(54) Title: A BODY TISSUE REPLACEMENT PRODUCT AND A METHOD OF PRODUCING THE PRODUCT

(57) Abstract

An integral body tissue replacement product constituted by an at least partially degradable, flexible material comprising a polymer matrix having a porous structure, characterized in that the rate of degradation of the polymer of the matrix varies with the distance from the exposed surface or surfaces of the product; and a method of producing such product.
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A Body Tissue Replacement Product and a Method of producing the product

The present invention relates to a body tissue replacement product constituted by a degradable, flexible material comprising a synthetic polymer matrix having a porous structure.

In using synthetic polymers as replacement materials for various types of human tissue it is desirable to design materials, which degrade in the body at a controlled rate. In this connection it is desirable, e.g. on the one hand, to ensure relatively fast degradation so that endothelization or epithelialization can take place as rapidly as possible. On the other hand, however, constructional integrity of the material must be maintained for the required period of time so that the growth of new tissue will be sufficient for satisfactory performance before the replacement material has degraded.

The general concept of this invention is to provide new products of varying rates of degradation. This can be achieved in different ways, one example of which is varying the molecular weight of the polymer.

Quite generally, a material of low molecular weight degrades faster than one with high molecular weight and in accordance with this invention a balance of the molecular weight can be provided to obtain a material which on the one hand maintains structural integrity for a sufficient period of time and on the other hand will degrade at a sufficient rate to permit fast endothelization or epithelialization to take place.

The present invention has for its main object to solve the problem outlined above while providing a body tissue replacement product which meets the requirements of its practical use.

To attain this object the invention provides a product, wherein the rate of degradation of the polymer of the matrix varies with the distance from the exposed surface
of the product.

The term "exposed surface" as used in this disclosure refers to one or two surfaces of the product to make it clear that the rate of degradation of the polymer varies throughout the thickness of the material as seen in a lateral direction. Thus, when the product is in the form of a wound dressing, the exposed surface of the product is the surface facing the wound. In regard to a vascular prosthesis there are exposed two surfaces, one constituted by the lumen side of the product, the other facing the surrounding tissue.

According to one aspect of the invention the rate of degradation may decrease or increase in the direction from one side to the other of the product. This is the case with for example a wound dressing, wherein it is desirable to have a higher degradation rate and higher pore size on the side of the dressing facing the wound, whereas it is desirable to use a polymer of lower rate of degradation or nondegradable and lower pore size on the outer side of the dressing to protect from e.g. bacterial invasion.

In some cases however it is desirable to provide a wound dressing which has higher degradation rate and lower pore size such as 5-10 μm on the exposed face of the dressing, higher degradation rate and higher pore size such as 50-100 μm in the intermediate part of the dressing and nondegradable protective outer layer with porosity of an order of 1 μm.

In a preferred embodiment of the invention the product is in the form of a multilayered but integral material, wherein each layer independently of the others contains polymer of same rate of degradation. By using such multilayering technique it is possible, as further outlined below, to build up a product by stepwise application and precipitation of layers wherein the desired gradient of degradation rate across the product will be obtained. In for example a vascular prosthesis it is thus possible to arrange layers on the
lumen side of the wall of the prosthesis containing polymers of a high degradation rate, to ensure rapid endothelization, some interior layers of the material containing polymer of lower rate of degradation so that the constructional integrity of the product will be maintained for a sufficient period of time. In this embodiment the degradation rate of the different layers may diminish outwardly from the center of the product or the product may contain at intervals layers of lower degradation rate alternating with layers of higher degradation rate.

The multilayered varieties of the product of this invention can be prepared starting from a solution of a copolymer in a suitable solvent and coating a substrate with a uniform thickness of such solution. The initial layer resulting from coating the substrate is then precipitated by treating the coating to displace solvent present in the coating with a precipitating solution which comprises a fluid which is miscible with said solvent but functions as a precipitating non-solvent with respect to the polymer. This procedure is then repeated the desired number of times to form a multilayered material.

It has been found that if some solvent is left in the precipitated polymer layer repeating the procedure to form another layer or coating results in the formation of a mechanically strong linkage between the first layer and the subsequent layers preventing progressive delamination of the graft wall when implanted in a living body. Such delamination is a disadvantage associated with the conventional art and generally results in the formation of extensive aneurism upon implantation.

In the products of the present invention the polymer used for preparing same can be any polymer useful in the context, viz. a polymer showing biocompatibility and in some cases blood compatibility and being degradab-
le in the desired manner when implanted. It is preferred, however, to use a copolyurethane, particularly a segmented copolyurethane. In coating the substrate it is preferred to use a solution containing less than 5% and especially less than about 3% by weight of polymer. The lower limit is not critical but is preferably not less than 0.1% by weight.

As a solvent there may be used any solvent having the ability to dissolve the polymer used, but preferred solvents are those selected from the group consisting of tetrahydrofuran, amide solvents and sulfoxide solvents. Among such solvents there may be mentioned in addition to tetrahydrofuran dimethylacetamide, dimethylformamide and dimethylsulfoxide.

As a non-solvent there may be used any fluid having the capacity to precipitate the polymer. A preferred solvent is water but also lower alkanols, such as ethanol, may be used, optionally in combination with water.

As previously indicated segmented aliphatic polyurethanes or segmented aromatic polyurethanes may be used in applying the technique of this invention. In order to obtain materials which are non-toxic, non-mutagenic and non-carcinogenic it is preferred to use segmented aliphatic polyurethanes or using another expression aliphatic segmented polymers.

The polymeric material for use in the invention may be conventionally prepared from aliphatic polyurethanes based on diisocyanates, e.g. 1,2-diisocyanatoethane, 1,5-diisocyanato pentane, hexamethylene diisocyanate, methane diisocyanato pentane, 1,9-diisocyanato nonane, 1,8-diisocyanato octane, 1,4-diisocyanato butane, 4,4'-methylenebiscyclohexyl diisocyanate, lysine diisocyanate, 1,4-trans-cyclohexane diisocyanate, dimethyl(diisocyanato silane, diethyl(diisocyanato silane. In addition to such diisocyanates there may be used polyols having average molecular weight within the range of 100 to 10 000, e.g. poly(ethylene adipate), poly(tetramethylene adipate), poly(1,4-
cyclohexyldimethylene adipate), poly(hexamethylene oxalate), poly(hexamethylene glutarate), poly(E-aprolactone), poly(tetramethylene oxide), poly(ethylene oxide), poly(1,2-propylene oxide). Chain extenders e.g. 1,4-butandiol, 2,4,6-tris(dimethylaminomethyl)phenol glycerol, 3,6-dioxoactane 1-8-diol, ethylene diol, diathylene diol, tetramethylene diamine, ethylene diamine, hexamethylene diamine, propylene diamine.

The copolyurethanes are conventionally formed by e.g. reacting a prepolymer such as a polyether diol, with a diisocyanate, and the product resulting from such reaction may then be chain extended by reacting with a diol or diamine. By such polymerization process copolymers may be produced having preferred molecular weights and preferred viscosity in solution. By varying the molecular weight and the viscosity of the polymer in solution the rate of degradation and porosity of the material prepared may be controlled. However, various polymers with different rates of degradation can be used in the different layers.

The selected polymer material is dissolved in a suitable solvent of the type indicated above and the proportions between polymer and solvent are suitably selected so as to give a percentage of solids in the resulting solution of less than 5% by weight and preferably less than 3% and suitably no less than 0.1% by weight. The coating solution is then used to coat a substrate to form an initial coating of uniform thickness. As a substrate there may be used any mechanical means of suitable type, such as a metal or glass plate or a metal or glass mandrel, preferably coated with a resistant plastic, such as polytetrafluoro ethylene. The coating can be provided by spraying, immersion or dipping or in some other conventional manner.

The molecular weight of the polymer used in preparing the products of this invention can vary within fairly wide limits but when using polyurethanes the average
molecular weight preferably lies within the range of from about 5x10^3 to 10^6. A particularly preferred range is from about 2x10^4 to 3x10^5.

The tissue replacement product of this invention can be used in a multitude of medicinal applications. Thus, it can be used as a vascular graft, as a skin graft or as a wound dressing. Moreover, it can be used as elastic membranes for ear drum replacement, as elements for orthopedic surgery and as anticoagulant tubing for blood transfusion.

The invention will now be further described by specific examples which, however, must not be construed to limit the scope of the invention. In this connection reference is also made to the appended drawing, wherein there is shown a casting device for the preparation of a multilayered material in accordance with the present invention.

The casting device shown in the drawing includes a frame carrying a rotary cylinder A. The cylinder may be of sintered glass or its surface may be covered with polytetrafluoroethylene, viz. "FLUON", manufactured by ICI Limited, England. Cylinder A is arranged to be driven by an electric motor C through gears and a gear shaft B. The rotational speed of cylinder A can be easily adjusted for controlling the coating formed on the cylinder. The level of polymer solution is indicated at D.

**Example I.**

**General Production Procedure.**

Using the casting device shown in the drawing the cylinder A is dip-coated at room temperature with a polymer solution, the polymer coating applied being then precipitated with a non-solvent possibly containing a minor amount of solvent. After the first layer of polymer is precipitated this procedure is repeated for the desired number of cycles to prepare superimposed layers of polymer coatings on the cylinder to produce a multilayered prosthesis material of the required mechanical strength and thickness. After the deposition of the desired number of layers on cylinder A the material produced is soaked in deionized water to remove all residual solvents and
non-solvents, and the material may then be washed with ethanol and dried on the cylinder at for example 30°C in a vacuum oven.

The average thickness of the individual polymer layer is in the range of about 0.01 to 0.2 mm, and the average pore size in the material prepared is in the range about 0.5 to 500 μm. For example, using a concentration of polyurethane of about 2% by weight an average pore size will be obtained lying within the range of about 30 to 50 μm.

In using the technique of this invention it is preferred that some solvent is always left in the precipitated polymer coating at the moment when the subsequent polymer coating is deposited on the underlying one.

The initial coating resulting from applying polymer solution on the substrate is precipitated by treating the coating to displace solvent present in the coating with a precipitating solution which comprises, as a major constituent, a fluid which is miscible with said solvent but functions as a precipitating non-solvent with respect to the polymer, and further comprising, as a minor constituent, a solvent for the polyurethane. This procedure is then repeated the desired number of times to form a multilayered material.

It has been found that if some solvent is left in the precipitated polymer layer repeating the procedure to form another layer or coating results in the formation of new fibres which form a mechanically strong linkage between the first layer and the subsequent layer. This will prevent progressive delamination of the graft wall when implanted in a living body. Such delamination is a disadvantage associated with the conventional art and generally results in the formation of extensive aneurisms upon implantation.
This strong linkage between the layer may be accomplished either by using a mixed solvent-non-solvent as outlined or by interrupting the treatment with precipitating solution to leave some solvent in the coating when applying the subsequent layer.

Although the invention is not limited to any specific theory or mechanism, there are different factors which might explain how the very strong linkage is achieved. It has thus been observed that there are many fibres in the boundary of two subsequent layers, which seem to be interlocked probably due to the fact that many tiny fibres in the outer surface of the first layer are partly dissolved in the highly diluted solvent contained in the non-solvent/solvent precipitation liquid system. As soon as the new fibres are precipitated in the subsequent precipitation step, also the partly dissolved fibres produced in the preceding step are reformed, thus giving an interlocking effect of the two subsequent layers. There are also fibres precipitated in the second subsequent layer, which are trapped in the pores of the first layer. At last there may also be a kind of gluing effect between fibres in the outer surface of the first layer and the inner surface of the second layer. This results from the presence of small amounts of solvent left in the precipitated polymer.

In practical use the product or material of this invention may, of course, include reinforcing materials, such as materials in fibrous, woven or pleated form. Such reinforcing material may be degradable or non-degradable.

It is to be noted that the invention is not limited to the casting technique described above but other methods of applying the polymer solution onto a substrate may be used equally well. Thus, application by spraying is also useful and brushing technique is also conceivable.
Example II.
Preparation of degradable Wound Dressings.

A series of casting solutions was prepared from polyester urethane based on hexamethylene diisocyanate, poly (hexamethylene glutanate)diol and 1,4-butane diol. Solutions were prepared from polyurethanes having molecular weights of $2 \times 10^4$, $4 \times 10^4$, $5 \times 10^4$, $6 \times 10^4$ and $3 \times 10^5$. These individual casting solutions contained 4, 3, 2, 2 and 1% by weight, respectively, of the said polyurethanes.

Another casting solution is prepared by dissolving Esthane-polyether urethane (Trade Mark, Goodrich) in tetrahydrofurane at room temperature. The polymer solution is stirred for half an hour and is then filtered and stored in dark, closed bottles until use thereof.

Using the casting solutions prepared a wound dressing is manufactured according to the procedure outlined in Example I using a casting device provided with a cylinder made of sintered glass. In the casting procedure the cylinder is continuously flushed with deionized water. Water penetrates through the pores of the sintered cylinder causing uniform precipitation of the polymer on the surface of the cylinder.

Using the five casting solutions of varying molecular weight of the polymer five subsequent layers were deposited on the cylinder giving an average porosity varying from about 70 to about 150 $\mu$m. The polymer membrane on the cylinder is then flushed with ethanol, which is subsequently evaporated.

Using the remaining casting solution another three layers of polymer are deposited on the glass cylinder, and drying these outer polymer layers leaves a semi-permeable membrane having a porosity within the range 0.5 - 1 $\mu$m. This membrane protects against bacterial invasion and allows the proper fluid transport through the membrane.
The whole composite polymer material deposited on the cylinder is finally washed with ethanol, deionized water and again with ethanol. The material is removed from the cylinder, dried at 30°C under a vacuum of 20 mbar and placed in a plastic bag for sterilization. When used as a wound dressing the material displays excellent adherence and flexibility. Due to the degradability of the polymer of the side exposed to the wound epithelization and growth of new skin tissue is enhanced.

This artificial wound dressing composed of two different membranes connected together is placed with the degradable face on the wound. This degradable layer ensures a proper epithelization and successive tissue ingrowth in the dressing and is finally replaced with newly synthesized stable connective tissue.

The upper layer made from non-degradable polyurethane ensures the proper fluid transport rate,
1 to 4 mg/hr/cm², and protects the wound against bacterial invasion.

This layer is finally stripped off the rehealed wound.

This artificial skin protects the wound for at least 20 to 60 days without rejection and without requiring an immune suppression.

It shows excellent adherence to the wound and high flexibility.

Example III.

Preparation of Degradable Vascular Prosthesis.

Two of the casting compositions described in Example II were used, namely that containing polyurethane of molecular weight 2 x 10⁴ and that of molecular weight 3 x 10⁵. The procedure described in Example I is used for the manufacture using a mandrel rather than a cylinder.

The prosthesis wall is composed of 30 layers of polyurethane having a molecular weight of 2 x 10⁴ on the lumen side of the prosthesis and 3 x 10⁵ on the opposite side of the prosthesis wall. In the manufacture the sixth, eleventh, sixteenth, twentyfirst, twentiesixth and the outermost layer are all made from polyurethane with a molecular weight of 3 x 10⁵. The other layers are made from polyurethane having a molecular weight of 2 x 10⁴.

Using the polymer with a lower molecular weight results in higher rate of degradation. High rate of degradation is desirable to ensure rapid endothelization and growth of tissue. On the other hand, high molecular weight of the polymer results in lower rate of degradation. The degradation process of the prosthesis is thus slowed down so that its mechanical integrity will be maintained for a sufficient period of time to fulfil its function until newly grown tissue will impart sufficient mechanical stability where implantation has been made.
Example IV.
Preparation of Partially Degradable Vascular Prosthesis.

A polyether urethane having an average molecular weight of $4 \times 10^5$ based on 4,4'-methylene-bis-cyclohexyl diisocyanate, poly(tetramethylene oxide) and 1,4-butane-diol is dissolved in tetrahydrofurane at room temperature and precipitated with water/ethanol(9:1v./v.). The precipitated polymer is washed with distilled water and dried under vacuum. The dried polymer is then dissolved in dichloromethane to produce a solution having a concentration of polymer of 2 % by weight. The polyurethane is precipitated with n-hexane and dried to constant weight.

The polyurethane thus prepared is used for preparing a casting solution by dissolving the purified polymer in tetrahydrofurane at room temperature, the concentration thereof being 1.8 % by weight.

Using the procedure outlined in Example I partially degradable vascular prostheses are prepared from the solution described above. However, before applying layers of polymer from such casting solution there are initially applied on the cylinder three layers from a casting solution containing degradable polyurethane of the type described in Example II but having an average molecular weight of about $3 \times 10^4$. This will form a membrane having small pores in the range of 5-10 \( \mu \)m on top of which there are then applied 35 to 50 layers using the casting solution described initially in the present example. The average pore size of these additional layers is larger than that of the initial membrane and within the range 30-60 \( \mu \)m.

Due to the fact that the lumen side of the prosthesis is based on material having a relatively small pore size and being degradable the rate of endothelization is enhanced while due to the following layers the prosthesis maintains its mechanical integrity for the
required period of time.

Example V.
Preparation of a partially degradable vascular prosthesis.

Two casting solutions were prepared from polyesterurethane based on hexamethylene diisocyanate 1,4-butane-diol and poly(ethylene adipate)dil with a molecular weight of 500 (solution A) and 1500 (solution B). These individual casting solutions contained 1.5 and 2.1 % by weight, respectively, of the said polyurethanes.

Vascular prostheses are prepared by casting on the mandrel 10 layers of solution B followed by depositing on these layers next 40 layers of solution A according to the procedure described in Example I as a mandrel instead of a cylinder.

Due to faster degradation of the material in the said 10 layers comprising the lumen part of the prosthesis the endothelization process is enhanced while the remaining part of the prosthesis prepared from the other material having a lower rate of degradation maintains the required mechanical integrity of the prosthesis during the healing process.

While the invention has been described with reference to certain specific examples using specific materials, solvents etc. and a specific technique for applying the different layers, it is to be noted that the invention is in no way limited to such specific features since obvious variations and modifications will be apparent to those skilled in the art. Therefore, the invention is not limited otherwise than as is defined by the scope of the appended claims.
PATENT CLAIMS.

1. An integral body tissue replacement product constituted by an at least partially degradable, flexible material comprising a polymer matrix having a porous structure; characterized in that the rate of degradation of the polymer of the matrix varies with the distance from the exposed surface or surfaces of the product.

2. The product of claim 1 in the form of a multilayered material, each layer independently containing polymer of same rate of degradation.

3. The product of claim 2, wherein some interior layers of the material contain polymer of lower degradation rate to prolong the constructional integrity of the product.

4. The product of any preceding claim in the form of a vascular prosthesis.

5. The product of any of claims 1-3 in the form of a wound dressing or skin graft.

6. The product of claim 4, wherein the matrix adjacent to the lumen face of the prosthesis is composed of a polymer of higher degradation rate than that of the interior part of the prosthesis.

7. The product of claim 6 based on a multilayered material, wherein the lumen side layer is composed of a polymer of higher degradation rate than those of the center part of the prosthesis, the pore size being correspondingly lower on the lumen side than in the center part.

8. The product of any preceding claim, wherein the variation of rate of degradation is provided by varying the molecular weight of the polymer.
9. The product of claim 8, wherein the variation of rate of degradation is provided by using different polymers of different molecular weight in the different layers.

10. The product of claim 8, wherein the number of layers is at least 5, some intermediate layers being composed of a polymer of higher molecular weight to prolong the structural integrity of the product when implanted.

11. The product of claim 6, designed as a multi-layered material, wherein the part of the matrix facing the living tissue is composed of a polymer of lower molecular weight than that adjacent to the outer face, the rate of degradation being correspondingly higher on the tissue side than on the outer side.

12. The product of any preceding claim, wherein the synthetic polymer matrix comprises a copolyurethane.

13. The product of claim 11, wherein the copolyurethane is a segmented copolymer.

14. A method of producing the product of any of claims 2-13, comprising the steps:
   (a) preparing a copolymer solution using a solvent;
   (b) coating a substrate with a uniform thickness of said solution;
   (c) precipitating the initial coating resulting from step (b) to form a physically stable structure having pores substantially uniformly distributed therein by treating the coating with a precipitating solution which is miscible in said solvent but functioning as a precipitating non-solvent with respect to the copolymer and then repeating steps (a)-(c), as required to form the multilayered material, characterized by preparing in step (a) a solution containing less than 5% by weight of polymer.
15. The method of claim 14, wherein the solution prepared in step (a) contains less than about 3% by weight and especially less than about 2% of polymer.

16. The method of claim 14 or 15, wherein some solvent is left in each preceding layer when the subsequent layer is applied.

17. The method of claim 16, wherein the precipitating solution comprises as a major constituent a fluid which is miscible in said solvent but functions as a precipitating non-solvent with respect to the polymer, and further comprises as a minor constituent a solvent for the polymer, whereby when repeating steps (a)-(c), due to the presence in the precipitating solution of some solvent, mechanical binding will be obtained between said initial coating and the subsequent one.
INTERNATIONAL SEARCH REPORT

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) *

According to International Patent Classification (IPC) or to both National Classification and IPC

A 61 L 27/00, A 61 F 2/02

II. FIELDS SEARCHED

Classification System | Classification Symbols
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IPC 3 | A 61 L 15/00, 01, 03, 04; A 61 F 1/00, 13/00; B 32 B 7/04, 27/06, 27/40

Documentation Searches other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched *

SE, NO, DK, FI classes as above

III. DOCUMENTS CONSIDERED TO BE RELEVANT *

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| A | US, A, 4 289 125 (INTERNATIONAL PAPER COMPANY) 15 September 1981, See claims 1 and 8 | 1, .../...

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- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step
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- "A" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search: 1985-03-19

Date of Mailing of this International Search Report: 1985-03-21

International Searching Authority: Swedish Patent Office

Signature of Authorized Officer: Inga-Karin Petersson

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See claim 1 | 1                     |
| A        | DE, C2, 2 802 295 (DELLALANDE S A)  
20 July 1978  
See claim 1 | 1                     |