Dec. 4, 1956 J. N. MASCI ET AL 2,772,999

HEMOSTATIC SURGICAL COMPOSITIONS AND DRESSINGS

Filed June 6, 1952

Fig. 1.

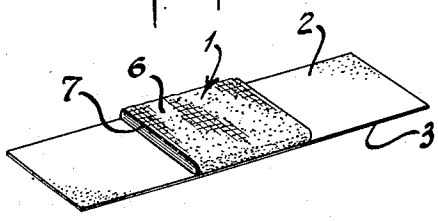


Fig. 2.

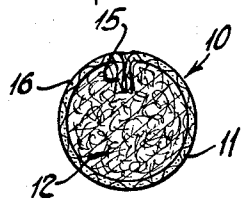


Fig. 3.

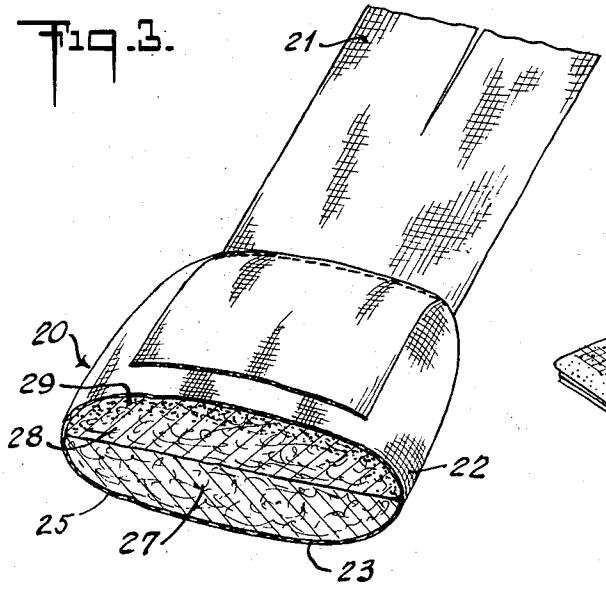
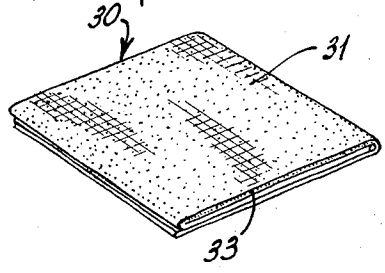


Fig. 4.



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HEMOSTATIC SURGICAL COMPOSITIONS AND DRESSINGS

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18 Claims. (Cl. 167—84)

This invention relates to hemostatic surgical compositions such as dressings, and a method for arresting the flow of blood from body wounds.

In checking the flow of blood from body wounds, it has been the well-known practice to apply to and hold with pressure against the affected areas suitable dressings which derive their effectiveness largely from the pressure employed. The principle of these conventional dressings has been to hold the blood within the general area of the wound until sufficient time has elapsed to permit the blood to coagulate and clot of its own accord. The blood, of course, permeates the dressing, be it gauze or other fibrous material, and when it clots acts as a bonding agent, securely uniting the dressing with the body. The fuzz which is normally associated with nonwoven and even woven dressings such as gauze, augments this bond.

Other types of dressings have been developed with a view to minimizing the tendency of the ordinary dressing to absorb an undue amount of the blood. Various gums or other gel-forming materials have been added to the dressing in an effort to localize the blood by physical retention thereof within a confined space bounded by the relatively impermeable gum-treated dressing. No difference in principle has been introduced by the latter type of dressings, since the dressings themselves do not possess any inherent blood clotting properties, but merely attempt to retain the blood within a relatively confined zone until the natural hemostatic qualities of the blood can come into play.

Each type of prior art dressing has often resulted in loss of an excessive amount of blood. Further, in many instances, it has been difficult, if not impossible, to keep the wound neat and sanitary for any length of time, and difficulties have arisen in removing the dressing caused by the tendency of the clot to adhere to the dressing and thereby start afresh the flow of blood.

Still other types of hemostatic materials include various articles made from human plasma fractions, fibrin and thrombin; for example, fibrin foam used as a carrier for thrombin, or as a dry, porous, brittle, cream-colored textile; water solutions of thrombin used as a spray; gelatin sponges used in conjunction with thrombin solution. However, an inherent weakness in each of these materials originating in the body is that they are ready-made breeding ground for bacteria and other undesirable organisms. Hence, extreme precautions must be taken to insure sterility at all times. Even then, deleterious side effects may come into play through their use. The materials mentioned are also subject to spoilage when stored, which is a limitation. They are unduly expensive. Source of supply is not adequate. Heat sterilization is often difficult or impossible.

An important object of the invention is to provide a surgical composition such as a dressing which possesses inherent hemostatic, i. e., blood congealing properties without the necessity of relying upon pressure and physical retention of the blood within the wound area for time sufficient to realize the normal tendency of the blood to congeal itself. A further object is to devise a novel method of hemostasis. Other objects will appear hereinafter.

In the invention, certain hemostatic agents have been discovered which congeal blood on contact therewith through inherent hemostatic activity. They are stable, heat sterilizable, relatively inexpensive, and prepared from readily available materials. They do not foster the growth of bacteria and also otherwise accomplish the above stated objects of the invention. The invention hemostatic agents are free acid cellulose glycolic acid ethers (also called free acid carboxymethyl cellulose) and free acid cellulose hydroxypropionic acid ethers (also called free acid carboxyethyl cellulose). Accordingly, the invention method comprises arresting the flow of blood from a wound by applying to the wound area one of the invention hemostatic agents, in the form of a powder (suitably a powder in the physical form of the native linters or fiber, that is, not dissolved and precipitated) or other hemostatic composition, e. g., impregnated surgical dressing, bone wax, etc. The surgical compositions, e. g., dressings, of the present invention contain free acid cellulose glycolic acid ether or free acid cellulose hydroxypionic acid ether so disposed as to contact the wound when the composition is placed in use. Each of these materials possesses remarkable and unexpected inherent blood clotting properties. Hence, the invention surgical compositions and method arrest bleeding much faster and possess properties described below which are substantially superior as compared with prior art dressings and methods. Preferred embodiments of the invention employ free acid cellulose glycolic acid ether (C. G. E.) as hemostatic agent.

In the specification terminology, the term cellulose glycolic acid ether (or carboxymethyl callulose) includes both the free acid cellulose glycolic acid ether and its salts. Similarly, cellulose hydroxypropionic acid ether (or carboxyethyl cellulose) includes both the free acid cellulose hydroxypropionic acid ether and its salts.

Certain embodiments of the invention may be conveniently understood by reference to the attached drawing, in which Fig. 1 represents a sectional perspective view of an invention Band-Aid adhesive bandage. Fig. 2 describes a hemostatic globular surgical sponge, shown in section, of the type commonly used in tonsillectomies. Fig. 3 shows a sectional perspective view of a battle dressing prepared according to the invention. Fig. 4 is an illustration of a rectangular folded gauze dressing of the present invention.

Reference No. 1 indicates generally a folded gauze pad secured to adhesive face 2 of backing strip 3 of the adhesive bandage. Wound contacting surface 6 of the dressing contains as an impregnant a hemostatic agent of the present invention, namely, free acid carboxymethyl cellulose or free acid carboxyethyl cellulose. The manner of incorporating this impregnant into the dressing will be described below. Zone 7 of pad 1 indicates the area of hemostatic agent-impregnated fibers. When the Fig. 1 adhesive bandage is placed on the body in wound-contacting position, exuding blood first contacts zone 7 and is quite promptly congealed, forming a block to further exudation of blood. Bleeding is therefore arrested with minimum loss and minimum penetration into the dressing. The bandage is preserved in substantially its original neat and cleanly condition. Further, when it is desired to remove the bandage, the small degree of penetration minimizes tendency of the clot to adhere to the dressing.

The surgical globular sponge shown generally at 10 comprises one or more layers of gauze 11 surrounding a core of gauze, cotton or other fibrous cellulosic material

12. The sponge may, if desired, be formed of all gauze or all cotton, suitably having the shell and core integral. The edges **15** of the gauze are tucked and tied or otherwise secured within the sponge. The gauze shell **11** is shown as containing in zone **16**, as impregnant, a hemostatic agent of the present invention. In use, this hemostatic zone contacts the wound and arrests the flow of blood in a manner similar to that of the afore-described adhesive bandage.

Fig. 3 shows a battle dressing **20** in transverse section. The dressing is formed of body portion **22** and provided with tabs or ties **21**. Body portion **22** is composed of shell **23** of gauze or other suitable material and core **25**. The latter may suitably be in two sections, a first section **27** of nonabsorbent cotton and a second section **28** of absorbent cotton. The ordinary function of section **28** would be to absorb and retain exuded blood and section **27** to prevent undue penetration of the blood into and through the dressing. According to the invention, the zone **29** comprising portion of gauze shell **23** and adjacent absorbent cotton contains as impregnant one of the hemostatic agents of the invention, i. e., free acid carboxymethyl cellulose or free acid carboxyethyl cellulose.

Dressing **30** of Fig. 4 is formed of a multiple of layers, which may be 8 to 16 or more in number, of folded gauze. The dressing has a wound-contacting surface **31** which is intended to be placed next to the body and held there by suitable bandage strappings or ties. Zone **33** adjacent surface **31** contains as impregnant in the fibers one of the invention hemostatic agents.

A use of the invention hemostatic agents is also found in preparation of bone wax compositions. The control of osseous hemorrhage has presented a serious problem to the medical profession because the hemostatic agents found effective for the control of soft tissue hemorrhage have not been effective for the control of bleeding from cut bone surfaces. One class of materials used for the control of this latter type of hemorrhage is called bone wax. Certain unavoidable disadvantages inhere in the bone wax compositions previously used or suggested. In accordance with the present invention is has been found that hemostatic bone wax compositions which have a specific hemostatic effect and in which the consistency may be varied as desired include as ingredients a water-soluble innocuous base, and free acid cellulose glycolic acid ether or free acid cellulose hydroxypropionic acid ether as hemostatic agent. The invention bone wax compositions may be prepared to be completely absorbable by the body tissues which is a further marked advantage as compared with certain prior art bone waxes. The base may be a single substance or a mixture of two or more water-soluble innocuous substances. Substances suitable as bases include non-volatile compatible poly-ol compounds such as glycerin, polymerized low molecular weight aliphatic glycols such as polymerized ethylene glycol, and low molecular weight ethers or esters of polyglycols such as the methyl, ethyl, or propyl ethers of polyethylene glycols and the acetic or propionic esters of polyethylene or polypropylene glycols. Polymerized ethylene glycol is the preferred water-soluble base, and polymerized ethylene glycols having a molecular weight in the range 200 to 4000 and a consistency varying from a liquid of low viscosity to that of a solid wax may be found suitable. If desired, a polymerized ethylene glycol having a molecular weight of 1000 to 4000 may be used in combination with a polymerized ethylene glycol having a molecular weight of 200 to 600.

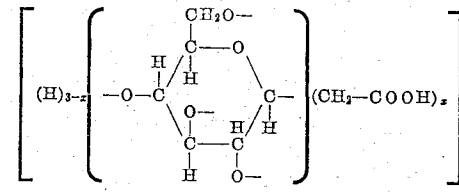
In addition to the hemostatic agent and innocuous base, preferred bone wax compositions also contain a tackifier such as cellulose glycolic acid ether salt or cellulose hydroxypropionic acid ether salt (preferably sodium salt) and water as a plasticizer. The cellulose ether sodium salt is important in producing a composition having just the right amount of tack and adhesion so that it will be easily manipulated in the hands of the surgeon, spread on the bone, and will adhere to the bone surface. The proportion of water to tackifier is also important in producing the desired consistency. A further function of the base or the water is to swell the free acid cellulose ether to a solvated or hydrated form, preferably to a clear jelly. We believe that this swelling or solvation tends to render the free acid cellulose ether completely absorbable by the body.

To summarize, suitable bone wax compositions may be found within the following ranges of ingredient proportions, expressed on a weight basis: free acid cellulose glycolic acid ether in hemostatic amount at least about 2%, preferably 5% or more; tackifier (cellulose glycolic acid ether sodium salt) at least about 8%; ratio of water to tackifier in the range from 1:1 to 6.5:1; base material to make 100%. The following compositions have been prepared and found to have acceptable properties.

Code	No. 1	No. 2	No. 3	No. 4	No. 5
C. G. E. Free Acid	11.5	13.7	11.45	11.65	11.75
Polyethylene Glycol 400	23.0	22.7	19.93	19.40	19.60
Glycerin			14.92	13.58	13.72
H_2O	54.0	54.5	40.75	42.75	41.21
C. G. E. Sodium Salt	11.5	9.1	12.95	12.62	13.72

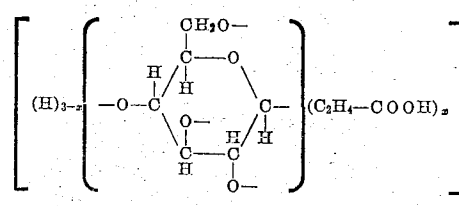
Composition Nos. 1, 2, and 5 were superior from the standpoint of hemostasis and bone affinity.

The free acid cellulose glycolic acid ether (free acid carboxymethyl cellulose), which is preferably used to prepare the surgical compositions of the invention may be described structurally as:



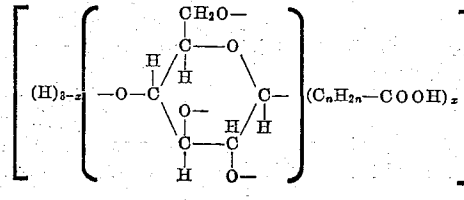
where x is not greater than 3 and y is a large whole number.

The ring structure represents the anhydroglucose residue which is linked in known manner to similar residues on either side to form a long chain cellulose structure. The bracketed H atoms are attached to oxygen atoms in the anhydroglucose residue in known fashion. Similarly, the (CH_2—COOH) groups are attached to the residue through oxygen linkage by substituting for the aforementioned H atoms. The free acid carboxyethyl cellulose (free acid cellulose hydroxypropionic acid ether), which is an alternate to the free acid carboxymethyl cellulose, may be described structurally as:



x, again, being not greater than 3 and y a large whole number. The C_2H_4 group is preferably —CH_2CH_2—.

The general formula of the materials used to prepare surgical dressings according to the invention is therefore:



where x is not greater than 3, n is 1 or 2, and y is a large whole number.

The degree of substitution (D. S.), a term commonly employed in connection with cellulose derivatives of the nature of the invention hemostatic agents, is an important property and indicates the average number of substituent groups per glucose unit in the cellulose molecular chain (i. e., the value of x in the above formulae). Since there are three hydroxyl groups and hence three possible points of substitution per glucose unit, the maximum D. S. is 3.0. It has been found according to the present invention that the degree of substitution is an important factor in determining the hemostatic activity of the particular cellulose ether. That is, as D. S. increases, hemostatic activity also increases. Hence, for the purpose of the present invention, material may be employed having D. S. which will afford adequate hemostatic activity. Preferably, since aqueous solutions (of the free acid or its salt) are conveniently used in adding the hemostatic material to the surgical dressing, material having D. S. which will afford water solubility of the salts (such as the ammonium or sodium salt) to produce suitable sizing solution is employed. Compounds having D. S. above about 0.5 generally have adequate hemostatic activity and further, are generally sufficiently soluble. Preferred cellulose ethers have D. S. about 0.7 and above. The preferred maximum D. S. is about 2.0.

For invention purposes, consideration is given to the degree of polymerization (D. P.) of the cellulose derivatives (the value of y in the above formulae). At very low D. P.'s, water solubility may become quite high with corresponding deterioration in physical properties of the cellulose ether. Further, low molecular weight material is more difficult to convert to the preferred insoluble form by the heat treatment described below. Hence, D. P. expressed as viscosity reading in seconds on a modified Ostwald-Fenske viscosimeter pipette ASTM D–445 #300 of a 0.50% by weight aqueous solution of the free acid in 0.50 normal NaOH solution at 25.50° C. should be at least about 5.7 seconds and may be as high as 36 seconds or greater, as compared with a zero pipette reading of 5.0 seconds for a 0.5 N. NaOH solution at the same temperature.

It is important to retain in the cellulose ether an adequate number of carboxyl groups whose hydrogen atoms are not replaced by salt-forming radicals such as ammonium or alkali metal. In other words, the degree of neutralization (D. N.) should be maintained below certain limits. These free carboxyl groups apparently play a part in blood congealing in the hemostatic surgical compositions of the invention. Further, a certain number of free carboxyl groups is believed to be necessary to make the compound susceptible to conversion to desired insoluble form as described below. D. N. is maintained not greater than about 60%, preferably 15% or lower and in any case sufficiently low so that the free carboxy content of the cellulose is at least 0.5 per glucose unit. As indicated below, however, the cellulose ether used to treat the surgical dressing or other composition in preparing the hemostatic material may be appreciably or completely neutralized so long as the D. N. is reduced in the final product.

The hemostatic agents, whose structure and properties are described above, may be incorporated into the surgical compositions by a variety of procedures. Each of the procedures involves adding by one way or another free acid carboxymethyl cellulose or free acid carboxyethyl cellulose to the composition. The acid cellulose ether may be so added, for example, by way of any of its soluble salts, soluble forms of the acid itself, or by synthesis of the cellulose ether in situ on cellulose fibers. A preferred procedure utilizes the ammonium salt of the cellulose ether, which may be made by direct contact of free acid carboxymethyl or carboxyethyl cellulose powder with concentrated aqueous ammonium hydroxide solution. The latter solution is used at least in amount to supply NH_3 equivalent to the free COOH groups on the selected free acid cellulose ether. The ammonium salt is then diluted with water to any desired concentration and used directly as a treating agent added to the surgical composition. If desired, the free acid carboxymethyl cellulose used for preparation of the ammonium salt may be synthesized by acidification of the sodium salt, using mineral acid if the acid cellulose ether has degree of substitution in the insoluble range, and mineral acid plus alcohol if the acid cellulose ether is soluble in water, and filtration of the acid cellulose ether.

Free acid carboxymethyl cellulose was prepared, for example, by steeping 20 parts (by weight) of sodium carboxymethyl cellulose in 500 parts of a mixture of 1,000 parts isopropanol to 200 parts concentrated hydrochloric acid for two hours. The liquid was then removed and steeping repeated with an equal and fresh amount of isopropanol=HCl. The solid material was then washed with a mixture of 80 parts isopropanol and 20 parts water until free of mineral acid and sodium chloride. The converted free acid carboxymethyl cellulose powder was then filtered and dried in air at room temperature. The dried powder was treated with ammonium hydroxide solution containing NH_3 in amount equivalent to the carboxyl groups in the acid carboxymethyl cellulose. The resulting solution of ammonium carboxymethyl cellulose was then diluted with water to 2% by weight strength.

The ammonium salt is incorporated into the surgical dressing in amounts indicated below. After treating and drying, the dressing material is heated at temperature to bring about decomposition of the ammonium salt into NH_3 and the free acid cellulose derivative. The latter is preferably further converted to a form which has been found to be quite insoluble in water and may be properly described as "refractory."

The formation of the refractory hemostatic agent is brought about by carefully controlling the temperature at and the time during which the cellulose ether is heated. In general, elevated temperatures are necessary to bring about the change. Formation of refractory acid begins to take place at an appreciable rate at about 175° F. At this temperature, it takes at least about 30 minutes to effect a substantial decrease in solubility of the free acid as compared with the non-heat treated material. Conversion takes place at a substantially faster rate at temperatures of at least about 200° F. Heating time in each case is preferably at least about 30 minutes. Within the heating time of about 2½ to 3 hours, optimum insolubility is obtained.

Temperatures above about 235° F. generally afford substantially higher rates of conversion of the soluble to the insoluble forms of hemostatic agent. Preferably, for fast operation and correspondingly short heating times, temperatures are maintained above about 300° F. The temperature in any case is maintained below levels at which excessive degradation of the cellulose ether, base fabric or other elements of the composition occurs within the minimum time in which the material can be handled at the elevated temperatures in question. Preferably it is held below about 350° F.

Any source of heat is suitable for insolubilizing the hemostatic agent. Hot air or infra-red ovens, induction heating devices, steam, hot plates, or heated irons may be used. In large scale operation, hot air ovens, which are standard equipment in many factories, are preferred.

Although the ammonium salt affords a convenient way of incorporating the free acid cellulose ether into surgical dressings, the invention is not limited to the use of the ammonium salt. An alternative procedure is to treat the surgical dressing material with the sodium salt, for example, in an aqueous solution, and thereafter form the free acid cellulose ether in situ on the fibers by addition of a stronger acid, such as hydrochloric acid or a mix-

ture of such acid and alcohol. The acidified material is washed thoroughly with water to remove excess reagents and dried. The treatment described is then preferably followed by heating to form the refractory free acid carboxymethyl cellulose just as in the case of the ammonium salt.

As a further alternative procedure, a water solution of the free acid cellulose ether may be prepared (if cellulose ether which is water soluble in the acid form is used) by adding an excess of HCl to a 2% solution of the sodium salt. This can be dialyzed using a semi-permeable membrane to remove the excess mineral acid and NaCl and leave free acid cellulose ether in solution. This free acid carboxymethyl cellulose solution is then used to treat the surgical dressing material. The material is then dried and preferably heated at the elevated temperatures indicated above to obtain invention surgical dressing having insoluble hemostatic agent impregnant.

Another method for incorporating the invention hemostatic agents into cellulosic surgical dressing materials such as cotton or gauze comprises first treating the cellulose derivative with caustic soda or potash to form the alkali metal derivative, then reacting this derivative with an alkali metal salt of chloroacetic acid. The conditions of the reaction can be controlled to maintain the physical state of the reacted fibers of cellulosic material which can then be washed free of reagents and converted to the free acid carboxymethyl cellulose by treatment with a solution of a mineral acid. Washing, drying, and preferably heat treatment to form the refractory cellulose derivative follow.

It will now be apparent that it is not necessary to impregnate the surgical dressing after it is fabricated. In fact, in most instances it will be found preferable to add the impregnant to the surgical dressing material before fabrication of the dressing. For example, in the case of the adhesive bandage of Fig. 1, zone **7** of the dressing pad **1**, containing hemostatic agent, may be a separate layer of gauze superjacent to other gauze which does not contain impregnant. Similarly, the gauze shell **11** of globular sponge **10** may be impregnated and treated as above prior to fabrication of the sponge.

The invention surgical dressings are advantageously but not necessarily formed of woven fibrous material, nonwoven fibrous material having a suitable bonding agent, or unbonded nonwoven fibrous material. However, the advantageous hemostatic properties of the invention surgical dressings may be found and surgical dressings formed, for example, of non-fibrous materials which have sufficient absorbency, permeability and other desired properties. Non-cellulosic dressings may be substituted for the usual cotton as a base material for the dressing.

In bandages having gauze as the base carrier material for hemostatic agent, the thread count of the gauze should be sufficiently high so that porosity is not excessive. On the other hand, the thread count should not be unduly high so as to produce harshness. In view of these considerations, it is preferred to utilize gauze having thread count in the range from about 14 x 10 to about 64 x 56. This range gives satisfactory dressings covering a suitable range of physical properties, texture, and efficacy. Within these limits there is a special preference for gauze of 20 x 12 or 28 x 24. The gauze count has some bearing on preferred amount of hemostatic agent incorporated into the dressing.

As indicated, the zone containing hemostatic agent is disposed adjacent the wound-contacting external surface. The precise location and depth of this zone is subject to considerable variation. It is, however, preferably disposed at or as nearly as possible adjacent to the outside surface of the dressing. For appreciable blood clotting effect, the hemostatic zone should contain at least about 0.3 mg. of hemostatic cellulose derivative per square inch of wound-contacting surface. A preferred amount is at least about 0.8 mg. per square inch. Larger amounts may be used, and the zone of hemostatic agent may be extended as far into and through the dressing as desired. For the purpose of retaining flexibility of the dressing, however, it is preferred to maintain the concentration of hemostatic agent in the zone of fibers containing the same not greater than 5% by weight based on the impregnated fibers. The optimum range of coating weight is influenced to some extent by thread count of the gauze. There is special preference for 3 to 3½% of free acid on a dry weight basis using 20 x 12 gauze. As the thread count is increased, the upper limit of practicable coating weight decreases. Thus, a coating weight of 3 to 4% on 44 x 36 gauze may still be satisfactory but somewhat harsh, whereas on the 14 x 10 gauze it would be considerably softer.

The various procedures illustrated above for incorporating carboxymethyl cellulose or carboxyethyl cellulose into surgical dressing material each involve forming an aqueous solution of the cellulose ether in one chemical form or another and treating the surgical dressing material with this aqueous solution. Other procedures may be used, however, if desired. For example, the carboxymethyl or carboxyethyl cellulose in suitable form may be dissolved in organic solvents in cases where it is soluble therein, and formed solutions used to treat the material, followed by drying and preferably heat treating.

The following examples illustrate the invention. Parts and percentages are expressed on a weight basis unless otherwise indicated.

Example 1

A sample of 44 x 36 cotton gauze was treated with a 1% by weight aqueous solution of the ammonium salt of cellulose glycolic acid ether (carboxymethyl cellulose) having degree of substitution of 1.17. The degree of polymerization of the carboxymethyl cellulose ammonium salt was indicated by viscosity of a 0.50% by weight aqueous solution of the free acid in 0.50 N. NaOH at 25.50° C. equal to 18.3 seconds as determined on a modified Ostwald-Fenske viscosimeter pipette ASTM D–445 #300, as compared with a zero pipette reading of 5.0 seconds for a 0.50 N. NaOH solution at the same temperature. The pickup of solution by the gauze was 150% of its weight. The gauze was dried on a stretcher in air under room conditions, heated under a flat iron at a temperature of about 300° F. for about 5 minutes to convert the ammonium salt to the free carboxymethyl cellulose acid and the latter to the insoluble form of acid, and tested for hemostatic activity in the liver of the adult albino rat. An incision was made for the treated gauze and a similar incision for the plain gauze untreated control. The gauzes were placed on the wounds without pressure, and the time was noted in minutes and seconds for the blood to cease flowing.

	Bleeding time
Untreated gauze control	7'3", 7'28"
Treated gauze	1', 1'30"

Example 2

A sample of 44 x 36 gauze was treated with an aqueous solution of carboxymethyl cellulose sodium salt having degree of substitution of 1.17 and degree of polymerization corresponding to viscosity of 18.3 seconds determined by the method outlined in Example 1. The treated material was dried and then steeped for 20 minutes in a mixture consisting of 500 parts ethanol, 125 parts concentrated aqueous hydrochloric acid, and 25 parts water. It was then steeped for 10 minutes in a mixture of 500 parts ethanol and 100 parts concentrated aqueous hydrochloric acid, and finally rinsed out in three portions of water, in amount sufficient to free the material of salt and mineral acid. The gauze was dried in air. The dried material contained 6.5% acid carboxymethyl cellulose. The treated gauze was used to fabricate Band-Aid Adhesive Bandages, the gauge being folded to form dressing pads having 4 plies. The control adhesive bandages

formed from untreated 44 x 36 gauze were of the same size and construction as the treated items. The comparison tests for hemostatic activity were carried out in the gluteus maximus muscle of the posterior limb of the rat. Flat wounds 5 square mm. in area in each case were covered by the respective bandages without pressure and the time in minutes and seconds for the blood to cease flowing was noted. Results were:

	Bleeding time
Untreated control:	
Rat 912	4′ 45″
Rat 913	5′ 5″
Treated Band-Aid adhesive bandage:	
Rat 912	1′ 15″
Rat 913	1′ 20″

Example 3

Sterile surgical absorbent cotton was saturated with a 2% solution of carboxymethyl cellulose sodium salt with degree of substitution of 1.17 and degree of polymerization corresponding to viscosity of 18.3 seconds as measured by the Example 1 procedure and dried in air. The dried material contained about 5% of the sodium salt. The material was washed for 2 hours in a mixture of 80 parts ethanol and 20 parts hydrochloric acid, and the sodium salt thereby converted to acid carboxymethyl cellulose. It was rinsed free of mineral acid and salt in water, dried, and used for testing hemostatic activity using untreated surgical cotton as a control. The time in minutes and seconds required to stop the flow of blood from similar wounds in the adult rat were as follows.

	Bleeding time
Untreated control cotton:	
Muscle	4′ 43″, 4′ 30″
Spleen	17′ 25″, 19′ 50″
Treated cotton:	
Muscle	55″, 55″
Spleen	1′ 45″, 2′ 20″

Example 4

Gauze of 44 x 36 mesh was treated with 5% aqueous solution of carboxymethyl cellulose sodium salt which had degree of substitution of 0.90 and degree of polymerization corresponding to viscosity of 8.4 seconds. The treated gauze was dried on a stretcher and assayed 8 milligrams of the sodium salt per square inch. It was then treated with aqueous alcoholic mineral acid and as in Example 1 to convert the sodium salt to the free cellulose derivative acid washed free of impurities. The gauze was dried and test strips of the treated gauze were then evaluated for hemostatic activity on rat liver and spleen as indicated above. The results were:

	Bleeding Time	
	Liver	Spleen
Plain Gauze (untreated control)	7′ 4″	19′ 17″
	6′ 24″	19′ 21″
Treated Gauze	1′ 5″	1′ 53″
	1′ 10″	1′ 53″

Example 5

Cellulose glycolic acid ether sodium salt in the form of the native cotton linters having a D. S. of 1.21 and D. P. indicated by a viscosity of 26.8 seconds, as determined by the above standard procedure, was suspended in a 10% HCl—70% ethyl alcohol aqueous solution at room temperature and stirred for 20 minutes. The cellulose ether was then filtered, washed once with 10% HCl—70% ethyl alcohol and then twice with equal portions of 95% ethyl alcohol to remove inorganic acid and salt. The free acid cellulose glycolic acid ether, which was still in the form of the native cotton linters, was then air dried. The powder obtained was ground in a Wiley mill to 60 mesh size. 11.5 parts of the powder obtained were kneaded together with 23.0 parts polyethylene glycol 400. When the dispersion was substantially uniform, 54.0 parts of water were added while continuing the kneading. Thereafter 11.5 parts cellulose glycolic acid ether sodium salt were added and the mixing continued until the dispersion was again uniform. The dough was then sealed into tubes and heated at 250° F. for 20 minutes to produce a clear hemostatic gel. The product was tested by applying it to an exposed linearly fractured portion of the shaft of the femur of a rabbit. It was found to have excellent adhesion to the bone surface and excellent hemostatic properties. The absorbability of the bone wax was evaluated by implanting 25 mg. samples under the skin of the back of a rat. Autopsies were performed 7 and 15 days after implantation. The bone wax was found to be completely absorbed in the autopsies of the 15th day postoperative period.

Example 6

Free acid cellulose glycolic acid ether in the form of the pulverized native cotton linters, having D. S of 0.90 and D. P. indicated by viscosity of 25 seconds as determined by the standard procedure, was prepared by the method described in Example 5. The powder was tested for hemostatic activity in the kidney, liver, and spleen of the adult albino rat according to the procedure of Example 1. Rectangular incisions of uniform size were made in the organs sufficient to produce a free flow of blood. 25 mg. samples of the free acid cellulose ether powder were then placed on each bleeding wound. For kidney incisions in four different animals, bleeding was arrested in each case from 1 minute 20 seconds to 1 minute 25 seconds after applying the hemostatic powder. In two different animals bleeding from liver incisions was arrested 1 minute 10 seconds and 0 minutes 55 seconds after applying the powder. In two different animals bleeding from spleen incisions was arrested 1 minute 20 seconds and 1 minute 38 seconds after applying the hemostatic powder. As a control a gelatin sponge sold by one well-known manufacturer was tested for hemostatic activity on the same type incisions. This material gave bleeding times of 3 minutes 56 seconds and 3 minutes 53 seconds in the liver, and 18 minutes in the spleen at which the rat had bled out. Implantation tests in rats showed the free acid cellulose ether to be completely absorbable by the body.

Example 7

An aqueous solution of cellulose hydroxypropionic acid ether sodium salt (carboxyethyl cellulose sodium salt) having D. S. above about 0.5 was acidified with concentrated HCl. 95% ethanol was then added to the solution until the free acid cellulose ether precipitated. The precipitate was washed to remove inorganic acids and salts and dried. The material was then evaluated for hemostasis on the rat by the Example 6 procedure. Bleeding was arrested in duplicate tests on rat spleen incisions in 5 minutes 20 seconds and 5 minutes 30 seconds.

The foregoing description is presented as illustrative and it will be apparent that there are many modifications within the spirit and scope of the invention. Hence, the invention is to be limited only by the appended claims. By the use of the term "consisting essentially of" in certain of the appended claims, it is intended to cover compositions which may include unspecified ingredients which do not materially affect the basic and novel hemostatic characteristics of the free acid cellulose ethers of the invention.

The claims are:

1. A surgical composition for coagulating blood containing a hemostatic amount, at least about 2%, of cellulose derivative of the group consisting of free acid cellulose glycolic acid ether and free acid cellulose hydroxypropionic acid ether having degree of substitution at least about 0.5, and degree of neutralization in the approxi-

mate range 0 to 60% but sufficiently low so that the free carboxy content of the cellulose is at least 0.5 per glucose unit.

2. A hemostatic surgical dressing containing cellulose derivative of the group consisting of free acid cellulose glycolic acid ether and free acid cellulose hydroxypropionic acid ether having degree of substitution at least about 0.5, and degree of neutralization in the approximate range 0 to 60% but sufficiently low so that the free carboxy content of the cellulose is at least 0.5 per glucose unit, adjacent wound-contacting external surface thereof, the amount of said ether being at least about 0.3 mg. per square inch of said surface.

3. A sterile fibrous surgical dressing containing a hemostatic amount of cellulose derivative of the group consisting of free acid cellulose glycolic acid ether and free acid cellulose hydroxypropionic acid ether having degree of substitution at least about 0.5, and degree of neutralization in the approximate range 0 to 60% but sufficiently low so that the free carboxy content of the cellulose is at least 0.5 per glucose unit, adjacent wound-contacting external surface thereof, the amount of said ether being at least about 0.8 mg. per square inch of said surface.

4. A surgical composition containing a hemostatic amount, at least about 2%, of free acid cellulose glycolic acid ether having degree of substitution at least about 0.5, and degree of neutralization in the approximate range 0 to 60% but sufficiently low so that the free carboxy content of the cellulose is at least 0.5 per glucose unit, adjacent wound-contacting external surface thereof.

5. A surgical dressing containing free acid cellulose glycolic acid ether having degree of substitution at least about 0.5, and degree of neutralization in the approximate range 0 to 60% but sufficiently low so that the free carboxy content of the cellulose is at least 0.5 per glucose unit, adjacent wound-contacting external surface thereof, the amount of said ether being at least about 0.3 mg. per square inch of said surface.

6. A surgical dressing containing cellulose derivative of the group consisting of free acid cellulose glycolic acid ether and free acid cellulose hydroxypropionic acid ether having degree of substitution at least about 0.5, and degree of neutralization in the approximate range 0 to 60% but sufficiently low so that the free carboxy content of the cellulose is at least 0.5 per glucose unit, adjacent wound-contacting external surface thereof in an amount at least about 0.3 mg. per square inch of said surface, said cellulose derivative having been heated, after treatment of the dressing therewith, at a temperature above about 175° F. for time sufficient to form cellulose derivative having substantially lower water solubility.

7. A surgical dressing having adjacent a wound-contacting external surface thereof, cellulose derivative of the group consisting of free acid cellulose glycolic acid ether and free acid cellulose hydroxypropionic acid ether in an amount at least about 0.3 mg. per square inch of said surface, said cellulose derivative having degree of substitution at least about 0.5 and degree of neutralization in the approximate range 0 to 60% and sufficiently low so that the free carboxy content of the cellulose is at least 0.5 per glucose unit, said cellulose derivative further having degree of polymerization indicated by viscosity of a 0.50% by weight solution of the free acid in a 0.50 N. NaOH solution at 25.50° C. of at least 5.7 seconds as determined in a modified Ostwald-Fenske viscosimeter pipette ASTM D–445 #300, as compared with a zero pipette reading of 5.0 seconds for a 0.50 N. NaOH solution at the same temperature.

8. A surgical dressing having free acid cellulose glycolic acid ether adjacent a wound-contacting external surface thereof in an amount at least about 0.3 mg. per square inch of said surface, said free acid cellulose glycolic acid ether having degree of substitution at least about 0.5 and degree of neutralization in the range 0 to 60% and sufficiently low so that the free carboxy content of the cellulose is at least 0.5 per glucose unit, said free acid cellulose ether further having degree of polymerization indicated by viscosity of a 0.50% by weight solution of the free acid in a 0.50 N. NaOH solution at 25.50° C. of at least 5.7 seconds as determined in a modified Ostwald-Fenske viscosimeter pipette ASTM D–445 #300, as compared with a zero pipette reading of 5.0 seconds for a 0.50 N. NaOH solution at the same temperature.

9. A sterile fibrous surgical dressing containing as an impregnant adjacent a wound-contacting external surface thereof, free acid cellulose glycolic acid ether in amount at least about 0.30 mg. per square inch of said surface, said free acid cellulose ether having degree of substitution at least about 0.5 and degree of neutralization in the range 0 to 60% and sufficiently low so that the free carboxy content of the cellulose is at least 0.5 per glucose unit, said free acid cellulose ether further having degree of polymerization indicated by viscosity of a 0.50% by weight solution of the free acid in a 0.50 N. NaOH solution at 25.50° C. of at least 5.7 seconds as determined in a modified Ostwald-Fenske viscosimeter pipette ASTM D–445 #300, as compared with a zero pipette reading of 5.0 seconds for a 0.50 N. NaOH solution at the same temperature.

10. A sterile fibrous surgical dressing containing as an impregnant adjacent a wound-contacting external surface thereof, free acid cellulose glycolic acid ether in amount at least about 0.30 mg. per square inch of said surface, said free acid cellulose ether having degree of substitution at least about 0.7 and degree of neutralization in the range 0 to 60% and sufficiently low so that the free carboxy content of the cellulose is at least 0.7 per glucose unit, said free acid cellulose ether further having degree of polymerization indicated by viscosity of a 0.50% by weight solution of the free acid in a 0.50 N. NaOH solution at 25.50° C. of at least 5.7 seconds as determined in a modified Ostwald-Fenske viscosimeter pipette ASTM D–445 #300, as compared with a zero pipette reading of 5.0 seconds for a 0.50 N. NaOH solution at the same temperature.

11. A sterile fibrous surgical dressing containing as an impregnant adjacent a wound-contacting external surface thereof, free acid cellulose glycolic acid ether in amount at least about 0.8 mg. per square inch of said surface but not greater than about 5% by weight based on impregnated fibers, said free acid cellulose ether having degree of substitution at least about 0.7 and degree of neutralization in the range 0 to 15% and sufficiently low so that the free carboxy content of the cellulose is at least 0.7 per glucose unit, said free acid cellulose ether further having degree of polymerization indicated by viscosity of a 0.50% by weight solution of the free acid in a 0.50 N. NaOH solution at 25.50° C. of at least 5.7 seconds as determined in a modified Ostwald-Fenske viscosimeter pipette ASTM D–445 #300, as compared with a zero pipette reading of 5.0 seconds for a 0.50 N. NaOH solution at the same temperature.

12. A sterile fibrous surgical dressing containing as an impregnant adjacent a wound-contacting external surface thereof, free acid cellulose glycolic acid ether in amount at least about 0.8 mg. per square inch of said surface but not greater than about 5% by weight based on impregnated fibers, said free acid cellulose ether having degree of substitution at least about 0.7 and degree of neutralization in the range 0 to 15% and sufficiently low so that the free carboxy content of the cellulose is at least 0.7 per glucose unit, said free acid cellulose ether further having degree of polymerization indicated by viscosity of a 0.50% by weight solution of the free acid in a 0.50 N. NaOH solution at 25.50° C. of at least 5.7 seconds as determined in a modified Ostwald-Fenske viscosimeter pipette ASTM D–445 #300, as compared with a zero pipette reading of 5.0 seconds for a 0.50 N. NaOH solution at the same temperature and having been

heated, after treatment of the dressing therewith, at a temperature above about 175° F. for time sufficient to form cellulose derivative having substantially lower water solubility.

13. A hemostatic composition for use in control of tissue and osseous hemorrhage comprising a water-soluble innocuous base and a hemostatic amount at least about 2%, of cellulose derivative of the group consisting of free acid cellulose glycolic acid ether and free acid cellulose hydroxy propionic ether having degree of substitution at least about 0.5, and degree of neutralization in the approximate range 0 to 60% but sufficiently low so that the free carboxy content of the cellulose is at least 0.5 per glucose unit, said cellulose derivative being in solvated form.

14. A hemostatic composition for use in control of tissue and osseous hemorrhage comprising a water-soluble innocuous base selected from the group consisting of glycerin, polymerized low molecular weight aliphatic glycols, and low molecular weight ethers and esters of polyethylene glycol and polypropylene glycol; and a hemostatic amount, at least about 2% of free acid cellulose glycolic acid ether having degree of substitution at least about 0.5, and degree of neutralization in the approximate range 0 to 60% but sufficiently low so that the free carboxy content of the cellulose is at least 0.5 per glucose unit, said cellulose derivative being in solvated form.

15. A hemostatic composition for use in control of tissue and osseous hemorrhage comprising a water-soluble innocuous base, a compatible tackifier of the group consisting of a salt of cellulose glycolic acid ether and a salt of cellulose hydroxypropionic acid ether, water, and a hemostatic amount, at least about 25%, of free acid cellulose glycolic acid ether in hydrated form having degree of substitution at least about 0.5, and degree of neutralization in the approximate range 0 to 60% but sufficiently low so that the free carboxy content of the cellulose is at least 0.5 per glucose unit, the weight ratio of water to tackifier being not less than about 1:1 and not more than about 5:1.

16. A hemostatic composition for use in control of tissue and osseous hemorrhage comprising, in weight percentage, a hemostatic amount, at least about 2%, free acid cellulose glycolic acid ether having degree of substitution at least about 0.5 and degree of neutralization not greater than about 60% but sufficiently low so that the free carboxy content of the cellulose is at least 0.5 per glucose unit, and in hydrated form; at least about 8% cellulose glycolic acid ether sodium salt as tackifier; water in amount corresponding to ratio of water to tackifier in the range from at least about 1:1 to not more than about 6.5:1; and as a water-soluble innocuous base, material selected from the group consisting of glycerin, polymerized low molecular weight aliphatic glycols, low molecular weight ethers and esters of polyethylene glycol and polypropylene glycol having molecular weight in the range 200 to 4000.

17. A sterile hemostatic powder consisting essentially of cellulose derivative of the group consisting of free acid cellulose glycolic acid ether and free acid cellulose hydroxypropionic acid ether having degree of substitution of at least about 0.5, and degree of neutralization in the approximate range 0–60% but sufficiently low so that the free carboxy content of the cellulose is at least 0.5 per glucose unit.

18. A sterile hemostatic powder according to claim 17 in which the cellulose derivative is free acid cellulose glycolic acid ether.

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