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2,731,015

ARTIFICIAL SPONGE AND METHOD OF MAKING IT

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This invention relates to an artificial sponge. More particularly, the invention relates to a dextran sponge having the general characteristics of a conventional sponge, but which is absorbable and readily assimilable by living animal bodies.

In the practice of medicine and surgery, it is often necessary to insert a porous material into different parts of the body for the purpose of bringing a therapeutic agent into contact with certain tissues and organs and/or for picking up fluids in a wound area, such as blood and exudates.

Surgeons have the problem of keeping the amount of blood present around a surgical incision at a minimum since the blood impedes the surgeon's work. A common practice is to apply a coagulating agent such as thrombin to the area for the purpose of clotting the blood. This practice involves various problems. If the coagulating agent is poured into the incision, it tends to interfere with the surgeon's work almost as much as does blood itself, and if a clot is formed, it is quickly washed away. To avoid this, it has been proposed to soak a porous material of the appropriate size in the coagulating agent and then place the material carrying the agent, thrombin or the like, at strategic points within the incision. While this technique may facilitate the surgeon's task, it presents the difficulty that most available porous materials, such as conventional sponges, are not absorbable and assimilated by the body, which means that they must be removed before the incision is closed. The very act of removing a conventional sponge from the body often initiates hemorrhaging. On the other hand, real damage results if the non-absorbable materials are not removed.

One object of this invention is to eliminate these and other problems by providing a new porous or sponge-like material having a large number of intercommunicating cells or interstices, which may be cut into convenient swabs or packs, and which is absorbable and readily assimilated by the human body without harmful effects so that if it is placed in an incision, for example, the latter may be closed without removal of the porous material.

Another object is to provide a new sponge-like material which may be deliberately left within an incision in order to keep a constant supply of therapeutic agent at a given point therein, as well as to preclude hemorrhage occasioned by its removal.

A further object is to provide a new absorbable, readily assimilated sponge-like material which can be made economically.

A still further object is to provide a sponge-like material as described and which can be subjected to sterilizing conditions without undergoing damage.

Another object is to provide a new sponge-like material adapted to a variety of uses.

These and other objects of the invention are accomplished by providing a sponge-like material comprising a dextran or a dextran derivative.

The dextrans are high molecular weight polysaccharides comprising anhydroglucopyranosidic units linked by car-

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bon-to-carbon linkages some, and apparently 50% or more of these linkages being alpha-1,6 carbon-to-carbon linkages. The dextrans may vary with respect to their molecular structural repeating alpha-1,6 to non-1,6 linkages ratios, molecular weight, sensitivity to water and osmotic pressure in liquids.

The dextran sponge of the invention, in its final form, is insoluble in water. It may comprise a dextran which is initially insoluble in water or one which is initially water-soluble but which has been rendered insoluble in water by suitable chemical treatment.

One method of making the dextrans involves the steps of inoculating a selected nutrient medium with a microorganism and incubating the mixture at the temperature most favorable to growth of the microorganism until the maximum of dextran is obtained, as may be determined by periodically precipitating samples of dextran from the culture medium by the addition of alcohol or acetone to the medium, and drying and weighing the samples. Suitable microorganisms are those of the *Leuconostoc mesenteroides* and *L. dextranicum* types.

Using microorganisms of these types, the culture medium must contain particular nitrogenous substances, certain inorganic salts, and some sucrose, which may be either refined or crude, or which may be in the form of a sucrose-containing substance such as molasses. The required nitrogen may be added to the medium in the form of commercial peptone, beef extract or other nitrogen-containing substance. If molasses is used as the sucrose source, the quantity of nitrogenous compounds present therein may be sufficient to provide the nitrogen required by the microorganism, so that the addition of other nitrogen sources may not be necessary. Salts such as dipotassium phosphate and sodium chloride are also added. A specific example of a suitable nutrient is an aqueous medium containing: 5–10% sucrose, 0.5% peptone, 0.2% dipotassium phosphate and 0.1% sodium chloride. Other growth factor supplements, such as liver, yeast and malt extracts also may be included, for instance at 0.5% concentration. The pH of the medium is preferably adjusted to slightly on the alkaline side of neutrality, and production of the dextran is favored by maintaining the medium slightly alkaline throughout the fermentation period, which may be accomplished by the periodic addition of alkali to the fermenting medium or by using an excess of calcium carbonate in the medium. The time required for maximum dextran production will vary with the organism employed, the temperature of the incubation, the concentration of sucrose in the medium and other factors. When the maximum of dextran has been formed, an equal amount of alcohol or acetone may be added to the medium at a pH of 2.5 to 4.5 to precipitate, or complete the precipitation of, the dextran in pure form and substantially free from occluded or absorbed bacteria, nitrogenous materials and inorganic elements. Any water-miscible aliphatic alcohol, such as methyl, ethyl or isopropyl alcohol may be used to precipitate the dextran. In order to further purify the precipitated dextran, it may be mixed with water and reprecipitated with alcohol at a pH of about 7.0, the pH of the dextran-water mixture being adjusted by means of sodium hydroxide, for instance, prior to the reprecipitation. In some instances, it may be desirable to reprecipitate the dextran several times. The final precipitate may be dried free of alcohol and water, and reduced to particulate condition for use in this invention.

The dextran as obtained initially is a high molecular weight substance which may be soluble or insoluble in water, depending on the conditions under which it is obtained and particularly the microorganism. The dextran obtained using the microorganisms *Leuconostoc mesenteroides* B-1120; *L. mesenteroides* B-1144; *L.*

mesenteroides B-523; and *Betabacterium vermiforme* B-1139 (Northern Regional Research Laboratory classification) are initially substantially water-insoluble and may be used as such in practicing the invention, or after hydrolysis by means of acid or enzymatically to a lower molecular weight such that the dextran remains substantially water-insoluble. On the other hand, the dextrans obtained using the microorganisms *Leuconostoc mesenteroides* B-512, B-1146, B-119 and B-1146 (NRRL classification) are initially soluble in water and are insolubilized for use as a sponge substitute in accordance with the invention. For example, the dextran may be insolubilized by treatment with formaldehyde, a water-insoluble dextran polyformal being produced. Or the dextran may be converted to other water-insoluble or substantially water-insoluble derivatives, which may or may not be adsorbed and assimilated by the living body. For example, the dextran derivative may be a calcium salt of dextran or a calcium salt of carboxymethyl dextran which may be absorbed safely and which also serve to facilitate blood coagulation. A method for the production of water-insoluble calcium salts of dextrans is described in the pending application of L. J. Novak et al., Ser. No. 281,505, filed April 10, 1952. The calcium salts of carboxymethyl dextran, which is disclosed in the pending application of M. H. Hiler, Ser. No. 327,938, filed December 18, 1952, may be made by similar methods.

Since the dextran may be water-insoluble as obtained, or rendered water-insoluble by appropriate treatment, and dextrans having a wide range of molecular weights may be used, the invention is not limited to the method by which the dextran is obtained. The dextran may be prepared enzymatically in the absence of bacteria. For example, a suitable bacterium may be cultivated to obtain a dextran-producing enzyme which is separated from the culture and introduced into a medium in which dextran is formed by the action of the enzyme. Or the dextran may be obtained by bacterial conversion of 1,4 linkages of starch-derived dextrans to 1,6 bonds of dextran. These various dextrans may be used in substantially pure form and after sterilization, as such, or in the form of their water-insoluble or substantially water-insoluble conversion products, when the sponge is intended for therapeutic use. The purity and sterile condition are less important in the case of sponges destined for household or industrial use.

The sponge-like material is prepared by dissolving or dispersing the water-insoluble dextran or dextran derivative in a solvent or dispersing medium which may be aqueous or non-aqueous, to obtain a product of thick, creamy or latex-like consistency, and then treating the dissolved or dispersed dextran or conversion product to induce inflation or foaming thereof, followed by drying of the foam.

Various foaming or inflating treatments may be used. For example, the dextran solution or dispersion may be beaten vigorously to produce a firm foam which may be dried in circulating air under controlled humidity conditions. According to other useful embodiments, the foamy or inflated condition of the dextran or conversion product may be brought about by treating the solution or dispersion thereof with immiscible volatile solvents or liquids which, on volatilization, induce foaming of the mass. Another useful method involves the use of chemical agents such as sodium bicarbonate, ammonium carbonate, ammonium carbamate, ammonium bicarbonate, a mixture of sodium nitrite and ammonium chloride, and the like, which evolve as a gas on heating. Further, there may be used inert gases such as nitrogen, carbon dioxide, nitrous oxide (N_2O) etc., which are forced into the solution or dispersion under high pressure and from vacuoles upon release of the pressure. The volatile immiscible liquids and gas-evolving materials such as sodium bicarbonate, usually require heating of the mass for producing the foamy or inflated

effect, whereas when methods utilizing the inert gases of the nitrous oxide type are used, heating is generally not essential to the production of a final product having, throughout its cross-section, myriad small voids or pores forming a honeycomb or sponge-like structure. For example, an aqueous slurry of a water-insoluble dextran may be impregnated in a closed container with nitrous oxide and as soon as the impregnated material is released, as through a hose nozzle, it immediately foams and, on drying, a strong, soft sponge of homogeneous character and having fine interconnecting pores or cells is obtained.

Regardless of the foaming or inflating method employed, the final, dried products of the invention are firm, resilient structures comprising cells defined by walls which do not tend to collapse during use of the sponge. The products can be cut to pieces of any desired size and shape. In some cases, for example when the dextran solution or dispersion is impregnated with nitrous oxide or the like under pressure, the impregnated mass may be cast directly to the size and shape of sponge required, and having any predetermined thickness, by casting the mixture of gas and solution or dispersion of the dextran directly from the impregnating or mixing vessel into which the gas is introduced under pressure, into the cavity of an open mold having the predetermined dimensions.

The dextran or dextran conversion product may be mixed with an organic solvent to obtain an essentially non-aqueous mass which is subjected to the inflating or foaming treatment. Formamide and other lower acyl amides, as well as the alkylated and dialkylated, specifically methylated and dimethylated lower acyl amides, such as dimethylacetamide and dimethyl formamide, are examples of such solvents which may be used in preparing the mass but other organic solvents may also be used and are selected so that they are readily evaporated from the inflated or foamy mass during drying thereof. In general, it will be preferred to disperse or slurry the particulate water-insoluble dextran or dextran conversion product in water and bring the aqueous mass to the inflated foamed condition. Water-soluble dextrans or their water-soluble conversion products may be brought to the water-insoluble state after the foam is formed.

The following examples will illustrate specific embodiments of the invention.

Example I

A substantially pure, water-insoluble dextran in particulate condition is mixed with water to produce a thick slurry. The slurry is impregnated in a pressure cylinder equipped with an agitating device with nitrous oxide at from 80 to 250 lbs. pressure, with constant agitation of the mass to ensure thorough and uniform distribution of the gas in the slurry. The impregnated, expanded slurry is discharged through a hose having a relatively small bore nozzle into an open mold to obtain a sponge-like mass of a shape and size corresponding to the mold cavity. The expanded foam settles evenly into the mold cavity. The molded or shaped foam is then dried by evaporation of the water. The firm, dried material, which is cellular in cross-section, can be die-cut to any shape or sliced, as desired.

Example II

A water-soluble dextran is dissolved in a sufficient amount of water to produce a thick, creamy solution. Between 0.01% and 10.0% (on the weight of the dextran) of formalin (40% aqueous solution of formaldehyde) is added and the mixture is allowed to stand for about two hours, with warming, if desired. The mix is then placed in a vessel equipped with a beater and beaten vigorously until a firm foam is formed. The foam is placed on screens in a drying oven in which dry air (10% relative humidity) is circulated constantly. In order to expedite reaction of the formaldehyde and dextran to produce a

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water-insoluble dextran formal, the dried foam is sprayed with a dilute aqueous solution of sulfuric acid and heated at elevated temperature between 110° and 120° C. until a substantial reaction product of the dextran and formaldehyde is produced. The insolubilized cellular material is then rinsed free of acid, and dried.

Those dextran sponges which are intended for therapeutic use may be packaged for marketing and may be sterilized before or after packaging.

The dextrans are ideally suited to use as therapeutic sponges. They are bland, stable, non-irritating materials which, in the pure condition, are non-toxic. They are heptanes and hence are immunologically active materials which do not induce allergic reactions. The dextrans are not stored in body tissues and appear to be completely broken down in the body, probably to glucose and apparently by enzyme action. The sponges made from them can be inserted in incisions which are then closed, without damage. They have the additional advantage of a high liquid pick-up and retention capacity and when they are soaked in a therapeutic agent and then placed in an incision or in a body cavity, the therapeutic agent is released to the area to be treated gradually, at a more or less controlled rate, and over a long period of time. Also because of the high moisture pick-up and retention capacity of the dextrans, the sponges are particularly advantageous in taking up blood around an incision or the like, since they pick up and hold a considerable amount of blood without requiring frequent replacement. The sponges may be pre-treated with a deodorant in order to neutralize or "kill" the odors caused by suppuration.

It will be understood that although the sponges in accordance with the invention have been discussed in detail in connection with those which are useful in the medical and surgical arts and particularly suited to such use by virtue of being readily absorbed in and assimilated by living animal bodies, the sponges of the dextran conversion products which are not absorbed by living bodies may be used for any other purpose for which sponges are commonly employed, for example in household applications.

Additional examples of dextran derivatives which may be treated as described herein to produce a firm, stable foam include water-insoluble ethers, esters, and ether-esters such as are described in U. S. Patents 2,203,702-5, 2,229,941 and 2,236,386 to G. L. Stahly and W. W. Carlson, including benzyl dextran, dextran benzyl ether-phthalyl ester, dextran butyl ether-benzoyl ester, etc., lower fatty acid esters of dextran such as dextran acetate, higher fatty acid esters of dextran and higher fatty acid esters of carboxyalkyl dextrans. Examples of water-insoluble dextran derivatives suitable for use in making sponges adapted to therapeutic use include such higher fatty esters as dextran palmitate and dextran laurate and the palmitic and lauric acid esters of carboxymethyl dextran. When the dextran is of the inherently water-soluble type, the ester groups may be selected so that the esterified product is insoluble or substantially insoluble in water. When the sponge is intended for therapeutic use, the dextran derivative is one which is physiologically innocuous and readily and wholly absorbed in or assimilated by living animal bodies. Examples of such derivatives are the higher fatty acid esters such as dextran palmitate and dextran laurate containing, per anhydroglycopyranosidic group, an average of from less than 1.0 to 3.0 palmityl or lauryl groups, and carboxymethyl dextran palmitates and laurates in which the palmityl and lauryl groups predominate, i. e., ether-esters containing an average of less than 1 to 1.0 carboxymethyl group and from about 1.5 to 2.0 palmityl or lauryl groups. The dextran derivatives may be caused to foam and expand in the same manner as the dextrans. They may be dispersed in aqueous media or dissolved in a suitable solvent, prior to the inflating or foaming treatment. For example, benzyl dextran is

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soluble in such solvents as acetone and ethyl acetate, which may be used.

Various adjuvants may be mixed with the medium before the foaming treatment, particularly when the sponge is intended for uses other than therapeutic uses. Such adjuvants include pigments and other effect materials.

Various changes and modifications may be made in practicing the invention without departing from its spirit and scope and it is to be understood, therefore, that I desire to comprehend within my invention all such modifications as may be necessary to adapt it to varying conditions and uses.

I claim:

1. A firm, water-permeable, substantially water-insoluble sponge-like product consisting essentially of a porous mass of a substance selected from the group consisting of dextrans and dextran conversion products, said mass having, in cross-section, a cellular, foam-like structure.

2. A firm, water-permeable, substantially water-insoluble sponge-like product consisting essentially of a porous mass of dextran, said mass having, in cross-section, a cellular, foam-like structure.

3. A firm, water-permeable, substantially water-insoluble sponge-like product consisting essentially of a porous mass of a dextran conversion product, said mass having, in cross-section, a cellular, foam-like structure.

4. A substantially water-insoluble therapeutic sponge consisting essentially of a sterile, porous mass of a substantially pure dextran absorbable without deleterious effect by living bodies, said mass having, in cross-section, a cellular, foam-like structure.

5. A substantially water-insoluble therapeutic sponge consisting essentially of a sterile porous mass of a substantially pure dextran conversion product absorbable without deleterious effect by living bodies, said mass having, in cross-section, a cellular, foam-like structure.

6. A firm, water-permeable, substantially water-insoluble sponge-like product consisting essentially of a porous mass of a carboxymethyl dextran, said mass having, in cross-section, a cellular, foam-like structure.

7. A firm, water-permeable, substantially water-insoluble sponge-like product consisting essentially of a porous mass of a dextran ether, said mass having, in cross-section, a cellular, foam-like structure.

8. A firm, water-permeable, substantially water-insoluble sponge-like product consisting essentially of a porous mass of a dextran ester, said mass having, in cross-section, a cellular, foam-like structure.

9. A firm, water-permeable, substantially water-soluble sponge-like product consisting essentially of a porous mass of a dextran higher fatty acid ester, said mass having, in cross-section, a cellular, foam-like structure.

10. A firm, water-permeable, substantially water-insoluble sponge-like product consisting essentially of a porous mass of a dextran high fatty acid ester of carboxymethyl dextran, said mass having, in cross-section, a cellular, foam-like structure.

11. In a method of making a firm, water-permeable, substantially water-insoluble sponge-like product having, in cross-section, a cellular, foam-like structure, the steps of (a) mixing a dispersion of a substance selected from the group consisting of dextrans and dextran conversion products in a liquid which is chemically inert to the dextran and dextran conversion products with an inflating agent, (b) removing the inflating agent to leave the mass in the form of a foam, and drying the inflated, cellular, foam-like mass of dextran or dextran conversion product remaining after removal of the inflating agent.

12. In a method of making a firm, water-permeable, substantially water-insoluble sponge-like product having, in cross-section, a cellular, foam-like structure, the steps

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of (a) beating air into a dispersion of a substance selected from the group consisting of dextrans and dextran conversion products in a liquid which is chemically inert to the dextran and dextran conversion products, until a firm foam is formed, and (b) drying the foam.

13. In a method of making a firm, water-permeable, substantially water-insoluble sponge-like product having, in cross-section, a cellular, foam-like structure, the steps of (a) introducing a gas under pressure into a mass comprising a substance selected from the group consisting of dextrans and dextran derivatives dispersed in a liquid which is chemically inert to the dextran and dextran conversion products while agitating the mass, (b) abruptly releasing the pressure to cause foaming of the mass, and (c) drying the foamed mass.

14. A method according to claim 13 in which the gas is nitrous oxide.

15. A method of making a firm, water-permeable, substantially water-insoluble sponge-like product having, in cross-section, a cellular, foam-like structure, which comprises forming a thick slurry of a particulate, substantially water-insoluble dextran in water, beating air into the slurry until a foam is formed, and drying the foam.

16. A method of making a firm, shaped, water-

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permeable, substantially water-insoluble sponge-like product having, in cross-section, a cellular foam-like structure, which comprises introducing a gas under pressure into a thick slurry of a particulate, water-insoluble dextran in water, while agitating the slurry, casting the mass containing the gas directly into an open mold to effect release of the gas and foaming of the mass, and drying the foam to obtain a product having substantially the shape and size of the mold cavity.

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