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(21) International Application Number: PCT/US93/04829 (22) International Filing Date: 20 May 1993 (20.05.93) (30) Priority data: 4/127156 20 May 1992 (20.05.92) JP (71) Applicant (for all designated States except US): SHERWOOD MEDICAL COMPANY [US/US]; 1915 Olive Street, St. Louis, MO 63103-1642 (US). (72) Inventor; and (75) Inventor/Applicant (for US only) : OGAWA, Masaki [JP/JP]; 569-29, Kimune, Hamakita-City, Shizuoka Prefecture 434 (JP). (74) Agents: SMITH, Montgomery, W.; Sherwood Medical Company, 1915 Olive Street, St. Louis, MO 63103-1642 (US) et al.		(81) Designated States: AU, BB, BG, BR, CA, CZ, FI, HU, JP, KP, KR, LK, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SK, UA, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published With international search report.
(54) Title: ARTIFICIAL WINDPIPE (57) Abstract A light-weight artificial windpipe with excellent biocompatibility has adapters at both ends and an elastomer tube in the middle. The adapter of the artificial windpipe is made primarily of an organic polymer selected from among organic polymers containing sulfone groups and/or carboxyl groups or organic polymers containing esters in the principal-chain and/or side-chains, and is coated with 3-10μm thick hydroxyapatite.		

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Artificial Windpipe

Technical Field

The present invention concerns an artificial windpipe to be used for reconstructing a part of or entire windpipe in case of diseases or accidents.

Background Art

In recent years, windpipe resections (e.g., the pharyngeal cancer, etc.) have been on the rise. If the length removed is less than 30 mm, the remaining part is stretched and stitched. If the length resected is 30 mm or larger, however, this method cannot be utilized. While an artificial windpipe equipped with a silicone cuff (manufactured by Neville Co.) is well known, it has been rarely used in Japan due to extremely poor clinical results.

Improved artificial windpipes are disclosed in Japanese Patent Application Publication No. Kokai Sho 63[1988]-27014 and Japanese Patent Disclosure No. Tokkai Hei 1[1989]-291858.

Various methods for manufacturing hydroxyapatite were also published. Among them are: a sintering method in Japanese Patent Application Publication No. Kokai Hei 2[1990]-13580; a method for plasma-spraying metal implants in Japanese Patent Application Publication No. Kokai Sho 58[1983]-50737; methods for plasma-melt-spraying ceramic core materials in Japanese Patent Application Publication No. Kokai Sho 59[1984]-46911 and Japanese Patent Disclosure No. Tokkai Sho 62[1987]-34559, Sho 62[1987]-57548, and Sho 63[1988]-46165.

A sputtering method is disclosed in Japanese Patent Disclosure No. Tokkai Sho 58[1983]-109049; a flame melt-spray method in The Proceedings from the 1988 First Fall Symposium of the Japan Ceramic Society, pp. 401-402; and a glass frit baking method in The Proceedings from the 9th Biomaterial Society Convention (1987), p. 6.

An electrophoretic method is disclosed in Japan Ceramic Society, 1988, pp. 417-418.

Methods for depositing hydroxyapatite from an artificial body fluid composed of ions of the same types and concentrations as those of human blood plasma are disclosed in Japanese Patent Application Publication No. Kokai Sho 52[1977]-10939 and Hei 1[1989]-54290 and Japanese Patent Disclosure No. Tokkai Hei 2[1990]-255515.

Disclosure of Invention

Although various techniques have been published regarding artificial windpipes, there remain many problems to be resolved.

Japanese Patent Application Publication No. Kokai Sho 63[1988]-27014 presented an attempt to provide an artificial windpipe for long-term or permanent uses, in which by coating collagen on a mesh/silicone composite is coated with collagen to improve the biocompatibility and to prevent unsatisfactory excessive granulation growths. The performances, however, are unsatisfactory, and they have yet to be used for general clinical purposes. Japanese Patent Disclosure No. Tokkai Hei 1[1989]-291858 has disclosed an artificial windpipe which consists of a ceramic composite of porous and dense materials containing hydroxyapatite. However, because hydroxyapatite, which exhibits excellent biocompatibility, has a low strength and is brittle, there are severe restrictions on shapes. In order to secure sufficient strengths, therefore, the weight must be increased. Since this, in turn, increases the load on patients, the success of artificial windpipe reconstruction becomes less likely. Other ceramics which have sufficient strengths, on the other hand, do not yield satisfactory biocompatibilities, and their successful clinical use is also not expected.

Methods for manufacturing and coating hydroxyapatite are difficult to apply to the artificial windpipe of the present invention due to the following problems.

(a) The plasma melt-spray method requires an expensive and complicated apparatus and yet does not readily produce fine apatite coating. In addition, since the hydroxyapatite source is first melted at high temperature, a coating of apatite different from the apatite inside the body is formed.

(b) In the sputtering method, an expensive and complicated apparatus is required. Since the hydroxyapatite is first melted at high temperature, a coating of apatite different from the apatite inside the body is formed.

(c) The sintering method and glass frit method, require heat treatments at temperatures 850°C or above, and therefore, these methods are applicable only to substrates with high heat resistances. Since the hydroxyapatite source is melted at high temperature, a coating of apatite different from the apatite inside the body is formed. Also a terminal made from the sintered material are subjected to severe restrictions on the structure and shape because the strength of hydroxyapatite is low.

(d) The electrophoretic method can be applied only to metal substrates with good electric conductivity because it uses the substrate itself as an electrode. Since a sintered apatite is used as a feed material, a coating of apatite different from the apatite inside the body is formed.

(e) The method of precipitation from an artificial body fluid, has a drawback that no substrates other than a CaO/SiO₂ glass which provide good adhesion with the hydroxyapatite generated have been found.

It has long been acknowledged that an unprecedented implant material can be manufactured by coating an organic polymer with hydroxyapatite having a composition virtually identical to that of the human body. This method, however, could not be implemented in practice because of the

difficulties to attain sufficient adhesive strengths between hydroxyapatite and organic polymers.

The objective of the present invention, which has been proposed in order to resolve the aforementioned problems inherent in conventional artificial windpipes, is to provide an innovative light-weight artificial windpipe with an excellent biocompatibility.

The present invention concerns an artificial windpipe with the following characteristics: an artificial windpipe consisting of adapters at both ends and an elastomer tube in the middle, in which the adapter of said artificial windpipe is primarily made of an organic polymer selected from among organic polymers containing sulfone groups and/or carboxyl groups or organic polymers containing esters in the principal-chain and/or side-chain and is coated with 3-100 μm thick hydroxyapatite.

Preferably, the artificial windpipes satisfy the following conditions (1) - (10).

1. The said adapter is fitted over and fixed to the elastomer tube with an overlapping between them and at least two, preferably at least four, through holes are present on its circumferential surface.

2. The adhesive strength between the hydroxyapatite coating and the organic polymer material is at least 2 MPa.

3. No metallic components are used.

4. The Shore hardness of said elastomer is 30A to 70D.

5. The said elastomer tube has thicker wall segments for reinforcement and/or is reinforced by a stent.

6. The said organic polymer containing sulfone group is selected from among polyethersulfone, polysulfone, and/or a compound containing organic polymers selected from between them.

7. The said organic polymer containing carboxyl group is a polymer while is obtained through a copolymerization of an olefin and carboxylic acid containing vinyl group and

subsequent cross-linking with metal ions and/or a compound containing an organic polymer.

8. The said organic polymer containing esters in the principal-chain is allyl resin, oxybenzoyl polyester, polyacrylate, polybutylene terephthalate, polycarbonate, or polyethylene terephthalate.

9. The said organic polymer containing esters in side-chains is selected from among AAS resin (acrylic ester-acrylonitrile-styrene copolymer), cellulosic plastics such as cellulose acetate, cellulose butyrate and ethyl cellulose, ethylene-vinyl acetate-vinyl chloride copolymer, ethylene-acrylic ester copolymer, acrylic ester-butadiene-styrene copolymer, methacrylic resin, and vinyl acetate resin.

10. A part of phosphate groups, or hydroxyl groups of hydroxyapatite is substituted by carbonate groups.

Brief Description of Drawings

Figure 1 shows a partial sectional view of one embodiment of an artificial windpipe according to the present invention.

Figure 2 shows a partial sectional view of another embodiment of an artificial windpipe according to the present invention.

Figure 3 shows a partial sectional view of still another embodiment of an artificial windpipe according to the present invention.

The scope of the present invention is limited to an artificial windpipe which consists of adapters at both ends and an elastomer tube in the middle for the following reasons: the gist of the present invention lies in the fact that an excellent biocompatibility which has not been achieved in conventional techniques is attained by coating an organic polymer with a relatively low specific weight hydroxyapatite having a composition virtually identical to that of human body, and materials which can be coated by

said hydroxyapatite with sufficient adhesive strengths are limited to materials with relatively large elastic constants. Elastomers are selected as tubes connecting said adapters to obtain the overall compliance of the artificial windpipe similar to that of an actual artificial windpipe.

Best Modes for Carrying Out the Invention

The primary material of the adapter is limited to an organic polymer selected from among organic polymers containing sulfone groups and/or carboxyl groups or organic polymers containing esters in the principal-chain and/or side-chain. This is required to attain sufficient adhesive strength with hydroxyapatite for practical use. However, since the intended function of these organic polymers is to improve the adhesion with hydroxyapatite, it is only necessary for such polymers to have sulfone or carboxyl groups, or esters on the surface. For example, when polypropylene selected as an organic polymer receives a plasma treatment at 0.1 Torr, 8 cc/min., and 150 mA for 3 minutes, carboxyl groups are introduced into approximately 7% of carbon atoms on the surface and sufficient adhesive strength with hydroxyapatite is attained.

Examples of organic polymers containing sulfone groups or carboxyl groups include polyethersulfone, polysulfone, ionomer, carboxylic acid-modified polyolefins (e.g., brand name: Mitsui Lonply), etc. However, other polymers may be used as long as sulfone groups or carboxyl groups are present on the surface in contact with hydroxyapatite.

Examples of organic polymers containing esters in the principal-chain include allyl resin, oxybenzoyl polyester, polyacrylate, polybutylene terephthalate, polycarbonate, and polyethylene terephthalate.

Examples of organic polymers containing esters in side-chains include AAS resin (acrylic ester-acrylonitrile-styrene copolymer), cellulosic plastics such as cellulose acetate, cellulose butyrate and ethyl cellulose, ethylene-

vinyl acetate-vinyl chloride copolymer, ethylene-acrylic ester copolymer, acrylic ester-butadiene-styrene copolymer, methacrylic resin, and vinyl acetate resin.

It is desirable that the thickness of the
5 hydroxyapatite film be 3-100 μm . If the thickness is less than 3 μm , it may be eroded and disappear while it remains inside the body. If the thickness exceeds 100 μm , a significant strain is produced due to difference in expansion coefficients between the substrate and
10 hydroxyapatite in response to temperature and humidity variations. As a result, the hydroxyapatite layer becomes more easily cracked, and the film separation may result from such cracks. Moreover, the prolonged time required for forming such thick hydroxyapatite layer inflates the
15 production costs, making the thicker coating unpracticable.

An ionomer obtained by cross-linking an ethylene-methacrylic acid copolymer with metal ions (e.g., Himirane, trademark of Mitsui-DuPont Chemical Co.) is desirable in the present invention since the highest adhesive strength with
20 hydroxyapatite is attained.

It is desirable that a part of phosphate groups or hydroxyl groups of the hydroxyapatite of the present invention be substituted with carbonate groups, because in such form, it is closer to the hydroxyapatite in the human
25 body and has better biocompatibility.

In the present invention, adapters are locked with and fixed to the elastomer tube in an overlapping fashion, and at least two, preferably at least four, through holes are present on the circumferential surface. There is no need,
30 however, to open holes on the tube. If holes are present on hard adapters, which needles go through, then even if no holes are present in the tube, which needles can easily go through, the needles can easily penetrate when the artificial windpipe is fixed to a real windpipe via
35 needles/sutures, and the artificial windpipe can be effectively sealed (extremely difficult surgical skills are

required for fixing elastomer tubes which have no overlapping with adapters by using needles/sutures).

It is necessary that the number of holes be at least 2, preferably at least four, since it is desirable that four or more holes be present to obtain an air tight suture between an artificial windpipe-real windpipe. The holes do not have to be circular and may be elliptical and hyperelliptical.

It is desirable that absolutely no metallic components be present in the artificial windpipe of the present invention since such components may obstruct diagnoses by X-ray CT, MRI, etc., which are expected to be more widely used in the future.

It is desirable that the Shore hardness of the elastomer used for the artificial windpipe of the present invention be 30A to 70D since the artificial windpipe must have a flexibility comparable to those of real windpipes. If the hardness is lower than 30A, the size of the inner cavity may locally decrease. If the hardness exceeds 70D, an excessive load is exerted on a real windpipe at the suture, prolonging the healing of the wound.

It is desirable for said elastomer tube to have locally thicker wall segments for reinforcement and/or be reinforced by a stent. This is to prevent the narrowing of the inner cavity under an external pressure. If the thickness of the entire tube is increased, the flexibility of the artificial windpipe decreases, and the load is concentrated at the suture, consequently, the healing of the wound may be delayed, or in an extreme case, the artificial windpipe may come off.

Tables I and II show data obtained corresponding to the following examples, in which the thickness of hydroxyapatite coating and the adapter material were varied.

Application Examples 1 through 5

Figure 1 shows a partially sectioned view of an embodiment of an artificial windpipe according to the

present invention. Figures 2 and 3 show partially sectioned views of other embodiments of an artificial windpipe. In the Figures, (1), (2), and (3) are an adapter, a tube, and through holes, respectively.

5 The artificial windpipe of the present invention is prepared as follows. The adapter (1) at both ends of the artificial windpipe is composed of polyethersulfone (PE S4100G, manufactured by ICI Japan). Two of such artificial windpipe adapters are buried into a glass powder with
10 particle diameters 100-600 μm (this technique is disclosed in Japanese Patent Disclosure No. Tokkai Hei 2[1990]-25515). In said glass powder, the ranges of CaO and SiO₂ compositions are: CaO: 20-60 mol%; SiO₂: 40-80 mol%. The sum of CaO and SiO₂ is at least 70 mol%. At least 80% of
15 the glass powder has particle diameters 100-600 μm .

 The glass composition was as follows: CaO: 49.87 mol%; SiO₂: 35.46 mol%; P₂O₅: 7.153 mol%; MgO: 7.111 mol%; CaF: 0.399 mol%.

 Artificial body fluid A, which was virtually
20 supersaturated with hydroxyapatite, was added (quantity of addition: 30 equivalents of an apparent volume of the aforementioned glass powder). and the resulting mixture was left at 37°C for 48-hours.

 The composition of the artificial body fluid was as
25 follows (with respect to 1 L of water): artificial body fluid A: 7.996 g of NaCl, 0.350 g of NaHCO₃, 0.224 g of KCl, 0.228 g of K₂HP0₄·3H₂O, 0.305 g of MgCl₂, 0.071 g of Na₂SO₄, approximately 45 mL of 1 N HCl, and 6.057 g of tris(hydroxymethyl)aminomethane; artificial body fluid B:
30 11.99 g of NaCl, 0.525 g of NaHCO₃, 0.336 g of KCl, 0.324 g of K₂HP0₄·3H₂O, 0.458 g of MgCl₂, 0.107 g of Na₂SO₄, approximately 68 mL of 1 N HCl, and 8.086 g of tris(hydroxymethyl)aminomethane.

 NaHCO₃ has also been added to the present artificial
35 body fluid as a carbonate. It has been confirmed that the

phosphate groups or hydroxyl groups of the hydroxyapatite layer derived from said artificial body fluid are partially substituted with carbonate groups. It is also known that the phosphate groups or hydroxyl groups of hydroxyapatite existing in the human body are partially substituted with carbonate groups as well.

The artificial windpipe was retrieved 48 hours later, and subsequently, it was immersed in artificial body fluid B for 1 week. One week later, the adapter was retrieved from the artificial body fluid B, washed with water and dried, it was then fitted over and glued to a tube of medical polyurethane (Tekoflex EG85A, manufactured by Thermedic Co.; Shore hardness: 85A [sic]). After the adhesive was dried, the jointed windpipe was then sterilized by gaseous ethylene oxide in a sterilized bag.

The thickness of the hydroxyapatite coating was controlled by varying the artificial body fluid immersion.

Application Example 6

An artificial windpipe not coated with hydroxyapatite was used in a comparative example. The thickness of hydroxyapatite coating and physical appearances (e.g., cracks, etc.) were measured or observed by using a scanning electron microscope.

When an artificial windpipe was coated with hydroxyapatite, a plate (length: 5 mm; width: 5 mm; thickness: 1 mm), consisting of a material identical to that of the adapter was also coated together, and the adhesive strength of the coating on this plate was measured in order to evaluate the adhesive strength between the artificial windpipe adapter and hydroxyapatite.

A part of windpipe of each adult dog was resected and replaced by an artificial windpipe, and the survival period and the presence of granulation growths were examined for each dog.

TABLE I

	Application Examples					
	6	1	2	3	4	5
Coating Thickness (μm)	--	2.5	3.5	12	95	110
Presence of Cracks	--	absent	absent	absent	absent	absent
Adhesive Strength (MPa)	--	4.8	5.2	5.5	4.0	1.9
Time of Death (Survival Period after Transplantation)	34 days 44 days	55 days 58 days	-- both alive after 6 months	-- both alive after 6 months	-- both surviving more than 6 months	-- 113 days and surviving more than 6 months
Extents of Granulation Growths	moderate, no clogging	medium, clogging has yet to occur	no problems	no problems	no problems	no problems
1 month						
2 months	--	significant, clogging has yet to occur	no problems	no problems	no problems	slight enlargement
6 months	--	--	no problems	no problems	no problems	no problems

Application Example 7

An artificial windpipe adapter with the shape identical to that in Application Example 1 was prepared by using polybutylene terephthalate (PBT1401-X06, manufactured by Toray, Inc.), and hydroxyapatite was coated under conditions identical to those in Application Example 2.

Application Example 8

An artificial windpipe adapter with the shape identical to that in Application Example 1 was prepared by using a polyacrylic resin (Delpet 60N, manufactured by Asahi Kasei Co.), and hydroxyapatite was coated under conditions identical to those in Application Example 2. A medical-grade soft polyvinyl chloride resin (RS3090, manufactured by Riken-Vinyl Industries Co.; Shore hardness: 60A) was used for the tube.

TABLE II

	Application Examples			
	7	7	8	8
Adapter Material	PBT	PBT	PMMA	PMMA
Coating Thickness (μm)	--	15	--	18
Presence of Cracks	--	absent	--	absent
Adhesive Strength (MPa)	--	3.2	--	2.9
Time of Death	30 days	--	28 days	--
(Survival Period after Transplantation)	39 days	both alive after 6 months	37 days	both alive after 6 months
Events of Granulation Growth				
1 month	moderate, no clogging	no problems	moderate, no clogging	no problems
2 months	--	no problems	--	no problems
6 months	--	no problems	--	no problems

*PBT: polybutylene terephthalate
 PMMA: polymethyl methacrylate

It is necessary that adapters at both ends of the artificial windpipe coated with hydroxyapatite of the present invention be coated with hydroxyapatite. In another embodiment, both the inner and outer surfaces of the tube
5 may be coated with hydroxyapatite.

Since the artificial windpipe of the present invention has the aforementioned characteristics, a light-weight artificial windpipe with an excellent biocompatibility was successfully obtained.

Claims

1. An artificial windpipe characterized in that at least a portion of said artificial windpipe is made primarily of an organic polymer selected from among organic polymers containing sulfone groups and/or carboxyl groups or
5 organic polymers containing esters in the principal-chain and/or side-chains and is coated with 3-100 μm thick hydroxyapatite.
2. The artificial windpipe described in Claim 1 further
10 characterized in that said artificial windpipe includes an elastomer tube and adapters at both ends of said tube, wherein at least a portion of at least one of said adapters is made primarily of an organic polymer selected from among organic polymers containing sulfone groups and/or carboxyl
15 groups or organic polymers containing esters in the principal-chain and/or side-chains and is coated with 3-100 μm thick hydroxyapatite.
3. The artificial windpipe described in Claim 2 characterized in that each said adapter coated with
20 hydroxyapatite is fitted over and fixed to the elastomer tube with an overlapping between said adapter and said tube and wherein at least two through holes are present on its circumferential surface.
4. The artificial windpipe described in Claim 3 further
25 characterized in that each said adapter coated with hydroxyapatite includes at least four of said through holes.
5. The artificial windpipe described in Claims 1, 2 or 3 characterized in that the adhesive strength between the hydroxyapatite coating and the organic polymer material is
30 at least 2 MPa.
6. The artificial windpipe described in Claims 1, 2, 3 or 5 characterized in that no metallic components are used.
7. The artificial windpipe described in Claims 1, 2, 3 or 5 characterized in that the Shore hardness of said
35 elastomer is 30A to 70D.

8. The artificial windpipe described in Claims 2, 3, 5, 6 or 7 characterized in that said elastomer tube has thicker wall segments for reinforcement and/or is reinforced by a stent.

5 9. The artificial windpipe described in Claims 1, 2 or 3 characterized in that said organic polymer containing sulfone group is polyethersulfone, polysulfone, and/or a compound containing organic polymers selected from between them.

10 10. The artificial windpipe described in Claims 1, 2, 3 or 9 characterized in that said organic polymer containing carboxyl group is a polymer which is obtained through copolymerization of an olefin and carboxylic acid containing vinyl group and subsequent cross-linking with metal ions
15 and/or a compound containing organic polymers.

11. The artificial windpipe described in Claims 1, 2, 3, 9 or 10 characterized in that said organic polymer containing esters in the principal-chain is an allyl resin, oxybenzoyl polyester, polyacrylate, polybutylene
20 terephthalate, polycarbonate, or polyethylene terephthalate.

12. The artificial windpipe described in Claims 1, 2, 3, 9, 10 or 11 characterized in that said organic polymer containing esters in side-chains is selected from among an AAS resin (acrylic ester-acrylonitrile-styrene copolymer),
25 cellulosic plastics such as cellulose acetate, cellulose butyrate and ethyl cellulose, ethylene-vinyl acetate-vinyl chloride copolymer, ethylene-acrylic ester copolymer, acrylic ester-butadiene-styrene copolymer, methacrylic resin, and vinyl acetate resin.

30 13. The artificial windpipe described in Claims 1, 2, 3, 9, 10, 11 or 12 characterized in that a part of phosphate groups, or hydroxyl groups of hydroxyapatite is substituted by carbonate groups.

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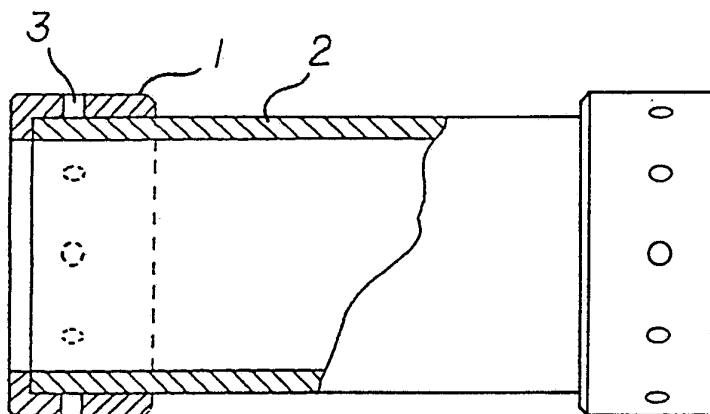


FIG. 1

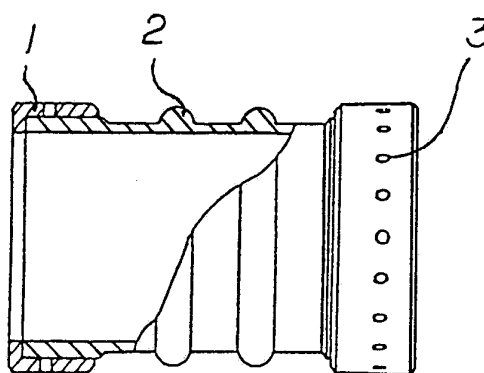


FIG. 2

2/2

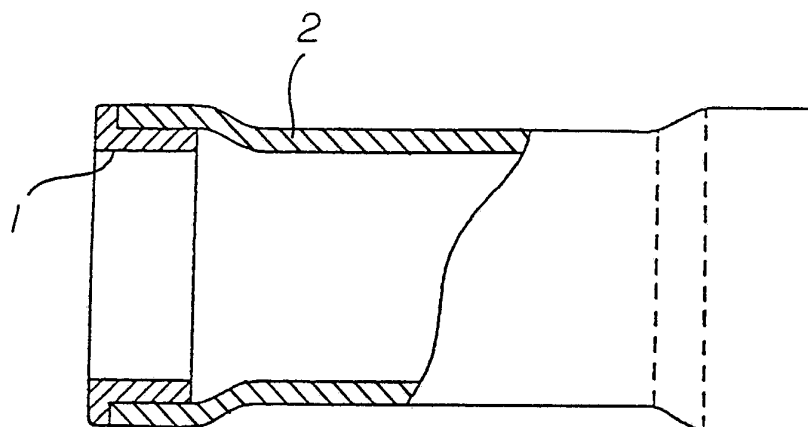


FIG. 3

INTERNATIONAL SEARCH REPORT

PCT/US 93/04829

International Application No

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC		
Int.Cl. 5 A61L27/00		
II. FIELDS SEARCHED		
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Int.Cl. 5	A61L	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
A	EP,A,0 389 713 (KYOTO UNIVERSITY) 3 October 1990 see page 6, line 41 - line 42 see page 7, line 24 ---	1
A	EP,A,0 437 975 (SUMITOMO) 24 July 1991 see column 4, line 43 - line 49; claim 7 ---	1
P,A	WO,A,9 307 916 (SHERWOOD MEDICAL) 29 April 1993 see page 9, line 1 - line 8; claims 1,2,12 ---	1
A	DATABASE WPIL Week 8606, Derwent Publications Ltd., London, GB; AN 86-039159 & JP,A,60 259 268 (ADV KAIHATSU KENKYU) see abstract -----	1
¹⁰ Special categories of cited documents : ¹⁰ "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "&" document member of the same patent family		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
24 AUGUST 1993	AUG 25 1993	
International Searching Authority	Signature of Authorized Officer	
EUROPEAN PATENT OFFICE	PELTRE CHR.	

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.**

US 9304829
SA 74476

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24/08/93

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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