinking and the
film is cooled and ground to a coarse powder. The crosslinked gelatin powder is used to prepare a 30% gelatin weight solution in distilled water by heating to 65°C with stirring. The resulting solution is deaerated and loaded into syringes as described in Example 4 to be used as a surgical adhesive. Two methods are utilized to produce a final sterile bioadhesive product. Both processes are performed using a series of aseptic steps to preclude any introduction of viable organisms to sterile product components. The first method is tyndallization. After the bioadhesive formulation is made by reconstituting the 145°C heat crosslinked powder using sterile filtered water, it is then loaded into sterile syringes and packaged in peel pouches. All steps are performed under aseptic conditions in a laminar flow hood with properly gloved and gownned personnel. This is a fractional method of sterilization involving exposure of the final product to moist 80°C - 100°C heat for 30 minutes for three consecutive days.

COMPARATIVE EXAMPLE

Tissue samples were bonded together according to the method used in Example 1 using an adhesive made according to the present invention which had a solids content of 20 weight percent and a melt index temperature of 35°C. The adhesive was heated to about 50°C, applied to the surfaces of the tissue to be bonded and the tissue samples were then placed together. Samples were also bonded together using Tisseel® according to the directions indicated by the manufacturer. The samples were then tested for their adhesive bonding strength by applying weight to the
samples in a fashion to create shear across the bonded area. The bond strength was taken as the weight required to cause failure in the sample. The bonding strength of the samples in grams was measured at 5 specified times from preparation. The results are reported in Table 2.

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As can be appreciated from the results, the adhesive strength of the adhesive is significantly higher than the commercially available Tisseel® medical adhesive.
What is claimed is:

1. An adhesive composition suited for surgical applications which consists essentially of:

   an aqueous solution of a biological polymer chosen from the group of biological polymers consisting of collagen and gelatin which has a melt index temperature within the range of 33°C to 60°C.

2. The adhesive composition of Claim 1 which has a viscosity less than 50,000 centipoise ten degrees above its melt index temperature.

3. The adhesive composition of Claim 1 wherein the melt index temperature of the aqueous solution is in the range of 35°C to 45°C.

4. The adhesive of Claim 1 wherein the critical melt index temperature characteristics of said composition are achieved by mixing blends of densely crosslinked biopolymers and noncrosslinked biopolymers.

5. The adhesive of Claim 4 wherein the densely crosslinked biopolymers is achieved by thermal crosslinking means.
6. The adhesive of Claim 4 wherein the non-crosslinked biopolymers comprises 50 weight percent of the total solids content of the composition.

7. The adhesive of Claim 4 wherein the non-crosslinked biopolymers comprises 25 weight percent of the total solids content of the composition.

8. The adhesive of Claim 4 wherein the non-crosslinked biopolymers comprises 20 weight percent of the total solids content of the composition.

9. The adhesive of Claim 4 wherein the non-crosslinked biopolymers comprises 15 weight percent of the total solids content of the composition.

10. The adhesive of Claim 4 wherein the non-crosslinked biopolymers comprises 5 weight percent of the total solids content of the composition.

11. The adhesive of Claim 1 wherein the critical melt index temperature characteristics are achieved by blending densely crosslinked gelatin with relatively non-crosslinked gelatin.

12. The adhesive composition of Claim 1 wherein the total biopolymers content of the solution is in the range of 5-30 weight percent.
13. The adhesive composition of Claim 1 wherein the total biopolymers content of the solution is in the range of 20 to 30 weight percent.

14. A method for closing wounds comprising the step of contacting at least one surface of a wound with an adhesive composition which is an aqueous solution consisting essentially of a biopolymer chosen from purified, naturally occurring collagen and gelatin and water wherein said solution has a melt index temperature between 35°C and 45°C, and a viscosity when heated 10 degrees above its melt index temperature of less than 50,000 centipoise.

15. A method for promoting healing of wounds which consists of contacting at least one surface of a wound with a composition which consists essentially of a solution of naturally occurring biopolymer collagen in water with cultured epithelium cells dispersed throughout said solution, wherein said composition has a melt index between 35°C and 45°C, and a viscosity, when heated 10 degrees above said melt index temperature of less than 50,000 centipoise.
16. A method for promoting healing of wounds comprising the step of contacting at least one surface of a wound with a composition which is an aqueous solution consisting essentially of purified, naturally occurring biopolymer, water, and growth factors, wherein said solution has a melt index between 35°C and 45°C, and a viscosity when heated ten degrees above its melt index temperature of less than 50,000 centipoise.
AMENDED CLAIMS

[received by the International Bureau on 3 June 1992 (03.06.92); original claims 1-16 replaced by amended claims 1-34 (6 pages)]

1. An adhesive composition suited for surgical applications which comprises:

   an aqueous solution of a biological polymer chosen from the group of biological polymers comprising collagen and gelatin which has a melt index temperature within the range of 33°C to 60°C.

2. The adhesive composition of Claim 1 which has a viscosity less than 50,000 centipoise ten degrees above its melt index temperature.

3. The adhesive composition of Claim 1 wherein the melt index temperature of the aqueous solution is in the range of 35°C to 45°C.

4. The adhesive of Claim 1 wherein the critical melt index temperature characteristics of said composition are achieved by mixing blends of densely crosslinked biopolymers and noncrosslinked biopolymers.

5. The adhesive of Claim 4 wherein the densely crosslinked biopolymers is achieved by thermal crosslinking means.

6. The adhesive of Claim 4 wherein the non-crosslinked biopolymers comprises 50 weight percent of the total solids content of the composition.

7. The adhesive of Claim 4 wherein the non-crosslinked biopolymers comprises 25 weight percent of the total solids content of the composition.
8. The adhesive of Claim 4 wherein the non-crosslinked biopolymers comprises 20 weight percent of the total solids content of the composition.

9. The adhesive of Claim 4 wherein the non-crosslinked biopolymers comprises 15 weight percent of the total solids content of the composition.

10. The adhesive of Claim 4 wherein the non-crosslinked biopolymers comprises 5 weight percent of the total solids content of the composition.

11. The adhesive of Claim 1 wherein the critical melt index temperature characteristics are achieved by blending densely crosslinked gelatin with relatively non-crosslinked gelatin.

12. The adhesive composition of Claim 1 wherein the total biopolymers content of the solution is in the range of 5-30 weight percent.

13. The adhesive composition of Claim 1 wherein the total biopolymers content of the solution is in the range of 20 to 30 weight percent.

14. A method for closing wounds comprising the step of contacting at least one surface of a wound with an adhesive composition which is an aqueous solution comprising a biopolymer chosen from purified, naturally occurring collagen and gelatin and water wherein said solution has a melt index temperature between 33°C and 60°C, and a viscosity when heated 10 degrees above its melt index temperature of less than 50,000 centipoise.
15. A method for promoting healing of wounds which comprises contacting at least one surface of a wound with a composition which comprises a solution of naturally occurring biopolymer collagen in water with cultured epithelial cells dispersed throughout said solution, wherein said composition has a melt index between 33°C and 60°C, and a viscosity, when heated 10 degrees above said melt index temperature of less than 50,000 centipoise.

16. A method for promoting healing of wounds comprising the step of contacting at least one surface of a wound with a composition which is an aqueous solution comprising purified, naturally occurring biopolymer, water, and growth factors, wherein said solution has a melt index between 33°C and 60°C, and a viscosity when heated ten degrees above its melt index temperature of less than 50,000 centipoise.

17. An adhesive composition suited for surgical applications which comprises:

an aqueous solution of a biological polymer chosen from the group of biological polymers comprising collagen and gelatin which has a melt index temperature within the range of 33°C to 60°C, and which contains at least one pharmacological agent.

18. The adhesive composition of Claim 17 which has a viscosity less than 50,000 centipoise ten degrees above its melt index temperature.

19. The adhesive composition of Claim 17 wherein the melt index temperature of the aqueous solution is in the range of 35°C to 45°C.
20. The adhesive of Claim 17 wherein the critical melt index temperature characteristics of said composition are achieved by mixing blends of densely crosslinked biopolymers and noncrosslinked biopolymers.

21. The adhesive of Claim 20 wherein the densely crosslinked biopolymers is achieved by thermal crosslinking means.

22. The adhesive of Claim 20 wherein the non-crosslinked biopolymers comprises 50 weight percent of the total solids content of the composition.

23. The adhesive of Claim 20 wherein the non-crosslinked biopolymers comprises 25 weight percent of the total solids content of the composition.

24. The adhesive of Claim 20 wherein the non-crosslinked biopolymers comprises 20 weight percent of the total solids content of the composition.

25. The adhesive of Claim 20 wherein the non-crosslinked biopolymers comprises 15 weight percent of the total solids content of the composition.

26. The adhesive of Claim 20 wherein the non-crosslinked biopolymers comprises 5 weight percent of the total solids content of the composition.

27. The adhesive of Claim 17 wherein the critical melt index temperature characteristics are achieved by blending densely crosslinked gelatin with relatively non-crosslinked gelatin.
28. The adhesive composition of Claim 17 wherein the total biopolymers content of the solution is in the range of 5-30 weight percent.

29. The adhesive composition of Claim 17 wherein the total biopolymers content of the solution is in the range of 20 to 30 weight percent.

30. A method for closing wounds comprising the step of contacting at least one surface of a wound with an adhesive composition which is an aqueous solution comprising a biopolymer chosen from purified, naturally occurring collagen and gelatin and water wherein said solution has a melt index temperature between 33°C and 60°C, and a viscosity when heated 10 degrees above its melt index temperature of less than 50,000 centipoise, and which contains at least one pharmacological agent.

31. A method for promoting healing of wounds which comprises contacting at least one surface of a wound with a composition which comprises a solution of naturally occurring biopolymer collagen in water with cultured epithelial cells dispersed throughout said solution, wherein said composition has a melt index between 33°C and 60°C, and a viscosity, when heated 10 degrees above said melt index temperature of less than 50,000 centipoise, and which contains at least one pharmacological agent.

32. A method for promoting healing of wounds comprising the step of contacting at least one surface of a wound with a composition which is an aqueous solution comprising purified, naturally occurring biopolymer, water, and growth factors, wherein said solution has a melt index between 33°C and 60°C, and a viscosity when heated ten degrees
above its melt index temperature of less than 50,000
centipoise, and which contains at least one pharmacological
agent.

33. An adhesive composition according to Claim 17,
wherein said pharmacological agent helps control the rate of
healing at a wound site.

34. An adhesive composition according to Claim 17,
wherein said pharmacological agent is an antibiotic.
INTERNATIONAL SEARCH REPORT

I. CLASSIFICATION OF SUBJECT MATTER

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.C1.5   A 61 L 25/00

II. FIELDS SEARCHED

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Documentation searched other than minimum documentation

to the extent that such documents are included in the fields searched

III. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>EP.A,0330344 (CEDARS-SINAI MEDICAL CENTER) 30 August 1989, see column 6, lines 3-6; column 7, lines 28-30</td>
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<td>A</td>
<td>DE.A,3146841 (BEIERSDORF) 1 June 1983, see claim 1</td>
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* "&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search: 24-03-1992

Date of Mailing of this International Search Report: 11.05.92

International Searching Authority: EUROPEAN PATENT OFFICE

Signature of Authorized Officer: [Signature]

Mme Dagmar FRANK
ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO. US 9109638
SA 56461

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For more details about this annex: see Official Journal of the European Patent Office, No. 12/82.