PATENT SPECIFICATION (11) 1 584 080

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(21) Application No. 50503/77 (22) Filed 5 Dec. 1977 (19)

(44) Complete Specification published 4 Feb. 1981

(51) INT. CL.³ A61K 37/02

(52) Index at acceptance

A5B 180 31X 31Y 38Y 39X J

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(54) ABSORBABLE HEMOSTATIC COMPOSITION

(71) We, ETHICON, INC., a Corporation organised under the laws of the State of New Jersey, United States of America, of Somerville, New Jersey, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:

This invention relates to a bone sealant, and more particularly, to an absorbable, semisolid composition for the control of osseous hemorrhage.

Various substances and compositions have been imployed by members of the medical profession to control the bleeding from cut bone surfaces. One class of materials used for the control of this type of hemorrhage is called bone wax. Bone waxes are used for the purpose of controlling hemorrhages from the cut surfaces of bones, such as those of the skull, by forcibly smearing the wax over the cut surface so that the material acts mechanically to occlude and seal the open ends of the bleeding osseous vessels and sinuses.

Bone waxes used in surgery today are generally prepared from refined beeswax which has been admixed with other non-absorbable and water insoluble hydrocarbons and vegetable oils. Certain disadvantages inhere in these bone wax compositions, as for example, relatively poor adhesion properties, separation of wax components and the hard, brittle state of the wax at room temperatures requiring use at elevated temperatures.

U.S. Patent No. 3,395,217 discloses non-absorbable bone wax compositions comprised of low molecular weight ethylene copolymer waxes containing from about 15 to about 40 percent by weight of another unsaturated constituent and having molecular weights in the range of 1000 to 4000. These waxes have a semisolid consistency such that they can be kneaded between the fingers when at room temperature and have the right amount of tack and adhesion so that they can be easily manipulated in the hands of the surgeon or applied by any suitable applicator such as a gloved finger, spatula or appropriate disposable applicator.

Absorbable bone waxes have also been suggested. U.S. Patent No. 2,772,999 describes a bone wax comprised of a water soluble innocuous base and free acid cellulose glycolic acid ether or free acid cellulose hydroxypropionic acid ether as a hemostatic agent. The composition also preferably contains a tackifier such as cellulose glycolic acid ether salt or cellulose hydroxypropionic acid ether salt (preferably sodium salt) and water as a plasticizer.

The Annals of Surgery *132*, 1128 (1950) describes an absobable hemostatic bone wax containing powdered oxidized cellulose as the hemostatic agent in a base of polyethylene glycol. The base is a mixture of high and low molecular weight polyethylene glycols selected to provide the malleability and consistency of material desired for this application.

The present invention provides a new absorbable bone sealant which is a putty-like semisolid at room temperature. The softness of the composition allows the material to be packaged in a syringe, plastic or coated paper envelope, or aluminum or glass tube from which it may be extruded or dispensed in desired amounts during use. The sealant has sufficient tack so that it adheres to bone surfaces, yet is easily manipulated in the hands of the surgeon without crumbling or sticking to the surgeon's gloves.

Absorbable bone sealant compositions of the present invention comprise a mixture of from 10 to 50 percent by weight of the total composition of a hemostatic powder in a water-soluble bicompatible base, optionally containing a small amount of tackifying agent, the hemostatic powder comprising a mixture of fibrin and collagen powders, preferably in substantially equal proportions. The base is preferably a mixture of water and a poly-ol such as glycerol, and the tackifying agent, if present, is preferably a polyglucoside such as dextran. The sealant is formulated to the consist-

ency of a semisolid which is extrudable from a large orifice syringe. The composition is packaged in a syringe, plastic envelope, or aluminum tube and sterilized by radiation. During use, small amounts of the sealant may be extruded from the package as required by the surgeon. The composition is effective to control osseous hemorrhage from cut bone and does not interfer with subsequent healing and rejoining of bone parts.

It is desirable that the hemostatic compositions of the present invention, which comprise a mixture of a hemostatic powder, an innocuous absorbable base, and, preferably, a tackifying agent, should be formulated to obtain a semisolid material which may be readily spread upon the surface of cut bone in order to arrest the flow of blood.

Fibrin powder useful in the present invention may be obtained from human or animal blood according to the method disclosed in U.S. Patent No. 3,523,807. The fibrin powder is preferably reduced to a particle size of 500 microns or smaller, and most preferably to a size of about 200 microns. The fibrin powder thus obtained comprises, together with the collagen powder, from 10 to 50 percent by weight of the total hemostatic composition.

Collagen powder, useful in the present invention, is a finely divided, fluffy material which may be prepared according to the method disclosed in U.S. Patent No. 3,742,955. The collagen powder is preferably reduced to a particle size of 2 mm or less, and most preferably to less than 1 mm.

The collagen powder and fibrin powder are preferably mixed in a ratio of 40–95 percent by weight fibrin, 5–60 percent by weight collagen, in order to obtain a final product having the desired characteristics of softness and malleability. In a particularly preferred composition of this invention, substantially equal proportions of fibrin and collagen powders are used with good results.

The base component of the hemostatic composition may be an aqueous solution of 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 glycerol, propylene glycol, 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. Glycerol and polyethylene glycols are the preferred base materials, and polymerized ethylene glycols having a molecular weight in the range of 200 to 4000 and a consistency varying from a liquid or low viscosity to that of a waxy solid may be found suitable. If desired, a polymerized ethylene glycol having a molecular weight of 100 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, the bone wax composition may also contain a tackifier such as a polyglucoside, gelatin or collagen gel, polyvinyl pyrrolidone, cellulose ester or other derivative of cellulose such as oxidized cellulose, a water-soluble starch, or a sugar. A preferred polyglucoside is dextran while a preferred cellulose derivative is cellulose glycolic acid ether salt or cellulose hydroxypropionic acid ether salt, most preferably the sodium salt.

The powdered fibrin hemostatic material and tackifying agent, if present, should desirably be thoroughly dispersed in the aqueous base to provide a semisolid composition which is readily spreadable on the surface of cut bone. The desired consistency of the composition is obtained by proper selection of the base material and the amount of water admixed therewith.

The following examples are provided to further illustrate preferred embodiments of the present invention:

EXAMPLE I

A hemostatic composition was prepared by thoroughly dispersing the following materials in the indicated proportions:

Hemostatic Agent	
Fibrin powder (200 microns)	17·5 g
Collagen powder (2 mm)	17·5 g
Tackifying Agent	
Dextran (MW 60,000–90,000)	8·0 g
Base	
Glycerol	30·0 g
Water	27·0 g
Total	100 g

The composition had a semisolid, putty-like, slightly sticky consistency. When loaded in a 1 cc hypodermic syringe with the needle removed, the mixture was readily extruded through the 1·6 mm diameter opening of the syringe to form a ribbon of material ready for use.

EXAMPLE II

An extruded ribbon, 10 mm in length by 1·6 mm in diameter of the hemostatic composition of Example I was implanted in the lumbar muscles of 12 CFY strain rats weighing 250–300 kg. Two rats were sacrificed after 3, 7, 14, 28, 49, and 70 days, and

the implant sites examined to determine absorption rates and tissue reaction to the bone sealant. The bone sealant was substantially completely absorbed by the 14th day with only few remnants of collagen being detectable. No trace of the sealant was found after 28 days. No abnormal tissue reaction was observed during the test.

EXAMPLE III

Fourteen white male CFY rats, weighing 200–250 g, were anesthetized, and under surgically sterile conditions, the frontal and parietal bones of the skull were exposed. Four holes were made, one in each quadrant of the skull, using a 2 mm burr on an electric drill. The parietal hole on one side was filled with a complete plug of the bone sealant of Example I, and the parietal hole on the other side plugged with a commercial bone wax control. One frontal hole was treated by spreading a small amount of the bone sealant of Example I on the cut surface, while the other hole was similarly treated with the bone wax control.

After 14 days, 12 rats were sacrificed and the wounds examined to determine the histological effects of the bone sealant and bone wax. The remaining 2 rats were sacrified and examined after 28 days. The following results were noted with no significant differences between the 14- and 28-day examination periods.

A. *Bone Sealant of Example I*

i. Plugged holes. Holes filled with tissue and bony edges lined with a layer of osteoblasts. There was considerable evidence of new bone formation in the area.

ii. Smeared holes. Similar to plugged holes, but connective tissue depressed below the level of the skull surface.

B. *Bone Wax Control*

i. Plugged holes. Holes remained filled with a solid plug of wax which was easily removed. Hole was thickly roofed by connective tissue with evidence of a much thinner tissue floor. There was no indication of any significant tissue activity in plug area.

ii. Smeared holes. Generally filled with connective tissue, but with fragments of wax visible in many cases.

The composition of Example I is a specific illustration of a generally preferred hemostatic composition having the following range of formulation:

Fibrin powder	— 15–25%
Collagen powder	— 15–25%
Dextran	— 5–10%
Glycerol	— 20–40%
Water	— 20–30%

The precise composition illustrated in Example I was selected from the above general formulation to provide a desirable combination of properties, particularly consistency and adhesion or tack. Optimum formulations may vary somewhat from that given in Example I depending upon the particular properties of the individual ingredients.

WHAT WE CLAIM IS:—

1. An absorbable hemostatic composition for use in the control of osseous hemorrhage comprising from 10 to 50 percent by weight of the total composition of a hemostatic powder in a water-soluble, biocompatible base, said hemostatic powder comprising a mixture of fibrin and collagen powders.

2. The composition of Claim 1 wherein the particle size of the fibrin powder is less than about 500 microns, and the particle size of the collagen powder is less than about 2 mm.

3. The composition of Claim 1 wherein said biocompatible base comprises a mixture of water and a poly-ol.

4. The composition of Claim 3 wherein said poly-ol is selected from the group consisting of glycerol, propylene glycol, low molecular weight poly(alkylene) glycols, and low molecular weight ethers or esters of poly(alykylene) glycols.

5. The composition of Claim 3 wherein the poly-ol is glycerol and the ratio of glycerol to water is from 2:1 to 1:2.

6. A composition of Claim 1 comprising, in addition to the hemostatic powder and base, a tackifier.

7. A composition of Claim 6 wherein the tackifier is selected from the group consisting of polyglucosides, gelatin, collagen gels, polyvinyl pyrrolidone, cellulose esters, oxidized cellulose, water-soluble starches, and sugars.

8. A composition of Claim 7 wherein the tackifier is dextran.

9. A composition of Claim 8 wherein the dextran is present in an amount of from 5 to 10 percent by weight of the composition.

10. A composition of Claim 1 wherein the hemostatic powder comprises from 40 to 95 percent by weight fibrin powder and from 5 to 60 percent by weight collagen powder.

11. An absorbable hemostatic composition for use in the control of osseous hemorrhage comprising, by weight,

15–25% fibrin powder
15–25% collagen powder
5 –10% dextran
20–40% glycerol
20–30% water.

12. The composition of Claim 11 where-

the implant sites examined to determine absorption rates and tissue reaction to the bone sealant. The bone sealant was substantially completely absorbed by the 14th day with only few remnants of collagen being detectable. No trace of the sealant was found after 28 days. No abnormal tissue reaction was observed during the test.

EXAMPLE III

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After 14 days, 12 rats were sacrificed and the wounds examined to determine the histological effects of the bone sealant and bone wax. The remaining 2 rats were sacrified and examined after 28 days. The following results were noted with no significant differences between the 14- and 28-day examination periods.

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ii. Smeared holes. Generally filled with connective tissue, but with fragments of wax visible in many cases.

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1. An absorbable hemostatic composition for use in the control of osseous hemorrhage comprising from 10 to 50 percent by weight of the total composition of a hemostatic powder in a water-soluble, biocompatible base, said hemostatic powder comprising a mixture of fibrin and collagen powders.

2. The composition of Claim 1 wherein the particle size of the fibrin powder is less than about 500 microns, and the particle size of the collagen powder is less than about 2 mm.

3. The composition of Claim 1 wherein said biocompatible base comprises a mixture of water and a poly-ol.

4. The composition of Claim 3 wherein said poly-ol is selected from the group consisting of glycerol, propylene glycol, low molecular weight poly(alkylene) glycols, and low molecular weight ethers or esters of poly(alykylene) glycols.

5. The composition of Claim 3 wherein the poly-ol is glycerol and the ratio of glycerol to water is from 2:1 to 1:2.

6. A composition of Claim 1 comprising, in addition to the hemostatic powder and base, a tackifier.

7. A composition of Claim 6 wherein the tackifier is selected from the group consisting of polyglucosides, gelatin, collagen gels, polyvinyl pyrrolidone, cellulose esters, oxidized cellulose, water-soluble starches, and sugars.

8. A composition of Claim 7 wherein the tackifier is dextran.

9. A composition of Claim 8 wherein the dextran is present in an amount of from 5 to 10 percent by weight of the composition.

10. A composition of Claim 1 wherein the hemostatic powder comprises from 40 to 95 percent by weight fibrin powder and from 5 to 60 percent by weight collagen powder.

11. An absorbable hemostatic composition for use in the control of osseous hemorrhage comprising, by weight,

15–25% fibrin powder
15–25% collagen powder
5 –10% dextran
20–40% glycerol
20–30% water.

12. The composition of Claim 11 where-

in the particle size of the fibrin powder is less than about 500 microns and the particle size of the collagen powder is less than about 2 mm.

13. The composition of Claim 11 wherein the molecular weight of the dextran is in the range of from 60,000 to 90,000.

14. A hemostatic composition as claimed in any of Claims 1 to 13 and substantially as described in the foregoing Examples.

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Printed for Her Majesty's Stationery Office by Burgess & Son (Abingdon), Ltd.—1981.
Published at The Patent Office, 25 Southampton Buildings, London, WC2A 1AY,
from which copies may be obtained.