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(54) Benævnelse: **Absorberbar hæmostatisk plaster**

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Description

[0001] The present invention relates to a method of making a reinforced absorbable multilayered hemostatic wound dressing.

[0002] The control of bleeding, as well as sealing of air and various bodily fluids, is essential and critical in surgical procedures to minimize blood loss, to seal tissue and organ structures, to reduce post-surgical complications, and to shorten the duration of the surgery in the operating room.

[0003] In an effort to provide dressings with enhanced hemostatic and tissue sealing and adhering properties, therapeutic agents, including, but not limited to, thrombin, fibrin and fibrinogen have been combined with dressing carriers or substrates, including gelatin-based carriers, polysaccharide-based carriers, glycolic acid or lactic acid-based carriers and a collagen matrix. Examples of such dressings are disclosed in USP 6,762,336, USP 6,733,774 and PCT publication WO 2004/064878 Al.

[0004] Due to its biodegradability and its bactericidal, tissue sealing, tissue repairing, drug delivering and hemostatic properties, it is desirable to utilize cellulose that has been oxidized to contain carboxylic acid moieties, hereinafter referred to as carboxylic-oxidized cellulose, as a topical dressing in a variety of surgical procedures, including neurosurgery, abdominal surgery, cardiovascular surgery, thoracic surgery, head and neck surgery, pelvic surgery and skin and subcutaneous tissue procedures.

[0005] However, when carboxylic-oxidized cellulose is utilized in combination with thrombin and fibrinogen, the acidic moieties that may be present in the cellulose denature the activity of the thrombin and fibrinogen. Therefore, it is desirable to shield the thrombin and fibrinogen from such acid moieties to maintain their hemostatic activities.

[0006] EP-A-0059265 describes a hemostat prepared by coating a collagen carrier with a mixture of fibrinogen and thrombin. The coating may be carried out by dispersing particles of fibrinogen and thrombin in a non-aqueous solvent and coating the dispersion onto the collagen carrier, followed by evaporation of the solvent.

[0007] As used herein, the term "nonwoven fabric" includes, but is not limited to, bonded fabrics, formed fabrics, or engineered fabrics, that are manufactured by processes other than spinning, weaving or knitting. More specifically, the term "nonwoven fabric" refers to a porous, textile-like material, usually in flat sheet form, composed primarily or entirely of staple fibers assembled in a web, sheet or batt. The structure of the nonwoven fabric is based on the arrangement of, for example, staple fibers that are typically arranged more or less randomly. The tensile, stress-strain and tactile properties of the nonwoven fabric ordinarily stem from fiber to fiber friction created by entanglement and reinforcement of, for example, staple fibers, and/or from adhesive, chemical or physical bonding. Notwithstanding, the raw materials used to manufacture the nonwoven fabric may be yarns, scrims, netting, or filaments made by processes that include spinning, weaving or knitting.

[0008] The present invention is directed to a method of making a multi-layered wound dressing, said wound dressing comprising: a first absorbable nonwoven fabric comprising fibers comprised of aliphatic polyester polymers or copolymers of one or more monomers selected from the group consisting of lactic acid, lactide (including L-, D-, meso and D, L mixtures), glycolic acid, glycolide, ε-caprolactone, p-dioxanone, and trimethylene carbonate; and a second absorbable woven or knitted fabric attached to said first absorbable nonwoven fabric, said second absorbable woven or knitted fabric comprising oxidized cellulose, the method comprising: suspending thrombin and fibrinogen powders together in a perfluorinated hydrocarbon carrier fluid in which they are not soluble, and applying the resulting suspension to the first absorbable nonwoven fabric.

[0009] The figure shows the pressure required to disrupt/burst the seal formed between the tissue and hemostatic wound dressings made in accordance with the invention.

[0010] The multilayered dressings obtainable by the methods described herein provide and maintain effective hemostasis when applied to a wound requiring hemostasis. Effective hemostasis, as used herein, is the ability to control and/or abate capillary, venous, or arteriole bleeding within an effective time, as recognized by those skilled in the art of hemostasis. Further indications of effective hemostasis may be provided by governmental regulatory standards and the like.

[0011] In certain embodiments, multilayered dressings obtainable by the present invention are effective in providing and maintaining hemostasis in cases of severe or brisk bleeding. As used herein, severe bleeding is meant to include those cases of bleeding where a relatively high volume of blood is lost at a relatively high rate. Examples of severe bleeding include, without limitation, bleeding due to arterial puncture, liver resection, blunt liver trauma, blunt spleen trauma, aortic aneurysm, bleeding from patients with over-anticoagulation, or bleeding from patients with coagulopathies, such as hemophilia.

[0012] The reinforced absorbable multilayered dressing comprises a nonwoven fabric and a reinforcement fabric. The reinforcement fabric provides a backing to which the nonwoven fabric may be attached, either directly or indirectly, wherein thrombin and fibrinogen are substantially homogeneously dispersed throughout the nonwoven fabric and/or are disposed on the surface of the nonwoven fabric. The reinforcement fabric provides strength to the dressing sufficient to permit the user of the dressing to place and manipulate the dressing on or within a wound or directly onto tissue of a patient requiring hemostasis, or tissue sealing and adhering.

[0013] In addition to serving as a carrier for the thrombin and fibrinogen, the nonwoven fabric also serves to shield the thrombin and fibrinogen from acidic moieties present in the carboxylic-oxidized cellulose used as the reinforcement fabric.

[0014] The nonwoven fabric functions as the first absorbable nonwoven fabric of the reinforced absorbable multilayered dressing described herein. The first absorbable nonwoven fabric is comprised of fibers comprising aliphatic polyester polymers, copolymers, or blends thereof synthesized in a ring opening polymerization of monomers selected from lactic acid, lactide (including L-, D-, meso and D, L mixtures), glycolic acid, glycolide, ε-caprolactone, p-dioxanone (1,4-dioxan-2- one), and trimethylene carbonate (1,3-dioxan-2-one).

[0015] Preferably, the first absorbable nonwoven fabric comprises a copolymer of glycolide and lactide, in an amount ranging from 70 to 95% by molar basis of glycolide and the remainder lactide.

[0016] Preferably, the nonwoven fabric is made by processes other than spinning, weaving or knitting. For example, the nonwoven fabric may be prepared from yarn, scrims, netting or filaments that have been made by processes that include spinning, weaving or knitting. The yarn, scrims, netting and/or filaments are crimped to enhance entanglement with each other and attachment to the second absorbable woven or knitted fabric. Such crimped yarn, scrims, netting and/or filaments may then be cut into staple that is long enough to entangle. The staple may be between 2-5 and 63 mm (0.1 and 2.5 inches) long, preferably between 13 and 44 mm (0.5 and 1.75 inches), and most preferably between 25 and 33 mm (1.0 and 1.3 inches). The staple may be carded to create a nonwoven batt, which may be then needlepunched or calendared into the first absorbable nonwoven fabric. Additionally, the staple may be kinked or piled.

[0017] Other methods known for the production of nonwoven fabrics may be utilized and include such processes as air laying, wet forming and stitch bonding. Such procedures are generally discussed in the Encyclopedia of Polymer Science and Engineering, Vol. 10, pp. 204-253 (1987) and Introduction to Nonwovens by Albin Turbank (Tappi Press, Atlanta GA 1999).

[0018] The thickness of the nonwoven fabric may range from 0.25 to 2 mm. The basis weight of the nonwoven fabric ranges from 16 to 310 g/m^2 (0.01 to 0.2 g/in^2), preferably from 47 to 155 g/m^2 (0.03 to 0.1 g/in^2), and most preferably from 62 to 124 g/m^2 (0.04 to 0.08 g/in^2). The weight percent of first absorbable nonwoven fabric may range from about 5 to 50 percent, based upon the total weight of the reinforced absorbable multilayered dressing having thrombin and fibrinogen.

[0019] The second absorbable woven or knitted fabric functions as the reinforcement fabric and comprises oxidized cellulose. For example, the cellulose may be carboxylic-oxidized or aldehyde-oxidized cellulose. Preferably, oxidized regenerated cellulose may be used to prepare the second absorbable woven or knitted fabric. Regenerated cellulose is preferred due to its higher degree of uniformity versus cellulose that has not been regenerated. Regenerated cellulose and a detailed description of how to make oxidized regenerated cellulose are set forth in USP 3,364,200, USP 5,180,398 and USP 4,626,253.

[0020] Examples of fabrics that may be utilized as the reinforcement fabric include, but are not limited to, Interceed® absorbable adhesion barrier, Surgicel® absorbable hemostat; Surgicel Nu-Knit® absorbable hemostat; and Surgicel® Fibrillar absorbable hemostat; each available from Johnson & Johnson Wound Management Worldwide or Gynecare Worldwide, each a division of Ethicon, Inc., Somerville, New Jersey.

[0021] The reinforcement fabric utilized in the present invention may be woven or knitted, provided that the fabric possesses the physical properties necessary for use in contemplated applications. Such fabrics, for example, are described in USP 4,626,253, USP 5,002,551 and USP 5,007,916. In preferred embodiments, the reinforcement fabric is a warp knitted tricot fabric constructed of bright rayon yarn that is subsequently oxidized to include carboxyl or aldehyde moieties in amounts effective to provide the fabrics with biodegradability.

[0022] In an alternative embodiment, the reinforcement fabric comprises oxidized cellulose fibers in combination with fibers comprised of aliphatic polyester polymers, copolymers, or blends thereof.

[0023] The second absorbable woven or knitted fabric preferably comprises oxidized regenerated cellulose and may have a basis weight ranging from 1.6 to 310 g/m^2 (0.001 to 0.2 g/in^2), preferably in the range of 16 to 155 g/m^2 (0.01 to 0.1 g/in^2), and most preferably in the range of 62 to 109 g/m^2 (0.04 to 0.07 g/in^2).

[0024] The first absorbable nonwoven fabric is attached to the second absorbable woven or knitted fabric, either directly or indirectly. For example, the nonwoven fabric may be incorporated into the second absorbable woven or knitted fabric via needlepunching, calendaring, embossing or hydroentanglement, or chemical or thermal bonding. The staple of the first absorbable nonwoven fabric may be entangled with each other and imbedded in the second absorbable woven or knitted fabric. More particularly, for methods other than chemical or thermal bonding, the first absorbable nonwoven fabric may be attached to the second absorbable woven or knitted fabric such that at least about 1% of the staple of the first absorbable nonwoven fabric are exposed on the other side of the second absorbable woven or knitted fabric, preferably about 10-20% and preferably no greater than about 50%. This ensures that the first absorbable nonwoven fabric and the second absorbable woven or knitted fabric remain joined and do not delaminate under normal handling conditions. The reinforced absorbable multilayered fabric is uniform such that substantially none of the second absorbable woven or knitted fabric is visibly devoid of coverage by the first absorbabale nonwoven fabric.

[0025] One method of making the multilayered fabric described herein is by the following process. Absorbable polymer fibers, having a dtex (denier) per fiber of 1.1 to 4.4 (1 to 4), may be consolidated to 88 to 132 dtex (80 to 120 denier) multifilament yarn and then to 880 to 1320 dtex (800 to 1200 denier) yarns, thermally crimped and then cut to a staple having a length between 19 and 38 mm (0.75 and 1.5 inch). The staple may be fed into a multiroller dry lay carding machine one or more times and carded into a uniform nonwoven batt, while humidity is controlled between about 40-60% at a room temperature of 60 to 75°C. For example, the uniform nonwoven batt may be made using a single cylinder roller-top card, having a main cylinder covered by alternate rollers and stripper rolls, where the batt is doffed from the surface of the cylinder by a doffer roller and deposited on a collector roll. The batt may be further processed via needlepunching or any other means such as calendaring. Thereafter, the first absorbable nonwoven fabric may be attached to the second absorbable woven or knitted fabric by various techniques such as needlepunching. The reinforced absorbable multilayered fabric may then be scoured by washing in an appropriate solvent and dried under mild conditions for approximately 30 minutes.

[0026] It is desirable to control process parameters such as staple length, opening of the staple, staple feed rate, and relative humidity. For example, the consolidated yarns may have from 2 to 20 crimps per cm (5 to 50 crimps per inch) and preferably from 4 to 12 crimps per cm (10 to 30 crimps per inch). Efficient cutting of the crimped yarns is desirable, as any long and incompletely cut staple tends to stick on the carding machine and cause pilling. A preferred range of the staple length is from 19 to 38 mm (0.75 to 1.5 inches), and preferably from 25 to 33 mm (1.0 to 1.3 inches).

[0027] To optimize uniformity and minimize the build-up of static electricity, the relative humidity may be controlled during batt processing, preferably during carding to form the uniform nonwoven batt. Preferably, the nonwoven batt is processed using a dry lay carding process at a relative humidity of at least 40% at a room temperature of 60 to 75°C. More preferably, the nonwoven batt is processed at a relative humidity of from 50% to 60%.

[0028] The multilayered fabric is scoured using solvents suitable to dissolve any spin finish. Solvents include, but are not limited to, isopropyl alcohol, hexane, ethyl acetate, and methylene chloride. The multilayered fabric is then dried under conditions to provide sufficient drying while minimizing shrinkage.

[0029] The reinforced absorbable multilayered fabric may have an average thickness of between 0.75 and 3.0 mm, preferably between 1.00 and 2.5 mm, and most preferably between 1.2 and 2.0 mm. The basis weight of the reinforced absorbable multilayered fabric is between 78 and 388 g/m^2 (0.05 and 0.25 g/in^2), preferably between 124 and 310 g/m^2 (0.08 and 0.2 g/in^2), and most preferably between 155 and 280 g/m^2 (0.1 and 0.18 g/in^2). The reinforced absorbable multilayered fabric is uniform such that there is no more than about 10% variation (relative standard deviation of the mean) in the basis weight or thickness across each square inch.

[0030] The thrombin and fibrinogen may be animal derived, preferably human, or may be recombinant. The thrombin activity on the multilayered dressing may be in the range of about 20 to 500 IU/cm^2, preferably about 20 to 200 IU/cm^2, and most preferably about 50 to 200 IU/cm^2. The fibrinogen activity on the multilayered dressing may be in the range of about 2 to 15 mg/cm^2, preferably about 3 to 10 mg/cm^2, and most preferably about 4 to 7 mg/cm^2.

[0031] The basis weight of the multilayered dressing having the thrombin and fibrinogen powders is between 155 and 1550 g/m^2 (0.1 and 1.0 g/in^2) preferably between 155 and 775 g/m^2 (0.1 and 0.5 g/in^2), and most preferably between 155 and 465 g/m^2 (0.1 and 0.3 g/in^2). The multilayered dressing having the thrombin and fibrinogen may be sterilized, for example, by radiation, preferably by electron beam radiation.

[0032] The air porosity of the multilayered dressing having the thrombin and fibrinogen powders ranges from about 50-250 cm^3/sec/cm^2, preferably between 50-150 cm^3/sec/cm^2, and most preferably 50-100 cm^3/sec/cm^2.

[0033] When the reinforced absorbable multilayered dressing is used internally, about 50 to 75% of its mass is absorbed after about 2 weeks. The percent of mass loss may be measured by using a rat implantation model. Here the dressing is inserted into the rat by first making a midline incision (approximately 4 cm) in the skin over the lumbosacral vertebral column of a rat. The skin is then separated from the underlying connective tissue, bilaterally, to expose the superficial gluteal muscles. An incision is then made in the dorso-lateral fascia, which is located above the gluteal muscles and directly adjacent to the vertebral column. Using blunt dissection, a small pocket is created between the fascia and the gluteal muscle lateral to the incision. The multilayered dressing is placed in the gluteal pocket. The fascia is then sutured in place. After two weeks, the rat is euthenized and the multilayered dressing is explanted to determine the percent mass loss over the two week period.

[0034] The first absorbable nonwoven fabric retains solid thrombin and solid fibrinogen powder without separation and with minimal loss of the powder from its surface. Thrombin and fibrinogen containing solutions are separately lyophilized. The lyophilized materials are then ground into powders using a superfine mill or a cooled blade mill. The powders are weighed and suspended together in a carrier fluid in which the proteins are not soluble. The carrier fluid is a perfluorinated hydrocarbon, including but not limited to HFE 7000, HFE 7001 HFE 7003 and PF50/60 (commercially available from 3M of Minnesota). The suspension is thoroughly mixed and applied to the first absorbable nonwoven fabric via conventional means such as wet, dry or electrostatic spraying, dip coating, painting, or sprinkling, while maintaining a room temperature of 16 to 24°C (60 to 75 degrees F) and relative humidity of 10 to 45%. The multilayered dressing is then dried at ambient room temperature and packaged in a suitable moisture barrier container. The multilayered dressing having the thrombin and fibrinogen contains no more than 25% moisture, preferably no more than 15% moisture, and most preferably no more than 5% moisture.

[0035] The amount of thrombin and fibrinogen powder applied to the nonwoven fabric is sufficient to cover its surface such that no area is visibly devoid of coverage. The powder may sit mostly on top of the nonwoven fabric or may penetrate into the nonwoven fabric as far as the surface of the second absorbable woven or knitted fabric. However, the bulk of the powder does not contact the second absorbable woven or knitted fabric, and no more than trace amounts of the powders penetrate to the underside of the second absorbable woven or knitted fabric.

[0036] As a surgical dressing, the multilayered dressing described herein may be used as an adjunct to primary wound closure devices, such as arterial closure devices, staples, and sutures, to seal potential leaks of gasses, liquids, or solids as well as to provide hemostasis. For example, the multilayered dressing may be utilized to seal air from tissue or fluids from organs and tissues, including but not limited to, bile, lymph, cerebrospinal fluids, gastrointestinal fluids, interstitial fluids and urine.

[0037] The multilayered dressing described herein has additional medical applications and may be used for a variety of clinical functions, including but not limited to tissue reienforcement and buttressing, i.e., for gastrointestinal or vascular anastomoses, approximation, i.e., to connect anastomoses that are difficult to perform (i.e. under tension), and tension releasing. The dressing may additionally promote and possibly enhance the natural tissue healing process in all the above events. This dressing can be used internally in many types of surgery, including, but not limited to, cardiovascular, peripheral-vascular, cardio-thoracic, gynecological, neuro- and general surgery. The dressing may also be used to attach medical devices (e.g. meshes, clips and films) to tissues, tissue to tissue, or medical device to medical device.

Example 1.

[0038] Poly (glycolide-co-lactide) (PGL, 90/10 mol/mol) was melt-spun into fiber. A 80 denier multifilament yarn was consolidated into a 880 dtex (800 denier) consolidated yarn. The consolidated yarn was crimped at approximately 110 degree C. The crimped yarn was cut into staple having a length of about 32 mm (1.25") in length. 20 g of the crimped staple was accurately weighed and laid out uniformly on the feed conveyor belt of a multi-roller carding machine. The environmental conditions (21°C (70°F)/55% RH) were controlled. The staple was then carded to create a nonwoven batt. The batt was removed from the pick-up roller and cut into 4 equal parts. These were re-fed into the carder perpendicular to the collection direction. After this second pass the batt was weighed (19.8 g: 99% fabric yield) and then compacted into a felt. The compact felt was precisely laid onto an ORC fabric and firmly attached via 2 passes in the needlepunching equipment. The multilayered fabric was trimmed and scoured in 3 discrete isopropyl alcohol baths to remove spin finish and any machine oils. The scoured multilayered fabric was dried in an oven at 70 degree C for 30 minutes, cooled and weighed.

[0039] 18.93 g of BAC-2 [(Omrix Biopharmaceuticals, Inc.) specific activity (by Clauss) 0.3g/g] and 1.89 g of thrombin were mixed thoroughly with about 420 ml of HFE7000. The slurry was sprayed through a nozzle onto the multilayered fabric weighing about 12g and sized to 20 cm x 30 cm (8" x 12"). The multilayered hemostatic wound dressing was air dried for about 30 minutes. The environmental conditions were maintained at 24°C (75°F)/55% RH throughout the process. The multilayered hemostatic wound dressing was cut into appropriate sizes and packed in a tray. The tray is specifically designed such that the clearance between the top and the bottom of the tray is slightly less than the overall thickness of the dressing to ensure minimized motion of the dressing during shipping and handling. The tray is further packaged in a foil pouch, which is thermally sealed with dessicants as needed. The dressing was stored at 2-8 degrees C until needed.

[0040] The "thickness" of the multilayered fabric/dressing was measured as described herein. The measurement tools were:

(1) Mitutoyo Absolute gauge Model number ID-C125EB [Code number-- 543-452B]. The 2-5 cm (1") diameter foot was used on the gauge.

(2) A magnetic holder was used to lock in place and set the caliper up to the die platen.

(3) Two metal plates ~7 cm x 5 cm x 1.5 cm (2.75" x 2" x 0.60"), weighing between 40.8g to 41.5g [combined total of ~82.18g].

[0041] The multilayered fabric/dressing was placed on a platen surface that is a smooth and machined surface. The two metal plates were placed on top of each other on the multilayered fabric/dressing and gently pressed at their corners to make sure the multilayered fabric/dressing is flat. The gauge foot was placed onto the top of the metal plates and was then re-lifted and re-placed, at which time a reading was made.

Example 2

[0042] In general, anesthetized pigs were dissected to expose the abdominal aorta. A biopsy punch was used to remove a 4 mm section of the aorta. The blood was allowed to flow freely, and the dressing to be tested was quickly applied to the wound site while aspirating any excessive pooling blood. Manual pressure was applied to hold the dressing to the wound site for 3 minutes. At the end of the three-minute period, pressure was removed. The test was considered a "pass" if the dressing adhered well to the wound and achieved full hemostasis with no rebleeding.

Sample ID	Thrombin Activity (IU/cm^2)	Fibrinogen Activity (mg/cm^2)	Hemostatic Performance-Porcine Aortic Punch
1	~50	4.86	Pass
2	~50	6.23	Pass
3	~50	5.36	Pass
4	~50	5.49	Pass
5	~50	6.19	Pass
6	~50	7.80	Pass
7	~50	7.90	Pass
8	~50	6.77	Pass
9	~50	6.97	Pass
10	~50	3.31	Fail
11	~50	5.99	Pass
12	~50	5.89	Pass
13	~50	8.52	Pass
14	~50	7.11	Pass
15	~50	11.07	Fail
16	~50	12.47	Pass
17	~50	8.43	Pass
18	~50	11.77	Fail
19	~50	8.61	Fail

Sample ID	Thrombin Activity (IU/cm^2)	Fibrinogen Activity (mg/cm^2)	Hemostatic Performance-Porcine Aortic Punch
20	~50	8.70	Pass
21	~50	8.52	Fail
22	~50	6.50	Pass
23	~50	6.68	Pass
24	~50	9.13	Fail
25	~50	7.68	Pass
26	~50	6.59	Pass
27	~50	7.03	Pass
28	~50	7.55	Pass
29	~50	6.85	Pass
30	~50	5.0-10.0***	pass
31	~50	5.0-10.0***	pass
32	~50	5.0-10.0***	pass
33	~50	5.0-10.0***	pass
34	~50	5.0-10.0***	pass
35	~50	5.0-10.0***	pass
36	~50	5.0-10.0***	pass
37	~50	5.0-10.0***	fail*
38	~50	5.0-10.0***	flail*
39	~50	5.0-10.0***	pass
40	~50	5.0-10.0***	pass
41	~50	5.5 - 7.5	pass
42	~50	5.5 - 7.5	pass
43	~50	5.5 - 7.5	fail*
44	~50	5.5 - 7.5	fail*
45	~50	5.5 - 7.5	fail**
46	~50	5.5 - 7.5	pass
47	~50	5.5 - 7.5	pass
48	~50	5.5 - 7.5	pass

*Failure occurred due to inadequate aspiration of pooling blood at the puncture site
** Failure occurred due to inadequate aspiration of pooling blood at the puncture site as a result of suction hose failure
*** Targeted range during production

[0043] All animals were euthenized after conclusion of the test, except for Sample ID 46 and 47, which survived for at least 2 weeks post surgery.

Reference Example 3

Non-woven PGL fabric with ORC reinforcement fabric.

[0044] Poly (glycolide-co-lactide) (PGL, 90/10 mol/mol) was melt-spun into fiber. The fiber was cut into small staple and then carded to create a very fine nonwoven fabric of about 1.25 millimeters thick and had a density of about 98.1 mg/cc. The nonwoven fabric was then needle punched into a knitted carboxylic-oxidized regenerated cellulose fabric, available from Ethicon, Inc., under the tradename Interceed®, to secure the nonwoven fabric to the ORC fabric. The final construct comprised about 60 weight percent of the nonwoven fibers.

Reference Example 4

Analysis of Adhesive/Sealant Properties of Samples Coated with Fibrinogen and Thrombin

[0045] The material described in Example 3 was coated with dry particles consisting mostly of fibrinogen (7 to 8 mg/cm^2) and thrombin (50IU/cm^2), and then tested using a Hydraulic Burst Leak Test (HBLT). Samples were cut into circular pieces of 18 mm (¾ inch) diameter. The samples were placed onto a tissue substrate derived from bovine pericardium with a hole in the center of the tissue. The pierced tissue substrate was placed over an airtight chamber into which saline was pumped. The pressure required to disrupt/burst the seal formed between the tissue and the sample was measured (see Figure 1). Samples without protein coating do not adhere to the tissue.

[0046] While the examples demonstrate certain embodiments of the invention, they are not to be interpreted as limiting the scope of the invention as defined in the accompanying claims, but rather as contributing to a complete description of the invention. All reinforcement fabrics described in the examples are the nonsterile materials of the corresponding commercial products referred by their tradenames.

Patentkrav

1. Fremgangsmåde til fremstilling af en flerlagssårforbinding, hvor sårforbindingen omfatter:
et første absorberbart ikke-vævet tekstil, omfattende fibre, som består af alifatiske polyesterpolymerer eller copolymerer af en eller flere monomerer, der er udvalgt fra gruppen bestående af mælkesyre, lactid (omfattende L-, D-, meso- og D-, L- blandinger), glykolsyre, glycolid, ε-caprolacton, p-dioxanon og trimethylencarbonat; og
et andet absorberbart vævet eller strikket tekstil, der er fastgjort til det første absorberbare ikke-vævede tekstil, hvor det andet absorberbare vævede eller strikkede tekstil omfatter oxideret cellulose,
hvor fremgangsmåden omfatter: suspension af thrombin- og fibrinogen-pulvere sammen i en perfluoreret carbonhydrid som bærerfluid, i hvilken de ikke kan opløses, og
påføring af den resulterende suspension til det første absorberbare ikke-vævede tekstil.

2. Fremgangsmåde ifølge krav 1, hvor thrombin- og/eller fibrinogen-pulveret fremstilles ved at lyofilisere thrombin og/eller fibrinogen separat, efterfulgt af maling af de lyofiliserede materialer under anvendelse af en ekstrafin mølle eller en afkølet bladmølle.

3. Fremgangsmåde ifølge et af de foregående krav, hvor fluidsuspensionen påføres på en sådan måde, at massen af pulverne ikke kommer i kontakt med det andet absorberbare vævede eller strikkede tekstil, og ikke mere end at spormængder af pulveret trænger ind i undersiden af det andet absorberbare vævede eller strikkede tekstil.

4. Fremgangsmåde ifølge krav 4, hvor det første absorberbare ikke-vævede tekstil omfatter glycolid-/lactidcopolymer.

5. Fremgangsmåde ifølge et af de foregående krav, hvor det andet absorberbare vævede eller strikkede tekstil omfatter oxideret regenereret cellulose.

6. Fremgangsmåde ifølge krav 1, hvor det første absorberbare ikke-vævede tekstil omfatter glycolid-/lactidcopolymer, og det andet absorberbare vævede eller strikkede tekstil omfatter oxideret regenereret cellulose.

7. Fremgangsmåde ifølge krav 6, hvor det første absorberbare ikke-vævede tekstil har en basisvægt på mellem 16 og 310 g/m^2 (0,01 til 0,2 g/in^2); det andet absorberbare vævede eller strikkede tekstil har en basisvægt på mellem 1,6 og 310 g/m^2 (0,001 til 0,2 g/in^2); og flerlagsforbindingen, som har thrombin og/eller fibrinogen derpå, har en basisvægt på mellem 155 og 1550 g/m^2 (0,1 til 1,0 g/in^2).

8. Fremgangsmåde ifølge et af de foregående krav, hvor mængden af thrombin- og/eller fibrinogenpulver, der påføres til det ikke-vævede tekstil, er tilstrækkelig til at dække overfladen deraf, således at der ikke er nogen zone, som synligt mangler dækning.

9. Flerlagssårforbinding, der kan opnås med fremgangsmåden ifølge et af de foregående krav.

Analysis of HBLT Burst Pressure (mmHg) Data

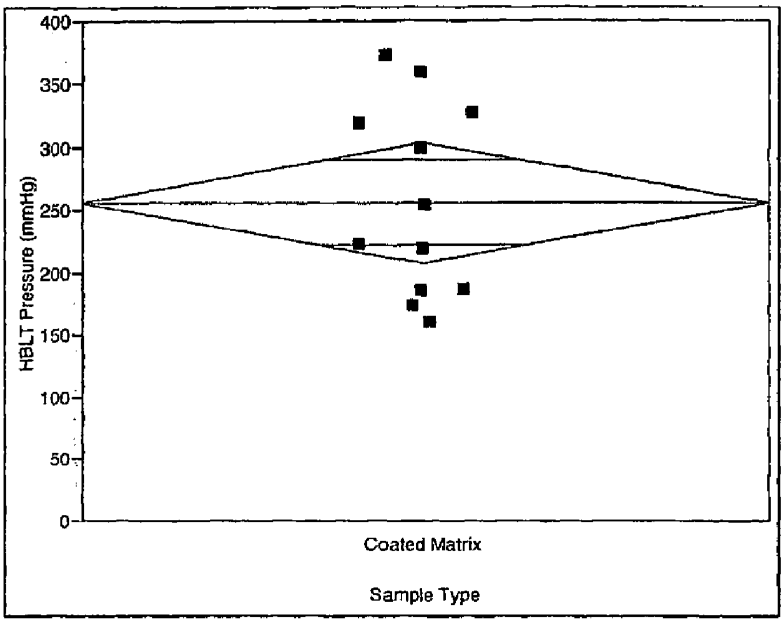

FIG. 1