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(54) PERMSELECTIVE STRUCTURALLY ROBUST MEMBRANE MATERIAL

PERMSELEKTIVES STRUKTURELL ROBUSTES MEMBRANMATERIAL

MATIERE DE MEMBRANE STRUCTURELLEMENT ROBUSTE PERMSELECTIVE

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Description

TECHNICAL FIELD

[0001] The present invention has to do, in general, with a biocompatible hydrophilic segmented block multi polymer that may formed into a permselective membrane for use as part of an indwelling analyte sensor.

BACKGROUND ART

[0002] U.S. Patents 5,428,123; 5,589,563; and 5,756,632, issued June 27, 1995; December 31, 1996 and May 28, 1998, respectively, together disclose a type of material and a way of engineering this material to have a particular permselectivity US 5589563 for example relates to surface active endgroup containing polymers for use in the manufacture of medical devices. US5962620 discloses a polymer useful in the manufacture of biocompatible medical films, the polymer having an intermediate water uptake. When efforts were made, however, to use this material in an indwelling glucose sensor application it was found that the requirement for high oxygen and glucose permeability was at conflict with the requirement for structural strength and integrity after exposure to an oxidative environment. More specifically it was found that when the material was made sufficiently oxygen permeable it became too weak and tended to break apart on the sensor, after being placed in the body's interstitial fluid for more than a few hours.

[0003] Within biological solutions such as blood or interstitial fluid there exist a number of reactive materials and enzymes that may bring about cleavage of the polymer's molecular chains and thus result in loss of membrane or fiber strength and integrity. Some of the reactive materials and enzymes that may bring about polymer degradation and cleavage include small molecules such as superoxide (O_2^-) and acids, and enzymes such as proteases and oxidases that react with the various types of linkages in the polymer. This loss of membrane or fiber integrity is deleterious to applications which depend on the permselectivity of the polymeric material and the exclusion of solids and larger biological molecules, such as the detection of the levels of glucose within the body fluids of a living human body.

DISCLOSURE OF INVENTION

[0004] In a first separate embodiment, the present invention is a biocompatible hydrophilic segmented block multi polymer, having a backbone comprising about 10 to 45 wt % of at least one hard segment and about 55 to 90 wt % of soft segments. The soft segments are divided into three groups, 5 to 25 wt %, of total soft segment weight, of an oxygen permeable soft segment; 5 to 25 wt %, of total soft segment weight, of a hydrophilic soft segment; and 50 to 90 wt %, of total soft segment weight, of a biostable, hydrophobic soft segment, wherein said multipolymer is capable forming a membrane having water absorption of from 2 to 25% of dry weight. The invention thus provides a biocompatible multipolymer in accordance with claim 1. Advantageous are in accordance with the dependent claims.

[0005] The foregoing and other objectives, features and advantages of the invention will be more readily understood upon consideration of the following detailed description of the invention, taken in conjunction with the accompanying drawings.

BRIEF DESCRIPTION OF DRAWINGS

[0006]

Drawing 1 is an illustration of a possible arrangement of the hard segments and soft segments of several polymer chains in a biocompatible multipolymer according to the present invention.

BEST MODES FOR CARRYING OUT THE INVENTION

[0007] In its preferred embodiments, the present invention is a multipolymer 10, a high molecular weight polymeric organic material consisting of different types of monomeric units, suitable for use in a glucose sensor or in an oxygen sensor which is immersed for substantial periods of time in blood or interstitial fluids of the human body. Referring to FIG. 1 multipolymer 10 includes hard segments 1, polyurethane domains with highly crystalline or glassy nature that associate with each other either interchain to provide the physical tensile strength of membranes made from the polymer. The energetically favorable associations between the individual molecular backbones provide regions that hold the chains together and require a substantial energy input to disrupt. Soft segments of the three soft segments **4,** are randomly situated in the individual molecular chains. Any type of soft segment may be directly attached to a hard segment, or to another type of soft segment. There may be multiple domains of each kind of segment, hard or soft, in the polymer material. The soft segments have a low associative energy with other soft segments or with hard segments, so a lesser degree of force would be required to dissociate the soft segments, giving membranes prepared from the polymer a rubbery or flexible character. The less crystalline or glassy nature of regions containing soft segments are the regions where oxygen and aqueous solutions may freely permeate the membrane. The polycarbonate soft segments **4** likewise are less crystalline or glassy than the hard segments **1,** but their resistance to degradation by the reactive chemicals and enzymes found in the tissue fluids of living human beings gives a greater degree of biostability to membranes prepared from the polymer of the present invention containing such polycarbonate domains.

[0008] Again referring to FIG. 1, more specifically, in one preferred embodiment the multipolymer consists of (1) hard segments or domains of substantially crystalline or glassy structure **1,** that would have a high melting points or glass transition temperatures if prepared as homopolymers, and (2) soft segments, of substantially amorphous structure 2, **3,** and **4,** that would have low melting or glass transition temperatures if prepared as homopolymers, that are permeable to aqueous solutions containing organic solutes such as glucose, and to dissolved oxygen, and are substantially stable to degradation in a biological separate the hard domains **1** of the multipolymer, which further comprise three distinct types or classes of polymeric materials: (i) polymer domains **2** that confer oxygen permeability to the material, (ii) polymer domains **3** that confer hydrophilicity to the material, and (iii) polymer domains **4** that confer biostability to the material, specifically domains comprising polycarbonate-type structures.

[0009] The hard domains **1** of the multipolymer confer physical strength and durability allowing the casting of dense, non-porous semi-permeable membranes or hollow fibers with sufficient tensile strength and elasticity for use over relatively long periods of times immersed in fluids of the human body. The hard domains of the multipolymer comprise polyurethane structures that may also contain some urea-type linkages (N-(CO)-N) as well as urethane-type linkages (N-(CO)-O). These polyurethane-type polymers result from the reaction of various types of difunctional isocyanates (isocyanate group: R-N=C=O) with difunctional amines (R-NH2) or alcohols (ROH), where R may be aliphatic, cycloaliphatic, aryl, hetero-aryl, or alkylaryl in nature. Such polyurethane structures are known to be strong, durable materials suitable for uses where they are in contact with biological solutions in living organisms, as described in U.S. Patent 5,428,123.

[0010] The soft domains **2, 3,** and **4** of the block copolymer confer permeability for both water solutions of compounds and for oxygen, but the dense non-porous nature of membranes cast from these polymers are adequate to exclude insoluble materials such as cells and suspensions of solid materials. Thus the membranes or fibers made from the multipolymers of the present invention allow aqueous solutes and oxygen to permeate the membranes while disallowing solid materials to pass through, as disclosed in U.S. Patent 5,428,123.

[0011] In the present invention the resistance of the multipolymer and thus the resistance of membranes and fibers prepared from the multipolymer to biological degradation is increased by inclusion of domains of soft, biostable, relatively hydrophobic segments **4** consisting of polycarbonate-type materials (R-O-(CO)-O-R). Polycarbonates are oligomeric or polymeric materials where difunctional alcohols are linked via the difunctional carbonate group, where carbonate esters are formed linked to the difunctional alcohols through both available oxygen atoms of the carbonate moiety.

[0012] In the present invention, it has been discovered that multipolymers synthesized with specified proportions of the hard segment materials **1** and of the three distinct types of soft segment materials **2, 3,** and **4** possess the desired properties of strength and durability, permeability to aqueous solutes and to oxygen, and chemical/physical stability while in contact with biological fluids in living organisms. The present invention comprises block copolymers or multi polymers wherein the hard segments **1** comprise 10-45 wt% of the total, and the soft segments 55-90 wt% of the total, where among the soft segments, the three necessary components comprise 5-25 wt% of total soft segment dry weight of oxygen-permeable materials **2,** 5-25 wt% of total soft segment dry weight of hydrophilic materials **3,** and 50-90 wt% of total soft segment dry weight of biostable, relatively hydrophobic materials **4,** specifically polycarbonate-type materials.

[0013] The first preferred embodiment of the present invention for use in glucose sensors in contact with blood or interstitial fluids of the human body is characterized by the various types of suitable soft segment material types for the soft segment domains of the multipolymer. These include for the oxygen-permeable soft segments **2,** oligomeric polysiloxane domains where the silicon-oxygen backbone may be substituted with various carbon-containing functional groups $(\text{-O-Si}(R_2)\text{-})_n$ where R is an alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, or heteroaryl group and which oligomer is terminated with siloxy (Si-OH) moieties that may be combined via linkages such as ester, ether, or urethane with other segments of the polymer backbone; for the hydrophilic soft segments **3,** poly-(oxyalkylene) chains such as poly-(oxyethylene) $(OCH_2CH_2\text{-})_n$ or poly-(oxytetramethylene) $(OCH_2CH_2CH_2CH_2\text{-})_n$ oligomeric or polymeric materials; for the biostable, relatively hydrophobic soft segments **4,** polycarbonate chains where difunctional carbonate esters link difunctional alcohols such as ethylene, propylene, butylenes and higher glycols $(\text{-O}(CH_2)_n\text{-O(CO)-})_m$.

[0014] The specific properties of the polymers and of the membranes or fibers prepared from them can vary according to the specific nature and proportions of the various domains of the block copolymer, for instance if enhanced oxygen permeability is desired for a given use, the proportion of oxygen permeable polysiloxane soft segment **2** content can be increased; if increased biostability is desired, the proportion of biostable polycarbonate soft segment material **4** can be increased in the multipolymer. However in all cases the multipolymers of the present invention prepared according to these specifications possess properties of enhanced biostability relative to previously disclosed polymer compositions in applications where strength/durability, selective permeability of aqueous solutes and oxygen, and suitability for long-term exposure to biological fluids in living organisms are required.

[0015] In a second preferred embodiment of the present invention, the multipolymer may be used in sensors used for detecting the oxygen content of various biological fluids in the human body. In this embodiment of the invention, an oxygen-sensing electrode may be contained within a coating of the multipolymer, whose oxygen-permeable soft segment component 2 proportion has been adjusted to provide for a high degree of oxygen permeability enabling accurate detection of oxygen level, whose hydrophilic soft segment component 3 proportion has been adjusted to allow for free diffusion of the aqueous solutions of body fluids containing the dissolved oxygen through the multipolymer membrane, and whose biostable polycarbonate soft segment component **4** proportion has been adjusted to provide membrane stability in the presence of the reactive materials and enzymes contained within the body fluid in which the sensor is immersed.

[0016] These multipolymers can be prepared as outlined below in Example 1. More generally, the oligomeric polycarbonate soft segment domains may be included in the multipolymer through introduction of oligomeric polycarbonate materials into the reaction mixtures forming the multipolymer; the polycarbonate oligomers possess terminal reactive hydroxyl groups which can react with the isocyanate groups of the hard segment oligomers forming urethane linkages. The proportions of the polycarbonate soft segments in the multipolymer of the present invention may be controlled just as for the other soft segments of polysiloxanes and polyoxyalkylenes as described therein through control of the relative proportions of these components in the multipolymer-forming reaction.

[0017] The above described multipolymers may have sufficient permeability to oxygen and glucose, and adequate physical strength and durability for use in biological sensors of various types, and with resistance to biological degradation and oxidative breakdown in the human body.

SYNTHESIS: GENERAL CONSIDERATIONS

[0018] An exemplary synthetic method is presented hereinbelow, based upon polyurethane chemistry, to teach how to make the polymers of this invention. Those skilled in the art will readily understand, however, based upon this disclosure, how to append surface-modifying endgroups (SMEs) to other segmented and block copolymers, random copolymers, graft copolymers, and homopolymers. The polymers of this invention may be prepared as solution-based polymers (dissolved in organic solvent), as thermoplastic polymers (100% solids, no solvent), as water-borne emulsions or dispersions (polymer dispersed in a water phase), or as two-component castable polymers. Synthetic procedures, which would enable the preparation of a multitude of polymers by changing soft segments, isocyanates, chain extenders, and/or endgroups, are described below. More details relating to the synthetic methods that may be employed to make the SME-containing polymers of this invention may be found in US 5,589,563.

Synthetic Example 1 - Solution-Based Synthesis.

[0019] In this Example, the soft segments are polyhexyl ethyl carbonate diol (PHECD) having a molecular weight of 2000, polyethylene glycol (PEG) - having a molecular weight of 1500, and polydimethylsiloxane diol (PDMSD) -having a molecular weight of 1000, the hard segment is composed of 4,4'-diphenylmethane diisocyanate (MDI) having a molecular weight of 250.26 and ethylene diamine (ED) having a molecular weight of 60.1, and the endgroups are methoxy polyethylene glycol (mPEG) having a molecular weight of 2000 and mono-functional OH-terminated polydimethyl siloxane (mPDMS) -having a molecular eight of 2000. A reactor is charged with 8.6 moles of PHECD, 6.9 moles of PDMSD, 0.044 moles of mPDMS and 3.8 moles of PEG. The reactants are dried under vacuum with a nitrogen purge. Then 32.7 moles of 4,4'-diphenylmethane diisocyanate solution in dimethylacetamide is added to the reactor, and the contents of the reactor are further diluted with additional dimethylacetamide solvent. The ingredients are stirred for 3 hours at 55°C. The contents of the reactor are then diluted with more dimethylacetamide solvent, and cooled to 40°C. Polymer synthesis is completed by adding 12.5 moles of ethylene diamine in dimethylacetamide solvent and stirring at 40°C for 30 minutes.

[0020] The resulting polymer has the following characteristics:

Reactant	Molecular Weight	Weight-%	Moles
PDMSD	1000	18.8	6.9
MDI	250.26	22.3	32.7
ED	60.1	2.1	12.5
mPDMS	2000	0.24	0.044

Claims

1. A biocompatible multipolymer suitable for use in an aqueous solute sensor adapted for immersion in body fluid, having a backbone comprising:

   (a) 10 to 45 wt % of at least one hard segment;
   (b) 55 to 90 wt% of soft segments, including:

      (i) 5 to 25 wt %, of total soft segment weight, of an oxygen permeable soft segment comprising polydimethylsiloxane;
      (ii) 5 to 25 wt %, of total soft segment weight, of a hydrophilic soft segment having the chemical form $[O(CH_2)_N]_M$, where N < 4; and
      (iii) 50 to 90 wt%, of total soft segment weight, of a biostable, hydrophobic soft segment comprising a polycarbonate.

2. The multipolymer of claim 1, wherein said hydrophilic soft segment comprises polyethylene oxide.

3. The multipolymer of claim 1, further comprising capping end groups.

4. The multipolymer of claim 3, wherein said capping end groups comprise less than about 10 wt% of said multipolymer.

5. The multipolymer of claim 1, capable of forming a membrane having a tensile strength of from 21.1 to 70.3 kg/cm^2 (300 to 1,000 psi).

6. The multipolymer of claim 1, capable of forming a membrane having an ultimate elongation of 100 to 1,000 %.

7. The multipolymer of claim 1, capable of forming a membrane having water absorption of from 2 to 25% of dry weight.

8. The multipolymer of claim 1, capable of forming a membrane having the characteristic that its water absorption and hydrophilic soft segment volume are less than 75% of the total dry polymer volume.

9. The multipolymer of claim 1 wherein said aqueous solute comprises glucose.

Patentansprüche

1. Biologisch verträgliches Multipolymer, das für die Verwendung in einem für das Eintauchen in Körperfluid ausgelegten wässrig-gelöster-Stoff-Sensor geeignet ist und das ein Rückgrat aufweist, umfassend:

   (a) 10 bis 45 Gew.-% von wenigstens einem harten Segment;
   (b) 55 bis 90 % an weichen Segmenten, umfassend:

      (i) 5 bis 25 Gew.-% des weiches-Segment-Gesamtgewichts an einem sauerstoffdurchlässigen weichen Segment, umfassend Polydimethylsiloxan;
      (ii) 5 bis 25 Gew.-% des weiches-Segment-Gesamtgewichts an einem hydrophilen weichen Segment mit der chemischen Form $[O(CH_2)_N]_M$, wobei N < 4; und
      (iii) 50 bis 90 Gew.-% des weiches-Segment-Gesamtgewichts an einem biologisch stabilen hydrophoben weichen Segment, umfassend ein Polycarbonat.

2. Multipolymer gemäß Anspruch 1, wobei das hydrophile weiche Segment Polyethylenoxid umfasst.

3. Multipolymer gemäß Anspruch 1, ferner umfassend abdeckende Endgruppen.

4. Multipolymer gemäß Anspruch 3, wobei die abdeckenden Endgruppen weniger als etwa 10 Gew.-% des Multipolymers bilden.

5. Multipolymer gemäß Anspruch 1, das fähig ist, eine Membran mit einer Zugfestigkeit von 21,1 bis 70,3 kg/cm^2 (300 bis 1.000 psi) zu bilden.

6. Multipolymer gemäß Anspruch 1, das fähig ist, eine Membran mit einer Reißdehnung von 100 bis 1.000 % zu bilden.

7. Multipolymer gemäß Anspruch 1, das fähig ist, eine Membran mit einer Wasserabsorption von 2 bis 25 % des Trockengewichts zu bilden.

8. Multipolymer gemäß Anspruch 1, das fähig ist, eine Membran mit der Eigenschaft zu bilden, dass ihr Wasserabsorptions- und hydrophiles-weiches-Segment-Volumen weniger als 75 % des Gesamt-Trockenvolumens des Polymers beträgt.

9. Multipolymer gemäß Anspruch 1, wobei der wässrig gelöste Stoff Glucose umfasst.

Revendications

1. Multipolymère biocompatible convenable pour être utilisé dans un capteur de soluté aqueux adapté à l'immersion dans du liquide corporel, ayant un squelette comprenant :

(a) 10 à 45 % en poids d'au moins un segment dur ;
(b) 55 à 90 % en poids de segment mou, y compris :

(i) 5 à 25 % en poids, par rapport au poids total de segment mou, d'un segment mou perméable à l'oxygène comprenant le polydiméthylsiloxane ;
(ii) 5 à 25 % en poids, par rapport au poids total de segment mou, d'un segment mou hydrophile ayant la forme chimique $[O(CH_2)_N]_M$, où N < 4 ; et
(iii) 50 à 90 % en poids, par rapport au poids total de segment mou, d'un segment mou hydrophobe, biostable comprenant un polycarbonate.

2. Multipolymère selon la revendication 1, **caractérisé en ce que** ledit segment mou hydrophile comprend l'oxyde de polyéthylène.

3. Multipolymère selon la revendication 1, comprenant en outre des groupements terminaux coiffants.

4. Multipolymère selon la revendication 3, **caractérisé en ce que** lesdits groupements terminaux coiffants comprennent moins d'environ 10 % en poids dudit multipolymère.

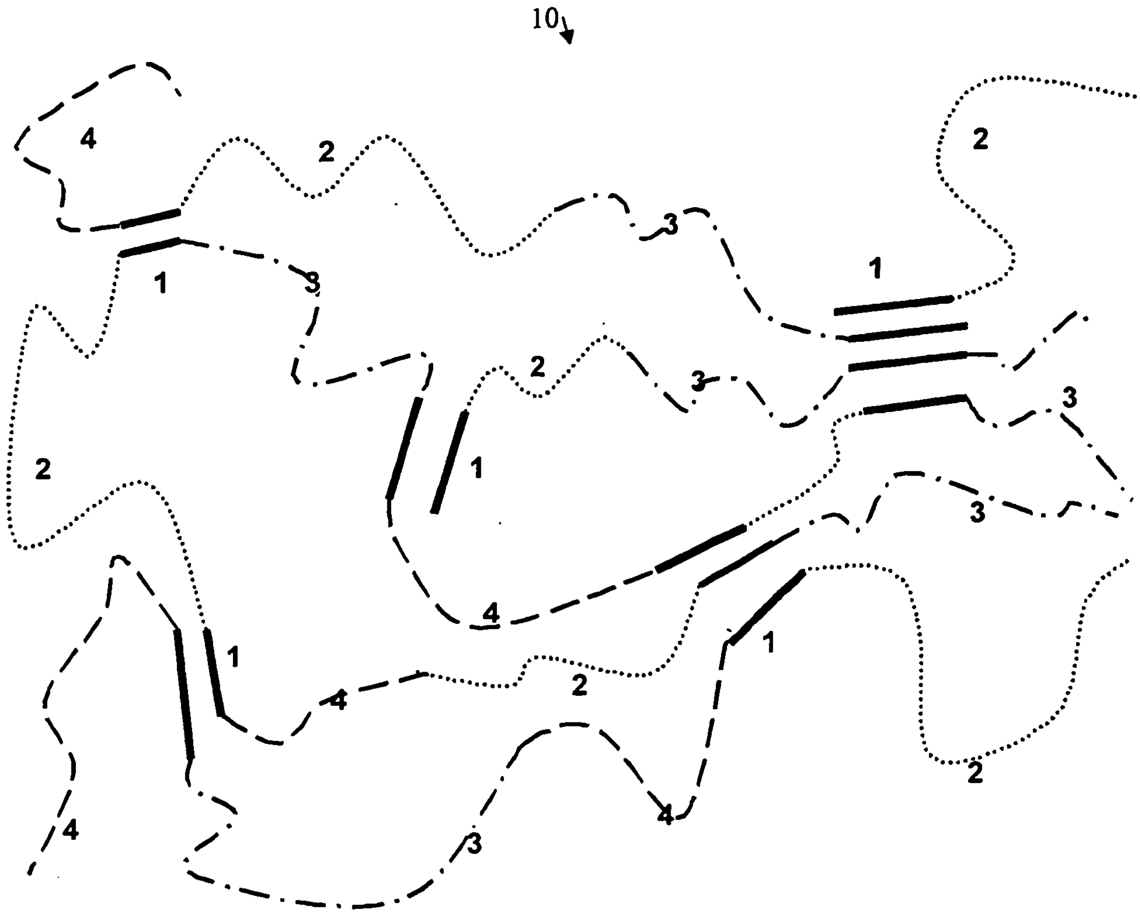
5. Multipolymère selon la revendication 1, capable de former une membrane ayant une résistance à la traction de 21,1 à 70,3 kg/cm^2 (300 à 1 000 psi).

6. Multipolymère selon la revendication 1, capable de former une membrane ayant un allongement à la rupture de 100 à 1 000 %.

7. Multipolymère selon la revendication 1, capable de former une membrane ayant une absorption d'eau de 2 à 25 % de poids sec.

8. Multipolymère selon la revendication 1, capable de former une membrane ayant la caractéristique selon laquelle son absorption d'eau et son volume de segment mou hydrophile sont inférieurs à 75 % du volume total de polymère sec.

9. Multipolymère selon la revendication 1, **caractérisé en ce que** ledit soluté aqueux comprend le glucose.



1 polyurethane hard segments

2 oxygen permeable soft segments

3 hydrophilic soft segments

4 biostable polycarbonate soft segments

FIG. 1

REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

- US 5428123 A **[0002] [0009] [0010]**
- US 5589563 A **[0002] [0018]**
- US 5756632 A **[0002]**
- US 5962620 A **[0002]**

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摘要(译)

一种生物相容性多聚物，其主链包含约10至45wt%的至少一个硬链段和约55至90wt%的软链段。软链段分为三组，总软段重量的5至25wt%，透氧软段;亲水性软链段的总软段重量的5至25wt%;生物稳定的，相对疏水的软链段的总软链段重量的50至90wt%。

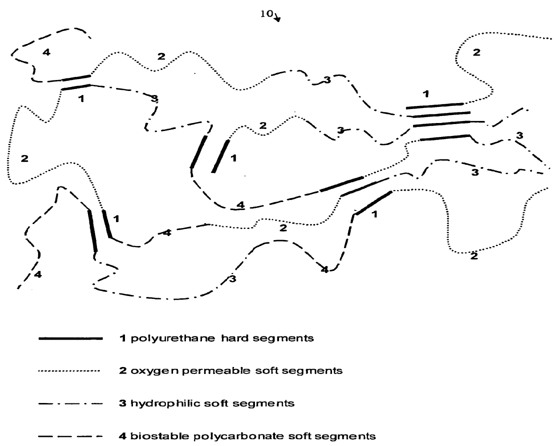

FIG. 1