



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup> :</b> <b>B01J 20/26, C08F 5/20</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 99/39823</b> <b>(43) International Publication Date:</b> 12 August 1999 (12.08.99)
<b>(21) International Application Number:</b> PCT/US98/27739 <b>(22) International Filing Date:</b> 30 December 1998 (30.12.98) <b>(30) Priority Data:</b> 09/019,583                      6 February 1998 (06.02.98)                      US <b>(71) Applicant:</b> ADVANCED RENAL TECHNOLOGIES, LLC [US/US]; 320 East 65th Street, New York, NY 10021 (US). <b>(72) Inventors:</b> DAVANKOV, Vadim; Leningradskoe Shosse, 112/1-3-825, Moscow, 125445 (RU). TSYURUPA, Maria; Serafimovicha, 2-320, Moscow, 109072 (RU). PAVLOVA, Ludmila; Zemlyanoi Vat, 2/50-64, Moscow, 103064 (RU). <b>(74) Agent:</b> ZBOROVSKY, Ilya; 6 Schoolhouse Way, Dix Hills, NY 11746 (US).		<b>(81) Designated States:</b> CA, CN, CZ, JP, UA, Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).  <b>Published</b> <i>With international search report.</i> <i>With amended claims and statement.</i>
<b>(54) Title:</b> METHOD OF PRODUCING MATERIAL FOR PURIFICATION OF PHYSIOLOGICAL LIQUIDS OF ORGANISM, AND METHOD OF PRODUCING THE MATERIAL  <b>(57) Abstract</b>  <p>Purification of physiological liquids of organism is performed by passing a physiological liquid with toxicants removed from a patient through a material which has a size, a shape, and a structure selected so as to remove toxic compounds in the molecular range of 300 to 30000 Dalton from the physiological liquid and which is composed of a porous hydrophobic divinylbenzene copolymer which initially has surface exposed vinyl groups in which thereafter the vinyl groups are chemically modified so as to form different surface exposed functional groups with a greater hydrophilicity and greater biocompatibility than those of the vinyl groups.</p>		

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METHOD OF PRODUCING MATERIAL FOR PURIFICATION OF PHYSIOLOGICAL LIQUIDS OF ORGANISM, AND  
METHOD OF PRODUCING THE MATERIAL

### Technical Field

The present invention relates to a method of and material for purification of physiological liquids of organism, and method of producing the material.

### 5      Background Art

10      It is well known that physiological liquids of organisms such as blood, plasma, peritoneal liquid etc., accumulate and transport various toxicants in the case of poisoning the organism as well as in the case of diseases, in particular diseases of liver and kidneys. It is therefore advisable to remove the toxicants from the physiological liquids to significantly improve the situation of the patient. A plurality of methods have been invented and have been utilized for removing toxicants from blood, plasma and other physiological liquids. One of the most efficient methods is hemodialysis. This method, however, is generally restricted to removing small toxic  
15      molecules, whereas toxins belonging to the so-called middle-size molecules (between 500 and 30000 Dalton molecular weight) are eliminated too slowly, even with modern "high flux" dialyser membranes. It is believed to be advisable to further improve the existing methods so as to provide an efficient purification of the physiological liquid of organism, especially with

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respect to above toxicants having larger molecular sizes, for the purpose of preventing propagation of diseases or curing the disease.

According to the present invention, a wider spectrum of toxic compounds should be removable from blood or other physiological fluids, if conventional hemodialysis procedure is supplemented with an adsorption procedure. The latter should be responsible for removing larger toxins which diffusion through the membrane of the dialyser is too slow.

The adsorbing material should both exhibit high adsorption capacity toward toxins in the middle range of molecular weights and display sufficient compatibility with blood or the corresponding physiological fluid. Designing suitable polymeric adsorbing material is one of the aims of present invention.

Macroporous styrene-divinylbenzene copolymers represents the most popular type of polymeric adsorbing materials. Many companies manufacture adsorbents of this category. Amberlite XAD-4 (by Rohm and Haas) being probably the best known one. Equally interesting, though less abandoned, are macroporous adsorbing materials manufactured by copolymerization of divinylbenzene (DVB) with other monomers, i.g., buthyl methacrylate, acrylo nitrile and others.

In order to maintain the porous architecture and nearly constant volume of polymeric particles under various conditions of usage, the three-dimensional network of these polymers has to be sufficiently rigid, i.e., it must contain a high proportion of crosslinking divinylbenzene. The latter product, when in pure state, is rather expensive. The more available technical

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product contains up to 30-40% of ethylvinyl styrene, so that commercially available macroporous adsorbents should be better referred to as copolymers of DVB, ethylvinyl styrene and styrene. Usually, this monomer mixture is provided with organic solvents serving as the diluters which cause a micro phase separation during the polymerization procedure and thus resulting in the macroporous structure of the final material.

It has been shown repeatedly that the radical polymerization procedure does never consume all the vinyl groups of DVB introduced into copolymerization. On the average, about 30% of DVB species fail to serve as crosslinking bridges and remain involved into the network with only one of its two vinyl groups. The presence of a relatively high amount of pending vinyl groups is therefore a characteristic feature of the macroporous adsorbents. It can be expected that these free vinyl groups are preferably exposed to the surface of the polymer beads and their macropores and should be readily available to chemical modification.

The chemical modification of the surface of macroporous DVB-copolymers relies on chemical reactions of the surface-exposed pendant vinyl groups and aims at converting these groups into more hydrophilic functional groups. This conversion provides the initial hydrophobic adsorbing material with the property of hemocompatibility, since the hydrophilic surfaces adsorb less blood cells and plasma proteins and do not activate the clotting cascades as rapidly as does the initial hydrophobic surface.

Some solutions were disclosed in our earlier patent application serial no. 08/756,445.

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Disclosure of the Invention

Accordingly, it is an object of present invention to provide a method of and a material for purification of physiological liquids of organism, and method of producing the material, which are further improvements in the above specified field.

In accordance with the present invention, the method of purification of physiological liquids of organism comprises removing a physiological liquid containing toxicants from a patient; passing the physiological liquid through a porous hydrophobic divinylbenzene copolymer which initially has surface exposed vinyl groups and thereafter the vinyl groups are chemically modified so as to form different surface exposed functional groups with a greater hydrophilicity and a greater biocompatibility than those of the vinyl groups.

In accordance with a further feature of the present invention, the material for purification of physiological liquids of organism is proposed, which is composed of a porous hydrophobic divinylbenzene copolymer which initially has surface exposed vinyl groups in which thereafter the vinyl groups are chemically modified so as to form different surface exposed functional groups with a greater hydrophilicity and greater biocompatibility than those of the vinyl groups.

Finally, a method for producing the material for purification of physiological liquids of organisms is proposed, in accordance with which a porous hydrophobic divinylbenzene polymer initially has surface exposed vinyl groups, and thereafter the vinyl groups are chemically modified so as

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to form different surface exposed functional groups with a greater hydrophilicity and greater biocompatibility than those of the vinyl groups.

When the method of and material for purification of physiological liquids of organism and a method of producing the material are provided in accordance with the applicant's invention, they provides for highly advantageous results.

#### Best Mode of Carrying Out the Invention

In accordance with the present invention, a purification of physiological liquids of organism by removing toxicants is proposed. A patient's blood is withdrawn from an arterial blood circulatory access point, passed through a material in accordance with the present invention which removes toxicants, and re-enters the patient through a venous access point. Preferably, the material has a size, a shape, and a structure selected so as to remove the toxic compounds in the molecular range of 300 to 30,000 Dalton from the physiological liquid.

The material in accordance with the present invention which is used in the inventive method for purification of physiological liquids of organism and which is produced in accordance with the inventive production method, is a porous hydrophobic divinylbenzene copolymer which initially has surface exposed vinyl groups in which thereafter the vinyl groups are chemically modified so as to form different surface exposed functional groups with a greater hydrophilicity and greater biocompatibility than those of the vinyl groups.

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According to the present potential invention, the modification of the surface vinyl groups was made in aqueous or aqueous organic media in the following three principal directions:

- grafting hydrophilic polymer chains by a radial polymerization of 2-hydroxyethyl methacrylate, N-vinylpyrrolidone, N-vinylcaprolactame, or other water soluble monomers,
- oxidation of the vinyl groups to epoxy groups with the subsequent reaction of the epoxy groups with water, ethylene glycol, amines or 2-amonoethanol molecules, and
- depositing high-molecular-weight hemocompatible polymer, in particular poly(trifluoroethoxy) phosphazene onto the surface of the polymeric beads.

In any case the hydrophilic nature of thus modified surfaces could be visualized by the easy wetting of dried modification material with water, whereas the initial dry unmodified adsorbent cannot be wetted by an immediate contact with water.

In the following examples, a mesoporous divinylbenzene-ethylstyrene-styrene copolymer, a typical polystyrene-type adsorbing material and a copolymer of DVB with buthyl methacrylate with surface exposed double bonds were taken for the modification.

The surface-modified materials were shown to exhibit good hemocompatibility, i.e., they did not change noticeably the coagulation time of blood, caused no hemolysis and showed no cytotoxicity effects. When contacted with plasma or whole blood, the materials effectively removed the

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pool of middle-sized molecules, as could be easily followed by conventional spectrophotometric measurements.

#### Preparation of mesoporous divinylbenzene copolymers

##### Example 1

5                   A solution of 130 g p-ethylstyrene, 132 g divinylbenzene (a mixture of para and metha-isomers of about 1:1) and 2.62 g benzoyl peroxide in a mixture of 150 ml toluene and 100 ml iso-amyl alcohol was suspended in 4 liters of pure water containing 1% cellulose stabilizer. After 39 min stirring at room temperature, the mixture was heated at 40°C for 1  
10                   hours, 60°C for 2 hours, 80°C for 5 hours and 90°C for 2 hours. After cooling the mixture to room temperature, the beads of the material obtained were filtered and washed with hot water, methanol and water. The polymer was dried in an oven at 80°C within one day.

##### Example 2

15                   A solution of 75 g buthyl acrylate, 51 g divinylbenzene (a mixture of para and metha-isomers of about 1:1) and 1 g benzoyl in 250 ml of toluene was suspended in 2.4 liters of pure water containing 15 g of cellulose stabilizer at room temperature. After 30 min stirring, the mixture was heated stepwise at 60, 80 and 95°C within 3 hours for each temperature.  
20                   After cooling to room temperature, the beads obtained were filtered, washed with hot water, methanol and water. The beads were dried in oven for 7 hours at 80°C.

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Grafting hydrophilic polymeric chains to the surface exposed vinyl groups

### Example 3

The polymer prepared in Example 1 was washed with ethanol and then rinsed with water, which results in a material fully wetted by water with all its pores filled with water. The material contains 40% polymer and 60% water. To 1 g of the polymer thus wetted with water, 1 ml of 3% aqueous solution of 2-hydroxyethyl methacrylate (HEMA) and 0.1 ml of 10% aqueous ammonium persulfate were added, and, under constant stirring of the mixture with a magnetic stirrer, provided with an aqueous solution of sodium sulfite (2 moles per mole of persulfate). The mixture was slowly mixed at a temperature of 40°C for 2 hours or at a temperature of 10°C for 10 h. The polymer was filtered, washed with water and dried at a temperature below 80°C.

### Example 4

To 1 g of dry polymer prepared in Example 1, 3, 5 ml of ethanol and then 1.6 ml of 6% aqueous solution of HEMA, 0.3 ml of 10% aqueous solution of ammonium persulfate, and finally 0.3 ml of 1 M aqueous solution of sodium sulfite (or 0.3 ml of 0.5 M solution of ascorbinic acid) were added. The mixture was stirred for 10 h at a temperature of 10°C. The polymer was filtered, washed with water and dried at 70°C.

The copolymer of divinylbenzene with buthyl methacrylate prepared in Example 2 was grafted with HEMA in exactly the same manner.

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## Example 5

To 1 g of the wetted with water polymer prepared in Example 1, 1.0 ml of 6% aqueous solution of N-vinylpyrrolidone, and 0.2 ml of 10% aqueous solution of ammonium persulfate were added, and the mixture was stirred for 2 h at a temperature of 40°C. The polymer was filtered, washed with water and dried.

## Example 6

To 1 g of the polymer wetted with water and prepared in Example 1 2.0 ml of 3% N-vinylpyrrolidone, 0.3 ml of aqueous 10% solution of sodium persulfate and 0.3 ml of sodium sulfite solution were added and the mixture was stirred at 25°C for 2 h. The polymer was filtered and treated as above.

Polymer analogous reactions on the surface exposed double bonds

## Example 7

To 1 g of the polymer wetted with water and prepared in Example 2, 2.0 ml of 3% N-acrylamide, 0.3 ml of aqueous 10% solution of sodium persulfate and 0.3 ml of 1 M aqueous solution of sodium sulfite were added and the mixture was stirred at 25°C for 2 h. The polymer was filtered and treated as above.

## Example 8

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To 6 g of dry polymer prepared in Example 1, 25 ml of acetic anhydride were added, the mixture was cooled to 0°C, slowly provided with 2 ml of aqueous 40% solution of hydrogen peroxide, and stirred at 10-15°C for 8 h. The polymer was filtered, washed with glacial acetic acid to result in epoxy groups containing material.

2 g of the above epoxy modified polymer, swollen with glacial acetic acid, were provided with 10-15 ml water and 2 drops of concentrated sulfuric acid and heated under stirring 50-70°C for 3-5 h, thus converting epoxy groups into diol groups. The polymer was filtered, carefully washed with water and dried.

#### Example 9

To 2 g of the epoxy modified (according to Example 7) polymer, swollen with glacial acetic acid, 1 ml of ethylene glycol in 5 ml glacial acetic acid (or 5 ml dry ethyl acetate) were added, provided with 2 drops of concentrated sulfuric acid and heated under stirring for 5-8 h at 50-70°C. This procedure results in the addition of ethylene glycol to the epoxy functional group. The polymer is filtered, washed with water, ethanol and again with water, and dried.

#### Example 10

2 g of the epoxy modified (according to Example 7) polymer, swollen with glacial acetic acid) were carefully washed with dry ethyl acetate and provided with 1 ml of 2-hydroxyethyl amine in 4 ml ethyl acetate. The mixture was stirred at 40°C for 5h, which results in the addition of the

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hydroxyethylamino group to the epoxy group. The polymer was filtered, washed with water, 1 N HCl and again water to neutral pH.

In a separate experiment, diethylamine was taken, instead of 2-hydroxyethyl amine. The product was washed with water 1N HCl and water as described above.

Depositing poly(trifluoroethoxy) phosphazene onto the surface of the polymer (molecular weight  $20 \cdot 10^6$  Dalton)

#### Example 11

The product obtained in Example 9 was dried in vacuum. A solution of 0.3 mg poly(trifluoroethoxy) phosphazene (molecular weight  $20 \cdot 10^6$ ) in 10 ml ethyl acetate were added quickly to 3 g of the dried polymer and agitated until the whole of the solvent was totally absorbed by beads of the polymer. The material was then dried under reduced pressure and washed with ethanol.

#### Example 12

3 g of dry unmodified polymer prepared in Example 2 were quickly provided with a solution of 1 mg poly(trifluoroethoxy) phosphazene in 10 ml ethyl acetate and then dried from the solvent as described in Example 10.

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It will be understood that each of the elements described above, or two or more together, may also find a useful application in other types of methods and products differing from the types described above.

5 While the invention has been illustrated and described as embodied in method of and material for purification of physiological liquids of organism, and method of producing the material it is not intended to be limited to the details shown, since various modifications and structural changes may be made without departing in any way from the spirit of the present invention.

10 Without further analysis, the foregoing will so fully reveal the gist of the present invention that others can, by applying current knowledge, readily adapt it for various applications without omitting features that, from the standpoint of prior art, fairly constitute essential characteristics of the generic or specific aspects of this invention.

15 What is claimed as new and desired to be protected by Letters Patent is set forth in the appended claims.

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Claims

1                   1. A method of purification of physiological liquids of organism,  
2                   comprising the steps of removing a physiological liquid with toxicant from a  
3                   patient; passing the physiological liquid with the toxicants through a material  
4                   which has a size, a shape, and a structure selected so as to remove toxic  
5                   compounds in the molecular range of 300 to 30000 Dalton from the  
6                   physiological liquid and which is composed of a porous hydrophobic  
7                   divinylbenzene copolymer which initially has surface exposed vinyl groups  
8                   in which thereafter the vinyl groups are chemically modified so as to form  
9                   different surface exposed functional groups with a greater hydrophilicity and  
10                  greater biocompatibility than those of the vinyl groups; and returning the  
11                  liquid to the patient.

1                   2. A material for purification of physiological liquids of  
2                   organism, comprising the step of passing a physiological liquid through said  
3                   material, which has a size, a shape, and a structure selected so as to remove  
4                   toxic compounds in the molecular range of 300 to 30000 Dalton from the  
5                   physiological liquid and which is composed of a porous hydrophobic  
6                   divinylbenzene copolymer which initially has surface exposed vinyl groups  
7                   in which thereafter the vinyl groups are chemically modified so as to form  
8                   different surface exposed functional groups with a greater hydrophilicity and  
9                   greater biocompatibility than those of the vinyl groups.

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1                   3. A material as defined in claim 1, wherein said porous  
2 hydrophobic divinylbenzene copolymer comprises a copolymer of  
3 divinylbenzene with comonomers selected from the group which includes  
4 styrene, ethylstyrene, acrylo nitrile, buthyl methacrylate.

1                   4. A material as defined in claim 1, wherein said surface  
2 exposed functional groups with a greater hydrophilicity and greater  
3 biocompatibility than those of vinyl groups are grafted hydrophilic polymeric  
4 chains selected from a group which includes polymers of 2-hydroxyethyl  
5 methacrylate, N-vinylpyrrolidone, N-vinylcaprolactame, N-acrylamide.

1                   5. A material as defined in claim 1, wherein said surface  
2 exposed functional groups with a greater hydrophilicity and greater  
3 biocompatibility than those of vinyl groups are products of oxidation of said  
4 vinyl groups to epoxy groups and subsequent addition of polar compounds  
5 selected from a group which includes water, ethylene glycole, small primary  
6 or secondary amines, 2-hydroxyethyl-amine.

1                   6. A material as defined in claim 4, wherein said surface  
2 exposed functional groups with a greater hydrophilicity and greater  
3 biocompatibility than those of vinyl groups are products of oxidation of said  
4 vinyl groups to epoxy groups and subsequent addition of small primary or

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1 secondary amines or 2-hydroxyethyl-amine and depositing high-molecular-  
2 weight poly(trifluoroethoxy) phosphazene.

1 7. A method of producing a material for purification of  
2 physiological liquids of organism comprising providing a porous hydrophobic  
3 divinylbenzene copolymer which has a size, a shape, and a structure  
4 selected so as to remove toxic compounds in the molecular range of 300 to  
5 30,000 Dalton from a physiological liquid and which initially has surface  
6 exposed vinyl groups; and thereafter chemically modifying the vinyl groups  
7 so as to form different surface exposed functional groups with a greater  
8 hydrophilicity and greater biocompatibility than those of the vinyl groups.

1 8. A method of producing the material as defined in claim 1,  
2 wherein said chemical modification of vinyl groups resulting in the formation  
3 of different surface exposed functional groups with a greater hydrophilicity  
4 and greater biocompatibility than those of vinyl groups, without affecting  
5 noticeably the porous structure and hydrophobic interior of the initial  
6 divinylbenzene copolymer, includes graft polymerization in an aqueous or  
7 aqueous organic media of water soluble monomers selected from a group  
8 comprising 2-hydroxyethyl methacrylate, N-vinylpyrrolidone, N-  
9 vinylcaprolactame, N-acrylamide.

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1                   9. A method of producing the material as defined in claim 1,  
2 wherein said chemical modification of vinyl groups resulting in the formation  
3 of different surface exposed functional groups with a greater hydrophilicity  
4 and greater biocompatibility than those of vinyl groups, without affecting  
5 noticeably the porous structure of the initial divinylbenzene copolymer,  
6 includes oxidation of said vinyl groups to epoxy groups followed by addition  
7 to the epoxy group of polar compounds selected from the group which  
8 includes water, ethylene glycole, small primary or secondary amines, 2-  
9 hydroxyethyl-amine.

1                   10. A method as defined in claim 7, wherein said oxidation of  
2 said vinyl groups to epoxy groups is followed by addition to the epoxy groups  
3 of small primary or secondary amines or 2-hydroxyethyl-amine and then  
4 depositing high-molecular-weight poly(trifluoroethoxy) phosphazene from its  
5 solution in an organic solvent via complexing the above polyphosphazene  
6 with the surface exposed amino groups.

**AMENDED CLAIMS**

[received by the International Bureau on 11 July 1999 (11.07.99);  
original claims 1 and 2 amended; remaining claims unchanged (2 pages)]

1. (amended) A method of purification of physiological liquids of organism, comprising the steps of removing a physiological liquid with toxicant from a patient; passing the physiological liquid with the toxicants through a material which has a size, a shape, and a structure selected so as to remove toxic compounds in the molecular range of 300 to 30000 Dalton from the physiological liquid and which is composed of a porous hydrophobic divinylbenzene copolymer which initially has surface exposed vinyl groups in which copolymer thereafter the vinyl groups are chemically modified so as to form different surface exposed functional groups with a greater hydrophilicity and greater biocompatibility than those of the vinyl groups; and returning the liquid to the patient.

2. (amended) A material for purification of physiological liquids of organism, comprising the step of passing a physiological liquid through said material, which has a size, a shape, and a structure selected so as to remove toxic compounds in the molecular range of 300 to 3000 Dalton from the physiological liquid and which is composed of a porous hydrophobic divinylbenzene copolymer which initially has surface exposed vinyl groups in which copolymer thereafter the vinyl groups are chemically modified so as to

form different surface exposed functional groups with a greater hydrophilicity and greater biocompatibility than those of the vinyl groups.

**STATEMENT UNDER RULE 19**

In the International Search Report the Examiner cited U.S. patent to Reed no. 4,427,793, U.S. patent to Maroldo 5,037,857 and U.S. patent to Schneider 5,079,274 as documents of particular relevance.

In accordance with the present invention, the material which is used for purification of physiological liquids and is produced by the inventive method is a porous hydrophobic divinylbenzene copolymer which initially has surface exposed vinyl group, in which copolymer the vinyl groups are chemically modified to form different surface exposed functional groups with a greater hydrophilicity and greater biocompatibility than the original vinyl groups.

In the patent to Reed, linear addition polymer beads have repeating units of vinyl benzyl alcohol and at least one other structure, wherein the cross-linked beads are functionalized to provide ion exchange properties. Also, the macronet adsorbant is proposed in which the cross-linked beads are post-crosslinked and treated in the presence of a Freidel-Crafts catalysts. In the material in accordance with the present invention, exclusively the surface of the porous polymers is modified to form different surface exposed functional groups with a greater hydrophilicity and biocompatibility than the original vinyl groups. These features are not disclosed in the patent to Reed.

The patent to Maroldo describes preparation of a high-surface area fiber by an extensive cross-linking of the polystyrene matrix, by subjecting to chloromethylation procedure. In this reference also there is no disclosure for modification in which the initial surface exposed vinyl groups are modified to form different surface exposed functional groups with a greater hydrophilicity and biocompatibility.

Finally, the patent to Schneider discloses preparation of adsorptive porous resins beads in which cross-linked microporous beads of copolymer are haloalkylated, purified, and swollen and post-crosslinked by reaction in an inert organic liquid in the presence of a Fedel-Craft catalysts. This reference also does not teach the above mentioned new features of present invention.

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US98/27739

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(6) : B01J 20/26; C08F 5/20  
US CL : 502/402, 400; 521/30, 32

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 502/402, 400; 521/30, 32

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched  
NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
APS

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4,427,793 A (REED et al.) 24 January 1984, columns 2-6.	1-10
X	US 5,037,857 A (MAROLDO et al.) 06 August 1991, columns 3-5.	1-10
X	US 5,079,274 A (SCHNEIDER et al.) 07 January 1992, columns 4-8.	1-10

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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