(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
27 April 2006 (27.04.2006)

PCT

(10) International Publication Number
WO 2006/044879 A2

(51) International Patent Classification:
A61L 15/32 (2006.01) *A61L 15/64* (2006.01)
A61L 15/42 (2006.01)

(21) International Application Number:
PCT/US2005/037403

(22) International Filing Date: 17 October 2005 (17.10.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/620,539	20 October 2004 (20.10.2004)	US
60/696,258	1 July 2005 (01.07.2005)	US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: HEMOSTAT

(57) Abstract: The present invention is directed towards a hemostat comprising an absorbable foam, an absorbable woven or knitted fabric, thrombin and fibrinogen.

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HEMOSTAT

This application claims priority from U.S. Provisional Application Serial No. 60/620539, filed on 20 October 2004, and U.S. Provisional Application Serial No. 60/696258, filed on 01 July 2005.

FIELD OF THE INVENTION

The present invention relates to a hemostat.

BACKGROUND OF THE INVENTION

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.

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 A1.

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.

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.

SUMMARY OF THE INVENTION

The present invention is directed towards a hemostat comprising an absorbable foam, an absorbable woven or knitted fabric, thrombin and fibrinogen.

DETAILED DESCRIPTION OF THE INVENTION

The hemostat described herein provides and maintains 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.

In certain embodiments, hemostats of 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.

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

In addition to serving as a carrier for the thrombin and fibrinogen, the foam also serves to shield the thrombin and fibrinogen from acidic moieties that may be present in the reinforcement fabric, such as is the case where carboxylic-oxidized cellulose is used as the reinforcement fabric.

The foam may be a biocompatible, water-soluble, or water-swellable polymer and a foaming agent/surfactant. Preferred biocompatible, water-soluble, or water-swellable polymers used to fabricate the foam include polysaccharides. Such polysaccharides include, without limitation, cellulose, alkyl cellulose, e.g. methylcellulose, alkylhydroxyalkyl cellulose, hydroxyalkyl cellulose, cellulose sulfate, salts of carboxymethyl cellulose, carboxymethyl cellulose, and carboxyethyl cellulose. Additionally, albumin, chitin, carboxymethyl chitin, hyaluronic acid, salts of hyaluronic acid, alginate, alginic acid, propylene glycol alginate, glycogen, dextran, dextran sulfate, curdlan, pectin, pullulan, xanthan, chondroitin, chondroitin sulfates, carboxymethyl dextran, carboxymethyl chitosan, chitosan, heparin, heparin sulfate, heparan, heparan sulfate, dermatan sulfate, keratan sulfate, carrageenans, chitosan, starch, amylose, amylopectin, poly-N-glucosamine, polymannuronic acid, polyglucuronic acid polyguluronic acid, and derivatives of any of the above, may be utilized. Even more preferably, biocompatible, water-soluble, or water-swellable polymers are an alkali or alkali earth metal salts of carboxylmethyl cellulose, most preferably sodium carboxylmethyl cellulose (CMC-Na).

The foaming agent/surfactant may be a cationic, anionic, amphoteric, zwitterionic or nonionic surfactant, or natural or modified proteins, including but without limitation, albumin, sodium lauryl sulfate, sodium laureth sulfate, or ammonia lauryl sulfate. A preferred foaming agent/surfactant is albumin, and more preferably, human serum albumin (HSA).

The reinforcement fabric is an absorbable woven or knitted fabric and comprises oxidized polysaccharides, in particular oxidized cellulose and the neutralized derivatives thereof. For example, the cellulose may be carboxylic-oxidized or aldehyde-oxidized cellulose. More preferably, oxidized regenerated polysaccharides,

including but without limitation 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, the contents each of which is hereby incorporated by reference as if set forth in its entirety.

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).

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, the contents of which are hereby incorporated by reference herein as if set forth in its entirety. 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.

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

The reinforcement fabric preferably comprises oxidized regenerated cellulose and may have a basis weight ranging from about 0.001 to 0.2 g/in^2, preferably in the range of about 0.01 to 0.1 g/in^2, and most preferably in the range of about 0.04 to 0.07 g/in^2.

In preparing the hemostats, a foam slurry may be prepared from, for example, CMC-Na and HSA, and then spread on the surface of, for example, an oxidized regenerated cellulose fabric. The ratio of the water-soluble or water-swellable polymer to the foaming agent may range from about 1:8 to 8:1 by weight, and preferably from about 2:1 to 1:2 by weight. The foam slurry is then dried either by lyophilization or in an oven at elevated temperature to form a solid foam substrate. The foam substrate may be treated with a chemical cross-linking agent such as glutaraldehyde for increased strength or may be partly cross-linked by heating. The density of the hemostat may be from about 5 to 20 mg/cm^3.

The thrombin and fibrinogen may be animal derived, preferably human, or may be recombinant. The thrombin activity on the hemostat 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 hemostat 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.

Thrombin powders may be prepared by lyophilization of thrombin solutions. Fibrinogen may be prepared by lyophilizaton of solutions containing fibrinogen, such as those described in USP 6,121,232 and PCT Application Publication No. WO 02/095019. Dry powders of fibrinogen and thrombin suspended in an organic solvent such as PF5060 or HFE 7000—7300 series are then sprayed onto the surface of the foam. Alternatively, the thrombin and fibrinogen may be incorporated into the foam during the foam production.

In an alternate embodiment, the hemostat may comprise a first foam having incorporated thereon or therein a first therapeutic agent, e.g., fibrinogen, and a second foam separate (unattached) from the first foam that may have upon or incorporated therein powders of a second therapeutic agent, e.g. thrombin. Alternatively, a hemostat may comprise a reinforcement fabric having a first foam adjacent thereto and second foam on the other side of the first foam. While either thrombin or fibrinogen may be incorporated into first foam, fibrinogen is preferred. While either thrombin or fibrinogen may be incorporated with the second foam, thrombin is preferred. In such an

embodiment, the foam slurries used to prepare the first and second foams are selected such that the second foam is less dense than the first foam so that it liquefies or melts quickly after coming into contact with blood at the wound site to start the clotting process. The second foam contacts the bleeding site first, then the combined reinforcing layer and first foam keeps the clot from being washed away by the blood flow.

The hemostat may optionally include without limitation, procoagulant enzymes, proteins and peptides, may be naturally occurring, recombinant, or synthetic, and may be selected from the group consisting of prothrombin, fibrin, fibronectin, heparinase, Factor X/Xa, Factor VII/VIIa, Factor IX/IXa, Factor XI/XIa, Factor XII/XIIa, tissue factor, batroxobin, ancrod, ecarin, von Willebrand Factor, collagen, elastin, albumin, gelatin, platelet surface glycoproteins, vasopressin and vasopressin analogs, epinephrine, selectin, procoagulant venom, plasminogen activator inhibitor, platelet activating agents, synthetic peptides having hemostatic activity, derivatives of the above and any combination thereof.

The hemostat described herein may also 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 hemostat 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.

The hemostat 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 hemostat may additionally promote and possibly enhance the natural tissue healing process in all the above events. This hemostat 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

hemostat 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. Lyophilized CMC-Na/ HSA foam with ORC fabric

In a mixing bowl were added 190 mL of a 2% solution of sodium carboxy methylcellulose (CMC-Na) (Aqualon, catalog No. 7M8SFPH) and 10 mL of a 20% solution of human serum albumin (HSA) (ALBUTEIN™, Alpha Therapeutic Corporation). The mixture was whipped mechanically to generate a foamed slurry. The foamed slurry was transferred to a rectangular frame having a piece of knitted carboxylic-oxidized regenerated cellulose fabric, available from Ethicon, Inc. under the tradename Interceed®, disposed at the bottom. The foamed slurry was then spread evenly across the whole frame to yield a thickness of about 3 mm. The foamed slurry was then lyophilized to remove solvent, thus yielding a solid CMC-Na/HSA foam adjacent and attached to the ORC fabric.

Example 2. Heat-treated CMC-Na/ HSA foam with ORC fabric

In a mixing bowl were added 190 mL of 2% solution of sodium carboxy methylcellulose (CMC-Na) (Aqualon, catalog No. 7M8SFPH) and 10 mL of 20% solution of human serum albumin (HSA) (ALBUTEIN™, Alpha Therapeutic Corporation). The mixture was whipped mechanically to generate a foamed slurry. The foamed slurry was transferred to a rectangular frame having a piece of carboxylic-oxidized regenerated cellulose fabric, available from Ethicon, Inc. under the tradename Interceed®, at the bottom. The foamed slurry was then spread evenly across the whole frame to yield a thickness of about 3 mm. The foamed slurry was then heated in an oven at 65°C for an hour to remove solvent and thus yielded a solid CMC-Na/HSA foam adjacent and attached to the ORC fabric.

Example 3. Reinforced Foams with active clotting factors

Hemostatic agents were applied to the constructs prepared in Examples 1 and 2 as below. The constructs were cut into 3" x 4" pieces. Lyophilized thrombin and Biological Active Components 2 (BAC-2) containing fibrinogen were ground to powder separately. The thrombin powder and the BAC-2 powder were passed through

a 45-micrometer sieve. The two powders were weighed to provide a final fibrinogen concentration of 6 mg/cm^2, 7 mg/cm^2 or 8 mg/cm^2, and a thrombin activity of 50 IU/cm^2. The powders were then mixed and suspended in a per-fluorinated solvent HFE 7000 in a flask. The suspension then was sprayed onto the various constructs and then dried under nitrogen at room temperature for 1 hour.

Example 4. Hemostasis test in a swine spleen linear incision model

Linear incisions (1.5 cm long and 0.3 cm deep) were made on a swine spleen. After spraying the wound with 0.9% saline solution, various test materials from Example 3 were applied to the wounds. Tamponade was applied for 30 seconds followed by a 30-second observation. When hemostasis was not achieved, additional tamponade was applied to stop the bleeding. A piece of surgical gauze and a commercial product Tachocomb® surgical patch (commercially available from Nycomed Pharma GmbH) were used as controls. Table 1 lists the experimental results.

Table 1. Hemostasis test results in a swine spleen model.

Test material	Average number of tamponade	Average time to hemostasis (min:sec)
Surgical gauze	21	>12:00
CMC-Na/HSA lyophilized foam/Interceed® fabric backing 6 mg/cm^2 fibrinogen 50 IU/cm^2 thrombin	4	2:33
CMC-Na/HSA lyophilized foam/Interceed® fabric backing 8 mg/cm^2 fibrinogen 50 IU/cm^2 thrombin	3	2:13
CMC-Na/HSA heat-treated foam/Interceed® fabric backing 7 mg/cm^2 fibrinogen 50 IU/cm^2 thrombin	2	1:03
Tachocomb® Surgical Patch (having 5.5 mg/cm^2 fibrinogen 2.0 IU/cm^2 thrombin)	7	5:55

Example 5. CMC-Na/HSA foam with thrombin

In a mixing bowl were added 190 mL of a 2% solution of sodium carboxy methylcellulose (CMC-Na) (Aqualon, catalog No. 7M8SFPH) and 10 mL of a 20% solution of human serum albumin (HSA) (ALBUTEIN™, Alpha Therapeutic Corporation). The mixture was whipped mechanically to generate a foamed slurry. A portion of the foamed slurry was transferred to a glass beaker. Thrombin powder was folded into the foamed slurry to yield an estimated activity of 1,000 IU/cm^3. The final mixture was lyophilized in aluminum weighing dishes with a height of 0.5 cm to form a solid foam comprising the thrombin dispersed therethrough.

Example 6. CMC-Na/HSA foam with fibrinogen

In a mixing bowl were added 190 mL of 2% solution of sodium carboxy methylcellulose (CMC-Na) (Aqualon, catalog No. 7M8SFPH) and 10 mL of 20% solution of human serum albumin (HSA) (ALBUTEIN™, Alpha Therapeutic Corporation). The mixture was whipped mechanically to generate a foamed slurry. A portion of the foamed slurry was transferred to a glass beaker. Five grams of fibrinogen powder was folded into the foam. The final mixture was placed in an aluminum weighing dish with a height of 0.5 cm and a having a piece of ORC fabric at the bottom. The foamed slurry then was lyophilized to form a solid foam comprising the fibrinogen dispersed therethrough.

Example 7. Hemostasis test with CMC-Na/HSA/Thrombin foam and CMC-Na/HSA/Fibrinogen.foam

A severe bleeding wound was made on a swine liver. The defect was created by making a triangular cut with a surgical scalpel. Each side measured about 1 inch and the depth measured 5mm. After the triangular liver tissue was removed, CMC-Na/HSA/Thrombin foam (1" x 1") was quickly applied to the wound. A piece of CMC-Na/HSA/Fibrinogen foam was then applied on top of the thrombin foam followed by manual compression. Hemostasis was achieved in 2 minutes.

We claim:

1. A hemostat comprising an absorbable foam, an absorbable woven or knitted fabric, thrombin and fibrinogen.

2. The hemostat of claim 1, where the foam comprises one or more polymers selected from the group consisting of polysaccharides, albumin, chitin, carboxymethyl chitin, hyaluronic acid, salts of hyaluronic acid, alginate, alginic acid, propylene glycol alginate, glycogen, dextran, dextran sulfate, curdlan, pectin, pullulan, xanthan, chondroitin, chondroitin sulfates, carboxymethyl dextran, carboxymethyl chitosan, chitosan, heparin, heparin sulfate, heparan, heparan sulfate, dermatan sulfate, keratan sulfate, carrageenans, chitosan, starch, amylose, amylopectin, poly-N-glucosamine, polymannuronic acid, polyglucuronic acid polyguluronic acid, and derivatives of any of the above.

3. The hemostat of claim 2, where the foam comprises a polysaccharide selected from the group consisting of methylcellulose, alkylhydroxyalkyl cellulose, hydroxyalkyl cellulose, cellulose sulfate, salts of carboxymethyl cellulose, carboxymethyl cellulose, carboxyethyl cellulose.

4. The hemostat of claim 3, where the absorbable woven or knitted fabric comprises oxidized polysaccharides.

5. The hemostat of claim 4, where the absorbable woven or knitted fabric comprises oxidized cellulose.

6. The hemostat of claim 5, where the absorbable woven or knitted fabric comprises oxidized regenerated cellulose.

7. The hemostat of claim 5, where the absorbable woven or knitted fabric is an absorbable knitted fabric comprising oxidized regenerated cellulose.

8. The hemostat of claim 1, where the foam comprises carboxymethyl cellulose and albumin, the absorbable woven or knitted fabric comprises oxidized regenerated cellulose, and the thrombin and fibrinogen are incorporated into or sprayed onto the foam.

9. The hemostat of claim 8, where the weight ratio of carboxymethyl cellulose to the albumin ranges from about 1:8 to 8:1 by weight.

10. The hemostat of claim 8, wherein the thrombin activity on the hemostat ranges from about 20 to 500 IU/cm^2, and the fibrinogen activity ranges from about 2 to 15 mg/cm^2.