



(22) Date de dépôt/Filing Date: 2001/04/30  
(41) Mise à la disp. pub./Open to Public Insp.: 2001/10/28  
(45) Date de délivrance/Issue Date: 2008/01/29  
(30) Priorités/Priorities: 2000/04/28 (US60/200,207);  
2000/06/13 (US09/592,344); 2001/01/19 (US09/766,513)

(51) Cl.Int./Int.Cl. *A61K 33/26* (2006.01),  
*A61L 15/18* (2006.01), *A61L 15/44* (2006.01),  
*A61P 7/04* (2006.01)

(72) Inventeurs/Inventors:  
PATTERSON, JAMES A., US;  
REDING, JAMES W., US;  
THOMPSON, JOHN A., BS;  
BENSON, JAMES V., US;  
KEENE, TALMADGE KELLY, US

(73) Propriétaire/Owner:  
BIOLIFE, L.L.C., US

(74) Agent: R. WILLIAM WRAY & ASSOCIATES

(54) Titre : AGENT HEMOSTATIQUE, METHODE ET EXCIPIENT POUR L'APPLICATION D'UN AGENT DE  
COAGULATION  
(54) Title: HEMOSTATIC AGENT, METHOD AND CARRIER FOR APPLYING A BLOOD CLOTTING AGENT

(57) **Abrégé/Abstract:**

A hemostatic agent, method and carrier for arresting the flow of blood and other protein containing body fluids flowing from an open wound and for promoting wound healing. A broad aspect is directed to a substantially anhydrous admixture of an oxyacid salt and a hydrophilic proton donor which will hydrate in the presence of blood and body fluid to produce cations to promote blood clotting. The preferred oxyacid salts are alkali and alkaline earth salts of transition metals and halogen oxyacids with oxidizing capabilities sufficient to accelerate blood clotting. Another embodiment of the invention includes the compound containing an oxysalt plus a hydrophilic polymer such as carboxy methylcellulose, polyvinyl, alcohol, an alginate, and all soluble gums. Still another embodiment of the invention includes the compound formed of an oxyacid salt in combination with a hydrophilic proton donor and a solid desiccant which further accelerates blood coagulation reaction rates. The cation exchange material or an admixture of an alkali metal oxyacid salt plus acidic inorganic salt produces a scab or protective coating over the wound for protection and enhanced healing. Oxygen produced during the reaction substantially reduces the level of bacteria, virus and fungus at the wound. The resin is performance-enhanced for greater fluid uptake and more rapid coagulation.



**ABSTRACT OF THE DISCLOSURE**

A hemostatic agent, method and carrier for arresting the flow of blood and other protein containing body fluids flowing from an open wound and for promoting wound healing. A broad aspect is directed to a substantially anhydrous admixture of an oxyacid salt and a hydrophilic proton donor which will hydrate in the presence of blood and body fluid to produce cations to promote blood clotting. The preferred oxyacid salts are alkali and alkaline earth salts of transition metals and halogen oxyacids with oxidizing capabilities sufficient to accelerate blood clotting. Another embodiment of the invention includes the compound containing an oxysalt plus a hydrophilic polymer such as carboxy methylcellulose, polyvinyl, alcohol, an alginate, and all soluble gums. Still another embodiment of the invention includes the compound formed of an oxyacid salt in combination with a hydrophilic proton donor and a solid desiccant which further accelerates blood coagulation reaction rates. The cation exchange material or an admixture of an alkali metal oxyacid salt plus acidic inorganic salt produces a scab or protective coating over the wound for protection and enhanced healing. Oxygen produced during the reaction substantially reduces the level of bacteria, virus and fungus at the wound. The resin is performance-enhanced for greater fluid uptake and more rapid coagulation.

## HEMOSTATIC AGENT, METHOD AND CARRIER FOR APPLYING A BLOOD CLOTTING AGENT

This invention relates generally to topically applied agents for promoting blood clotting to arrest blood flow from an open wound, and more particularly to a method of applying an anhydrous hemostatic agent which may be mixed with an aqueous media just prior to its application directly over an open bleeding wound or a wound from which body fluid is flowing to accelerate flowing blood and body fluid clotting and enhance healing.

### PRIOR ART

In addition to conventional bandages, adhesive means, compresses and the like which are applied with pressure directly against a bleeding open wound, considerable effort has been directed toward the development of chemical agents in various forms which accelerate or enhance the coagulation of blood flowing from an open wound to arrest blood flow. Many of these agents are in the "clotting cascade", i.e., fibrinogen, thrombin, Factor VIII and the like. Others are based upon the use of collagens. Edwardson, in U.S. patents 5,763,411, 5,804,428, and 5,962,026, for example, teaches the use of fibrin in conjunction with a solid support in the '411 patent, and as an enzyme free sealant in the '428 patent, and as a solid hemostatic agent substantially free of catalytic enzymes.

Three U.S. Patents invented by Martin, U.S. 5,692,302, 5,874,479 and 5,981,606, are generally directed to the use of pyruvate in combination with fatty acids and an anti-oxidant as a therapeutic wound healing hemostatic agent.

Stilwell, in U.S. Patent 5,484,913 teaches the use of calcium-modified oxidized cellulose to promote faster hemostasis. In U.S. Patent 5,474,782, Winter, et al. teaches a wound healing hemostatic agent or its salt present in a pharmaceutically acceptable carrier, the preferred embodiment being a salt of sodium. Winter provides a wound dressing with a taspine compound for promoting healing rather than clotting.

In U.S. Patent 2,163,588, Cornish teaches a wound pad having very fine fibers carrying a viscous agent and a septic for arresting and clotting blood flow. Eberl, et al., in U.S. Patent 2,688,586, teaches an improved hemostatic surgical dressing with alginic acid as a clotting agent. Masci, et al. in U.S. Patents 2,772,999



and 2,773,000 also teaches hemostatic surgical dressing including a pad and free acid cellulose glycolic acid.

A patent for another hemostatic wound dressing is taught by Shelley in U.S. patent 3,206,361 having an active agent in the form of methylaminoacetocatechol hydrochloride. Likewise, Anderson, in U.S. Patent 3,328,259, another wound dressing containing a film of cellulose glycolic acid ether is provided as the hemostatic agent.

The hemostatic agent taught by Sugitachi, et al. as disclosed in U.S. Patent 4,265,233 is blood coagulation Factor VIII plus either fibrin or thrombin. A ready-to-use bandage is taught by Altshuler in U.S. Patent 4,363,319 which also contains thrombin as an active agent, the bandage all of which is contained within a sealed package.

Invented by Lindner, et al., a wound pad which is impregnated with tissue-compatible protein such as collagen and lyophilized Factor XIII, thrombin and fibrinogen, are taught in U.S. Patent No. 4,600,574. The use of collagen as a hemostatic agent within a pad that has been freeze dried is taught by Sawyer in U.S. Patent 4,606,910.

In U.S. Patent 4,616,644, Saferstein, et al. teaches the use of an adhesive bandage with high molecular weight polyethylene oxide applied to the surface of the perforated plastic film wound release cover of the bandage to arrest blood flow from minor cuts. Yet another hemostatic agent including a carrier in the shape of a flake or fiber having thrombin and Factor XIII affixed thereto is taught by Sakamoto in U.S. Patent 4,655,211. The use of an ultra-pure, clean thrombin solution as a hemostatic agent is taught in U.S. Patent 5,525,498 invented by Bactor. Two recent patents invented by Pruss, et al., U.S. 5,643,596 and 5,645,849 both teach the use of hemostatic dressings which incorporate thrombin and epsilon aminocaproic acid (EACA) and calcium chloride on gelatin.

An absorbable spun cotton-like topical hemostat is taught by Shimuzu, et al. in U.S. Patent 5,679,372. This disclosure is directed to an absorbable dressing made of acetocollagen fibers which are innately adhesive to a bleeding surface. In a patent to Bell, et al, U.S. 5,800,372, a dressing made of microfibrillar collagen and a superabsorbant polymer provides both blood absorption and clotting inducement.

One embodiment of the present method utilizes an improved ion exchange resin, preferably in the form of a styrene divinylbenzene copolymer which has been sulfonated. The collective teaching of making this prior art resin is to be found in an earlier patent to co-inventor, Patterson, U.S. 4,291,980 which was based at least in part on the production of spherical beads comprised of copolymer styrene and divinylbenzene as taught in U.S. Patents 2,366,007 and 3,463,320. This collective teaching is incorporated herein by reference. An improvement better adapting this resin to the present invention is in the form of substantially reduced cross-linking down to about 0.25%.

Another primary aspect of the present method incorporates an oxyacid salt, preferably potassium ferrate ( $2K_2FeO_4$ ). The teaching of a process for producing alkali metal ferrates is taught by another co-inventor, Thompson, in U.S. Patent 4,545,974. See also U.S. Patent 6,187,347 by co-inventors herein.

It is submitted that the above-referenced prior art, either taken individually or collectively in any combination thereof fail to teach an enhanced hemostatic agent, method or carrier for a flowing blood or body fluid clotting agent which includes an admixture of a salt ferrate which produces a trivalent  $Fe^{+++}$  ion which reacts with the blood to accelerate coagulation and clotting of the blood. Moreover, the utilization of an enhanced insoluble cation exchange material, e.g. a sulfonated ion exchange resin, in combination with the salt ferrate to form the enhanced hemostatic agent, additionally produces a protective matrix covering over the wound and also supplies an oxidative capacity which acts as an antibacterial, antiviral and antifungal agent. Further, the presence of selected salts neutralize hydroxide radicals as clotting occurs so as to eliminate any substantial stinging sensation.

The "protective matrix" is formed by the interaction of the components of the invention with the liquid and solid components of the blood and tissue associated with the wound or trauma. The term clot and/or clotting includes both or either the product of the natural blood clotting cascade and the protective matrix formed by the invention. A "wound" includes all traumas resulting in the egress of blood, plasma and/or lymph from blood vessels and/or tissues, especially through the skin. "Body fluids include complete blood (red blood cells, white blood cells, platelets and



plasma), plasma alone, lymph alone (including suspended cells) and other body fluids, excluding urine, saliva and vaginal fluid. "Blood" refers to complete blood, plasma and/or lymph. Bleeding refers to the egress of bodily fluids including blood, plasma and/or lymph. A "hemostatic agent:" refers to natural and/or artificial material  
5 which brings about stoppage of blood loss.

Neither does prior art teach another broad aspect of this invention which includes a flowing blood or body fluid clotting (hemostatic) agent which includes an admixture of an oxyacid salt, in combination with a cation exchange resin, an organic acid or an acidic inorganic salt, which reacts with the blood or protein in blood to  
10 accelerate coagulation and clotting of the blood. The utilization of the insoluble cation exchange material, in combination with the oxyacid salt, also produces a protective matrix covering over the wound and also supplying oxidative capacity which acts as an antibacterial, antiviral and antifungal agent. In yet another aspect, the presence of a selected hydrophilic proton donor neutralizes hydroxide radicals  
15 as clotting occurs so as to eliminate any substantial stinging sensation.

This invention is directed to a method, carrier and enhanced hemostatic agent for arresting the flow of blood and other body fluid from an open wound and for promoting wound healing. In the method, the substantially anhydrous hemostatic agent of a salt ferrate and an enhanced cation exchange resin is provided for unique  
20 use which will hydrate in the presence of blood or other protein-containing body fluids.  $\text{Fe}^{+++}$  is produced, thereby promoting clotting of the blood and other body fluids when applied to the open wound for a time sufficient to promptly arrest substantial further flow of bodily fluids from the wound. The anhydrous hemostatic agent includes a monovalent, divalent, or trivalent salt ferrate ( $\text{M}_2 \text{Fe O}_4$ ,  $\text{M Fe O}_4$  or  
25  $\text{M}_2 (\text{Fe O}_4)_3$  taken from the cationic group consisting of H, Li, Na, K, Rb, Cs and Fr. However, to decrease or eliminate stinging sensation, the compound may be formed having a salt taken from the cationic group consisting of Be, Mg, Ca, Sr, Ba, Ra, Ti, V, Cr, Mn, Fe, Co, Ni, Cu, Zn, Ga, Ge, Zr, Nb, Mo, Tc, Ru, Rh, Pd, Ag, Cd, In, Sn, Hf, Ta, W, Re, Os, Ir, Pt, Au, Hg, Tl, Pb, Bi, Al, As,  $\text{NH}_4$ , and  $\text{N}(\text{C}_4\text{H}_9)_4$ . One preferred  
30 hemostatic agent includes the substantially anhydrous salt ferrate compound and an enhanced sulfonated ion exchange resin as an admixture which will rapidly hydrate in the presence of blood or other aqueous media to produce  $\text{Fe}^{+++}$ , thereby

promoting clotting. The resin produces a protective matrix coating over the wound for protection and promotes healing. Oxidative capacity produced during the reaction substantially reduces the level of bacteria, virus and fungus at the wound.

Another broad aspect of this invention is directed to a substantially anhydrous admixture of an oxyacid salt and a hydrophilic proton donor which will hydrate in the presence of blood and body fluid to provide protons which neutralize hydroxides and promote blood clotting. The preferred oxyacid salts are alkali and alkaline earth salts of transition metals and halogen oxyacids with oxidizing capabilities sufficient to promote blood clotting. A variation includes the compound containing an oxyacid salt plus a non-ionic hydrophilic polymer such as carboxy methylcellulose, polyvinyl alcohol, an alginate, starch, sugar and all soluble gums. Still another embodiment includes the compound formed of an oxyacid salt in combination with a hydrophilic proton donor and a solid desiccant which promotes clot formation. The enhanced cation exchange material or an admixture of an alkali metal oxyacid salt plus acidic inorganic salt produces a scab or protective coating over the wound for protection and enhanced healing.

It is therefore an object of this invention to provide a method of utilizing a salt ferrate as a clotting agent for arresting blood flow from an open surface wound.

It is another object of this invention to provide a method of arresting blood and body fluid flow utilizing a salt ferrate hemostatic agent which is substantially sting-free when applied onto an open wound.

It is still another object of this invention to provide an anhydrous hemostatic agent utilizing a salt ferrate combined with an enhanced insoluble cation exchange material which may be mixed with an aqueous media just prior to use for arresting blood flow from an open skin wound.

Still another object of this invention is to provide a method for preparing a localized rapid forming protective coating or covering that has antibacterial, antifungal and antiviral properties.

It is therefore an object of this invention to provide a method of utilizing an oxyacid salt as a blood clotting agent for arresting blood flow from an open surface wound.



It is another object of this invention to provide a method of arresting blood and body fluid flow utilizing an oxyacid salt hemostatic agent which is substantially sting-free when applied onto an open wound.

It is still another object of this invention to provide a composition utilizing an oxyacid salt combined with an enhanced insoluble cation exchange material or an organic acidic or an inorganic salt to arrest blood flow from an open skin wound.

Another object of this invention is to provide a composition of an oxyacid salt and an insoluble cation exchange material which, in addition to promoting blood clotting to arrest blood flow from an open wound, also provides antiseptic and a protective matrix over the wound.

It is a yet further object of this invention to enhance the fluid uptake capacity of resin mixed with a salt ferrate by use of a lower cross-linked resin and/or appropriate treatment of the resin.

In accordance with these and other objects which will become apparent hereinafter, the instant invention will now be described.

Figure 1 is a schematic flow diagram of material hemostatic agent additives and delivery modes for specific applications of the invention.

Figure 2 depicts a preferred delivery mode of the invention in the form of individual sealed ampules.

Figure 3 depicts the enhanced moisture uptake of resin as a result of boiling treatment in hydrogen peroxide ( $H_2O_2$ ) prior to admixture with a salt ferrate.

#### MECHANISM OF BLOOD COAGULATION

The following is offered as a brief explanation of one possible alternative mechanism which would explain the effectiveness of the present invention as described herebelow in full detail.

#### ALTERNATE THEORY

#### MECHANISM OF HEMOSTASIS

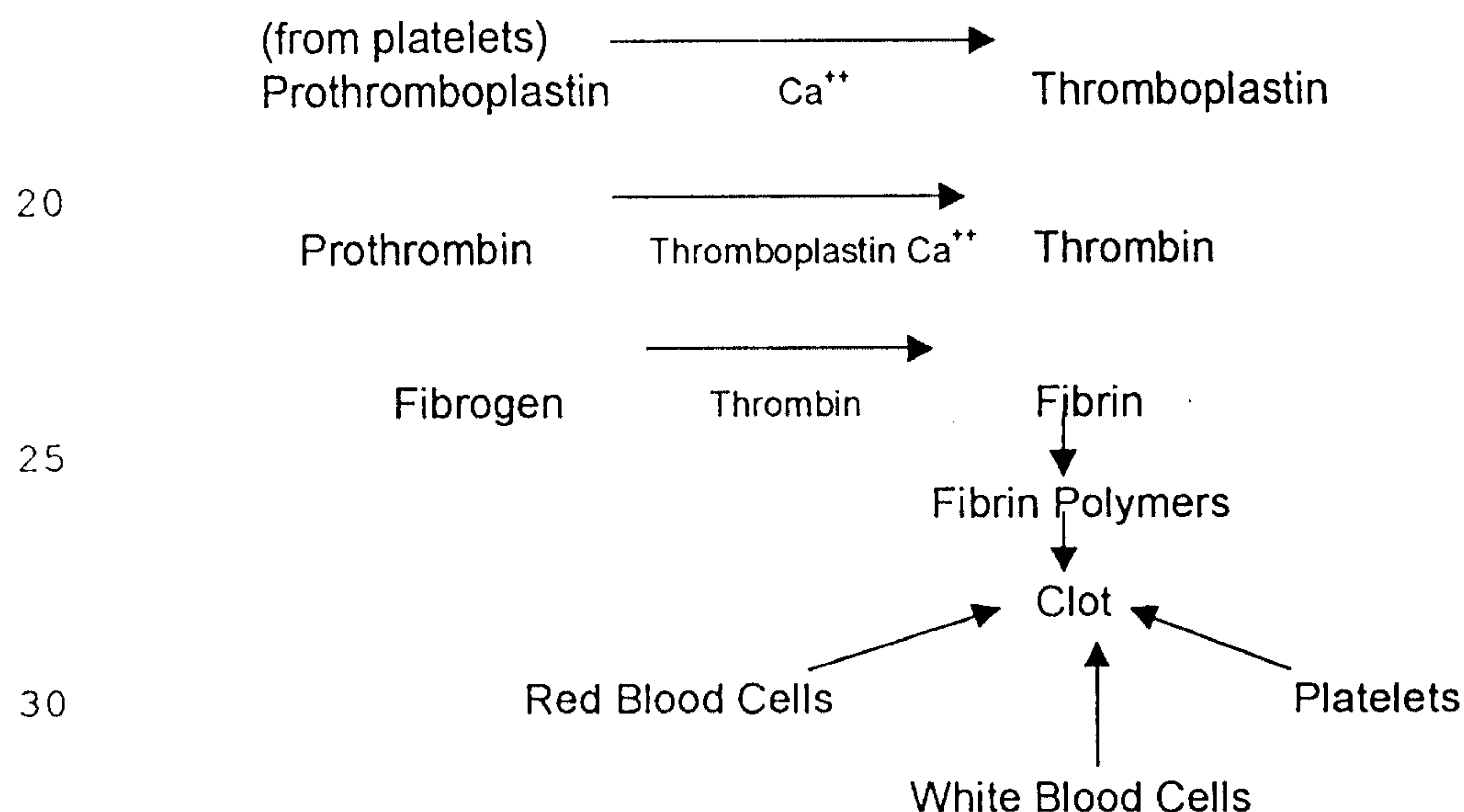
Blood contains both a solid and a liquid component. The liquid component is called plasma and contains a very broad variety of proteins. Among them are albumin, immunoglobulin and an assortment of proteins which participate in blood clotting. The solid components of the blood include red



blood cells (erythrocytes), white blood cells (leucocytes), and platelets. Of these, only platelets participate directly in blood clotting.

When blood clots, depending upon the immediate cause, the proteins in the plasma which are involved (which are proteolytic enzymes) act in a chain reaction (i.e. protein #1 activates protein #2 which activates, in turn, protein #3, etc.). This is called the cascade mechanism of blood clotting. Simplifying the process, the last three steps are as follows:

Irritation and disruption of platelets cause the release of Prothromboplastin. Calcium ions ( $\text{Ca}^{++}$ ), which are normally present in the plasma, cause the conversion of inactive Prothromboplastin into the active proteolytic enzyme, Thromboplastin. Thromboplastin, in the presence of calcium ions ( $\text{Ca}^{++}$ ) causes the activation of Prothrombin into Thrombin. Thrombin (also a proteolytic enzyme) acts upon Fibrinogen (present in great quantity in the plasma) to remove a portion of that protein, thus converting it to Fibrin, which then actively polymerizes with itself. A simple diagram of this clotting process is shown below.



Fibrin molecules are, as the name implies, arrayed in long strands. These molecules are a very "sticky" protein causing them to adhere to the tissue surrounding the wound (both epithelial tissue and deeper laying muscle and other connective tissue). Additionally, Fibrin molecules stick not only to tissue

adjacent to the wound, but also to themselves. This "self-sticking" forms a molecular web which expands and becomes stronger as more and more Fibrin strands become enmeshed across the wound. As blood continues to flow from the wound, the solid components of the blood become enmeshed, trapped and stuck upon the Fibrin "web", thus eventually blocking the egress of blood from the wound...forming a clot.

The clot naturally falls off when the damaged tissues underneath the clot (the callus of dedifferentiated wound tissue) becomes reorganized into repaired tissue.

## 10 ALTERNATE THEORIES

### MECHANISM OF ACTION OF THE INVENTION

The invention includes a non-drug, non-biological powder that covers a wound to control bleeding and fluid loss, absorbs wound exudate and protects against abrasion, friction, desiccation and contamination. This powder is composed of a uniform admixture of a hydrophilic polymer and an inorganic Ferrate ionic material. In one delivery mode, the granules/powder are used by sprinkling directly onto the wound site or in the nose by using a moist cotton/Dacron applicator containing the admixture. The admixture and its constituents are applied topically and is not metabolized by the body.

20 The mechanism of this invention is independent of the normal clotting mechanism, the clotting cascade. The invention creates a synthetic plug or barrier by providing its own means of binding with the skin, wound tissue and blood components. The invention provides for linking trivalent ions with tissue and blood components to the resin, rapidly forming a matrix regardless of anticoagulant usage. Being independent of the normal blood clotting mechanism, it may be functional for use by persons using anti-coagulants which interfere with, and prevent coagulation and by persons afflicted with genetic defects in the blood clotting mechanism such as hemophilia. It should be noted that normal blood clotting (unless inhibited by patient therapies or prevented by genetic defects) can and does occur beneath, and simultaneously with, the invention's artificial matrix/clot formation.



A possible secondary mechanism may be that the trivalent ferric ions irritate platelets to release not only Prothromboplastin, but also biologicals involved with wound healing, thereby promoting the reconstruction/regeneration of the damaged tissue. Other possibilities include the chemical stimulus by  
5 trivalent Ferrate ions of the precursors to active coagulation components.

The trivalent ferric ionic component of the invention may bind to the skin and the tissues exposed by the open wound. As red and white blood cells and platelets are carried out of the wound in the plasma, they bind with the ferric ions and the resin to form a water-resistant barrier, an artificial clot to the escaping  
10 blood. The tissue exudates and plasma (the lymph and the liquid component of the blood, which is mostly water), are absorbed by the resin polymer. This absorption of fluid by the resin polymer causes it to swell vigorously. This swelling, in turn, occludes the wound site, thus controlling/stopping the flow of blood.

15 The protective matrix of the ferric ions, the water-swollen resin, natural solid blood components (fibrin plus the red cells, white cells and platelets) combine to cause the rapid formation of a protective matrix. In accomplishing this, the invention helps promote healing, protects against infection and minimizes the pain and discomfort to the wound area.

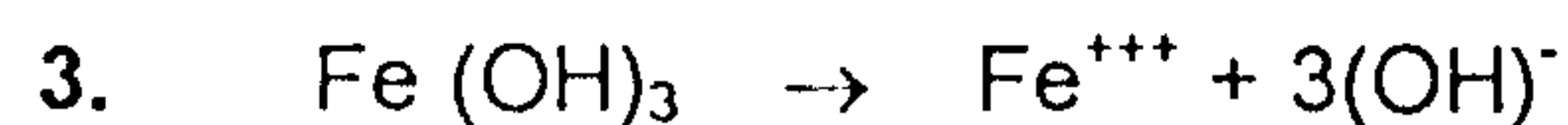
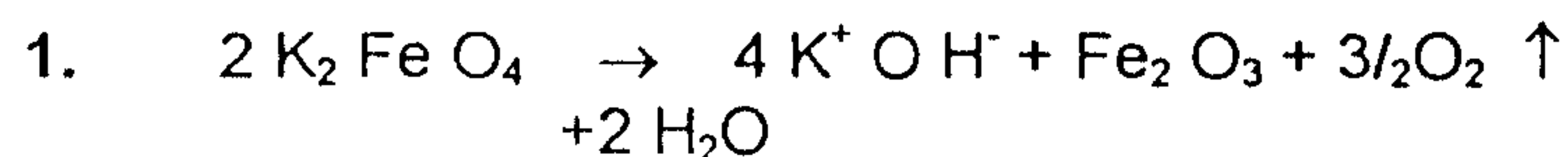
20 All polyvalent cations can induce the natural blood clotting cascade. It is known that the decomposition of potassium ferrate produces the finest particles of iron oxide ( $\text{Fe}_2\text{O}_3$ ) available. (See U.S. Patent 4,545,974). Upon addition to water,  $\text{K}_2\text{FeO}_4$  becomes  $\text{Fe}^{+++}$  in the form of  $\text{FeOOH}$ , which upon drying, yields  $\text{Fe}_2\text{O}_3$ . The  $\text{FeOOH}$  (or  $\text{Fe}_2\text{O}_3 \cdot \text{H}_2\text{O}$ ) is a solid in suspension and this ultra-fine  
25 material seems to be an ideal irritant for platelet membranes, thereby releasing the prothromboplastin that is needed to initialize the natural clotting cascade. It is possible that they may tend to rupture the platelets themselves, thereby causing a massive release of clotting factors as does the rough surface of a wound achieve the same end.

30 The  $\text{Fe}^{+++}$  ion is an example of a polyvalent cation that will induce coagulation of blood. Trivalent ions, by lowering the zeta potential of a particle in solution, allow the particles (platelets) to aggregate more easily. Platelets are

small disks of cytoplasm found in the blood of mammals. After a wound is received they begin to aggregate and stick around the wound area, causing the aggregation and sticking of another cytoplasmic component, the thrombocyte. During this aggregation process, certain phospholipids from the membrane of the platelets contribute to the overall clotting process, combined with the inactive plasma enzyme, Factor XII. Mechanical abrasion of the platelet membranes is important in freeing the phospholipid component from the platelets.

#### RANGE OF USEFUL SALT FERRATES

Initially, applicants have found that the utilization of potassium ferrate, again likely based upon the above-recited theory, effectively accomplishes the accelerated clotting of blood flowing from an open wound. The apparent chemical ferrate reaction with water found in blood is as follows:



One of the important results is the production of the trivalent  $Fe^{+++}$  ion which appears to be the beneficial clotting agent provided in this aspect of this invention. Moreover, it has been determined that the present invention acts on all body fluids containing protein, such as that which flows from an open skin blister or burn.

A broadening of this aspect of the inventive compound would be to substitute the potassium salt with others which possess the same cation properties as does the potassium cation. Those salt elements which will substitute for the potassium cation are shown in Tables I and II herebelow.



TABLE I

	H	Hydrogen
	Li	Lithium
	Na	Sodium
5	K	Potassium
	Rb	Rubidium
	Cs	Cesium
	Fr	Francium

TABLE II

10	Be Beryllium	Mg Magnesium	Ca Calcium
	Sr Strontium	Ba Barium	Ra Radium
	Ti Titanium	V Vanadium	Cr Chromium
	Mn Manganese	Fe Iron	Co Cobalt
	Ni Nickel	Cu Copper	Zn Zinc
15	Ga Gallium	Ge Germanium	Zr Zirconium
	Nb Niobium	Mo Molybdenum	Tc Technetium
	Ru Ruthenium	Rh Rhodium	Pd Palladium
	Ag Silver	Cd Cadmium	In Indium
	Sn Tin	Hf Hafnium	Ta Tantalum
20	W Tungsten	Re Rhenium	Os Osmium
	Ir Iridium	Pt Platinum	Au Gold
	Hg Mercury	Tl Thallium	Pb Lead
	Bi Bismuth	Al Aluminum	As Arsenic
	NH <sub>4</sub> Cation	N(C <sub>4</sub> H <sub>9</sub> ) <sub>4</sub> Cation	

25 In addition to the above salts in the cation form, all zeolites, sulfonated coal, and natural occurring membranes such as protein membranes will also act in compound form with ferrate to release the trivalent Fe<sup>+++</sup> ion to effect blood and body fluid coagulation.

## ELIMINATING STINGING EFFECT

In utilizing the  $K_2 Fe O_4$  as above described to arrest blood flow from a bleeding wound, equation 1 shows the presence of hydroxide  $(OH)^-$  radicals which are produced. The hydroxide  $(OH)^-$  radicals remain present in equation 3  
 5 and cause stinging at the wound site. Moreover, all of the cation salts of Table I produce the same result, i.e. stinging caused by the presence of the hydroxide ion.

All of the cation salts listed in Table II, however, produce a slightly altered chemical reaction which neutralizes all of the hydroxide ions produced. For  
 10 example, using a calcium cation salt to replace the potassium cation causes the following chemical reaction with water in blood:



As can be observed from Equation 4, no hydroxide ions are produced. Rather, all are neutralized and combined with calcium as shown in the equation.

15 As provided by the above compounds, a method of arresting blood and body fluid flow from an open skin wound is provided. An effective amount of any of the above salt ferrates, and preferably potassium ferrate in powder form, is applied directly onto the wound to interact with flowing blood or body fluid to accelerate its clotting.

## 20 SALT FERRATE COMBINED WITH RESIN

Although the above methodology and utilization of a salt ferrate greatly enhances blood clotting, the wound nonetheless remains opened and generally unprotected unless the salt ferrate is combined with a carrier such as a finger bandage, swab or the like which has been impregnated or coated with a dry  
 25 powder taken from one of the above chosen salt ferrate hemostatic agents.

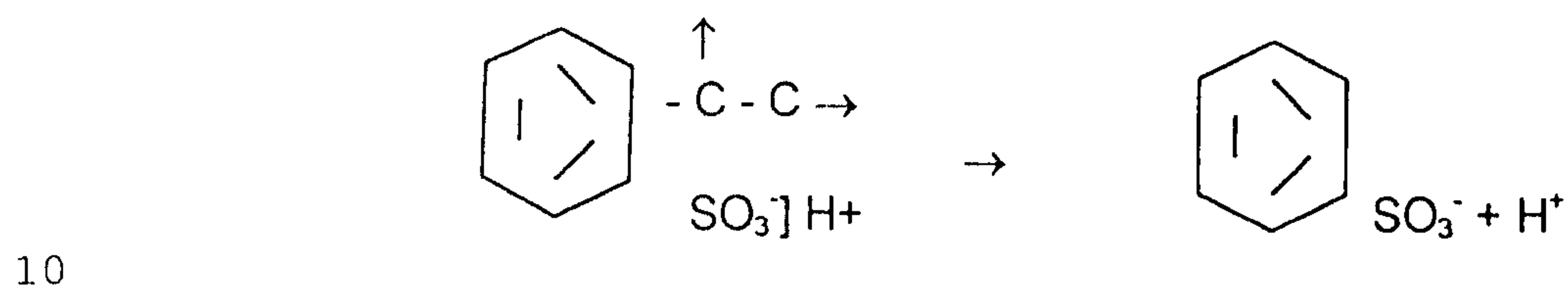
By the addition of an ion exchange resin R with the salt ferrate, an additional benefit of protective matrix formation or depositing of a substance produced by the reaction with water in the blood is accomplished over the open wound. Details of the hemostatic agent and method of producing the preferred  
 30 ion exchange resin R in the form of styrene divinylbenzene are disclosed in the previously referenced patents . As

described in formulas herebelow, the resin R may be shown in its chemical form

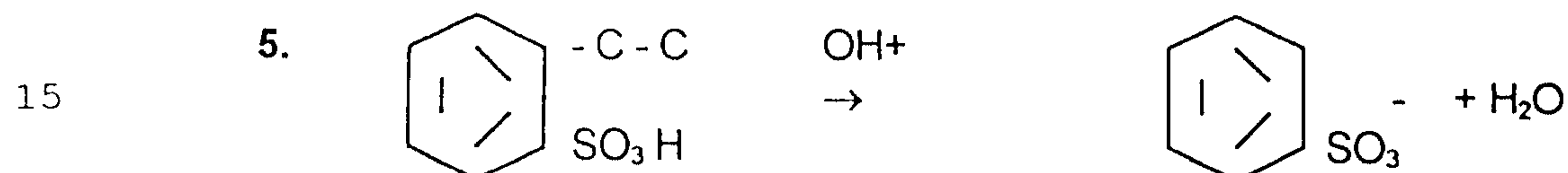


or generally designated by the symbol "R" for simplicity. The ion exchange resin R is sulfonated as is shown in chemical terms in each chemical equation herebelow.

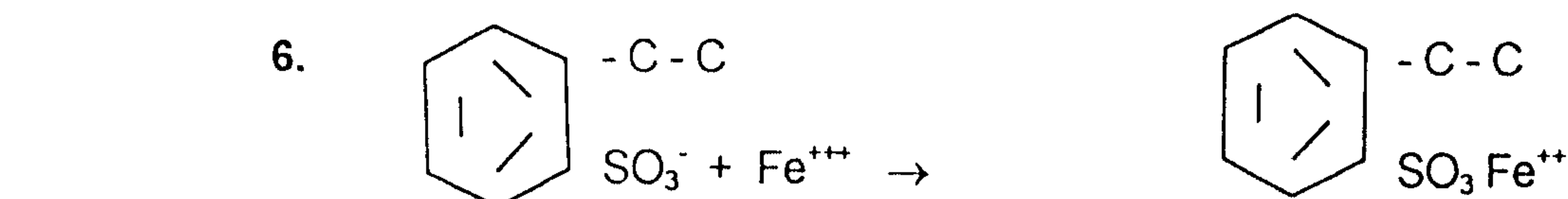
An acid form of the sulfonated ion exchange resin R in acid form is shown symbolically as follows:



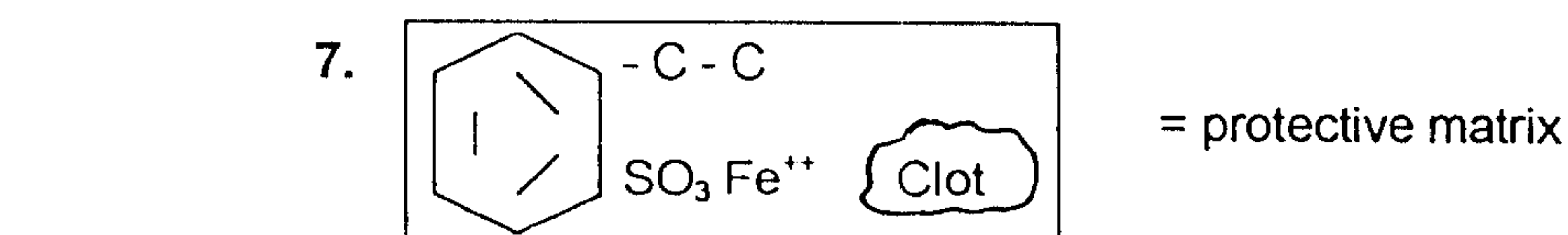
When the preferred hydrogen form of this sulfonated ion exchange resin R is in the presence of the salt ferrate and water within blood, the following reaction serves to neutralize the hydroxyl ions produced in equation 3 above.



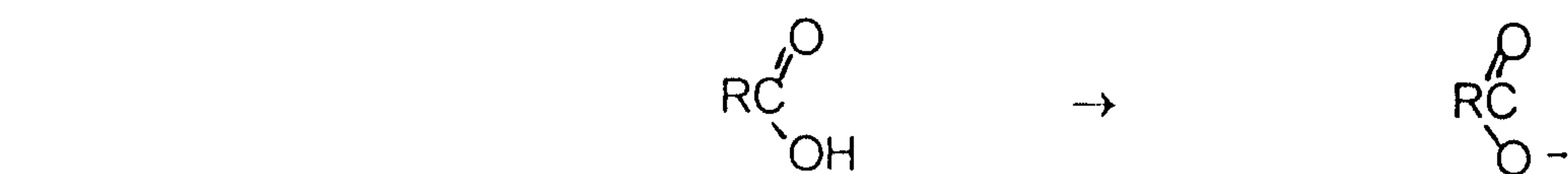
In addition to neutralizing hydroxyl ions by the presence of even trace amounts of the resin R to decrease or totally eliminate the stinging effect, excess trivalent  $\text{Fe}^{+++}$  ions interact with the resin as follows:



25 Thus, excess trivalent  $\text{Fe}^{+++}$  charged ion cross links with the clotting blood in accordance with the following equation:



The amino acids in the blood protein are shown to interact with the resin:

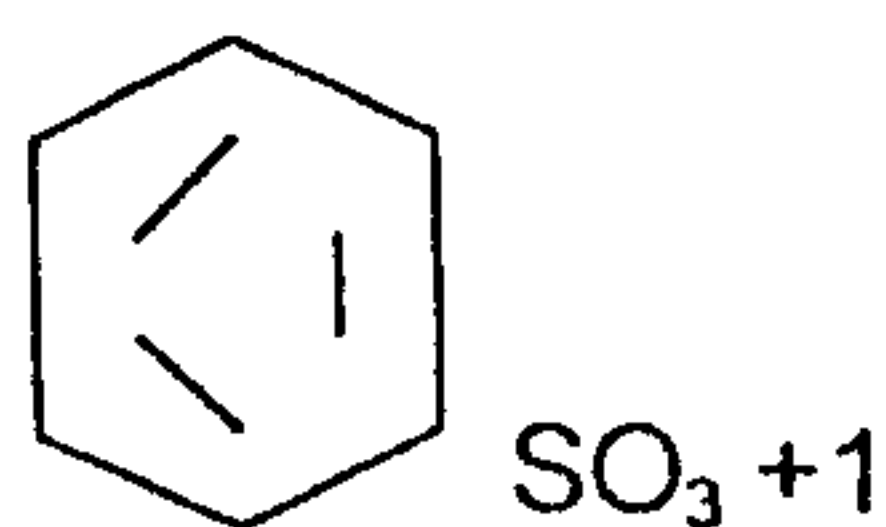


The  $\text{K}_2\text{FeO}_4$  is hygroscopic, small particles approximately 50 to 100 mesh size for best surface area. The ion exchange resin R is preferably in an acid form with some substitute Ca calcium ions as shown in equations 4 to 7. The cross

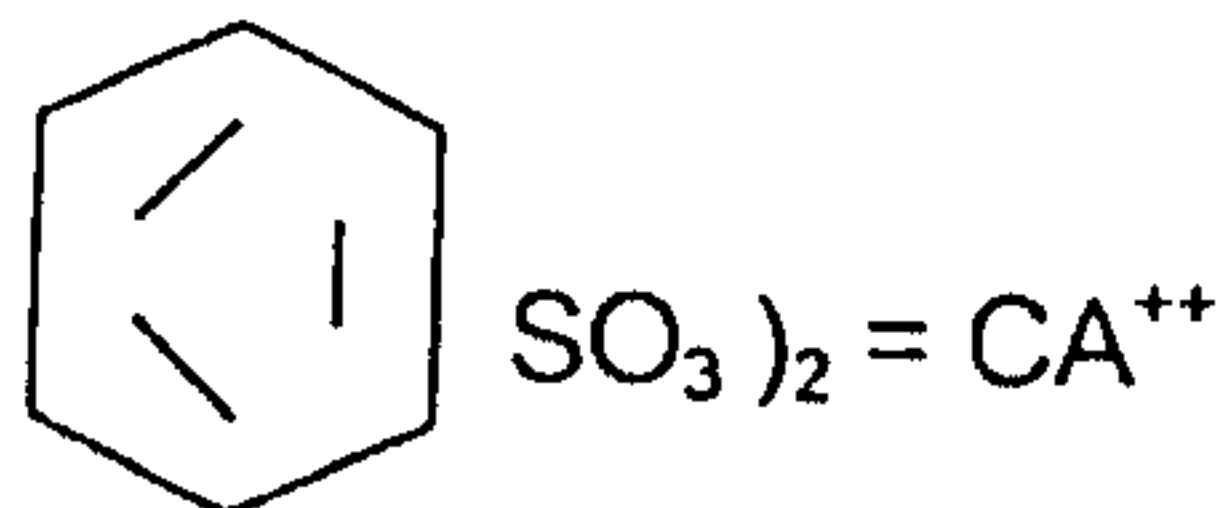
linking of the resin R should be below 4.0 and as low as 0.25% and hygroscopic. The weight ratio should favor the dry ion exchange resin R by at least 4 to 1 of dry salt ferrate. The ion exchange resin R is preferably a cation exchange resin.

In another embodiment, a small amount of divalent calcium  $\text{Ca}^{++}$  may be added as an additional coagulant. Heparins, EDTA (Ethylene Dismine Tetracacitic Acid), potassium oxalate, and warfarins are anticoagulants and are ionic in nature and remove Calcium  $\text{Ca}^{++}$  and trivalent ion  $\text{Fe}^{+++}$  by chelation to inhibit the natural clotting cascade. By supplying excess of polyvalent ions, the above anticoagulants and others can be overcome and clotting can occur. Also, in addition to the

hydrogen form of the resin R -



a given ratio of the calcium salt



can supply excess of this ion to further induce blood clotting. The ferrate in contact with the blood - water on the skin creates oxidative capacity which is a strong disinfectant to the wound.

## SUMMARY OF BENEFITS

By combining even a trace amount of the above-described sulfonated resin ( $\text{RSO}_3$ ) as an admixture with potassium ferrate ( $\text{K}_2\text{FeO}_4$ ), the following benefits are derived:

1. The trivalent  $\text{Fe}^{+++}$  + 3  $\text{RSO}_3$  produces a protective matrix and blood flow stoppage;
2. The oxidizing capacity produced by the reaction serves as an antibacterial, antiviral and antifungal agent;
3. The clotting with resin R produces a protective matrix that acts as a protective coating for the wound;
4. Resin ( $\text{RSO}_3$ ) in this admixture neutralizes hydroxyl ions to prevent stinging.



## EXAMPLE 1

## Anhydrous Powder Preparation

A ferrate - ion exchange resin admixture (moisture free) was prepared for direct application to a bleeding injury. The cation exchange resin R was prepared  
5 in the washed hydrogen form, and then dried at 110° for 24 hours and powdered in grinder to about 100 mesh.

This hemostatic agent was then applied directly to a fresh bleeding finger wound produced by a skin lancet having a penetration of 1.6 - 2.2 mm. The subject was 77 years old, skin condition non-flexible. Wound blood flow was at a rate of  
10 0.206g/30 seconds or .0412g per minute to .0606g per minute.

When a single penetration of the skin was made and blood flow started at 0.0412 to 0.0605 g per minute, application of 5 sec. of the above resin - ferrate hemostatic agent directly to the wound dropped blood to zero as determined with a blot pickup of 0.0020g within 1.0 minute. The resin- ferrate applied was on the order  
15 of 0.0175 - 0.0170 grams, forming a hard protecting sterilized coating over the penetration injury by the time that blood flow from the wound was stopped.

## DOSAGE ECONOMY

Pretreatment Blood Flow..... .0305g blood/30 sec. (.0605g/min)

After treatment Blood Flow..... .0010g blood/30 sec. (.0028g/min)

20 Dosage..... .0174g of anhydrous ferrate and resin admixture was used to treat wound.

At this dosage, a 30g quantity of the hemostatic agent will provide approximately 1724 separate treatments.

## METHOD OF PREPARATION

25 Just Prior to Use

The above-described anhydrous compound is preferably in the form of a combination of potassium ferrate ( $K_2FeO_4$ ) and the acid form of low cross-linked ion exchange resin particles. Both of the materials are in powder form and are stored together in an anhydrous form (no water). They have been previously applied  
30 directly to body fluids, i.e. blood, in the dry form (powder). Using this technique, this dry compound is difficult for control as to location of application and stability on a wound.

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Mix the resin and the  $K_2FeO_4$ . Then add the gelatin and mix. Within five (5) minutes, spread this paste-like mixture on the bleeding wound. The resin ferrate applied in this form controls bleeding.



## EXAMPLE 3

Compound ingredients:

0.1400 gm  $\text{RSO}_3$  [2.0% X-L]

0.0120 gm  $\text{K}_2\text{FeO}_4$

- 5 Mix the resin and  $\text{K}_2\text{FeO}_4$  with blood from a victim's wound and then apply this paste-like mixture to the wound from which the blood was previously obtained. Cover the wound evenly with the prepared paste mixture to control the bleeding.

## ACCELERATED BLOOD CLOTTING

- 10 The present invention, in one aspect, deals with the utilization of an inorganic acid containing oxygen known as an oxyacid in the salt form. Select oxyacid salts alone or in combinations as described herebelow, appear to have a similar beneficial effect upon accelerating the coagulation of blood and other protein based fluids flowing from an open wound.

- 15 The oxyacid salts which have been shown to produce this blood coagulation acceleration are as follows:

1. Alkali & alkaline earth salts;
2. Oxyacid salts of transition metals;
3. Halogen oxyacids;
4. Alkali & alkaline oxides, peroxides and superoxides.

## 20 ELIMINATION OF STINGING

- A hydrophilic proton donor may also be added which chemically combines to eliminate the sting caused by the presence of hydroxyl ions produced after the blood clotting reaction is in progress. In general, there are three categories of hydrophilic proton donors which will act as a matrix to accomplish the neutralization of the hydroxyl ions, where present, as follows:

1. Cation exchange resin (sulfonated, phosphorated or carbonated)
2. Acid producing salts
3. Organic acids.

- 30 Following are more specific examples of each of the three above-referenced general categories of compounds which will neutralize the hydroxyl acids present in the blood coagulation reaction of the present invention as follows:

1. Hydrogen form cation exchange resins (sulfonates)
2. Hydrogen form cation exchange resins (phosphonates)
3. Hydrogen form cation exchange resins (carbonates)
4. Acidic inorganic salts (e.g. NaHSO<sub>4</sub>)
5. Organic acids (e.g. Citric acid, carboxylic acids, amino acids, peptides, proteins)
6. Solid desiccants (e.g. CaCl<sub>2</sub>, CaSO<sub>4</sub>)
7. Porous hydrophilic matrix resins
8. Silicates (e.g. bentonite clay, hydroxy apatite)
9. Three component oxyacid, proton donor, solid desiccant
10. Polyvinyl alcohol
11. Carboxy methylcellulose

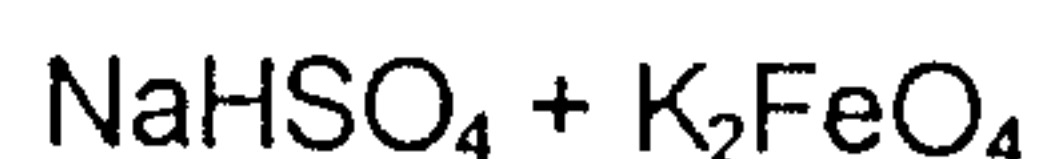
Solid desiccants also accelerate blood clotting further by water absorption from the blood.

#### 15 PROTECTIVE MATRIX FORMATION

Another preferred function of the present invention is to create an artificial scab atop the open wound as the blood is clotted to arrest blood flow while also serving as a potential anti-microbial agent in the form of an oxidant. Such artificial scab forming agents fall into two general categories. The first category is that of a cation exchange material in combination with:

1. K<sub>2</sub>FeO<sub>4</sub>;
2. KMnO<sub>4</sub>;
3. Na<sub>2</sub>O<sub>2</sub>;
4. KIO<sub>3</sub>
5. K<sub>2</sub>FeO<sub>4</sub> + KMnO<sub>4</sub>.

The second category is exemplified by the compound formed as an admixture of:



as a unique combination of an oxyacid salt and an acidic inorganic salt, respectively, also provide this artificial scab-forming agent function.

The two major types of oxyacid salts, namely transition metal salts and halogen salt, act differently with respect to the scab-forming aspect of this invention.



The transition metal oxyacid salts form metal oxides which are important in the matrix formation, or scab formation, when combined with the cation exchange material or any other hydrophilic proton donor. Halogen oxyacid salts do not possess this quality, nor do alkali or alkaline oxides, peroxides or superoxides. Although this later group does create an oxidizing environment that facilitates clotting, they do not act as efficiently as do the transition metal oxyacid salts to form a protective scab over the wound.

### MODES OF DELIVERY AND APPLICATIONS

Modes of product delivery and applications include the following:

10 Medical applications include a variety of hemostasis usages for arresting blood flow caused by minor wounds and potentially more serious wounds such as gunshots, stabs, or other severe lacerations creating blood loss. The material is expected to assist in stabilizing blood pressure and to allow the patient to maintain minimal blood loss in the most rapid manner possible.

15 A. Fine powder spray system.

Inert propellants such as nitrogen, nitrous oxide and/or carbon dioxide may be utilized to optimize product performance, stability and extended shelf life. The spray is highly controlled so that the operator can direct the spray and apply desired amount of product until satisfactory wound healing occurs. Canister size would be attractive and compact to fit in small EMT equipment container or into a small pocket. For example; the significant cost benefit of the spray embodiment will allow for larger use of the product. Military personnel equipped with such a spray will be able to keep a can of material for use in emergency situations. The smaller the size, the more attractive and mobile it would become, thereby achieving larger market appeal.

B. Bandage wound dressing.

Such delivery systems would contain the subject material in an impregnated form. The base material might be a biocompatible material such as natural or man-made material such as Dacron\* or cellulose that would provide additional tensile strength to an open wound. This added benefit could allow for more severe wounds to be treated. The impregnated bandage would need to be packaged in a way such that the material was not subjected to moisture in open air until immediately prior to

\* Trademark

use, maximizing effectiveness. Bandages of different sizes can be created to accommodate various size wounds.

C. Impregnated Sponge

Application of the hemostatic agent into a sponge or sponge-like material will enable the sponge to be easily manipulated within the body cavity during surgical operations offers distinct advantages. This embodiment would maintain the advantages of arresting blood flow from sources within the body in a structure that would retain its shape and create a barrier between the source of blood flow and the surgery area. The impregnated sponge would also absorb excess blood.

10 D. Tea Bag Form

The hemostatic agent can also be loaded into porous "tea bags" to achieve the maximum absorbency effect for blood or other body fluids inside the body. This concept can be applied to feminine hygiene products or the like.

E. Foam

15 The use of a foam has the benefit of conforming to the exact geometry that the body cavity or wound has created. The direct benefit of the hemostatic agent reacting immediately by direct application of a foam upon contact with blood and body fluids flowing from a wound requires a specialized applicator design such that the active powder and foam is co-applied simultaneously upon demand. The container may have two separate chambers that house the foam material and the dry hemostatic agent independently to prevent activation prior to use.

F. Pouring and Sprinkling

Direct dispensing of the hemostatic agent directly onto the wound will arrest blood flow and produce a clot.

25 G. Cotton Swab Applicator

This carrier embodiment consists of a bottle containing the dry coagulating agent into which a cotton swab could be dipped and then applied to smaller localized wound areas. Alternatively, powder may be poured onto gauze and the swab rolled in the powder. The use of the material for arresting nose bleeds could be in the form of a cotton swap applicator or the like which may have been moistened and previously been dipped into the material which is then applied directly to the nasal



cavity. This should prevent further damage to the sensitive membranes within the nose that is caused by the use of other products such as cauterization.

#### H. Direct Container Application

Another method of applying the invention is via a round plastic dispenser that fits snugly into a bleeding nose, the container filled with the hemostatic agent or dipped into the material immediately prior to application.

#### SPECIALIZED USES

The present invention is suitable for healing bed sores or decubitus ulcers by creating a protective surface barrier or temporary skin that is flexible while producing oxidative capacity at the surface of the wound, which in turn promotes healing. These ulcers sometimes have extreme difficulty in healing because of the lack of blood flow (especially in cases of diabetics) in the wound area. The product should stimulate wound recovery by providing oxidative capacity and killing bacteria as well as providing protection from contaminated air and other aerosolized or suspended infection carriers.

The present invention is also suitable for the treatment of skin and tissue burns through the creation of a protective surface or crust over the burn area and promoting natural tissue healing by producing oxidative capacity under the damaged tissue area.

Another use includes surgical sealants for mating and/or keeping trauma-separated surfaces together. This invention could be also used in conjunction with surgical staples and other such devices and with femoral artery plug systems useful during cardiac catheterization. Ferrate promotes tissue healing and growth by providing oxidative capacity under the surface of the hard clot that is created upon contact.

A further advantage of the combined ferrate and resin product is that of meaningful fluid absorbency upon contact with resin which expands as fluid is absorbed, further acting as a plug inside of a wound. This addition of pressure further enhances the ability to arrest the flow of blood. The crosslinking of the resin polymer, which is an insoluble acid, could also be changed to control the clot matrix and structure allowing for control of clot flexibility and rigidity which is useful for applying to the surface of a wound.

Fibers such as cellulose acetate, rayon, dacron, cotton, silk and the like may be included within the material hemostatic agent to provide additional structure. This would allow for further strength and/or flexibility of the clot matrix.

5 Use of the invention in conjunction with repair surgery systems would also stop blood flow around and in between surgical sutures and with respect to other similar surgical procedures. The hemostatic material is perfectly suited for specialty wound dressings and wound management systems.

10 Veterinary use would include applying this material directly to an animal wound promoting rapid healing. It offers significantly greater protection in preventing a wound site from opening-up again as the animal moves around. This is due to the material's bonding and related adhesive characteristics.

Figure 1 is a general flow diagram of the various embodiments of the modes of delivery of the hemostatic agent, including potential additives that would be complimentary for specific applications in final product form.

15 Figure 2 depicts an ampule-form of dispenser **10** and includes a molded plastic sealed hollow cavity **12** containing a quantity of dry hemostatic agent **18** in powder form. By separating one of the ampules dispensers **10** and fracturing and separating the removable end **14**, an opening **16** is formed from which the powder **18** may be dispensed.

## 20 RESIN ENHANCEMENT

Referring now to Figure 3, the enhancement of the resin in the form of substantially increased fluid uptake will now be described in detail. As seen in Figure 3, a typical strong acid cation resin (SAC) cross-linked at a nominal 2.0% exhibits a moisture uptake capacity of approximately 80% prior to any enhancement.

25 A 0.5% cross-link SAC resin exhibits a 95% moisture uptake capacity. These percentages are in terms of total weight of a fully water-saturated quantity of the resin. In other terms, at 80% saturation, the resin itself would represent 20% of the total weight, a weight ratio of 4:1 water-to-resin.

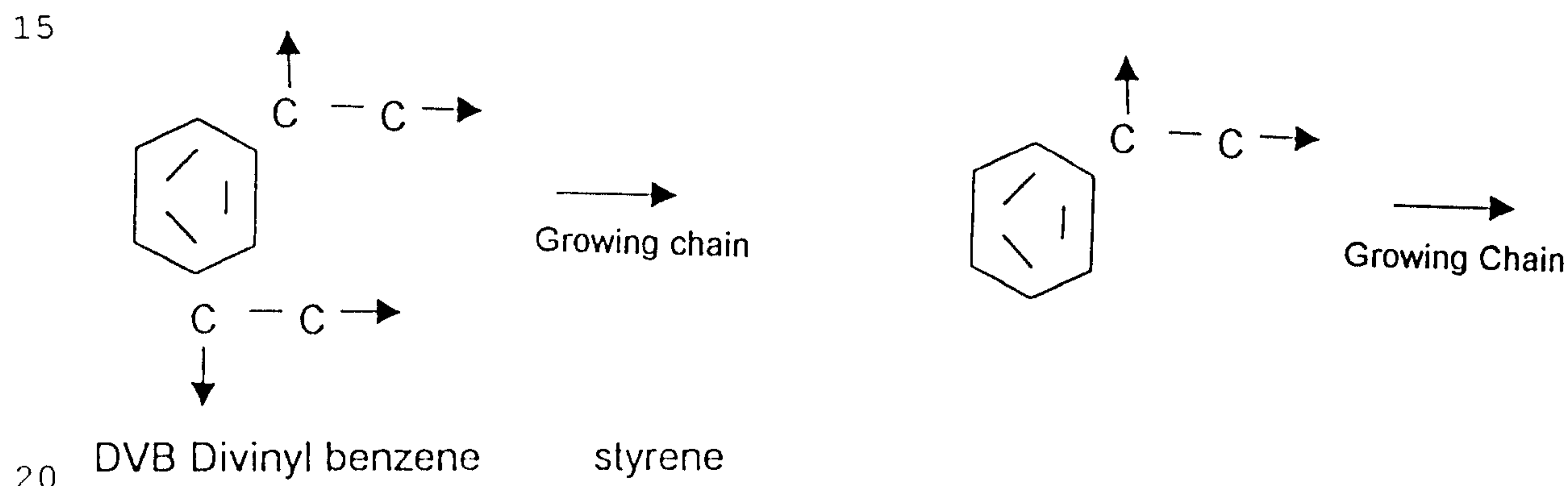
30 Because the fluid uptake or absorption of the resin is an extremely important aspect of this invention, increasing that moisture uptake capacity of the resin is highly desirable in accelerating the clotting action of the invention. To accomplish



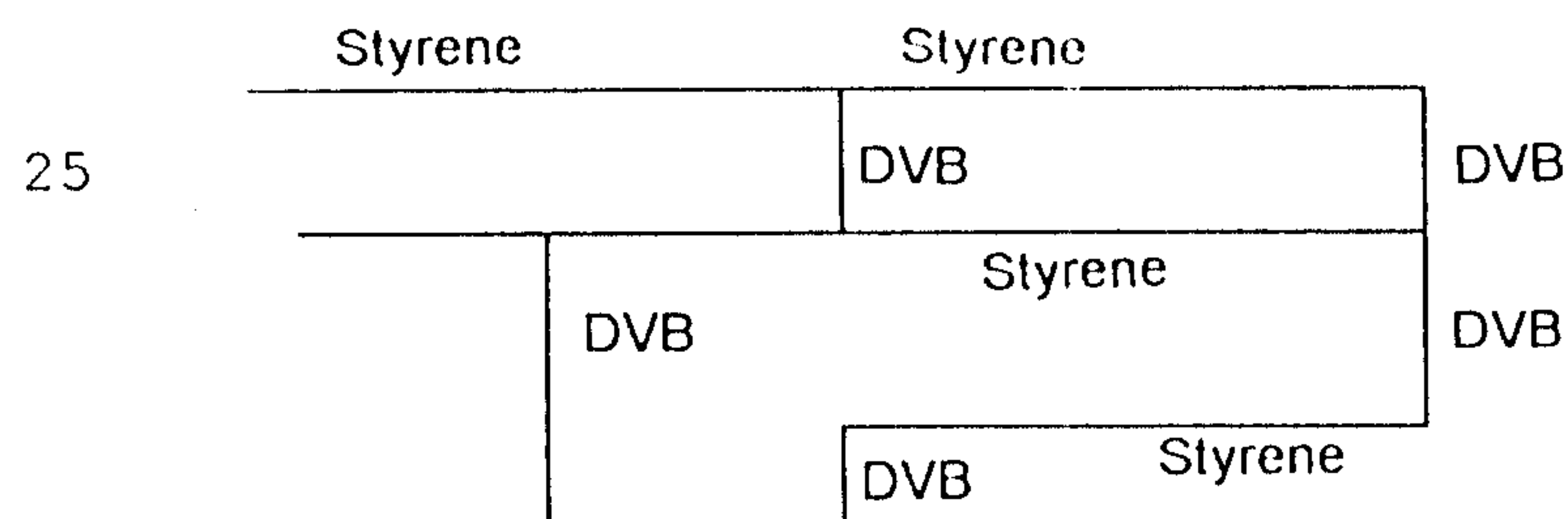
this enhancement, the resin is boiled in a time concentration of  $H_2O_2$  (hydrogen peroxide) for a time period of up to approximately 8 hours. After boiling, the resin is filtered, washed and dried, and then infused in an admixture process with the selected salt ferrate or oxy acid salt.

5 The process of enhancement with respect to the 2% cross-linked resin maintains the original spherical form of the bead; however, the original spherical form of the 0.5 cross-linked bead substantially deteriorates and loses its ability to absorb fluid almost entirely. Moreover, the manufacturing economy of 2% vs. 0.5% cross-linked resin is substantial in favor of 2% cross-linking and needs less waer to  
10 effect neutrolization fo the  $HOH^+$  radicals described hereabove.

The enhancement process may be viewed as breaking free radicals from the resin polymer which may also be accomplished by high energy light, sonic exposure, radiation and the application of immersion in bleach. A flow diagram of the process is shown herebeleow.



Shown diagrammatically, the process of resin enhancement is shown herebelow:



The benefit of this enhancement of the resin for increased moisture or fluid absorption is shown in Figure C. This benefit increases steadily with the time for boiling the resin in the heated hydrogen peroxide, increasing up to a percentage of moisture uptake of approximately 98% following boiling for approximately 450  
5 minutes with lesser levels of enhancement achieved with shorter boiling times as shown in Figure 3.

While the instant invention has been shown and described herein in what are conceived to be the most practical and preferred embodiments, it is recognized that departures may be made therefrom within the scope of the invention, which is  
10 therefore not to be limited to the details disclosed herein, but is to be afforded the full scope of the claims so as to embrace any and all equivalent apparatus and articles.



**CLAIMS:**

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows

1. The use of a mixture for arresting the flow of blood from a bleeding wound,
  - A. said mixture comprising a substantially anhydrous compound of an oxyacid salt ferrate (VI) that hydrates in the presence of blood or other protein-containing body fluids to produce  $\text{Fe}^{+++}$  with blood flowing from a wound;
  - B. the mixture from A to be applied to the wound for a working time of five minutes to effect sufficient clotting of the blood and to arrest substantial further blood flow from the wound.
2. The use of Claim 1, wherein:
 

said compound provided in Step A is formed of a salt selected from the group consisting of H, Li, Na, K, Rb, Cs and Fr.
3. The use of Claim 1, wherein:
 

said compound provided in Step A is formed having a salt selected from the group consisting of Be, Mg, Ca, Sr, Ba, Ra, Ti, V, Cr, Mn, Fe, Co, Ni, Cu, Zn, Ga, Ge, Zr, Nb, Mo, Tc, Ru, Rh, Pd, Ag, Cd, In, Sn, Hf, Ta, W, Re, Os, Ir, Pt, Au, Hg, Tl, Pb, Bi, Al, As,  $\text{NH}_4$  and  $\text{N}(\text{C}_4\text{H}_9)_4$ .
4. The use of Claim 1, wherein:
 

said compound provided in Step A is formed of a salt selected from the group consisting of H, Li, Be, Na, Mg, K, Ca, Rb, Sr, Cs, Ba, Fr, Ra, Ti, V, Cr, Mn, Fe, Co, Ni, Cu, Zn, Ga, Ge, Zr, Nb, Mo, Tc, Ru, Rh, Pd, Ag, Cd, In, Sn, Hf, Ta, W, Re, Os, Ir, Pt, Au, Hg, Tl, Pb, Bi, Al, As,  $\text{NH}_4$  and  $\text{N}(\text{C}_4\text{H}_9)_4$ .

5. The use of Claim 1, wherein;

said compound provided in Step A is  $K_2 Fe O_4$ .

6. The use of Claim 1, wherein:

said compound provided in Step A is formed of a salt which combines with water in the blood or aqueous media to eliminate substantially all hydroxide (OH) which cause a stinging sensation.

7. The use of Claim 1, wherein said aqueous media comprises:

whole blood, plasma, and/or lymph taken directly from the wound; deionized water; sodium chloride solution; aqueous dissolved gelatin; aqueous carboxy methacel; and aqueous carbohydrate solution.

8. The use of a mixture for arresting the flow of blood and other body fluids containing protein from an open skin wound,

- A. said mixture comprising a substantially anhydrous compound of a monovalent, divalent or a trivalent salt ferrate that hydrates in the presence of blood to produce  $Fe^{+++}$ , thereby promoting clotting of the blood, with a quantity of an aqueous media to form a paste;
- B. said paste to be applied to the wound for a working time of five minutes to effect sufficient clotting of the blood to arrest substantial further blood or body fluid flow from the wound.



9. A hemostatic agent for application directly onto a bleeding wound comprising:
- an oxyacid salt combined with an insoluble cation exchange material, said oxyacid salt combining with blood to promote blood clotting at the wound, said cation exchange material forming a protective cover over the wound as blood is thereby clotted.
10. A hemostatic agent as set forth in Claim 9, wherein said oxyacid salt is selected from the group consisting of:
- alkali and alkaline salts;  
oxyacid salts of transition elements;  
halogen oxyacids, and  
alkali and alkaline oxides, peroxides and superoxides.
11. A hemostatic agent as set forth in Claim 9, wherein said cation exchange material is an admixture of a cation exchange resin and a compound selected from the group that comprises:
- $K_2FeO_4$ ;  
 $KMnO_4$ ;  
 $Na_2O_2$ ; and  
 $KIO_3$ .
12. A hemostatic agent as set forth in Claim 9, wherein said hemostatic agent comprises:
- $K_2FeO_4$  as said oxyacid salt; and  
 $NaHSO_4$  as an acidic inorganic salt.

13. The use of a compound for arresting the flow of blood from a bleeding wound comprising:
  - A. providing a substantially anhydrous compound of an oxyacid salt combined with hydrophilic proton donor which hydrates in the presence of blood to thereby promote clotting of the blood;
  - B. said compound to be applied to the wound for a working time of five minutes to effect sufficient clotting of the blood to arrest substantial further blood flow from the wound.
14. A hemostatic agent for application directly onto a bleeding wound comprising:

an oxyacid salt combined with a hydrophilic proton donor material, said oxyacid salt combining with blood to promote blood clotting at the wound, said hydrophilic proton donor material combining with, and thereby neutralizing, hydroxylions formed as said oxyacid salt combines with blood to effect clotting.
15. A hemostatic agent as set forth in Claim 14, further comprising:

a solid desiccant combined with said oxyacid salt and said hydrophilic proton donor material, said solid desiccant further accelerating blood clotting by absorbing water in the blood.
16. A hemostatic agent for application directly onto a bleeding wound comprising:

a substantially anhydrous salt ferrate compound combined with an isoluble cation exchange material, said salt ferrate combining with blood to promote blood clotting at the wound, said cation exchange material forming a protective cover over the wound as blood is thereby clotted; said cation exchange material being a resin which is cross-linked greater than 0.5% and has been pretreated for increased moisture uptake to substantially exceed 80% by weight of the total weight of said resin when fully saturated with water.



17. A delivery vehicle for a hemostatic agent for application to bleeding wound, said hemostatic agent selected from a group comprising:

a substantially anhydrous compound of a monovalent, divalent or trivalent salt ferrate which hydrates in the presence of blood or an aqueous media to produce  $\text{Fe}^{+++}$ ;

a substantially anhydrous oxy acid salt combined with an insoluble cation exchange material; and

a substantially anhydrous oxy acid salt combined with a hydrophilic proton donor material;

said delivery vehicle taken from the group comprising:

a fiber material impregnated with said hemostatic agent;

a powder spray carrier within a pressurized container combining with said hemostatic agent as a dry powder upon discharging of the spray carrier from a spray nozzle of the container;

a cotton swab impregnated with said hemostatic agent;

a bandage impregnated with said hemostatic agent;

a sponge impregnated with said hemostatic agent;

a porous tea bag-like enclosure containing a quantity of said hemostatic agent; and

a foam carrier within a pressurized foam container combining with said hemostatic agent upon discharge of the foam carrier from a discharge nozzle of the foam container.

18. The use of a compound for arresting the flow of blood from a bleeding wound comprising:
- A. providing a substantially anhydrous compound of a salt ferrate which hydrates in the presence of blood to produce  $\text{Fe}^{+++}$  thereby promoting clotting of the blood;
  - B. said compound to be applied to the wound for a time sufficient to effect sufficient clotting of the blood to arrest substantial further blood flow from the wound.
19. The use of a compound for promoting healing of a bleeding wound comprising:
- A. providing a substantially anhydrous compound of salt ferrate and insoluble cation exchange material which will hydrate in the presence of blood to produce  $\text{Fe}^{+++}$  thereby promoting clotting of the blood and oxygen;
  - B. promoting blood clotting, followed by blood flow stoppage, by applying said compound to the bleeding wound;
  - C. substantially reducing the level of bacteria, virus and fungus at the wound during Step B by the presence of said oxygen;
  - D. forming a protective coating over the wound during Step B.
20. A composition which promotes healing of a bleeding wound consisting essentially of:
- a substantially anhydrous salt ferrate compound combined with an insoluble cation exchange material.



21. A hemostatic agent for application directly onto a bleeding wound comprising:

a salt ferrate combined with an insoluble cation exchange material, said salt ferrate combining with blood to form a trivalent  $\text{Fe}^{+++}$  ion which promotes blood clotting at the wound, said cation exchange material forming a protective cover over the wound as said trivalent  $\text{Fe}^{+++}$  ion is formed.

**R. WILLIAM WRAY & ASSOCIATES**

BOX 2760 - STATION D  
OTTAWA, CANADA K1P 5W8  
PATENT AGENT FOR THE APPLICANT

FIG 1

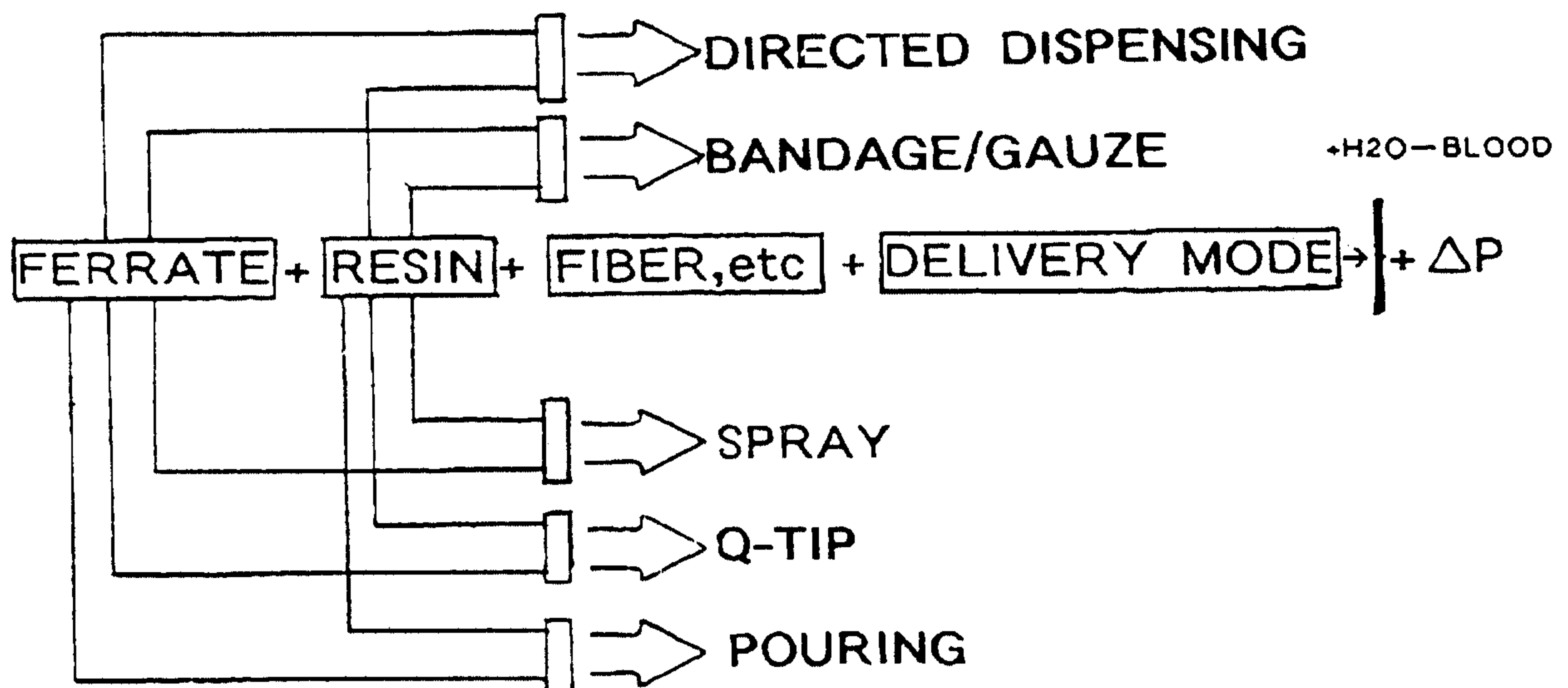


FIG 2

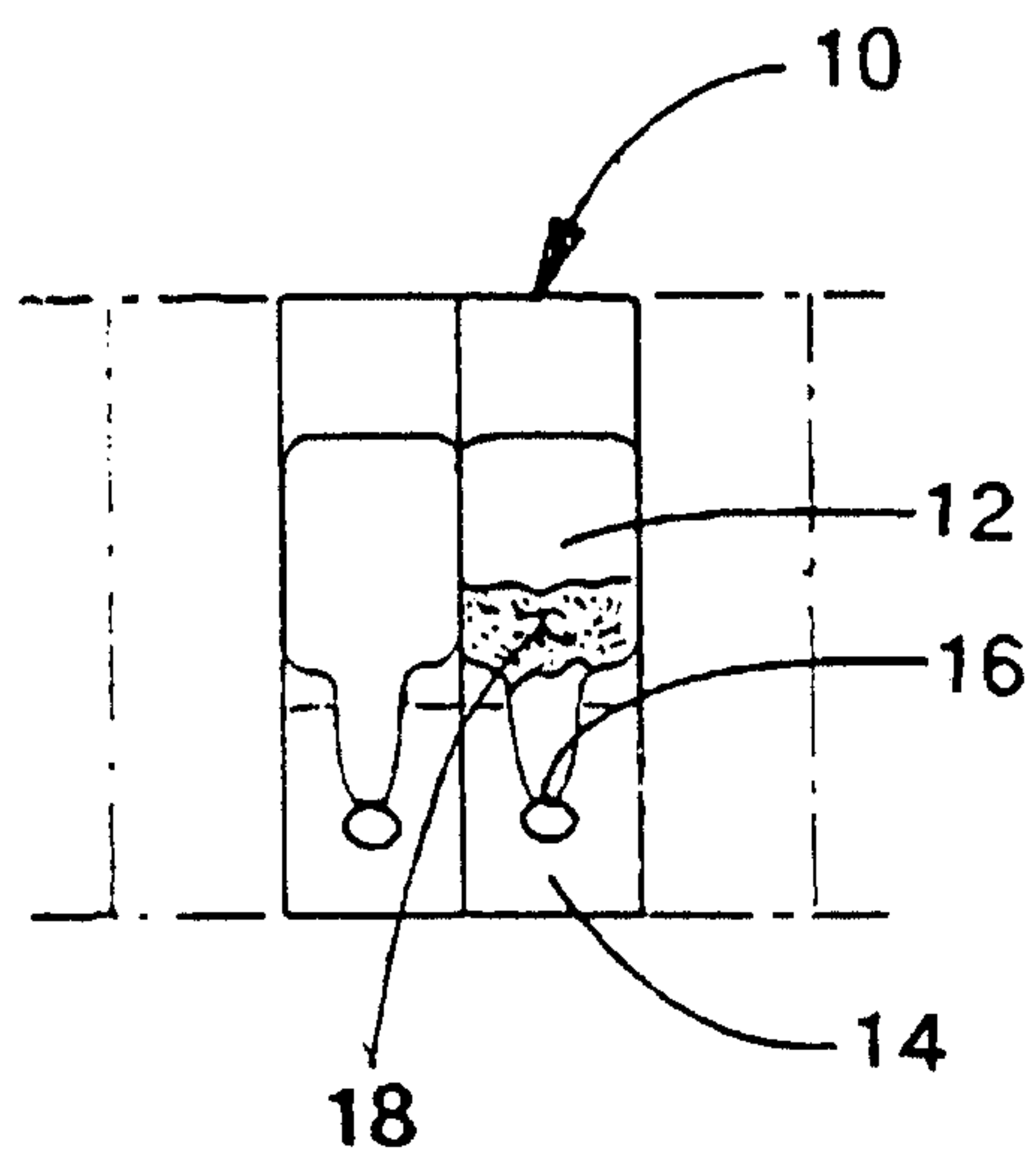




FIG 3

## 2% SAC - H+ Resin in Boiling 3% H2O2

