Patented June 26, 1951 2,558,395

UNITED STATES PATENT OFFICE

2,558,395

UNDENATURED GELATIN HEMOSTATIC SPONGE CONTAINING THROMBIN

André Studer, Basel, Switzerland, assignor to Hoffmann-La Roche Inc., Nutley, N. J., a corporation of New Jersey

No Drawing. Application March 26, 1948, Serial No. 17,366. In Switzerland June 3, 1947

3 Claims. (Cl. 167—65)

1

The present invention relates to a process for the manufacture of hemostatic tampons and bandages.

In surgery hemostatic tampons and bandages consisting of fibrin- and cellulose-derivative sponges which contain a thrombin solution are used. These tampons and bandages are prepared for use by dipping them into a thrombin solution immediately prior to application. This mode of use requires the sponges to consist of a material insoluble in water, because otherwise they would collapse during the contact with the aqueous thrombin solution. Such sponges have the disadvantage of being resorbed much more slowly by the organism than water soluble substances.

In order to avoid this disadvantage a soluble gelatine gel has been used in place of the said sponges. This gel is immersed in a thrombin solution immediately prior to application. However, it is difficult and takes a considerable amount of time to obtain the complete impregnation of such gels by the thrombin solution. Furthermore, such impregnated tampons cannot be stored because the thrombin is unstable in the presence of water and its activity quickly diminishes. Again it has been found that thrombin brings about a diminution of the jellifying quality of the gelatin.

It has now been found, according to the present invention, that hemostatic tampons and bandages may be prepared from undenatured water soluble gelatin by adding thrombin to an aqueous gelatin solution, transforming the solution obtained into foam and drying the foam obtained in vacuo at a low temperature. The form of the thrombonic gelatin sponge may be adapted to the requirements of the intended use. The present process yields hemostatic tampons and bandages consisting of an easily soluble mass of gelatin and thrombin and which is of a cotton-wool like appearance. These tampons and bandages need not be dipped into a thrombin solution but may be placed on any wound without prior treatment. The new tampons and bandages quickly cause hemostasis; the blood flowing from the wound is absorbed into the sponge, thereby dissolving the gelatin component; the thrombin which is thus released immediately causes the transformation of fibrinogen into fibrin. A fibrin film is thus formed over the wound, whereby the latter is closed and the flow of the blood is stopped. The film clings tightly to the surface of the wound, in many cases rendering the use of bandages or like means of protection unnecessary.

2

The efficiency of the tampons manufactured in accordance with the present invention may be demonstrated in vitro by the following experiment: In a test tube (about 1 cm. internal diameter) a few tampons are loosely stamped to form a column about 5 cm. high. 5 ccm. of plasma of 37° C. are poured thereon. The plasma is sucked into the sponge-like material and coagulates so quickly that the test tube may be turned upside down directly after filling in the plasma without any of the latter running out.

If so desired antiseptic agents may be added to the gelatin-thrombin product without influencing the activity of the tampons and bandages. Thymol, a mixture of p-hydroxybenzoic-acid-methyl- and propylester, or sulfamides, such as 5-sulfanilamido-3,4-dimethyl-isoxazole, are antiseptics which may be so used. The addition of substances accelerating cicatrization, such as panthenol, may also be found to be useful. Panthenol is the generic name for α,γ-dihydroxy-β,β - dimethyl - butyric - acid - (3' - hydroxypropyl) - amide.

The gelatin has a protective and stabilizing effect on the thrombin with which it is impregnated. It has been found, for instance, that the activity of an aqueous thrombin solution containing 5 per cent. gelatin falls away more slowly than in the case of such a solution containing no gelatin. The following table in which Th. U. stands for "thrombin units" (1 Th. U. being the amount of thrombin which causes 1 ccm. of plasma of bovine to coagulate within 30 seconds at a temperature of 37° C.), illustrates this fact:

	Aqueous thrombin solution, 5,500 Th. U.	Aqueous thrombin and gelatin solution, 7,500 Th. U.
	Th. U.	*Th. U.*
after 24 hours	4,000	7,500
after 48 hours	2,500	5,500
after 72 hours	350	4,000

Example 1

5 grams of gelatin in sheets are added to 100 ccm. of distilled water. The mixture is heated to 80° C. and filtered while still warm through a filter which retains bacteria. The filtrate is adjusted to a pH of 6.6. 10 ccm. of a thrombin solution containing 10,000 units per ccm. (vide supra) are added to 50 ccm. of the filtrate which has been cooled down to a temperature of 20° C. (This thrombin solution may be prepared from a

thrombin preparation showing on titration a content of 100 Th. U./mg.) The slightly turbid solution is passed through a filter which retains bacteria. The clear solution is transformed into a voluminous foam by blowing in sterile air through a glass plate. The froth is spread out over a sheet, frozen and dehydrated in high vacuo at low temperature.

Example 2

70 mg. of thymol are dissolved in 100 ccm. warm distilled water. 5 grams of gelatin are added to the solution and the mixture is heated to 80° C. Further working as described in Example 1.

Example 3

20 mg. of p-hydroxybenzoylmethylester and 80 mg. of p-hydroxybenzoylpropylester are dissolved in 100 ccm. of distilled water. 5 mg. of gelatin are added and the mixture is heated to 80° C. Further working as described in Example 1.

Example 4

5 grams of gelatin in 90 ccm. distilled water are heated to 80° C. 2 grams of finely pulverised 5-sulfanilamido-3,4-dimethylisoxazole are suspended in the warm solution. The solution is set to a pH of 6.6 by adding 5 to 10 ccm. of normal sodium hydroxide. The sulfanilamide then dissolves. The mixture is heated to 80° C. and worked further in accordance with Example 1.

Example 5

0.2 gram of panthenol is dissolved in 100 ccm. of distilled water. 5 grams of gelatin are added. The mixture is heated to 80° C. and worked further in accordance with Example 1.

I claim:

1. As a ready-to-use hemostatic sponge, a freeze-dried foam of an aqueous solution containing undenatured water-soluble gelatin and thrombin.

2. A preformed hemostatic sponge made by drying, at low temperature and under reduced pressure, a foam of an aqueous solution containing undenatured water-soluble gelatin and thrombin.

3. A preformed hemostatic sponge made by freezing a foam of an aqueous solution containing undenatured water-soluble gelatin and thrombin, and drying the frozen foam in vacuo at a low temperature.

ANDRÉ STUDER.

REFERENCES CITED

The following references are of record in the file of this patent:

UNITED STATES PATENTS

Number	Name	Date
2,166,074	Reichel	July 11, 1939
2,398,077	Smith	Apr. 9, 1946

FOREIGN PATENTS

Number	Country	Date
474,093	Germany	Mar. 26, 1929

OTHER REFERENCES

Lesser, Drug and Cosmetic Industry, March, 1947, page 329.

Bing, Acta Pharmacol., 1947, vol. 3, page 366.

"American Druggist," October, 1947, pages 95, 96 and 168.

Correll et al., Proc. Soc. Exper. Biol. and Medicine, 58, 233–5, March, 1945.

Bering, J. Clinical Investigation No. 4, July, 1944, pages 586–590.