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Sugawara

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(54) **BODY FLUID COMPATIBLE AND BIOCOMPATIBLE RESIN**

(75) Inventor: **Shuichi Sugawara**, Fuji (JP)

(73) Assignee: **Asahi Kasei Kabushiki Kaisha**, Osaka (JP)

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(51) **Int. Cl.**
C08G 65/34 (2006.01)

(52) **U.S. Cl.** **528/425**; 424/78.27; 424/85.2; 424/426; 525/54.1; 528/245; 527/205

(58) **Field of Classification Search** 528/220, 528/425, 245; 424/78.27, 85.2, 426; 525/54.1; 527/205
See application file for complete search history.

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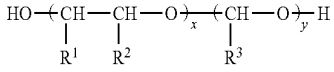
Primary Examiner—James Seidleck
Assistant Examiner—Gregory Listvoyb
(74) *Attorney, Agent, or Firm*—Birch, Stewart, Kolasch & Birch, LLP

(57) **ABSTRACT**

A body fluid compatible and biocompatible resin for use in a medical treatment involving a contact of said resin with at least one member selected from the group consisting of a body fluid and a biological tissue, which comprises at least one substituted oxyalkylene polymer having a weight average molecular weight of from 1,000 to 1,000,000 and represented by the following formula (1):



(1)

wherein each of R^1, R^2 and R^3 independently represents a hydrogen atom or a $—CH_2R^4$ group, and each R^4 independently represents a hydroxyl group or a $—OR^5$ group (wherein R^5 represents a group selected from the group consisting of a C_1-C_{10} aliphatic hydrocarbyl group, a C_6-C_{10} aryl group, a $—R^6COOH$ group and a derivative thereof, and a $—CH_2—O—CH_2—CH(OH)—CH_2—OR^7$ group, wherein R^6 represents a C_1-C_{10} aliphatic hydrocarbylene group and R^7 represents a C_1-C_{10} aliphatic hydrocarbyl group or a C_6-C_{10} aryl group), provided that all of R^1, R^2, and R^3 are not simultaneously hydrogen atoms; and $10 \leqq x \leqq 10{,}000$ and $0 \leqq y \leqq 10{,}000$.

3 Claims, 65 Drawing Sheets

BODY FLUID COMPATIBLE AND BIOCOMPATIBLE RESIN

This application is a Continuation-In-Part of copending Application No. PCT/JP03/08565 filed on Jul. 4, 2003. This Nonprovisional application claims priority under 35 U.S.C. §119(a) on Patent Application No(s). 2002-197308 & 2002-369933 filed in Japan on Jul. 5, 2002 & Dec. 20, 2002; respectively, the entire contents of which are hereby incorporated by reference and for which priority is claimed under 35 U.S.C. §120.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to a body fluid compatible and biocompatible resin. More particularly, the present invention is concerned with a body fluid compatible and biocompatible resin for use in a medical treatment involving a contact of the resin with at least one member selected from the group consisting of a body fluid and a biological tissue, which comprises at least one substituted oxyalkylene polymer having a specific structure and having a weight average molecular weight of from 1,000 to 1,000,000. The body fluid compatible and biocompatible resin of the present invention is advantageous not only in that the adhesion of biological substances (such as a biological tissue, a cell and a platelet) to the resin can be suppressed, and the activation of a platelet, a complement and the like by the resin can also be suppressed, but also in that the resin of the present invention is highly safe for living organisms and remains stable in a body fluid for a long time. Therefore, the body fluid compatible and biocompatible resin of the present invention can be advantageously used as an ingredient, a molding material or a coating material in the production of various biological and medical products. Specific examples of biological and medical products include a membrane for an artificial kidney, a plasma separation membrane, a membrane for an artificial lung, an artificial blood vessel, an anti-adhesion membrane, a wound dressing, an artificial skin, a virus removal membrane and a leukocyte removal membrane.

Further, the resin of the present invention is amphipathic and, hence, is soluble not only in water but also in organic solvents, such as an alcohol, an ether, an ester and an aromatic hydrocarbon. Therefore, the resin of the present invention can be used in a wide variety of medical application fields. For example, the resin of the present invention in the form of a film can be used for covering external wounds, such as bedsore, burn and ulcer, and can also be used for covering wounds caused by destruction of internal tissues, such as a corium, a hypoderm, a muscle, a tendon, an articulation and a bone. Further, by utilizing the hydrophilicity and moisture retention property of the resin, the resin of the present invention can be used for producing cosmetics, and can also be used for fiber treatments. Furthermore, by utilizing the ability of the resin to prevent adsorption of a protein thereto as well as the hydrophilicity of the resin, the resin of the present invention can also be used as a component of a contact lens washing solution.

As applications other than mentioned above, for example, the resin of the present invention can be used for various treatments of a polypeptide and a protein which are derived from organisms, such as a human, a mammal, a reptile, a microbe and an insect, wherein the treatments include a separation, a purification, a concentration, a filtration, a desalting/concentration and the like. Further, the resin of the present invention can also be used for treating a medicine, an active

pharmaceutical ingredient of a medicine and a raw material for a medicine, which contain the above-mentioned polypeptide or protein, wherein the treatments include a separation, a purification, a concentration, a filtration, a desalting/concentration and the like. Furthermore, the resin of the present invention can also be used as an additive for raw materials for producing an equipment used for the above-mentioned treatments or as a coating material for such an equipment.

When a compound having a pharmaceutical activity is bonded to the resin of the present invention through an amino acid or a peptide (i.e., the so-called "linker") to form a drug complex, such a drug complex enables the delivery of the compound having a pharmaceutical activity to a target tissue without being recognized by a biological tissue when the drug complex is administered to a living body.

2. Prior Art

In recent years, studies have been made on polymeric materials having body fluid compatibility and/or biocompatibility (hereinafter, referred to as "body fluid compatible/biocompatible materials"), and the development of the application of body fluid compatible/biocompatible materials in the fields of various biological and medical products (such as a membrane for an artificial kidney, a plasma separation membrane, a catheter, a membrane for an artificial lung, an artificial blood vessel, an anti-adhesion membrane, a wound dressing and an artificial skin) is expected. In the fields of the above-exemplified biological and medical products, the body fluid compatible/biocompatible material (e.g., a synthetic polymeric material), which is foreign to a living body, is contacted with a biological tissue and/or a body fluid during the use thereof. Therefore, the body fluid compatible/biocompatible material is required to possess a satisfactory body fluid compatibility and/or biocompatibility such that interaction and/or interference is not caused between the body fluid compatible/biocompatible material and a biological tissue and/or a body fluid.

The level of body fluid compatibility and/or biocompatibility which is required of a body fluid compatible/biocompatible material depends on the use of the material and the method for using the material. Further, when a body fluid compatible/biocompatible material is used, for example, as a material which is contacted with blood, such a body fluid compatible/biocompatible material is required to have the abilities to suppress the adsorption of a protein thereto, the blood coagulation, the adhesion of a platelet thereto, the activation of a platelet and a complement, and the like.

For example, Unexamined Japanese Patent Application Laid-Open Specification No. Hei 4-152952 describes an acrylate-type biocompatible material. However, conventional acrylate-type biocompatible materials pose problems in that the monomer used as a raw material is toxic, so that the acrylate-type biocompatible material exhibits toxicity when the monomer is not completely removed from the material, and in that the acrylate-type biocompatible material which is a polymeric material cannot be decomposed at all in a living body, so that the material remains and is accumulated in a living body.

Further, a polyalkoxyalkyl (meth)acrylate, which is one of the above-mentioned acrylate-type biocompatible materials, is known to have the abilities to suppress the adhesion of a platelet thereto, and the activation of a platelet and a complement, thereby exhibiting excellent blood compatibility. However, when the polyalkoxyalkyl (meth)acrylate is accumulated in an or gan, such as a liver or a spleen, there is a danger that the organ is damaged by the accumulated polyalkoxyalkyl (meth)acrylate. Specifically, there is a danger that the polyalkoxyalkyl (meth)acrylate is separated from a substrate

(e.g., by delamination of a polyalkoxyalkyl (meth)acrylate film from a substrate), so that the separated polyalkoxyalkyl (meth)acrylate is released into a body fluid and accumulated in an organ, such as a liver or a spleen. Conventionally, with respect to the polyalkoxyalkyl (meth)acrylate, only the abilities thereof to suppress the adhesion and activation of a platelet and the activation of a complement have been considered important, and the above-mentioned danger of damage to an organ has not been considered seriously. In an attempt to solve this problem, Unexamined Japanese Patent Application Laid-Open Specification No. 2001-000533 proposes a polyalkoxyalkyl (meth)acrylate product containing a specific amount of a polyalkoxyalkyl (meth)acrylate molecule having a specific high molecular weight. However, even such a polyalkoxyalkyl (meth)acrylate product is not free from the above-mentioned danger of damage to an organ and, hence, is not suitable as a biocompatible material.

WO02/22739 proposes to use an alkylene oxide copolymer in a medical equipment by utilizing the lubricity of an alkylene oxide copolymer, wherein the lubricity is exhibited due to the hydrophilicity and swelling property of the copolymer. More specifically, in this patent document, a medical equipment, a catheter and an implant are mentioned side-by-side with shaving devices and the like as examples of the use of an alkylene oxide copolymer. However, in the working example of this patent document in which the above-mentioned copolymer is synthesized, only the lubricity of the copolymer is evaluated, and there is no teaching or suggestion about the body fluid compatibility and biocompatibility of the copolymer.

Further, as an example of biodegradable and biocompatible polyacetal polymers, Japanese Patent Application prior-to-examination Publication (Tokuhyo) No. Hei 11-503481 describes the production of a polyacetal polymer obtained from an oxidized polysaccharide. This patent document describes that the polyacetal polymer has biodegradability and biocompatibility. However, in this patent document, the polyacetal polymer is only evaluated with respect to the degradability thereof using hydrochloric acid, and there is no teaching or suggestion about the biodegradability, body fluid compatibility and biocompatibility of the polymer.

On the other hand, an unsubstituted ethylene glycol homopolymer is a highly safe compound which has conventionally been used in the medical application fields. However, an unsubstituted ethylene glycol homopolymer is disadvantageous in that a drug can be introduced into this polymer only at the terminals thereof. That is, an unsubstituted ethylene glycol homopolymer is disadvantageous in that the maximum number of a drug compound which can be introduced per molecular chain of the polymer is as small as 2 (two). Therefore, when a drug complex is produced using the unsubstituted ethylene glycol homopolymer, the effective dose of the drug complex contains too large an amount of the unsubstituted ethylene glycol homopolymer such that the administration of the drug complex is practically impossible due to a heavy load on the patient. Further, an unsubstituted ethylene glycol homopolymer is generally water-soluble, so that, when used as a coating material for a shaped article, the unsubstituted ethylene glycol homopolymer is likely to dissolve out from the shaped article. Furthermore, when a mixture of an unsubstituted ethylene glycol homopolymer with a resin other than an unsubstituted ethylene glycol homopolymer is used to produce a shaped article, problems are likely to be caused due to the lack of a lipophilic subsituent in the unsubstituted ethylene glycol homopolymer, i.e., problems in that the compatibility of the unsubstituted ethylene glycol homopolymer and the other resin is poor, and in that, even when the unsubstituted ethylene glycol homopolymer and the other resin are compatibilized, the unsubstituted ethylene glycol homopolymer is likely to dissolve out from the shaped article.

With respect to a body fluid compatible/biocompatible material, not only is it demanded that the material has body fluid compatibility and biocompatibility which are appropriate for the intended use of the material and the method for using the material, but also the material is desired to be highly safe for living organisms. The reason for this is as follows. For example, when a body fluid compatible/biocompatible material is coated on a substrate and the resultant is in contact with a body fluid over a long period of time, a portion of the body fluid compatible/biocompatible material may be delaminated from the substrate and released into the body fluid. Therefore, even when the material has excellent body fluid compatibility, there is still a danger that the material is accumulated in an organ to damage the organ. Therefore, it has been desired to develop a body fluid compatible/biocompatible material which not only has the abilities to suppress blood coagulation, platelet adhesion, platelet activation and complement activation, but also exhibits high biological safety.

SUMMARY OF THE INVENTION

In this situation, the present inventor has made extensive and intensive studies with a view toward developing a resin having excellent body fluid compatibility and biocompatibility. As a result, it has unexpectedly been found that a resin which comprises at least one substituted oxyalkylene polymer having a specific structure and having a weight average molecular weight of from 1,000 to 1,000,000 has excellent body fluid compatibility and biocompatibility (that is, the resin is advantageous not only in that the resin is capable of suppressing the adsorption of a protein thereto, the adhesion of biological substances (such as a biological tissue, a cell and a platelet) thereto, and the activation of a platelet, a complement and the like, but also in that the resin exhibits high biological safety), and that, hence, the resin can be advantageously used in a medical treatment involving a contact of the resin with at least one member selected from the group consisting of a body fluid and a biological tissue. The present invention has been completed, based on these novel findings.

Accordingly, it is an object of the present invention to provide a body fluid compatible and biocompatible resin for use in a medical treatment involving a contact of said resin with at least one member selected from the group consisting of a body fluid and a biological tissue.

It is another object of the present invention to provide a resin composition comprising the above-mentioned body fluid compatible and biocompatible resin and a resin other than the body fluid compatible and biocompatible resin.

It is still another object of the present invention to provide use of the resin of the present invention in various treatments of a polypeptide and a protein which are derived from organisms, such as a human, a mammal, a reptile, a microbe and an insect, wherein the treatments include a separation, a purification, a concentration, a filtration, a desalting/concentration and the like, and to provide use of the resin of the present invention in treatments of a medicine, an active pharmaceutical ingredient of a medicine and a raw material for a medicine, which contain the above-mentioned polypeptide or protein, wherein the treatments include a separation, a purification, a concentration, a filtration, a desalting/concentration and the like.

The foregoing and other objects, features and advantages of the present invention will be apparent from the following description and appended claims taken in connection with the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

In the drawings:

FIG. **1** is a GPC chart which is obtained with respect to resin (86) of the present invention produced in Example 30;

FIG. **2** is a ^{1}H-NMR chart which is obtained with respect to resin (86) of the present invention produced in Example 30 (wherein the ^{1}H-NMR analysis is performed using heavy water as a solvent);

FIG. **3** is a GPC chart which is obtained with respect to resin (87) of the present invention produced in Example 31;

FIG. **4** is a ^{1}H-NMR chart which is obtained with respect to resin (87) of the present invention produced in Example 31 (wherein the ^{1}H-NMR analysis is performed using heavy water as a solvent);

FIG. **5** is a GPC chart which is obtained with respect to resin (88) of the present invention produced in Example 32;

FIG. **6** is a ^{1}H-NMR chart which is obtained with respect to resin (88) of the present invention produced in Example 32 (wherein the ^{1}H-NMR analysis is performed using heavy water as a solvent);

FIG. **7** is a ^{13}C-NMR chart which is obtained with respect to resin (88) of the present invention produced in Example 32 (wherein the ^{13}C-NMR analysis is performed using heavy water as a solvent);

FIG. **8** is an electron photomicrograph of a PET film obtained in Example 68, which PET film is coated with resin (15) of the present invention and has been subjected to a test for evaluating platelet adhesion;

FIG. **9** is an electron photomicrograph of a PET film obtained in Example 68, which PET film is coated with resin (33) of the present invention and has been subjected to a test for evaluating platelet adhesion;

FIG. **10** is an electron photomicrograph of a PET film obtained in Example 68, which PET film is coated with resin (34) of the present invention and has been subjected to a test for evaluating platelet adhesion;

FIG. **11** is an electron photomicrograph of a PET film obtained in Example 68, which PET film is coated with resin (37) of the present invention and has been subjected to a test for evaluating platelet adhesion;

FIG. **12** is an electron photomicrograph of a PET film obtained in Example 68, which PET film is coated with resin (48) of the present invention and has been subjected to a test for evaluating platelet adhesion;

FIG. **13** is an electron photomicrograph showing a non-coated PET film which is used in Example 68, which PET film has been subjected to a test for evaluating platelet adhesion;

FIG. **14** is a graph showing the results of the evaluation of HEK293 cell (human fetal renal cell) adhesion to various resins, which evaluation is made in Example 69;

FIG. **15** is a graph showing the results of the evaluation of HeLa cell (human cervical cancer cell) adhesion to various resins, which evaluation is made in Example 70;

FIG. **16** is a graph showing the results of the evaluation of human immunoglobulin adhesion to various resins, which evaluation is made in Example 71;

FIG. **17** is a graph showing the results of the evaluation of human fibronectin adhesion to various resins, which evaluation is made in Example 72;

FIG. **18** is a graph showing the results of the evaluation of human fibrinogen adhesion to various resins, which evaluation is made in Example 73;

FIG. **19** is a graph showing the results of the evaluation of human albumin adhesion to various resins, which evaluation is made in Example 74;

FIG. **20** is a graph showing the results of the evaluation of human immunoglobulin adhesion to PET films coated with various resins, which evaluation is made in Example 75;

FIG. **21** is a graph showing the results of the evaluation of toxicity of the resin of the present invention, which evaluation is made in Example 76;

FIG. **22** is a graph showing the results of the paclitaxel concentration test performed in Example 77 in which the paclitaxel concentration is measured with respect to tumor cells of mice to which resin (82) of the present invention and paclitaxel had been administered, respectively;

FIG. **23** is a graph showing the results of the paclitaxel concentration test performed in Example 78 in which the paclitaxel concentration is measured with respect to tumor cells of mice to which resin (83) of the present invention, resin (85) of the present invention and paclitaxel had been administered, respectively;

FIG. **24** is a graph showing the results of the evaluation of pharmacokinetics of resin (121) and resin (122), which evaluation is made in Example 82 and Comparative Example 1;

FIG. **25** is an electron photomicrograph of a non-coated PET film used in Example 83;

FIG. **26** is an electron photomicrograph of a PET film coated with resin (87) of the present invention, which PET film is obtained in Example 83;

FIG. **27** is an electron photomicrograph of a PET film coated with resin (108) of the present invention, which PET film is obtained in Example 83;

FIG. **28** is an electron photomicrograph of a PET film coated with resin (112) of the present invention, which PET film is obtained in Example 83;

FIG. **29** is a graph showing the results of the evaluation of HEK293 cell (human fetal renal cell) adhesion to various resins, which evaluation is made in Example 84;

FIG. **30** is a graph showing the results of the evaluation of human immunoglobulin adhesion to various resins, which evaluation is made in Example 85;

FIG. **31** is a graph showing the results of the evaluation of human fibronectin adhesion to various resins, which evaluation is made in Example 86;

FIG. **32** is a graph showing the results of the evaluation of human fibronogen adhesion to various resins, which evaluation is made in Example 87;

FIG. **33** is a graph showing the results of the evaluation of human immunoglobulin adhesion to PET films, which evaluation is made in Example 88;

FIG. **34** is a graph showing the results of the evaluation of toxicity of the resin of the present invention, which evaluation is made in Example 89;

FIG. **35** is a GPC chart of copolymer (160) obtained in Example 106;

FIG. **36** is a GPC chart of copolymer (161) obtained in Example 106;

FIG. **37** is a GPC chart of copolymer (162) obtained in Example 107;

FIG. **38** is a GPC chart of copolymer (163) obtained in Example 107;

FIG. **39** is a graph showing the results of the evaluation of HEL cell (human lung cell) adhesion to various resins, which evaluation is made in Example 115;

FIG. **40** is a graph showing the results of the evaluation of human immunoglobulin adhesion, which evaluation is made in Example 116;

FIG. **41** is a graph showing the results of the evaluation of toxicity of copolymer (125) and copolymer (138) of the present invention, which evaluation is made in Example 119;

FIG. **42** is an SEM photograph of a PET film coated with copolymer (139), which PET film is obtained in Example 120;

FIG. **43** is an SEM photograph of a PET film coated with copolymer (142), which PET film is obtained in Example 120;

FIG. **44** is an SEM photograph of a PET film coated with copolymer (145), which PET film is obtained in Example 120;

FIG. **45** is an SEM photograph of a PET film coated with copolymer (148), which PET film is obtained in Example 120;

FIG. **46** is an SEM photograph of a non-coated PET film used in Example 120;

FIG. **47**(*a*) is a graph showing the results of the evaluation of HEL cell (human lung cell) adhesion to copolymer (139), which evaluation is made in Example 121;

FIG. **47**(*b*) is a graph showing the results of the evaluation of HEL cell (human lung cell) adhesion to copolymer (142), which evaluation is made in Example 121;

FIG. **47**(*c*) is a graph showing the results of the evaluation of HEL cell (human lung cell) adhesion to copolymer (145), which evaluation is made in Example 121;

FIG. **47**(*d*) is a graph showing the results of the evaluation of HEL cell (human lung cell) adhesion to copolymer (148), which evaluation is made in Example 121;

FIG. **48** is a graph showing the results of the evaluation of human immunoglobulin adhesion, which evaluation is made in Example 122;

FIG. **49** is a graph showing the results of the evaluation of human fibrinogen adhesion, which evaluation is made in Example 123;

FIG. **50** is a graph showing the results of the evaluation of toxicity of copolymers of the present invention, which evaluation is made in Example 124;

FIG. **51** is a graph showing the results of the evaluation of toxicity of copolymers of the present invention, which evaluation is made in Example 128;

FIG. **52** is a graph showing the change with the lapse of time in the amount of the drug isolated from each of compound (177), compound (179), compound (181) and compound (183) in a mouse plasma having a temperature of 37° C., which change is evaluated in Example 146;

FIG. **53** is a graph showing the change with the lapse of time in the amount of the drug isolated from each of compound (177), compound (179), compound (181) and compound (183) in a human plasma having a temperature of 37° C., which change is evaluated in Example 146;

FIG. **54** is a graph showing the change with the lapse of time in the amount of the drug isolated from each of compound (177), compound (185), compound (187) and compound (189) in a mouse plasma having a temperature of 37° C., which change is evaluated in Example 147;

FIG. **55** is a graph showing the change with the lapse of time in the amount of the drug isolated from each of compound (177), compound (185), compound (187) and compound (189) in a human plasma having a temperature of 37° C., which change is evaluated in Example 147;

FIG. **56** is a graph showing the change with the lapse of time in the amount of the drug isolated from each of compound (197) and compound (200) in a mouse plasma having a temperature of 37° C., which change is evaluated in Example 148;

FIG. **57** is a graph showing the change with the lapse of time in the amount of the drug isolated from each of compound (197) and compound (200) in a human plasma having a temperature of 37° C., which change is evaluated in Example 148;

FIG. **58** is a graph showing the average tumor volume of each of a non-administered mouse group and test solution-administered mouse groups, which average tumor volume is evaluated in Example 149 after 6 days from the administration of the test solution;

FIG. **59** is a graph showing the change with the lapse of time in the average tumor volume of each of a non-administered mouse group and test solution-administered mouse groups, which change is evaluated in Example 150;

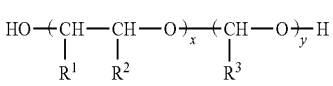
FIG. **60** is a graph showing the change with the lapse of time in the average tumor volume of each of a non-administered mouse group and test solution-administered mouse groups, which change is evaluated in Example 151;

FIG. **61** is a graph showing the change with the lapse of time in the amount of the drug isolated from each of compound (209), compound (212) and compound (215) in a mouse plasma having a temperature of 37° C., which change is evaluated in Example 163; and

FIG. **62** is a graph showing the results of the evaluation of human fibrinogen adhesion, which evaluation is made in Example 164.

DETAILED DESCRIPTION OF THE INVENTION

According to the present invention, there is provided a body fluid compatible and biocompatible resin for use in a medical treatment involving a contact of the resin with at least one member selected from the group consisting of a body fluid and a biological tissue, which comprises at least one substituted oxyalkylene polymer represented by the following formula (1):



(1)

wherein:

each of R^1, R^2 and R^3 independently represents a hydrogen atom or a —CH_2R^4 group,

wherein each R^4 independently represents a hydroxyl group or a —OR^5 group, wherein R^5 represents a group selected from the group consisting of a C_1-C_{10} aliphatic hydrocarbyl group, a C_6-C_{10} aryl group, a —R^6COOH group and a derivative thereof, and a —CH_2—O—CH_2—CH(OH)—CH_2—OR^7 group, wherein R^6 represents a C_1-C_{10} aliphatic hydrocarbylene group and R^7 represents a group selected from the group consisting of a C_1-C_{10} aliphatic hydrocarbyl group and a C_6-C_{10} aryl group,

provided that all of R^1, R^2, and R^3 are not simultaneously hydrogen atoms; and

x and y represent integers which satisfy the following requirements:

$10 \leqq x \leqq 10{,}000$ and

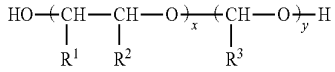
$0 \leqq y \leqq 10{,}000$,

the at least one substituted oxyalkylene polymer having a weight average molecular weight of from 1,000 to

1,000,000 as measured by gel permeation chromatography (GPC) using a calibration curve obtained with respect to standard polyethylene glycol (PEG) samples, each having a narrow molecular weight distribution.

For easy understanding of the present invention, the essential features and various preferred embodiments of the present invention are enumerated below.

1. A body fluid compatible and biocompatible resin for use in a medical treatment involving a contact of the resin with at least one member selected from the group consisting of a body fluid and a biological tissue, which comprises at least one substituted oxyalkylene polymer represented by the following formula (1):



(1)

wherein:

each of R^1, R^2 and R^3 independently represents a hydrogen atom or a $—CH_2R^4$ group,

wherein each R^4 independently represents a hydroxyl group or a $—OR^5$ group, wherein R^5 represents a group selected from the group consisting of a C_1-C_{10} aliphatic hydrocarbyl group, a C_6-C_{10} aryl group, a $—R^6COOH$ group and a derivative thereof, and a $—CH_2—O—CH_2—CH(OH)—CH_2—OR^7$ group, wherein R^6 represents a C_1-C_{10} aliphatic hydrocarbylene group and R^7 represents a group selected from the group consisting of a C_1-C_{10} aliphatic hydrocarbyl group and a C_6-C_{10} aryl group,

provided that all of R^1, R^2, and R^3 are not simultaneously hydrogen atoms; and

x and y represent integers which satisfy the following requirements:

$10 \leqq x \leqq 10{,}000$ and

$0 \leqq y \leqq 10{,}000$,

the at least one substituted oxyalkylene polymer having a weight average molecular weight of from 1,000 to 1,000,000 as measured by gel permeation chromatography (GPC) using a calibration curve obtained with respect to standard polyethylene glycol (PEG) samples, each having a narrow molecular weight distribution.

2. The body fluid compatible and biocompatible resin according to item 1 above, wherein x and y in the formula (1) satisfy the following requirements:

$x=y$,

$10 \leqq x \leqq 10{,}000$ and

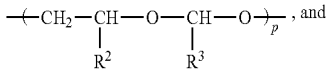
$10 \leqq y \leqq 10{,}000$, and

wherein the amount of the $—CH_2R^4$ group as any of R^1, R^2 and R^3 is from 0.01 to 2.5 mole, per mole of the total of $-(CHR^1—CHR^2—O)-$ unit and $-(CHR^1—CHR^2—O)-$ unit of the at least one substituted oxyalkylene polymer.

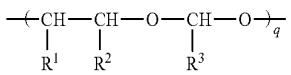
3. The body fluid compatible and biocompatible resin according to item 1 above, wherein the at least one substituted oxyalkylene polymer is a homopolymer.

4. The body fluid compatible and biocompatible resin according to item 1 above, wherein the at least one substituted oxyalkylene polymer is a copolymer.

5. The body fluid compatible and biocompatible resin according to item 2 above, wherein the at least one substituted oxyalkylene polymer is a copolymer comprised mainly of recurring units represented by formula (2) and formula (3);



(2), and



(3)

wherein:

R^2 and R^3 are as defined for formula (1),

wherein R^1 represents a $—CH_2R^4$ group, and

p and q are integers which satisfy the following requirements:

$10 \leqq p \leqq 10{,}000$ and

$10 \leqq q \leqq 10{,}000$,

wherein the molar ratio of recurring unit of formula (2) to recurring unit of formula (3) is 0.5.

6. The body fluid compatible and biocompatible resin according to item 1 above, wherein the at least one substituted oxyalkylene polymer is obtained by polymerizing an ethylene oxide derivative or by polymerizing an ethylene oxide derivative, followed by treatment with an acid.

7. The body fluid compatible and biocompatible resin according to item 1 above, wherein the at least one substituted oxyalkylene polymer is crosslinked by a crosslinking agent.

8. The body fluid compatible and biocompatible resin according to item 7 above, wherein the crosslinking agent is at least one compound selected form the group consisting of ethylene glycol diglycidyl ether and butanediol diglycidyl ether.

9. The body fluid compatible and biocompatible resin according to item 7 above, wherein the crosslinking agent is at least one compound selected form the group consisting of epichlorohydrin and epibromohydrin.

10. The body fluid compatible and biocompatible resin according to item 7 above, wherein the crosslinking agent is used in an amount of from 10 to 120% by weight, based on the weight of the at least one substituted oxyalkylene polymer.

11. The body fluid compatible and biocompatible resin according to item 1 above, wherein the at least one substituted oxyalkylene polymer is produced from a polysaccharide.

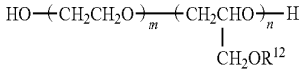
12. The body fluid compatible and biocompatible resin according to item 11 above, wherein the polysaccharide is a dextran or pullulan.

13. The body fluid compatible and biocompatible resin according to item 1 above, which is in the form of a film for preventing adhesion of a biological tissue or covering a wound.

14. The body fluid compatible and biocompatible resin according to any one of items 1, 3, 4 and 6 above, wherein y is 0, each R^1 is a hydrogen atom and each R^2 independently represents a $—CH_2R^8$ group,

wherein each R^8 independently represents a hydroxyl group, a $—O—CH_2COOH$ group, a $—O—CH_2COONa$ group or a $—O—CH_2COOR^{11}$ group, wherein R^{11} represents a group comprising an amino acid or peptide having bonded thereto a compound having a pharmaceutical activity.

15. The body fluid compatible and biocompatible resin according to any one of items 1, 3, 4 and 6 above, wherein a copolymer is represented by the following formula (4):



(4)

wherein:

each R^{12} independently represents a hydrogen atom, a —CH_2COOH group, a —CH_2COONa group or a —CH_2COOR^{13} group, wherein each R^{13} represents a group comprising an amino acid or peptide having bonded thereto a compound having a pharmaceutical activity; and

m and n are integers which satisfy the following requirements:

$10 \leqq m \leqq 10{,}000$ and

$10 \leqq n \leqq 10{,}000$.

16. The body fluid compatible and biocompatible resin according to item 14 above, wherein the compound having a pharmaceutical activity is a compound having an anticancer activity.

17. The body fluid compatible and biocompatible resin according to item 15 above, wherein the compound having a pharmaceutical activity is a compound having an anticancer activity.

18. The body fluid compatible and biocompatible resin according to item 14 above, wherein the compound having a pharmaceutical activity is an adrenocortical hormone, a vasodilator or an enzyme inhibitor.

19. The body fluid compatible and biocompatible resin according to item 15 above, wherein the compound having a pharmaceutical activity is an adrenocortical hormone, a vasodilator or an enzyme inhibitor.

20. The body fluid compatible and biocompatible resin according to item 4 above, wherein the at least one substituted oxyalkylene polymer is a copolymer having different R^2 groups, wherein each y is 0, each R^1 is a hydrogen atom and each R^2 independently represents a —CH_2OH group, a —CH_2OCH_3 group, a —$CH_2OCH_2CH_2CH_2CH_3$ group or a —$CH_2OC_6H_5$ group.

21. The body fluid compatible and biocompatible resin according to item 1 above, wherein each y is 0, each R^1 is a hydrogen atom and each R^2 represents a —CH_2OH group, wherein the —OH group in R^2 is formed by hydrolysis of a group selected from the group consisting of a tertiary butyl group, a trimethylsilyl group, a 1-ethoxyethyl group, a tetrahydropyranyl group and an acetyl group.

22. The body fluid compatible and biocompatible resin according to item 1 above, wherein the at least one substituted oxyalkylene polymer is a homopolymer obtained by subjecting an alkyl glycidyl ether or an aryl glycidyl ether to ring opening polymerization.

23. The body fluid compatible and biocompatible resin according to item 4 or 5 above, wherein the at least one substituted oxyalkylene polymer is a copolymer obtained by subjecting at least two different glycidyl ethers selected from the group consisting of an alkyl glycidyl ether and an aryl glycidyl ether to ring opening copolymerization.

24. The body fluid compatible and biocompatible resin according to item 1 above, which is for use as a coating material for a shaped article of a resin other than the body fluid compatible and biocompatible resin.

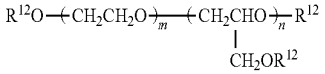
25. The body fluid compatible and biocompatible resin according to item 24 above, wherein the coating material is used in an amount of from 0.01 to 20% by weight, based on the weight of the resin other than the body fluid compatible and biocompatible resin.

26. The body fluid compatible and biocompatible resin according to item 24 or 25 above, wherein the resin other than the body fluid compatible and biocompatible resin is selected from the group consisting of a polyester, a polyamide, a polyimide, a polyether sulfone and a polysulfone.

27. A resin composition comprising the body fluid compatible and biocompatible resin of item 1 above, and a resin other than the body fluid compatible and biocompatible resin.

28. The resin composition according to item 27 above, wherein the resin other than the body fluid compatible and biocompatible resin is selected from the group consisting of a polyester, a polyamide, a polyimide a polyether sulfone and a polysulfone.

29. A body fluid compatible and biocompatible resin for use in a medical treatment involving a contact of the resin with at least one member selected from the group consisting of a body fluid and a biological tissue, which comprises at least one substituted oxyalkylene polymer represented by the following formula (5):



(5)

wherein:

each R^{12} independently represents a hydrogen atom, a-CH_2COOH group, a-CH_2COONa group or a —CH_2COOR^{14} group, wherein each R^{14} represents a group comprising an amino acid or peptide having bonded thereto a compound having a pharmaceutical activity; and

m and n are integers which satisfy the following requirements:

$10 \leqq m \leqq 10{,}000$ and

$10 \leqq n \leqq 10{,}000$,

the at least one substituted oxyalkylene polymer having a weight average molecular weight of from 1,000 to 1,000,000 as measured by gel permeation chromatography (GPC) using a calibration curve obtained with respect to standard polyethylene glycol (PEG) samples, each having a narrow molecular weight distribution.

30. The body fluid compatible and biocompatible resin according to item 29 above, wherein the at least one substituted oxyalkylene polymer is obtained by polymerizing an ethylene oxide derivative or by polymerizing an ethylene oxide derivative, followed by treatment with an acid.

31. The body fluid compatible and biocompatible resin according to item 29 or 30 above, wherein the compound having a pharmaceutical activity is a compound having an anticancer activity.

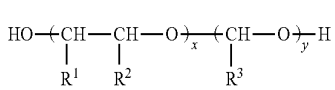
32. The body fluid compatible and biocompatible resin according to item 29 or 30 above, wherein the compound having a pharmaceutical activity is an adrenocortical hormone, a vasodilator or an enzyme inhibitor.

33. A resin composition comprising the body fluid compatible and biocompatible resin of item 29 above, and a resin other than the body fluid compatible and biocompatible resin.

34. The resin composition according to item 33 above, wherein the resin other than the body fluid compatible and biocompatible resin is selected from the group consisting of a polyester, a polyamide, a polyimide a polyether sulfone and a polysulfone.

Hereinbelow, the present invention is described in detail.

The body fluid compatible and biocompatible resin of the present invention is a resin which comprises at least one substituted oxyalkylene polymer represented by the following formula (1):



(1)

wherein:

each of R^1, R^2 and R^3 independently represents a hydrogen atom or a $—CH_2R^4$ group,

wherein each R^4 independently represents a hydroxyl group or a $—OR^5$ group, wherein R^5 represents a group selected from the group consisting of a C_1-C_{10} aliphatic hydrocarbyl group, a C_6-C_{10} aryl group, a $—R^6COOH$ group and a derivative thereof, and a $—CH_2—O—CH_2—CH(OH)—CH_2—OR^7$ group, wherein R^6 represents a C_1-C_{10} aliphatic hydrocarbylene group and R^7 represents a group selected from the group consisting of a C_1-C_{10} aliphatic hydrocarbyl group and a C_6-C_{10} aryl group,

provided that all of R^1, R^2, and R^3 are not simultaneously hydrogen atoms; and

x and y represent integers which satisfy the following requirements:

$10 \leqq x \leqq 10{,}000$ and

$0 \leqq y \leqq 10{,}000$,

the at least one substituted oxyalkylene polymer having a weight average molecular weight of from 1,000 to 1,000,000 as measured by gel permeation chromatography (GPC) using a calibration curve obtained with respect to standard polyethylene glycol (PEG) samples, each having a narrow molecular weight distribution.

The body fluid compatible and biocompatible resin of the present invention has features that the resin has a specific molecular weight and that the resin comprises at least one substituted oxyalkylene polymer mentioned above, which has a specific substituent. By virtue of such features, the resin of the present invention exhibits excellent body fluid compatibility and excellent biocompatibility. Therefore, the resin of the present invention can be advantageously used for a medical treatment involving a contact of the resin with at least one member selected from the group consisting of a body fluid and a biological tissue. Specific examples of body fluids include a blood, a lymph, a lacrimal fluid, an articulation fluid and a cerebrospinal fluid. Examples of biological tissues include various tissues other than an epidermis tissue. More specific examples of biological tissues include tissues of internal organs (such as a liver, a pancreas, a kidney and a spleen), an epithelial tissue, a connective tissue, a blood cell tissue, a myeloid tissue, a muscular tissue, a bone, a cartilage, a blood vessel, an eyeball, an adipose tissue, an alimentary tract, an alimentary tract mucosa and a nervous tissue.

The substituted oxyalkylene polymer contained in the resin of the present invention has a weight average molecular weight of from 1,000 to 1,000,000 as measured by GPC using a calibration curve obtained with respect to standard polyethylene glycol samples, each having a narrow molecular weight distribution (hereinafter, the thus measured weight average molecular weight is frequently referred to as a "weight average molecular weight determined by GPC using a PEG calibration curve"). When the weight average molecular weight of the polymer is less than 1,000, the solubility of the polymer in water becomes too high, thereby causing a disadvantage that, when the resin containing such a low molecular weight polymer is used for coating a shaped article produced from a hydrophobic resin other than the resin of the present invention, such a low molecular weight polymer is likely to get dissolved into a body fluid or the like. On the other hand, when the weight average molecular weight of the polymer is more than 1,000,000, the solubility of the polymer in water becomes too low, thereby causing a disadvantage that the body fluid compatibility and biocompatibility of a resin containing such a high molecular weight polymer is lowered. From the viewpoint of the coatability of the resin of the present invention to a substrate (such as the above-mentioned shaped article produced from a resin other than the resin of the present invention) and the miscibility of a resin other than the resin of the present invention (which is used to form a resin composition containing the resin of the present invention) with the resin of the present invention, it is preferred that the weight average molecular weight of the polymer contained in the resin of the present invention is in the range of from 1,000 to 500,000. Further, when the weight average molecular weight of the polymer contained in the resin of the present invention is measured by GPC using a calibration curve obtained with respect to standard pullulan samples, it is preferred that the weight average molecular weight is in the same range as in the case of the above-mentioned weight average molecular weight determined by GPC using a PEG calibration curve.

As mentioned above, from the viewpoint of the coatability of the resin of the present invention to a substrate and the miscibility of a resin other than the resin of the present invention with the resin of the present invention, it is preferred that the weight average molecular weight of the substituted oxyalkylene polymer contained in the resin of the present invention is in the range of from 1,000 to 500,000, as determined by GPC using a PEG calibration curve. The weight average molecular weight of the polymer is more preferably in the range of from 1,000 to 150,000, still more preferably from 1,000 to 100,000. From the viewpoint of the miscibility of the resin of the present invention with a resin other than the resin of the present invention, and the safety of the resin of the present invention for living organisms in the case where the resin of the present invention gets dissolved out from the substrate, it is preferred that the weight average molecular weight of the polymer is in the range of from 1,000 to 100,000, more advantageously from 1,000 to 65,000, as determined by GPC using a PEG calibration curve.

The above-mentioned preferred range of the weight average molecular weight influences the "biocompatibility" of the resin of the present invention, and is especially advantageous for achieving the high safety of the resin of the present invention. That is, in the present invention, the "biocompatible" resin means that the resin not only has less interaction and interference with living organisms, but also has a specific molecular weight which enables the rapid excretion of the resin from the kidney, so that the accumulation of the resin in organs and the like can be suppressed and the resin exhibits high safety. The reason for the high safety of the resin of the present invention is as follows. For example, when the resin of the present invention is released into a body fluid, a polymer having a weight average molecular weight which is lower than the molecular weight (about 67,000) of a blood plasma albumin present in a living organism can be rapidly excreted from the living organism. For this reason, the above-mentioned preferred range of the weight average molecular weight is especially advantageous for the renal excretion.

As examples of the method for controlling the weight average molecular weight of the polymer (determined by GPC using a PEG calibration curve) to be in the range of from 1,000 to 1,000,000, there can be mentioned a method in which raw materials are purified, and a method in which a high molecular weight fraction and/or a low molecular weight fraction is removed after the polymerization reaction for producing the resin of the present invention. With respect to the reaction conditions for producing the resin of the present invention, the type and amount of a polymerization initiator, the type and amount of a reaction solvent (if any), the reaction temperature, the reaction time, the concentrations of the raw materials, the polymerization initiator concentration, the reaction atmosphere, the reaction pressure, the manner of stirring, the stirring rate and the like can be appropriately selected so as to obtain a polymer having a desired weight average molecular weight. With respect to the above-mentioned method in which a high molecular weight fraction and/or a low molecular weight fraction is removed after the polymerization reaction, the fractionation of the polymer can be performed by various methods. Examples of methods for fractionation of the polymer include a chromatography, such as size exclusion chromatography (SEC); ultrafiltration with a UF module or the like; ultracentrifuge; a precipitation fractionation using a solvent or the like.

The weight average molecular weight determined by GPC using a PEG calibration curve means a molecular weight as measured by GPC using a calibration curve obtained with respect to standard polyethylene glycol (PEG) samples, each having a narrow molecular weight distribution. PEG is soluble not only in water but also in organic solvents and, hence, PEG is generally used as a standard substance for measuring a molecular weight of a hydrophobic polymer.

It is preferred that the substituted oxyalkylene polymer contained in the resin of the present invention has a molecular weight distribution of from 1.2 to 2.5 in terms of the Mw/Mn ratio, wherein Mw represents the weight average molecular weight (determined by GPC using a PEG calibration curve) of the polymer and Mn represents the number average molecular weight (determined by GPC using a PEG calibration curve) of the polymer. For surely achieving the desired excellent properties of the resin of the present invention, it is more preferred that the molecular weight distribution is in the range of from 1.2 to 2.2, still more advantageously from 1.2 to 2.0, most advantageously from 1.0 to 1.8. When the molecular weight distribution of the polymer is more than 2.5, such a polymer becomes a collection of high molecular polymer chains having widely varied molecular weights which range from a low molecular weight to a high molecular weight, so that it becomes difficult to surely obtain a resin having a satisfactory biocompatibility. On the other hand, with respect to the lower limit (1.0) of the molecular weight distribution, the production of a polyether having such a low molecular weight distribution is technically difficult.

Examples of raw material monomers used for producing the resin of the present invention which comprises the substituted oxyalkylene polymer represented by formula (1) include epoxy group-containing C_3-C_{100} compounds, such as ethylene oxide, an aliphatic hydrocarbon glycidyl ether (e.g., a C_1-C_{12} alkyl glycidyl ether) and an aromatic hydrocarbon glycidyl ether (e.g., a C_6-C_{12} aryl glycidyl ether). Specific examples of alkyl glycidyl ethers include methyl glydidyl ether, ethyl glycidyl ether, n-propyl glycidyl ether, i-propyl glycidyl ether, n-butyl glycidyl ether, i-butyl glycidyl ether, t-butyl glycidyl ether, allyl glycidyl ether, 2-ethylhexyl glycidyl ether, 2-methyloctyl glycidyl ether, ethylene glycol diglycidyl ether, butanediol diglycidyl ether, glycerol triglycidyl ether, acetyl glycidol (which is a reaction product of glycidol and acetyl chloride) and glycidyl methacrylate. These glycidyl ethers may be used individually or in combination. Specific examples of aryl glycidyl ethers include phenyl glycidyl ether and benzyl glycidyl ether. Further examples of raw material monomers include an alkylene oxide (such as propylene oxide), epichlorohydrin and epibromohydrin. For example, when epichlorohydrin is used as the raw material monomer, the resin of the present invention can be produced as follows. Epichlorohydrin is polymerized to produce a polyepichlorohydrin. The produced polyepichlorohydrin is dissolved in a solvent, such as diethylene glycol methyl ether and, then, potassium acetate is added to the resultant solution, followed by heating at 100 to 150° C., thereby converting chloromethyl groups of the polyepichlorohydrin to acetyloxy groups. Subsequently, the resultant is hydrolyzed with an aqueous sodium hydroxide solution at room temperature to convert the acetyloxy groups to hydroxyl groups, thereby producing a resin comprising the substituted oxyalkylene polymer represented by formula (1). Further, the resin comprising the substituted oxyalkylene polymer having alkyloxy groups introduced thereto can be produced in substantially the same manner as mentioned above, except that a potassium alkoxide or a sodium alkoxide is used instead of potassium acetate.

As examples of structures of the substituted oxyalkylene polymer represented by formula (1), there can be mentioned (i) a homopolymer, (ii) a copolymer comprised of the different recurring units which are, respectively, represented by formula (1), and (iii) a copolymer containing the recurring units of formula (1) and a monomer unit other than the recurring unit of formula (1). When the substituted oxyalkylene polymer represented by formula (1) is a copolymer of item (iii) above, the molar fraction of the monomer unit other than the recurring units of formula (1) present in the copolymer is preferably 80% or less, more preferably 60% or less, still more preferably 40% or less, based on the total molar amount of the recurring units of formula (1) and the monomer unit other than the recurring units of formula (1). As specific examples of monomer units other than the recurring units of formula (1), there can be mentioned monomer units which are, respectively, derived from an acrylic ester, a methacrylic ester, glycidyl methacrylate and vinyl ether. The copolymer of item (iii) above can be produced as follows. For example, the substituted oxyalkylene polymer represented by formula (1), wherein y is 0, and R_1 and R_2 are a hydrogen atom and a $—CH_2OCH_2CHCH_2$ group, respectively, is prepared. Then, the resultant polymer is subjected to radical polymerization with an acrylic acid, in which a double bond in the aryl group contained in R_2 is reacted with a double bond in the acrylic acid, thereby obtaining a copolymer of item (iii) above.

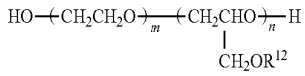
When the at least one substituted oxyalkylene polymer is a copolymer, the ratio of different monomer units constituting the copolymer can be controlled by appropriately adjusting the types and amounts of raw materials, the type and amount of a polymerization initiator, the type and amount of a reaction solvent (if any), the reaction temperature, the reaction time, the concentrations of raw materials, the polymerization initiator concentration, the reaction atmosphere, the reaction pressure, the manner of stirring, the stirring rate and the like.

When an ethylene oxide derivative is used to obtain the resin of the present invention, the production of the resin may be performed by any of the following methods: a method in which an ethylene oxide derivative is polymerized; and a method in which a polymer obtained by polymerization of an ethylene oxide derivative is treated in an organic solvent (such as dioxane) with hydrogen chloride or an acidic aqueous

solution, such as hydrochloric acid (e.g., 4 N HCl), or with a basic aqueous solution, such as 1 N aqueous sodium hydroxide solution.

The mechanism of various functions of the resin of the present invention is as follows. In the substituted oxyalkylene polymer contained in the resin of the present invention, the main chain and the hydrophilic side chain (having a primary hydroxyl group etc.) not only suppresses the adhesion of a polypeptide, a protein, a cell and a platelet to the resin, and the activation of platelet by the resin, but also improves efficiencies of various treatments (such as a separation, a removal and a recovery) for a polypeptide, a protein and a cell, and a platelet recovery. On the other hand, the presence of the hydrophobic group introduced into the side chain improves the liposolubility of the resin of the present invention, thereby rendering easy the mixing the resin of the present invention with a resin other than the resin of the present invention, or the coating of an equipment (used for the above-mentioned treatments) with the resin of the present invention.

In the resin of the present invention, the substituted oxyalkylene polymer may be a copolymer having a structure represented by the following formula (4):



(4)

wherein:

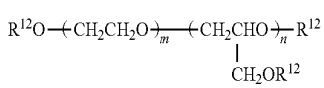
each R^{12} independently represents a hydrogen atom, a —CH_2COOH group, a —CH_2COONa group or a —CH_2COOR^{13} group, wherein each R^{13} represents a group comprising an amino acid or peptide having bonded thereto a compound having a pharmaceutical activity; and

m and n are integers which satisfy the following requirements:

$10 \leqq m \leqq 10{,}000$ and

$10 \leqq n \leqq 10{,}000$.

Further, the terminals of the substituted oxyalkylene polymer may be modified to form a copolymer having a structure represented the following formula (5):



(5)

wherein:

each R^{12} independently represents a hydrogen atom, a-CH_2COOH group, a-CH_2COONa group or a —CH_2COOR^{14} group, wherein each R^{14} represents a group comprising an amino acid or peptide having bonded thereto a compound having a pharmaceutical activity; and

m and n are integers which satisfy the following requirements:

$10 \leqq m \leqq 10{,}000$ and

$10 \leqq n \leqq 10{,}000$.

Each of the copolymers of formulae (4) and (5) can be produced by introducing a functional group into the terminal(s) of a side chain and/or a main chain of a substituted oxyalkylene polymer obtained from ethylene oxide and an epoxy group-containing C_3-C_{100} compound. Further, in each of the copolymers of formulae (4) and (5), ethylene oxide is used as a raw material and, hence, the number of the side chains can be reduced, thereby simplifying the structure of the copolymer. As examples of functional groups introduced into the terminal(s) of a side chain and/or a main chain of the substituted oxyalkylene polymer, there can be mentioned a hydrocarbyl group and a carboxymethyl group. The carboxymethyl group introduced into the copolymer represented by formula (4) or (5) can be used for binding a compound having a pharmaceutical activity (e.g., anti-cancer activity) to the copolymer through a linker, to form a drug complex. When such a drug complex is administered to a living organism, the resin of the present invention exhibits a characteristic that an interaction and interference of the drug complex with a biological tissue or body fluid do not occur. Specifically, as shown in the working example of the present specification, the resin of the present invention exhibits an advantage that the resin is not accumulated in an organ (such as a liver, a spleen or a bone marrow) in which side effects are caused by a drug metabolism and a drug. Further, by utilizing characteristics of a tumor tissue, such as EPR effect (see, Maeda, H., Advanced Drug Delivery Reviews, 6, pp. 181-202 (1991)), it becomes possible to deliver a drug selectively to a tumor site or an inflammatory site by administering the drug in the form of a drug complex which contains the copolymer represented by formula (4) or (5) to a living organism. The weight average molecular weight (determined by GPC using a PEG calibration curve) of the copolymer represented by formula (4) or (5) is in the range of from 1,000 to 1,000,000, preferably from 1,000 to 500,000. However, from the viewpoint of administration of the copolymer, the weight average molecular weight of the copolymer is more preferably in the range of from 1,000 to 150,000. Further, from the viewpoint of the safety of the copolymer to a living organism, it is preferred that the weight average molecular weight of the copolymer is in the range of from 1,000 to 100,000, more advantageously from 1,000 to 65,000. It is preferred that the copolymer represented by formula (4) or (5) has a molecular weight distribution of from 1.2 to 2.5, in terms of the Mw/Mn ratio, wherein Mw represents the weight average molecular weight (determined by GPC using a PEG calibration curve) of the polymer and Mn represents the number average molecular weight (determined by GPC using a PEG calibration curve) of the polymer. For surely achieving the desired excellent properties of the resin of the present invention, it is more preferred that the molecular weight distribution is in the range of from 1.2 to 2.2, still more advantageously from 1.2 to 2.0, most advantageously from 1.0 to 1.8. Further, with respect to the molar ratio (%) of the monomer units present in the copolymer of formula (4) or (5), the molar ratio ("m" in formula (4) or (5)) of ethylene oxide units is in the range of from 0.01 to 99.99%, and the molar ratio "n" in formula (4) or (5)) of an epoxy group-containing C_3-C_{100} compound units is in the range of from 99.99 to 0.01%, each based on the total molar amount of the ethylene oxide units and the epoxy group-containing C_3-C_{100} compound units.

The resin of the present invention, which contains the copolymer of formula (4) or (5), can be produced as follows. For example, the introduction of a carboxymethyl group into a side chain of the polymer represented by formula (1) can be performed by a method in which ethyl bromoacetate is reacted with the polymer represented by formula (1) in a solvent (such as toluene) in the presence of potassium t-butoxide and 18-crown-6-ether, and the ester linkage in the resultant reaction product is hydrolyzed with an alkali, thereby obtaining a polymer represented by formula (1) having introduced thereto a carboxymethyl group. Further, the

introduction of a carboxymethyl group into a side chain of the polymer represented by formula (1) can also be performed by a method in which sodium chloroacetic acid is reacted with the polymer of formula (1) in an aqueous solution thereof in the presence of a base, such as sodium hydroxide, thereby introducing the carboxymethyl group into the polymer represented by formula (1).

The substituted oxyalkylene polymer contained in the resin of the present invention may have a crosslinked structure. The crosslinked structure can be formed by a crosslinking agent. For example, the resin of the present invention which comprises a substituted oxyalkylene polymer having a side chain to which a hydrocarbyl group is introduced by an acid or base treatment can be crosslinked by various crosslinking agents, such as a crosslinking agent containing at least two epoxy groups in a molecule thereof, a crosslinking agent containing at least two carboxyl groups in a molecule thereof and a crosslinking agent containing at least two isocyanate groups in a molecule thereof. As preferred examples of copolymers to which a hydrocarbyl group is introduced at a side chain thereof by an acid or base treatment, there can be mentioned a copolymer of at least one member selected from the group consisting of t-butyl glycidyl ether, glycidyl trimethylsilyl ether, glycidyl tetrahydropyranyl ether, acetyl glycidol, glycidyl methacrylate and (1-ethoxy) ethyl glycidyl ether, with ethylene oxide or an epoxy group-containing C_3-C_{100} compound.

As preferred examples of crosslinking agents used for crosslinking the substituted oxyalkylene polymer contained in the resin of the present invention, there can be mentioned diglycidyl ether, a triglycidyl ether derivative, a dicarboxylic acid derivative, a tricarboxylic acid derivative, a diisocyanate and a triisocyanate. Examples of diglycidyl ethers include ethylene glycol diglycidyl ether and butandiol diglycidyl ether. Examples of carboxylic acids include polycarboxylic acids, such as succinic acid, malic acid, citric acid and adipic acid, and examples of isocyanates include tolylene diisocyanate and xylylene diisocyanate. As further examples of crosslinking agents, there can be mentioned epichlorohydrin and epibromohydrin. In general, when a polymer is reacted with the crosslinking agent as mentioned above, the resultant crosslinked product forms a gel. However, the hardness and swelling of the gel depend on the degree of a crosslinking and, hence, the hardness and swelling of the gel can be adjusted by appropriately selecting the type of the crosslinking agent and the reaction conditions. Further, the gel is transparent, and the water-solubility and strength of the gel can also be adjusted by appropriately selecting the crosslinking conditions. In the present invention, the crosslinking agent is used in an amount of from 5 to 300% by weight, preferably from 5 to 150% by weight, more preferably from 10 to 120% by weight, still more preferably from 25 to 75% by weight, based on the weight of the substituted oxyalkylene polymer. When the crosslinking agent is used in an amount within the above-mentioned range, the resultant crosslinked resin of the present invention is especially effective for suppressing the adhesion of biological substances (such as a biological tissue, a protein, a cell and a platelet) to the resin and the activation of platelet by the resin. Hereinbelow, an explanation is made with respect to a method for producing a crosslinked product of the resin of the present invention. In the explanation, resins produced from raw materials other than polysaccharide are taken as examples; however, the crosslinking method explained below can also be applicable to the hydrocarbyl group-containing resins of the present invention produced by oxidation reaction of a polysaccharide.

(1) Crosslinking of a Copolymer Having a Hydrocarbyl Group at a Side Chain Thereof:

For example, when the resin of the present invention comprises a copolymer obtained by copolymerizing t-butyl glycidyl ether as a protective monomer with ethylene oxide as a hydrophilic monomer, the copolymer is subjected to a conventional treatment for removing a protective group (t-butyl group), such as a treatment using a solution of hydrogen chloride in dioxane, hydrochloric acid or an ion exchange resin, thereby removing the t-butyl group from the copolymer. As a result, a copolymer having a side chain having a hydroxymethyl group (which has a primary hydroxyl group) is obtained. The obtained copolymer can be crosslinked using the below-mentioned crosslinking agent under various reaction conditions. By the crosslinking of the copolymer, for example, a hydrophilic or hydrophobic gel can be obtained. Also in the case where the protective monomer is glycidyl trimethylsilyl ether, glycidyl tetrahydropyranyl ether or (1-ethoxy)ethyl glycidyl ether, the protective group can be removed from the copolymer by the above-mentioned treatment with an acid, such as a solution of hydrogen chloride in dioxane, hydrochloric acid or an ion exchange resin, thereby obtaining a copolymer having a side chain to which a primary hydroxyl group is introduced. The thus obtained copolymer also can be crosslinked using the above-mentioned crosslinking agent.

On the other hand, when the protective monomer is a glycidyl carboxylate (such as acetyl glycidol) or a glycidyl ester of (meth)acrylic acid (such as glycidyl methacrylate), a copolymer obtained by a reaction between the protective monomer and the hydrophilic monomer is treated with a base solution, such as an aqueous sodium hydroxide solution or an aqueous potassium hydroxide solution, to remove an acetyl group from the copolymer, thereby obtaining a copolymer having a side chain having a hydroxymethyl group which has a primary hydroxyl group. The thus obtained copolymer also can be crosslinked using the above-mentioned crosslinking agent.

A glycidyl ether preferably used as the crosslinking agent is a diglycidyl ether having two epoxy groups in a molecule thereof or a triglycidyl ether having three epoxy groups in a molecule thereof. As examples of diglycidyl ethers, there can be mentioned ethylene glycol diglycidyl ether, diethylene glycol diglycidyl ether, propylene glycol diglycidyl ether, butandiol diglycidyl ether, 1,6-hexanediol diglycidyl ether and C_8-C_{20} diglycidyl ethers. Further, as examples of triglycidyl esters, there can be mentioned glycerol triglycidyl ether.

Among those which are exemplified above, from the viewpoint of the yield of a crosslinked product and the balance between the hydrophilicity and hydrophobicity of a crosslinked product, preferred are diglycidyl ethers, such as ethylene glycol diglycidyl ether, diethylene glycol diglycidyl ether and butanediol diglycidyl ether. The reason why these crosslinking agents are preferred is as follows. By using a crosslinking agent having an epoxy group, a hydroxyl group is generated after the crosslinking reaction and, hence, an increase in the liposolubility of the crosslinked product can be suppressed, thereby maintaining excellent body fluid compatibility and biocompatibility of the resin of the present invention even after the crosslinking reaction.

In the crosslinking reaction, the degree of crosslinking can be adjusted by appropriately selecting reaction conditions, such as the concentration of a copolymer having a side chain to which a hydroxymehtyl group (having a primary hydroxyl group) is introduced, the amount of a crosslinking agent, the type of a solvent, the amount of a crosslinking catalyst (such as an acid or a base) and the reaction temperature. Further, the

hydrophobicity of the crosslinked product can be adjusted by controlling the degree of crosslinking. That is, the degree of crosslinking can be changed by changing the amount of a crosslinking agent used for the crosslinking reaction, and the change in the degree of crosslinking leads to a change in the hydrophobicity of the crosslinked product. Therefore, a crosslinked product having a desired hydrophobicity can be obtained by using an appropriate amount of the crosslinking agent. It is even possible to obtain a crosslinked product in the form of a gel which has a poor water-solubility. Further, the crosslinked product can be molded into a film or a sheet.

Examples of bases which can be used as a crosslinking catalyst include potassium hydroxide, sodium hydroxide, cesium hydroxide, potassium carbonate, sodium methoxide, sodium ethoxide, sodium propoxide, sodium t-butoxide, potassium propoxide, potassium t-butoxide and potassium t-2-methyl-2-butoxide.

The crosslinking agent is used in an amount of from 5 to 300% by weight, preferably from 5 to 150% by weight, more preferably from 10 to 120% by weight, still more preferably from 25 to 75% by weight, based on the weight of the copolymer having a side chain to which a hydroxymethyl group (having a primary hydroxyl group) is introduced. When the crosslinked product of the resin of the present invention is produced using the crosslinking agent in an amount within the range mentioned above, the resin of the present invention exhibits especially excellent body fluid compatibility and biocompatibility, that is, the resin of the present invention is especially effective for suppressing the adhesion of biological substances (such as a biological tissue, a protein, a cell and a platelet) to the resin and the activation of platelet by the resin. Further, when such a crosslinked product is in the form of a film, such a film can be advantageously used for preventing the adhesion of a biological tissue, and can also be used for covering external wounds (such as bedsore, burn and ulcer) and for covering wounds caused by destruction of internal tissues (such as a corium, a hypoderm, a muscle, a tendon, an articulation and a bone).

(2) Crosslinking Reaction Performed Simultaneously with Copolymerization Reaction:

As another method for producing a crosslinked product of the resin of the present invention, there can be mentioned the following method. In the production of the body fluid compatible and biocompatible resin of the present invention, for example, when ethylene oxide and ethylene glycol diglycidyl ether or butanediol diglycidyl ether are used as raw material monomers, both of the raw material monomers are introduced into a pressure resistant reaction vessel and, then, subjected to ring opening copolymerization by a conventional method (such as a method described in E. J. Vandenberg, J. Polym. Sci., Polym. Chem. Ed., 23, 915-949 (1985); or E. J. Vandenberg, J. C. Mullis, R. S. Juvet, Jr., T. Miller and R. A. Nieman, J. Polym. Sci., Part A, 27, 3113-3149 (1989)), wherein the ring opening copolymerization is performed in the presence or absence of a reaction solvent (such as toluene, hexane, bis(2-methoxyethyl) ether, ethylene glycol dimethyl ether or ethylene glycol diethyl ether), in the presence of a polymerization initiator, on ice, at room temperature (if necessary, while heating) and under atmospheric pressure or superatmospheric pressure, thereby obtaining a copolymer in the form of a crosslinked product. As examples of polymerization initiators, there can be mentioned Lewis acid (such as tributylaluminum) and a strong base (such as a potassium t-butyl alcohol).

When a crosslinking reaction is performed simultaneously with a copolymerization reaction, the larger the amount of the crosslinking agent used, the higher the degree of crosslinking and the higher the hydrophobicity of a reaction product. It is even possible to obtain a crosslinked product in the form of a gel which has a poor water-solubility. It is preferred that the crosslinking agent is used in an amount of from 0.1 to 100% by weight, more advantageously from 0.1 to 50% by weight, based on the weight of the substituted oxyalkylene polymer. When the crosslinked product exhibits a poor water-insolubility, the crosslinked product may be melted by heating and shaped into a film. Thus obtained film also exhibits excellent body fluid compatibility and biocompatibility, that is, the film is especially effective for suppressing the adhesion of biological substances (such as a biological tissue, a protein, a cell and a platelet) to the resin and the activation of platelet by the resin. Further, the film can be advantageously used for preventing the adhesion of a biological tissue, and can also be used for covering external wounds (such as bedsore, burn and ulcer) and for covering wounds caused by destruction of internal tissues (such as a corium, a hypoderm, a muscle, a tendon, an articulation and a bone). With respect to the use of the resin of the present invention, it is possible to produce a medical equipment using only the resin of the present invention as a raw material. Alternatively, the resin of the present invention can be used as an additive for a resin composition used in the production of a medical equipment, or as a coating material for coating a portion of a medical equipment, which portion is contacted with a body fluid or a biological tissue.

The resin of the present invention may be produced from a polysaccharide. For example, the resin of the present invention may be produced from a natural polysaccharide, such as dextran or pullulan, by the so-called "Smith Degradation" which is a conventional method generally employed in the structural analysis of polysaccharides (with respect to the reaction conditions of the Smith Degradation, see, for example, S. Hase, N. Kikuchi, T. Ikenaka, K. Inoue, J. Biochem., Vol. 98 (1985), p. 863). Specifically, the resin of the present invention may be produced as follows. A polysaccharide is treated with an oxidizing agent (e.g., an excess amount of sodium metaperiodate) under conditions wherein the pH is appropriately adjusted to a weakly acidic value using an acetic acid buffer solution or the like, the temperature is from 4 to 40° C., the reaction time is from 4 hours to 1 week, and light is shielded, to thereby obtain a desired polyaldehyde. Then, the oxidizing agent is deactivated using ethylene glycol or the like, and the obtained polyaldehyde is subjected to reduction with sodium boron hydride, thereby obtaining the resin of the present invention.

The substituted oxyalkylene polymer of formula (1) which is present in the thus obtained resin of the present invention generally satisfies the following requirements:

$x=y$,

$10 \leqq x \leqq 10{,}000$ and

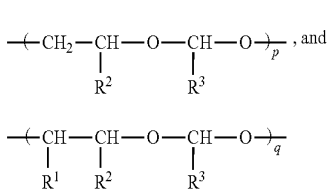
$10 \leqq y \leqq 10{,}000$, and

the amount of the $—CH_2R^4$ group as any of R^1, R^2 and R^3 is from 0.01 to 2.5 mole, per mole of $–(CHR^1—CHR^2—O–)$ unit of the substituted oxyalkylene polymer.

As mentioned above, the polysaccharides which are preferably used for producing the resin of the present invention are natural polysaccharides. Therefore, the produced resin tends to have a non-uniform structure. For example, in O. Larm, B. Lindberg, S. Sevensson, Carbohyd. Res., Vol. 20 (1971), pp. 39-48, it is reported that, with respect to dextran manufactured and sold by Pharmacia, Sweden, (which is a polysaccharide preferably used in the present invention), 5% of the recurring units thereof form not only an ordinary linkage (i.e., 1,6-α-D-glucan linkage), but also a branch linkage at the O-3 position.

With respect to a saccharide residue having such a branch linkage at the O-3 position, a cleavage reaction (i.e., ring opening polymerization) by an oxidizing agent (e.g., sodium metaperiodate) does not proceed. Therefore, a polymer comprised only of recurring units shown in formula (1) above cannot be obtained from a natural polysaccharide. For example, when a substituted oxyalkylene polymer is produced from the above-mentioned dextran (manufactured and sold by Pharmacia, Sweden), the produced polymer has a structure in which an uncleaved saccharide residue is sandwiched between recurring units shown in formula (1) above. In formula (1) above, such an uncleaved saccharide residue is not shown; however, the resin of the present invention may contain such an uncleaved saccharide residue.

When a substituted oxyalkylene polymer is produced from pullulan, due to the structural characteristics of pullulan, the polymer produced by the cleavage reaction using an oxidizing agent (e.g., sodium metaperiodate) is theoretically comprised mainly of recurring units represented by the following formulae (2) and (3);



(2)

(3)

wherein R^1, R^2 and R^3 are as defined for formula (1),

wherein p and q are integers which satisfy the following requirements:

$10 \leqq p \leqq 10{,}000$ and

$10 \leqq q \leqq 10{,}000$,

wherein the molar ratio of recurring unit of formula (2) to recurring unit of formula (3) is 0.5.

When the substituted oxyalkylene polymer represented by formula (1) above is reacted with any of the crosslinking agents exemplified above, the resultant product forms a gel. The thus obtained gel exhibits not only hydrophilicity and water regain, but also biocompatibility, thereby reducing adsorption of a protein, a cell and the like, which adsorption occur when the gel is contacted with a body fluid. Further, the gel is advantageous in that it has low toxicity, and in that the adhesion of a biological tissue to the gel is reduced. Therefore, the gel can be used in the form of a film for preventing the adhesion of a biological tissue or covering a wound. When such a film is used for covering a heat wound, such as a burn, the film exhibits effects of cooling the heat wound due to the hydrophilicity and water regain of the gel. Further, when such a film is used for covering a heat wound, the film absorbs an excess amount of a transudate from the wound so as to provide an appropriate moisture to the wound, thereby promoting the healing of the wound. Furthermore, the film is advantageous in that the patient feels less pain during the peeling off of the film from the wound.

With respect to the thickness of the above-mentioned film, there is no particular limitation. The thickness of the film is generally from 0.1 to 10 mm, preferably from 0.1 to 5 mm, more preferably from 0.2 to 1 mm. The film can be advantageously used as a medical product (e.g., an anti-adhesion membrane for use after an operation, and a wound dressing) and for producing cosmetics.

The resin of the present invention can be used in the form of a drug complex in which a compound having a pharmaceutical activity is bonded to the resin of the present invention through a linker, such as an amino acid or a peptide. Since such a drug complex has only an extremely weak interaction with living organisms, the drug complex enables the delivery of a compound having a pharmaceutical activity to a target tissue (e.g., a tumor cell, an inflamed tissue and a damaged tissue) without being recognized by a biological tissue when administered to a living body.

For example, when the resin of the present invention comprises a polymer which has a carboxyl group introduced thereto, sodium can be introduced to the carboxyl group by an ion exchange resin, to thereby improve the water-solubility of a drug complex which is produced by introducing a drug into the resin of the present invention.

Examples of the above-mentioned compounds having a pharmaceutical activity include compounds having an anti-cancer activity, such as compounds having a hydroxyl group or an amino group, and anti-cancer drug derivatives which have the above-mentioned functional group introduced thereto. Specific examples of compounds having an anti-cancer activity include taxanes and derivatives thereof, such as paclitaxel and docetaxel; anthracycline antibody drugs and derivatives thereof, such as doxorubicine; platinum anti-tumor drugs and derivatives thereof, such as mitomycin C and cisplatin; camptothecine and derivatives thereof; and anti-tumor drugs and derivatives thereof other than mentioned above, such as fluoropyrimidine antimetabolites, vinca alkaloids and folic acid antagonists. Further examples of compounds having a pharmaceutical activity include adrenocortical hormones, such as prednisolone and dexamethasone; vasolidators, such as nifedipine and dipyridamole; and enzyme inhibitors, such as angiotensin converting enzyme inhibitors (e.g., captoril) and HMG-CoA reductase inhibitors (e.g., mevalotin and lovastatin).

Examples of the above-mentioned linkers include amino acids and peptides having 2 to 4 amino acid residues. Specific examples of linkers include amino acids, such as glycine (gly), alanine (Ala), leucine (Leu), isoleucine (Ile) and phenylalanine (Phe); peptides having 2 amino acid residues, such as Phe-Gly, Ala-Gly and Leu-Gly; peptides having 3 amino acid residues, such as Gly-Phe-Gly and Gly-Gly-Gly; and peptides having 4 amino acid residues, such as Gly-Gly-Phe-Gly.

With respect to the above-mentioned compound having a pharmaceutical activity, in view of the ability of the drug complex to migrate into a tumor cell, the introduction ratio thereof is preferably from 0.001 to 30 mol %, more preferably from 0.01 to 30 mol %, still more preferably from 0.01 to 10 mol %, based on the total molar amount of recurring units shown in formula (1) above. Further, it is preferred that the amount of the above-mentioned compound having a pharmaceutical activity is from 0.1 to 50% by weight, more advantageously from 1 to 20% by weight, based on the weight of the polymer having the compound bonded thereto.

The dose and form of the drug complex and the schedule of administration of the drug complex are not particularly limited, and may vary depending on the type of the drug complex used. Further, with respect to the manner of administration of the drug complex, there is no particular limitation; however, it is preferred to employ a non-oral administration. Especially in the case of paclitaxel, it is preferred that the dose of the drug complex is from 20 to 1000 mg/m^2 (mg/body surface area) per adult, in terms of the amount of paclitaxel contained in the drug complex. However, in actuality, the appropriate dose of the drug complex depends on the composition of the drug complex, the manner of administration, the body portion to which the drug complex is delivered, and the type of tumor to

be treated. Further, with respect to the dose of the drug complex, it is required to consider various factors, such as the age, weight, gender, diet and physical condition of the patient, which factors may affect the drug action of the drug complex.

The resin of the present invention which comprises the substituted oxyalkylene polymer represented by formula (1) above may be produced, for example, by subjecting ethylene oxide and/or at least one alkyl or aryl glycidyl ether to a ring opening polymerization, if desired, in a solvent (such as toluene, bis(2-methoxyethyl) ether, ethylene glycol dimethyl ether or hexane) in the presence of a conventional polymerization initiator, such as a catalytic amount of a Lewis acid (e.g., tributyllithium aluminum), a potassium salt of a tertiary alcohol (e.g., a potassium salt of t-butanol) or a mixture thereof, wherein the ring opening polymerization is performed at room temperature or while cooling with ice or heating. Herein, the "catalytic amount" means an amount of from 0.001 to 30 mol %, preferably 0.01 to 20 mol %, based on the total molar amount of all monomers used in the ring opening polymerization (i.e., ethylene oxide and/or at least one alkyl or aryl glycidyl ether).

With respect to a substituted oxyalkylene polymer, it is reported that, when a glycidyl ether (such as an alkyl glycidyl ether and an aryl glycidyl ether) and ethylene oxide are used as raw material monomers, a 3-hydroxyoxetane derivative may be by-produced in a very small amount depending on the type of glycidyl ether used, the type of polymerization initiator used, the type of solvent and the reaction conditions (see, for example, E. J. Vandenberg, J. Polym. Sci., Polym. Chem. Ed., Vol. 23 (1985), pp. 915-949 and E. J. Vandenberg, J. C. Mullis, R. S. Juvet, Jr., T. Miller and R. A. Nieman, J. Polym. Sci., Part A, Vol. 27 (1989), pp. 3113-3149). However, the excellent effects of the resin of the present invention are achieved by the presence of the substituted oxyalkylene polymer, and are not adversely affected by such a 3-hydroxyoxetan derivative which is by-produced in a very small amount.

With respect to the body fluid compatible/biocompatible resin of the present invention, the hydrophilicity or hydrophobicity thereof can be adjusted by appropriately selecting the raw materials (e.g., a glycidyl ether, such as an alkyl glycidyl ether and an aryl glycidyl ether, and ethylene oxide) for producing the resin of the present invention. For example, when the resin of the present invention which is produced from an alkyl or aryl glycidyl ether having a highly lipophilic group (e.g., propyl glycidyl ether, butyl glycidyl ether or phenyl glycidyl ether) is coated on a shaped article of a hydrophobic resin other than the resin of the present invention, it is possible to prevent the resin of the present invention from being delaminated from the shaped article.

Specifically, when the resin of the present invention is produced from an alkyl or aryl glycidyl ether having a highly lipophilic group (e.g., propyl glycidyl ether, butyl glycidyl ether or phenyl glycidyl ether) for improving the compatibility of the resin of the present invention with a polyethylene terephthalate (PET) film, it becomes possible to prevent the resin of the present invention from being delaminated from the PET film over a long period of time, namely, for about 5 hours while vibrating the PET film, and for about 12 hours when the PET film is allowed to stand. Further, as shown in the working examples of the present invention, when the resin of the present invention is produced from an alkylene glycidyl ether having a highly lipophilic group, the produced resin is advantageous in that it has the abilities to suppress the adsorption of a protein and/or a cell thereto, the platelet adhesion and the platelet activation, even when it is coated on a shaped article of a resin other than the resin of the present invention.

Alternatively, when a substituted oxyalkylene polymer is produced from a polysaccharide, the saccharide structure of a large part of polysaccharide molecules are broken to form a large number of primary hydroxyl groups, so that the structural freedom of the produced polymer is increased. As a result, the produced polymer becomes highly hydrophilic. Therefore, when the substituted oxyalkylene polymer produced from a polysaccharide is coated on a shaped article of a hydrophobic resin other than the resin of the present invention, the substituted oxyalkylene polymer is delaminated from the shaped article due to the high hydrophilicity thereof, so that the excellent effects of the present invention cannot be achieved. Specifically, for example, when a substituted oxyalkylene polymer is produced from dextran is coated on a PET film and the coated PET film is vibrated in a physiological saline, the substituted oxyalkylene polymer is delaminated from the PET film (i.e., the hydrophilicity of the coated film surface is impaired) in about 3 hours, so that the abilities of the coated film to suppress the adsorption of a protein and/or a cell thereto, the platelet adhesion and the platelet activation are impaired. For preventing the resin of the present invention (produced from a polysaccharide) from being delaminated from a PET film, it is preferred to introduce a lipophilic group to the resin produced from a polysaccharide, to thereby improve the compatibility of the resin and the surface of the PET film. By introducing a lipophilic group to the resin of the present invention, it becomes possible to prevent the resin from being delaminated from the PET film over a long period of time, namely, for about 5 hours while vibrating the PET film, and for 12 hours or more when the PET film is allowed to stand. Examples of lipophilic groups include a propyl group, a butyl group and a phenyl group.

When the resin of the present invention is produced from a polysaccharide, a lipophilic group can be introduced thereto by alkylation reaction. When the alkylation reaction is performed using an alkyl halide and a basic compound, it is necessary to dissolve a hydrophilic polymer obtained from the polysaccharide and the alkyl halide (which is hydrophobic) simultaneously, so that it is difficult to introduce a long chain alkyl group to the polymer, which long chain alkyl group has a low solubility. However, by reacting a glycidyl ether derivative (e.g., butyl glycidyl ether or phenyl glycidyl ether) with the polymer produced from a polysaccharide, in the presence of a basic compound, it becomes possible to introduce a long chain alkyl group to the polymer produced from a polysaccharide. By the introduction of such a long chain alkyl group, it has, for the first time, become possible to impart a resin produced from a polysaccharide with excellent abilities to prevent the adsorption of a protein and/or a cell thereto, the platelet adhesion and the platelet activation (see the working examples).

When the resin of the present invention comprises the substituted oxyalkylene polymer of formula (1) above which is a copolymer comprising two types of recurring units, namely, a recurring unit in which R^2 is a methyl group, and a recurring unit in which R^2 is a butyl group, there is a tendency that the hydrophilicity of the copolymer increases in accordance with the increase in the molar ratio of methyl groups to all R^2 groups, thereby increasing the solubility of the copolymer in water, whereas the hydrophobicity of the copolymer increases in accordance with the increase in the molar ratio of butyl groups to all R^2 groups, thereby lowering the solubility of the copolymer in water. Specifically, when the molar amount of butyl groups, based on the total molar amount of all R^2 groups, is extremely high, for example, as high as 95 mol % or more, the liposolubility of the copolymer is improved, thereby improving the coatability of the resin of the present