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[54] **METHOD OF REPLACING OR REPAIRING THE BODY WITH BIORESORBABLE SURGICAL ARTICLES**

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[52] **U.S. Cl.** ..... **3/1;** 3/DIG. 1; 128/92 B; 128/92 C; 128/334 R; 128/335.5; 260/78 A

[51] **Int. Cl.** **A61f 1/24;** A61l 17/00

[58] **Field of Search** ..... 3/1, DIG. 1; 128/334 R, 128/334 C, 335.5, 92 C, 92 CA, 92 B, 92 D; 260/75 R, 75 T, 78 A

[56] **References Cited**

UNITED STATES PATENTS

2,071,250	2/1937	Carothers	260/78 A
3,463,158	8/1969	Schmitt et al.	3/1 X
3,620,218	11/1971	Schmitt et al.	128/334 R

OTHER PUBLICATIONS

"Polyesters," by V. V. Korshak, et al., Pergamon Press, Oxford London, Edinburgh, New York, Paris, Frankfurt, 1965, pp. 31 and 53.

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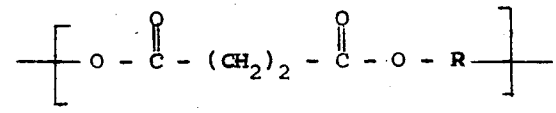
[57] **ABSTRACT**

Implantable surgical articles are provided which are at least partially bioresorbable and which consist at least partially of a polyester of succinic acid possessing a plurality of units of the general formula:



in which R represents a linear or branched alkylene radical containing 2 to 6 carbon atoms. They are particularly suitable as sutures.

15 Claims, No Drawings

METHOD OF REPLACING OR REPAIRING THE BODY WITH BIORESORBABLE SURGICAL ARTICLES

The present invention relates to surgical articles which are biologically partially or completely resorbable after implantation in living human or animal tissues.

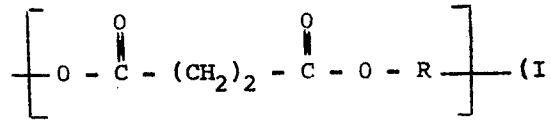
It is known that human or animal surgery is making use of more and more articles produced from natural or synthetic materials, in order to restore living tissues or to strengthen, repair and even replace various organs. For this purpose, surgical articles are placed in position either temporarily or permanently. In the case of temporary implantation, it has been considered preferable to make use of bioresorbable materials, that is to say materials which undergo degradation and which disappear after they have been implanted after a certain length of time, due to a biochemical process. It is important that the material used and its degradation products should not cause any unfavourable reaction of the surrounding tissues. With a permanent implantation, for example for replacing or strengthening a failing organ, non-resorbable articles are obviously used; it has been found, however, that in the majority of cases, the integration of the prosthesis and its joining to the adjacent tissues are facilitated if the prosthesis is made partly of a bioresorbable material which is gradually replaced by the adjacent tissues so as to form an intimate join between the latter and the implanted foreign body.

The elements for sutures and for ligatures intended for closing wounds and for repairing blood vessels, nerves and tendons are examples of surgical articles which are implanted temporarily. These elements are generally filaments, but they can also be in other forms, for example as clips or tapes. The most commonly used bioresorbable material for making suture or ligature filaments is catgut prepared from the collegen of mammals; the sub-muccous layer of the small intestine of sheep is most frequently employed. Catgut possesses numerous disadvantages, such as difficulty in obtaining it, the unfavourable reactions which it causes with living tissues and the lack of uniformity of its mechanical properties. Consequently, ways have been sought of replacing it by bioresorbable synthetic materials which can easily be converted into continuous filaments by extrusion techniques, and which possess readily reproducible mechanical properties. Various materials have been proposed for this purpose. Thus Belgian Pats. Nos. 679,726 and 758,156 describe elements for sutures and ligatures and other partially or completely bioresorbable surgical articles, which consist of polyesters of copolyesters derived from lactic acid and produced by polycondensation of a lactide (preferably a L-lactide) alone or combined with other derivatives of acid-alcohols such as glycolide, tetramethylglycolide, β-propiolactone and β-butyrolactone. Although they possess advantages relative to catgut, these polyesters are very sensitive to moisture and this has a detrimental effect on their mechanical properties so that it is necessary to store the surgical elements and especially the suture filaments made from them in hermetically sealed packaging. Hence they are not completely satisfactory.

In addition, it is known that it is important that the surgeon should have at his disposal various materials which provide him with a wide range of bioresorbable properties. In fact, the duration of the resorption varies

with the nature of the wound and with the nature of the tissues involved in the cicatrization process; it also varies from one individual to another and with the type of insertion in the case of prosthesis. The development of new bioresorabable materials increases the number of possibilities from which the surgeon can choose and there is, consequently, a demand for new bioresorbable materials.

According to the present invention there is provided a surgical article which can be used in human or animal surgery, which is completely or partially bioresorbable and which consists wholly or partially of a bioresorbable material consisting of a polyester of succinic acid possessing a plurality of units of the general formula:



(I)

in which R represents a linear or branched alkylene radical containing 2 to 6 carbon atoms. More specifically, R can be an ethylene, methylethylene, 1,2-dimethylethylene, trimethylene, 2-methyl-trimethylene, 2,2-dimethyl-trimethylene, 1-methyl-trimethylene, tetramethylene, pentamethylene or hexamethylene radical.

The bioresorbable character shown by the polyesters of formula (I), denoted hereafter by the general term "polysuccinate," is unexpected because it is known that polyesters such as polyethylene glycol terephthalate are not resorbed by human or animal tissues (see U.S. Pat. No. 3,463,158). It has been found that, in addition to their bioresorbable character, the polysuccinates are particularly well tolerated by the tissues in which they are implanted; thus no inflammatory reaction has been observed after a long-lasting implantation of polyethylene glycol succinate filaments in rats. Moreover, the polysuccinates possess excellent mechanical properties (notably tensile strength, tensile strength at knots and dimensional stability) and are insensitive to moisture, which make them particularly suitable for the manufacture of surgical articles and especially elements for sutures. Polysuccinate filaments are easy to handle and do not necessitate the use of special storage devices.

Polyglycol succinates have been known for a very long time (see, for example, U.S. Pat. No. 2,071,250; and V. V. KORSHAK and S. V. VINOGRADOVA, "Polyesters," edited by PERGAMON PRESS Ltd., 1965, pages 31 to 46). They can be prepared by the usual polycondensation processes such as those described by V. V. KORSHAK and S. V. VINOGRADOVA, loc. cit., or in HOUBEN WEYL, "Methoden der Organische Chemie - Makromolekulare Stoffe," volume 14/2, pages 1 to 29. Thus it is possible, for example, to use bulk polycondensation of glycols with free succinic acid or dimethyl succinate in the presence of the usual esterification or transesterification catalysts such as sulphuric or p-toluenesulphonic acids, or metal salts or oxides such as calcium oxide, strontium oxide, zinc oxide, aluminium oxide, bismuth oxide, iron oxide, titanium oxide, lead oxide, antimony oxide, cobalt oxide, calcium chloride, zinc acetate and zinc borates.

As glycols which can be used to prepare the polyesters used in the present invention, there may be mentioned ethylene glycol, propylene glycol, propane-1,3-diol, 2-methyl-propane-1,3-diol, 2,2-dimethyl-propane-1,3-diol, butane-1,4-diol, butane-1,3-diol, butane-2,3-diol, pentane-1,5-diol and hexane-1,6-diol. These various glycols can be used separately or as a mixture with one another. Use can thus be made of mixtures containing 1 to 99 mol % of ethylene glycol and 99 to 1 mol % of one or more other glycols such as 2-methylpropane-1,3-diol and 2,2-dimethyl-propane-1,3-diol.

The molecular weight of the polysuccinates used for the production of surgical articles according to the present invention can vary within very wide limits but it should generally be sufficiently high to render them suitable for the formation of films and fibres. Generally it should be sufficiently high for the polymer to be converted into filaments and films which can be orientated. The upper limit is not critical, subject to the condition that the product can be processed by the usual moulding or shaping techniques.

Polysuccinates can be used for the production of extremely diverse surgical articles, such as those described in "Handbook of Biomedical Plastics," H. LEE and K. NEVILLE, 1971, Pasadena Technology Press. They are particularly suitable for the production of elements for surgical sutures and ligatures, especially in the form of twisted or non-twisted filaments, tapes, bristles, tents or spun fibres. They can also be used in the form of single filaments, twisted filaments, stranded filaments, gathered filaments, texturized filaments or lapped filaments; these various terms are used in accordance with the definition which is given of them in French Standard Specification NF G 00-005. These various elements for sutures can consist wholly or partially of the bioresorbable polysuccinates. Thus use can be made of a filament of the polysuccinate or of a filament comprising a core of a non-resorbable synthetic material such as polyethylene glycol terephthalate, polyamide or polypropylene, and an outer coating of polysuccinates. It is likewise possible to use a composite element consisting of a yarn of natural material, e.g., linen or silk, or synthetic material covered with a polysuccinate, or of a yarn of variable structure comprising bioresorbable filaments and nonresorbable filaments.

Amongst the other surgical articles for which the polysuccinates of the formula (I) can be used, there may be mentioned knitted fabrics comprising resorbable yarns and optionally non-resorbable yarns or non-resorbable yarns covered with a layer of polysuccinate; non-woven fabrics prepared from non-bioresorbable fibres and a resorbable binder; and sheets made from non-resorbable materials covered on one or both faces by a polysuccinate. The wholly or partially resorbable knitted and woven fabrics can be used in the form of sheaths intended to facilitate the implantation of diverse prostheses such as that described in French Pat. Nos. 2,031,699 and 2,071,172 for correcting valvular illnesses, and especially of the mitral valve; tubes for the removal of biological liquids (in particular, artificial ureters) as described in French Pat. No. 2,133,083, and vascular prostheses such as those described in French Pat. No. 2,112,032.

The polysuccinates of formula (I) are also very suitable for the production of surgical articles such as tubes of various shapes, for example Y-shaped tubes and T-shaped tubes, bars, plates, rings and screws, intended to be implanted temporarily or permanently. Partially or completely bioresorbable tubular prostheses have been described in U.S. Pat. Nos. 2,127,903, 3,272,204, 3,304,557, 3,316,557, and 3,479,670 to which reference should be made for further details.

The shaping of the polysuccinates of formula (I) for the production of surgical articles can be carried out by the usual methods. Thus filaments, tapes or sheets can be produced by extrusion of the polymer in the molten state, followed by stretching at a sufficiently high ratio to cause the orientation of the chains of the polymer, and the fixing of the article thus produced.

The polysuccinates of formula (I) can contain various adjuvants such as fillers, dyestuffs and plasticizers which are chemically inert and do not bring about any reactions with the living tissues.

They can be used alone or mixed with non-bioresorbable materials, as indicated above, or with materials which are more or less resorbable in themselves, for example, respectively, polyesters of the polyethylene glycol terephthalate or adipate type, or of the polylactide or polyglycolide type.

The surgical articles according to the invention can be sterilized easily by the techniques usually employed in surgery, for example by radiation treatment.

The following Examples further illustrate the present invention.

EXAMPLE 1

1. Preparation of polyethylene glycol succinate

174g. (1 mol) of diethyl succinate, 93 g. (1.5 mols) of ethylene glycol, 0.280 g. of zinc acetate and 0.070 g. of antimony trioxide are introduced, under a stream of nitrogen, into a 300 cm^3 glass flask equipped with a scraping stirrer, a gas inlet tube, a gas outlet tube, a thermometer, a thermostatically controlled metal heating bath and a distillation column provided with a condenser and a receiving container. The contents of the flask are heated to 180°C., with stirring, and these conditions are maintained for 1 hour 30 minutes. The temperature of the reaction mixture is then raised to 240°C., over the course of 50 minutes and the apparatus is connected to a vacuum pump in order to reduce the pressure in the apparatus to 0.1 mm.Hg over the course of 30 minutes. The whole is maintained under these conditions for 6 hours 30 minutes. The viscous, light brown reaction mixture is dissolved in hot dioxane and then reprecipitated with methanol. A product is obtained which is filtered off and dried at 80°C. in a vacuum oven. In this way, 112 g. of polymer are obtained.

In all, 2 mols of ethanol, 0.368 mol of ethylene glycol and 0.07 mol of diethyl succinate are collected in the various distillates from the reaction. Taking account of the fact that a further 5 g. of polyester are recovered on the walls of the apparatus, the degree of polycondensation rises to 85.5%

The polyester thus obtained has a viscosity of 69 $cm^3/g.$, measured at 25°C., on a 4 g/l solution in chloroform and a viscosity of 70 cm/g, measured at 25°C. in a 2 g/l solution in meta-cresol. It melts at 104°C., and is not decomposed by heating under nitrogen at 300°C.

A filament of gauge 20 decitex is prepared from this polyester by melt spinning under 30 bars and stretching the yarn issuing from the spinneret in a ratio of 7 at

55°C. This filament possesses the following mechanical properties:

tensile strength in accordance with Standard Specification NF G 07,008, April 1961, 2 g/dicitex,

elongation at break in accordance with Standard Specification NF G 07,008, 50%,

tensile strength at knots, in accordance with Standard Specification NF G 07,008, 1.66 g/decitex,

shrinkage in water at 40°C. in accordance with Standard Specification BNMP 14,732/27 of February 1972 4%

2. Determination of the local tolerance of implant in rats

Using the polyethylene glycol succinate obtained as described above, a stretched filament of diameter 300 to 400 μ is produced and is sterilized by immersion for 1 hour in 70° GL ethyl alcohol.

Samples of length 1 cm are implanted, with a curved needle, in rats (Caesarean Originated, Barrier Sustained) weighing 250 to 350 g; the implantation is carried out, on the one hand, in the paravertebral muscles, and on the other hand, under the skin of one of the sides of each animal. Four rats (2 male and 2 female) each received two implants. Two months after the implantation, the animals are killed and the muscular implantation region (implant and paravertebral muscular mass) and the subcutaneous implantation region (skin, implant and underlying muscular portion) are removed in each case. The following examinations are carried out on each specimen removed:

a. Macroscopic examination after transverse section of one of the ends of the muscular mass (intramuscular implant) or detachment of the skin at one end (subcutaneous implant) of each specimen.

b. Histological examination after fixing the specimens in BOUIN liquid, inclusion in paraffin, cutting of 5 μ thick sections and colouration by means of hemalun-phloxine saffron. The following results were obtained:

a. Macroscopic examination

Two months after the implantation, no macroscopically detectable tissue reaction was observed either at the muscle level or at the subcutaneous tissue level.

b. Histological examination

Reaction of the tissues

This reaction is limited to a very inconspicuous fibrous sheath around the implant and to the presence of a few multinucleate giant macrophage and histiocyte cells situated in contact with the implant itself.

No change which could relate to a possible toxic effect of the material was detected on the sections.

In short, the local tolerance in rats is very good from the macroscopic point of view and from the histological point of view.

3. Determination of the bioresorbability "in vitro"

The bioresorbability of the polyethylene glycol succinate produced above is determined by measuring the variation in the reduced viscosity of a sample of polymer taken in the form of flakes and incubated for varying periods of time in an enzyme extract. The test was carried out in the following manner:

a. Preparation of the enzyme extract

"Fauves de Bourgogne" rabbits, of approximately 2.5 kg, are killed with chloroform. The muscles from the back and the thighs are removed and are frozen at −20°C. They are then ground rapidly in a meat mincing machine. 300 g. of ground material are dispersed in 500 ml. of 0.2 M citrate buffer of pH 4.1, which have previously been cooled to +2°. The suspension obtained is ground again twice for 1 minute (grinder turning at 2,000 revolutions/minute), with external cooling (ice and salt mixture at about −13°C.) to keep the temperature of the homogenized material below +10°C. during the operation.

The homogenized material is then subjected to an ultrasonic treatment (frequency: 20 kHz) for 2 minutes with the same cooling precautions. It is then centrifuged at 6,500 G, at 0° for 20 minutes. The supernatant liquid, filtered through glass wool, forms the enzyme extract; its pH is approximately 4.5.

b. Reaction between the product to be investigated and the enzyme extract

A sample of 100 mg. of the polymer to be investigated is incubated at 37°C., with agitation (shaking table turning at 80 revolutions/minute), in the following reaction mixture:

Enzyme extract	40 ml.
Streptomycin sulphate	2 mg.
Sodium salt of penicillin G	2 mg.
Sodium nitride	8 mg.

This reaction mixture is renewed every day; during each renewal, the samples are carefully washed with distilled water.

In parallel, other samples of 100 mg. of the product to be investigated are incubated in reaction mixtures in which the enzyme extract is replaced by an inactivated enzyme extract (heating for 30 minutes at 100°C.) or by 0.2 M citrate buffer of pH 4.5.

The product to be investigated, in the form of flakes, is enclosed in a guaze bag for the incubation.

c. Examination of the polymer after reaction

After 160 hours of incubation, the samples of the product to be investigated are recovered, washed several times with distilled water, drained on filter paper and dried under reduced pressure at 50°C.

The reduced specific viscosity of solutions of the product in 1,2-dichloro-ethane, at 40°C., as well as that of the product before incubation, is then determined.

The following results were obtained:

Nature of the incubation medium	Reduced specific viscosity
None	52
Citrate buffer	54
Inactivated enzyme extract	56
Active enzyme extract	34

It is found, under these conditions, that incubation in the active enzyme extract results in considerable degradation of the polyester.

EXAMPLES 2

1. Preparation of polybutane-1,4-diol succinate

174 g. of diethyl succinate, 135 g. of butane-1,4-diol, 0.270 g. of zinc acetate and 0.1 g. of SbF_3 are introduced into the apparatus described in Example 1 after it has been purged with nitrogen, and then the reagents are stirred for 20 minutes at ambient temperature. The contents of the flask are then heated to 190°–200°C. for

1 hour and then to 240°C. over the course of 30 minutes, and the pressure is reduced to 0.1 mm.Hg over the course of 40 minutes. After 4 hours 40 minutes under these conditions, the reaction is stopped.

In this way, 146.7 g. (degree of polycondensation 85.3%) of greyish polymer are obtained which are dissolved in 400 cm^3 of hot dioxane. The polymer is reprecipitated by introducing the solution into 3 l. of methanol, and is then filtered off and dried at 50°C., in vacuo. 138 g. of white polymer, having a viscosity of 94–97 cm^3/g, measured at 25°C., in a 2 g/l solution in meta-cresol, and having a melting point of 114°C., are recovered.

Filaments of gauge 21 decitex are prepared from the polymer thus produced by melt spinning under 61 bars and stretching at 85°C.

The filaments possess the following mechanical properties:

elongation at break (Standard Specification NF G 07,008, April 1961)	50%
tensile strength (Standard Specification NF G 07,008)	11.8 g/tex.

Braids of 20 strands are then prepared by twisting followed by fixing by heating at 50°C., for 10 minutes. The braids are then sterilized by irradiation under 2.5 Mrads and stored in heat-sealed polyethylene sachets.

2. Implantation of a braid in rats

The implantation is carried out on four rats of the same origin as in Example 1 and in a rigorously identical manner. After two months of implantation, the rats are killed and the same samples are removed and the same examinations carried out as in Example 1. The results obtained were as follows:

A. Macroscopic examination

Two months after the implantation, no macroscopically detectable tissue reaction was observed either at the muscle level or at the subcutaneous tissue level.

B. Histological examination

Reaction of the tissues

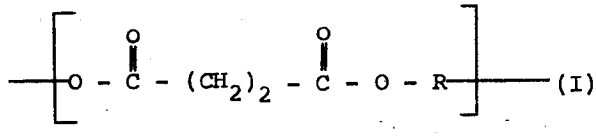
The local tolerance is good; reaction to the implantation is limited to the immediate periphery of the implant and remains inconspicuous. No change in the tissue due to a toxic effect of the products was detected.

Resorption of the implants

After two months of implantation, the number of strands visible in the sections of the intramuscular implants is 3 out of the 20 originally present.

We claim:

1. In a method of repairing or replacing a part of the body of a human of non-human animal by incorporating either temporarily or permanently, a surgical article, the improvement wherein the surgical article consists at least partially of a polyester of succinic acid possessing a plurality of units of the general formula:



(I)

in which R represents a linear or branched alkylene radical containing 2 to 6 carbon atoms having a film- or filament-forming molecular weight.

2. The method according to claim **1** in which the polyester is polyethylene glycol succinate.

3. The method according to claim **1** in which the surgical article is in the form of a suture element.

4. The method according to claim **3** in which the surgical article is in the form of a filament, bristle, single filament, twisted filament, stranded filament, gathered filament, texturized filament of lapped filament, tape, tent or spun fibre.

5. The method according to claim **1** in which the surgical article is in the form of a textile fabric.

6. The method according to claim **1** in which the polyester is combined with another material which is bioresorbable.

7. The method according to claim **6** in which the other material is selected from the group consisting of a polylactide or a polyglycolide.

8. The method according to claim **1** in which the polyester is combined with another material which is non-bioresorbable.

9. The method according to claim **8** in which the polyester is present as a coating over a core of non-bioresorbable material.

10. The method according to claim **8** in which the nonbioresorbable material is selected from the group consisting of polyethylene glycol terephthalate or adipate, polyamide or polypropylene.

11. The method according to claim **1** in which the surgical article is in the form of a tube.

12. The method according to claim **1** in which the surgical article is in the form of a bar.

13. The method according to claim **1** in which the surgical article is in the form of a plate.

14. The method according to claim **1** in which the surgical article is in the form of a screw.

15. The method according to claim **1** in which the surgical article is in the form of a ring.

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