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A1

WO 01/08604

(54) Title: **HYDROPHILIC BIOMEDICAL COMPOSITIONS**

(57) Abstract: A hydrophilic ethylenically unsaturated macromonomer is disclosed that is prepared by the addition polymerisation of addition polymerisable monomers that include monomers that have hydroxyl or amino functional groups, some of which may be subsequently reacted to provide (meth)acryl ethylenic unsaturation. The macromonomers may be used to form intraocular lenses *in situ* by polymerisation of the macromonomers.

HYDROPHILIC BIOMEDICAL COMPOSITIONS

Technical Field of the Invention

This invention relates to hydrophilic ethylenically unsaturated macromonomers that are suitable for use in biomedical applications.

5 Background of the Invention

The use of polymeric prostheses and biomedical mouldings has grown rapidly in recent times. Such mouldings may be used for contact lenses or for specific ophthalmic purposes. For example, they may be used for intraocular lenses and eye bandages. They may also be used for surgical mouldings such as heart 10 valves and artificial arteries. Other applications include wound dressings, biomedical adhesives and tissue scaffolds. Use in drug delivery is a further application.

Disease of the lens material of the eye is often in the form of cataracts. The ideal cataract procedure is considered to be one where the lens capsule bag is 15 maintained with the cataractous lens material removed through a small opening in the capsule. The residual lens epithelial cells are removed chemically and/or with ultrasound or lasers. A biocompatible material with appropriate optical clarity, refractive index and mechanical properties is inserted into the capsular bag to restore the qualities of the crystalline lens.

20 There have been recent advances in methods of inserting intraocular lens. For example, US Patent number 5,772,667 assigned to Pharmacia Lovision Inc, discloses a novel intraocular lens injector. This device compresses an intraocular lens by rolling the lens into a tight spiral. The device injects the compressed lens through a relatively small incision in the eye, approximately 2- 3 millimetres in 25 length, resulting from a phacoemulsification procedure. The intraocular lens is inserted into a receiving channel of the injector in an uncompressed state and is urged into a cylindrical passageway. As the intraocular lens advances into the cylindrical passageway, the lens will roll upon itself into a tightly rolled spiral within the confines of the cylindrical passageway. An insertion rod is inserted into 30 an open end of the cylindrical passageway and advances the compressed lens down

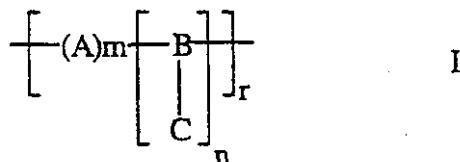
the passageway. As the lens exits the passageway and enters the eye, the lens will expand back to its uncompressed state.

To avoid the need for such injection devices, it has been proposed that intraocular lenses be formed *in situ* after being injected as a liquid flowable form 5 into the lens capsule bag. However, while this concept is attractive in that smaller incisions would be required, it raises further difficulties in that further polymeric reactions are required to take place and these are required to be not harmful to the patient. It is also a requirement that the reaction can take place over a relatively 10 short time under mild reaction conditions. A further requirement is that the reaction is not appreciably inhibited by oxygen. A still further requirement is that no byproducts or residues are produced that are leachable and which may have an adverse biological effect on the patient. It is desirable that the refractive index of the polymer composition for ophthalmic applications is close to 1.41 being the refractive index of the natural biological lens material.

15 Patent Application PCT/EP96/00246 in the name of AG Ciba-Geigy discloses water soluble cross-linkable polymers which may be crosslinked in solution to form moulded compositions. These compositions have particular application in contact lenses. The polymers are derivatives of polyvinyl alcohols. A portion of the hydroxyl groups are preferably reacted with 2-vinyl-4,4- 20 dimethylazlactone to produce ethylenically unsaturated macromonomers.

Summary of the invention

This invention provides in one form a hydrophilic ethylenically unsaturated macromonomer comprising units of structure:



25

where:

$m =$ an integer ≥ 1

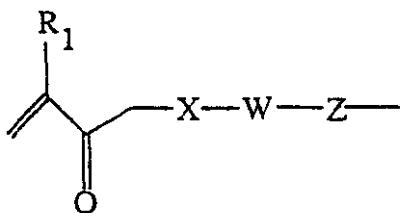
$n =$ an integer ≥ 1

$r =$ an integer ≥ 1

A is a non-reacted moiety resulting from the addition polymerisation of ethylenically unsaturated monomers.

B is a moiety resulting from the additional polymerisation of ethylenically unsaturated groups that possess hydroxyl or amino groups. Examples of suitable 5 monomers are hydroxybutylacrylate and N hydroxy ethylacrylamide

C has the following structure:



where:

10 R₁ = H, Me
 X = O, NH
 Z = O, NH, NR, S, CO₂ where R is C₁-C₈ alkyl
 W = linear, branched cyclic hydrocarbyl chains, polyether chains or heterochains, linear or cyclic.

15 It may include a mixture of moieties resulting from the use of a number of different ethylenically unsaturated monomers. The moieties are "non-reacted". By "non-reacted" we mean that under the reaction conditions that will allow appropriate side groups to be introduced into the copolymer backbone these "non-reacted" side groups will not form covalent bonds with other groups. Thus by this 20 definition certain chemical groups may be included as being "non-reacted". The A moiety may be "non-reacted" in that under the reaction conditions side groups will not form covalent bonds. However, the A moiety may also be "non-reacted" because of the stoichiometry of the side groups. Thus it is possible for the A and B moieties to be the same and the A moiety remains unreacted because the number of 25 equivalents of side groups is less than the equivalents of A and B. For example, A may include hydroxybutylacrylate and B may also be hydroxybutylacrylate.

The balance of the addition copolymer backbone, namely that part of the composition consisting of A and B moieties may be a random or block copolymer.

Examples of W are polyethylene glycol, polyethylene, cyclic and heterocyclic species such as phenyl rings or piperidine or mixtures of hydrophilic or hydrophobic polymers prepared by processes that allow control over end groups such as chain transfer chemistries and substituted variants thereof.

5 C may contain optional groups that are not ethylenically unsaturated polymerisable groups.

Preferably C is formed by suitable reaction of 2-vinyl-4,4-dimethylazlactone, acryloyl or methacryloyl chloride or related compounds with the complimentary hydroxyl or amino groups on the copolymer backbone. Other methods include 10 suitable reaction of isocyanatoethylmethacrylate, methacrylate anhydride, acrylate anhydride, active esters of acrylates or methacrylates. These can be prepared prior to reaction with the polymer or can be prepared *in situ* and attached to the copolymer by conventional coupling chemistries, for example the coupling of acrylic acid to alcohol groups on the backbone copolymer using carbodiimide 15 chemistry.

The macromonomer is hydrophilic. By hydrophilic we mean the macromonomer may be diluted 10% w/w with water without affecting the visual clarity of the macromonomer when viewed through a 100 ml measuring cylinder.

In an alternative form this invention provides a method of treating 20 presbyopia by removing a patient's lens from the lens capsule bag via an incision in the cornea, injecting into the lens capsule bag a macromonomer of Formula I and wherein the molecular weight of the macromonomer is in the range 10,000 – 300,000, and wherein the ethylenically unsaturated groups are provided by (meth)acrylamides, (meth)acrylate and styrenic moieties, and polymerising the 25 macromonomer to a polymer having an E modulus in the range 0.01 – 100 kPa, preferably 0.1 – 10 kPa, and more preferably 0.5 – 5kPa.

In a further alternative form this invention provides ethylenically unsaturated 30 macromonomers comprising units of Formula I wherein the macromonomer or macromonomer solution has a viscosity at 25°C in the range 1,000 – 20,000 cSt, and more preferably 1,000 – 10,000 cSt and after polymerisation to form

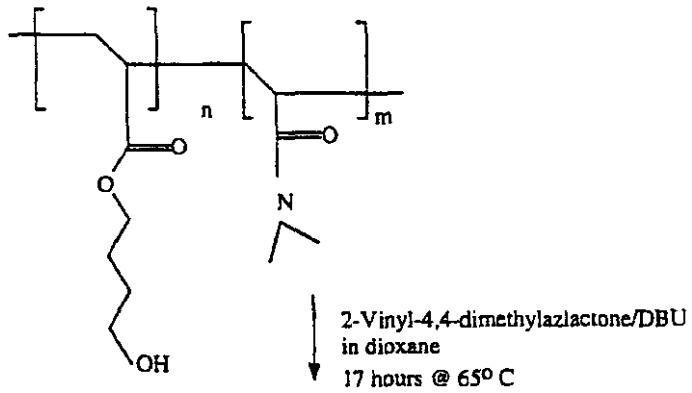
biocompatible polymers having an E modulus in the range 0.01 – 100 kPa, preferably 0.1 – 10kPa and more preferably 0.5 – 5kPa.

In a still further embodiment this invention provides a method of preparing intraocular lenses *in situ* by injecting a flowable macromonomer composition of Formula 5 I where the macromonomer composition has a viscosity at 25°C in the range 1,000 – 20,000 cSt, more preferably 1,000 – 10,000 cSt and after polymerisation having to form a polymer having an E modulus in the range preferably 0.1 – 10 kPa and more preferably 0.5 – 5kPa.

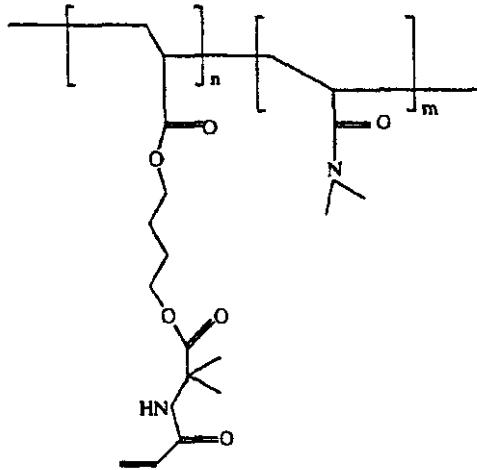
Preferably in the macromonomer the mole percentage of hydroxyl monomer 10 is in the range 0.5 – 5% and more preferably 1.0 – 3.0%.

Detailed description of the invention

The preferred scheme of reaction is set out below:



15



Acrylamide derivatives are preferred polymerisable groups as these tend to lead to less oxygen inhibition of the composition during crosslinking. This is particularly important for *in situ* crosslinking as is required when the preferred compositions are used as injectable intraocular compositions.

5 Crosslinked gels with different mechanical properties can be produced by irradiation of the macromonomer, depending on the degree of acrylamide functionalised and water content of the macromonomer formulation. The water content is preferably 10 – 70% w/w and more preferably 20 – 60%. The elasticity of the cured macromonomer is, as measured by the E modulus, in the range 0.01 –
10 100 kPa, preferably 0.1 – 10kPa and more preferably 0.5 – 5kPa. The E modulus is conveniently measured by equipment such as the Bohlin controlled stress rheometer.

This crosslinking has the advantage of being rapid and relatively insensitive to inhibition by oxygen.

15 The crosslinking process is therefore preferably carried out in such a way that the essentially aqueous solution of the water-soluble polymer comprising crosslinking groups is free or essentially free from undesired constituents, in particular from monomeric, oligomeric or polymeric starting compounds used for the preparation of the water-soluble, cross-linkable polymer, or from by-products 20 formed during the preparation of the water-soluble, cross-linkable polymer, and/or that the solution is used without addition of a comonomer.

In the case of photo cross-linking, it is expedient to add an initiator which is capable of initiating free-radical crosslinking and is readily soluble in water. Examples thereof are known to the person skilled in the art; suitable photoinitiators 25 which may be mentioned specifically are benzoin, such as benzoin, benzoin ethers, such as benzoin methyl ether, benzoin ethyl ether, benzoin isopropyl ether and benzoin phenyl ether, and benzoin acetate; acetophenones, such as acetophenone, 2,2-dimethoxyacetophenone and 1,1-dichloroacetophenone; camphorquinone; benzil, benzil ketals, such as benzil dimethyl ketal and benzil diethyl ketal, 30 anthraquinones, such as 2-methylanthraquinone, 2-ethylanthraquinone, 2-tert-butylanthraquinone, 1-chloroanthraquinone and 2-amylanthraquinone; furthermore

triphenylphosphine, benzoylphosphine oxides, for example 2,4,6-trimethylbenzoyl-diphenylphosphine oxide, benzophenones, such as benzophenone and 4,4'-bis(N,N-dimethylamino)benzophenone; thioxanthones and xanthones; acridine derivatives; phenazine derivatives; quinoxaline derivatives and 1-phenyl-1,2-propanedione 2-O-benzoyl oxime; 1-aminophenyl ketones and 1-hydroxyphenyl ketones, such as 1-hydroxycyclohexylphenyl ketone, phenyl 1-hydroxyisopropyl ketone, 4-isopropylphenyl 1-hydroxyisopropyl 1-hydroxyisopropyl ketone, 2-hydroxy-1-[4-2(-hydroxyethoxy)phenyl]-2-methylpropan-1-one, 1-phenyl-2-hydroxy-2-methylpropan-1-one, and 2,2-dimethoxy-1,2-diphenylethanone, all of which are known compounds.

Particularly suitable photoinitiators, which are usually used with UV lamps as light sources, are acetophenones, such as 2,2-dialkoxybenzophenones and hydroxyphenyl ketones, in particular the initiators known under the trade names IRGACURE®2959 and DAROCURE®1173.

Another class of photoinitiators usually employed when argon ion lasers are used are benzil ketals, for example benzil dimethyl ketal.

The photoinitiators are added in effective amounts, expediently in amounts of from about 0.3 to about 2.0% by weight, in particular from 0.3 to 0.5% by weight, based on the total amount of the water-soluble, cross-linkable polymer.

The water-soluble, cross-linkable polymers which are suitable in accordance with the invention can be crosslinked by irradiation with ionising or actinic radiation, for example electron beams, X-rays, UV or VIS light, ie electromagnetic radiation or particle radiation having a wavelength in the range from about 280 to 650 nm. Also suitable are UV lamps, He/Dc, argon ion or nitrogen or metal vapour or NdYAG laser beams with multiplied frequency. It is known to the person skilled in the art that each selected light source requires selection and, if necessary, sensitisation of the suitable photoinitiator. It has been recognised that in most cases the depth of penetration of the radiation into the water-soluble, cross-linkable polymer and the rate of curing are in direct correlation with the absorption coefficient and concentration of the photoinitiator.

If desired, the crosslinking can also be initiated thermally with an appropriate thermal free radical initiator, or by redox processes well known in the art. It should be emphasised that the crosslinking can take place in a very short time in accordance with the invention, for example, in less than five minutes, preferably in 5 less than one minute, in particular in up to 30 seconds, particularly preferably as described in the examples.

In general hydrophilic copolymers are preferably prepared by standard free radical polymerisation of dimethyl acrylamide with the active hydrogen comonomer, hydroxy butyl acrylate or N-hydroxy ethyl acrylamide, in dioxane to 10 afford white powdery polymers. The feed ratio of monomers is varied to afford a range of copolymers with differing uptake of the hydroxyl monomer into the copolymer.

The copolymers can then be activated by the 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) catalysed condensation in dioxane of 2-Vinyl-4,4-dimethylazlactone 15 with the pendant hydroxy functions of the macromolecules. The resultant acrylamide active macromer is isolated by precipitation, and dried *in vacuo* at 40°C for 4 hours. The acrylamide functionalised polymer was then dissolved in an excess of water (ca. 50 wt%) 0.3 wt% of the photoinitiator Irgacure 2959 was added, and then the aqueous solution was evaporated down to the appropriate water content,

20 The invention will be further described by reference to preferred embodiments set out in the following examples.

Example 1

This Example illustrates the preparation and testing of a composition according to the present invention.

25 A hydrophilic poly(HBA-*co*-DMA) copolymer was synthesised by dissolving 2.0013g 4-hydroxybutyl acrylate monomer (Aldrich Cat. No. 27,557-3) and 6.0755g N,N-dimethylacrylamide monomer (Aldrich Cat. No. 27,413-5) in 120 ml 1,4-dioxane in a 250ml round bottom flask equipped with a stirrer bar. 0.123g (1 mole per cent) of azobisisobutyronitrile (AIBN) initiator was added, and the 30 monomer solution was freeze-thaw degassed four times. After reaction at 70°C for

16 hours, the copolymer was isolated by precipitation into hexane, and was dried *in vacuo* at 40°C for 4 hours to yield 6.25g of a white, powdery polymer.

1.88g of the polymer was dissolved in 20 ml 1,4 dioxane in a 50ml round bottom flask equipped with a stirrer bar and nitrogen purge. 70 milligrams of 1,8-
5 diazabicyclo[5.4.0]-undec-7-ene (DBU) (Aldrich Cat. No. 13,900-9) was added, followed by 0.4801g 2-vinyl-4,4-dimethylazlactone. The reaction mixture was heated at 70°C for 17 hours and the polymer was isolated by pouring the reaction mixture into excess hexane. The polymer was then dried *in vacuo* at 40°C for 4 hours. The acrylamide functionalised polymer was then dissolved in water to give a
10 30 wt% solution, and 0.3 wt% of the photoinitiator Irgacure 2959 was added. The polymer solution was placed into polypropylene moulds (designed to give a flat polymeric disc of 20.7mm diameter and 1.0mm depth) and polymerised for ten minutes under irradiation from a 365nm UV lamp. After polymerisation was complete, a transparent, rubbery polymer disc was removed from the moulds. The
15 shear modulus of the polymer was measured with a Bohlin controlled stress rheometer (CS-10) and the results are set out in Table 1.

Table 1

DMA/Active Hydrogen Copolymers					
	Mole % Functionalised	Wt% Solids	Viscosity (cSt)	Refractive Index	Polymer Shear Modulus (kPa)
HBA ¹	1	75.9	125,000	1.4389	0.54
	2	41.0	850	1.3901	47
	3	50.1	14,600	1.4026	90.4
NHEA ²	1.6	65.3	117,000	1.4161	36
	1.6	49.0	16,000	1.4014	14.5

¹ Hydroxyl butyl acrylate

20 ² N-hydroxy ethyl acrylamide

Examples 2 and 3

These Examples illustrate the preparation and testing of two further compositions according to the present invention.

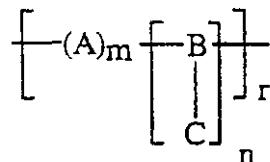
5 Example 1 was repeated except that the solids content was reduced to 25% (Example 2) and 20% (Example 3) to produce the results set out in Table 2.

Table 2

Example	Mole % acrylamide functionalised	Formulation solids content (wt%)	Shear modulus (kPa)
2	5	25	16.0
3	5	20	2.1

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1.



5 where:

$m =$ an integer ≥ 1

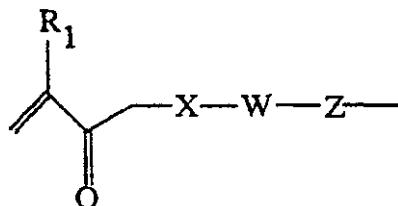
$n =$ an integer ≥ 1

$r =$ an integer ≥ 1

10 A is a non-reacted moiety resulting from the addition polymerisation of ethylenically unsaturated monomers.

B is a moiety resulting from the additional polymerisation of ethylenically unsaturated groups that possess hydroxyl or amino groups

D has the following structure:



15

where:

$\text{R}_1 = \text{H, Me}$

$\text{X} = \text{O, NH}$

$\text{Z} = \text{O, NH, NR, S, CO}_2$ where R is $\text{C}_1\text{-C}_8$ alkyl

20 $\text{W} =$ linear, branched cyclic hydrocarbyl chains, polyether chains or heterochains, linear or cyclic.

2. An ethylenically unsaturated hydrophilic macromonomer comprising units of Formula I as defined in claim 1 wherein the macromonomer or macromonomer solution has a viscosity at 25°C in the range 1,000 – 20,000 cSt and after

polymerisation forms a biocompatible polymer having an E modulus in the range 0.01 – 100 kPa.

3. An ethylenically unsaturated hydrophilic macromonomer as defined in claim 5 wherein the viscosity is in the range 1,000 – 10,000 cSt.

4. An ethylenically unsaturated hydrophilic macromonomer as defined in claim 2 or claim 3 wherein the biocompatible polymer has an E modulus in the range 0.1 – 10 kPa.

10

5. An ethylenically unsaturated hydrophilic macromonomer as defined in any one of claims 2 – 4 wherein the polymer formed after polymerisation has an E modulus in the range 0.5 – 5 kPa.

15 6. A method of treating presbyopia by removing a patient's lens from the lens capsule bag via an incision in the cornea, injecting into the lens capsule bag a macromonomer of Formula I and wherein the molecular weight of the macromonomer is in the range 10,000 – 300,000, and wherein the ethylenically unsaturated groups are provided by (meth)acrylamides, (meth)acrylate and styrenic 20 moieties, and polymerising the macromonomer to a polymer having an E modulus in the range 0.01 – 100 kPa.

7. A method of treating presbyopia as defined in claim 5 wherein the E modulus of the polymer is in the range 0.1 – 10 kPa.

25

8. A method of preparing intraocular lenses *in situ* by injecting a flowable macromonomer composition of Formula I where the macromonomer composition has a viscosity at 25°C in the range 1,000 – 20,000 cSt, more preferably 1,000 – 10,000 cSt and after polymerisation having to form a polymer having an E modulus in the 30 range preferably 0.1 – 10 kPa.

9. A method of preparing intraocular lenses as defined in claim 8 wherein the viscosity of the macromonomer composition has a viscosity in the range 1,000 – 10,000 cSt.

5 10. A method of preparing intraocular lenses as defined in claim 8 or claim 9 wherein the E modulus of the polymer is in the range 0.1 – 10 kPa.

11. A method of preparing intraocular lenses as defined in any one of claims 7 to 10 wherein the refractive index of the polymer is in the range 1.39 to 1.45.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU00/00916

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl. 7: A61F 2/14, 2/16, C08F 8/02, 8/10, 8/14, 8/16, 8/30, 8/32, 220/28, 220/36, 220/56

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)

IPC A61F 2/14, 2/16, C08F 8/02, 8/10, 8/14, 8/16, 8/30, 8/32, 220/28, 220/36, 220/56

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
AU: IPC AS ABOVEElectronic data base consulted during the international search (name of data base and, where practicable, search terms used)
DERWENT WPAT AND JPAT: INTRAOCULAR LENS PRESBYOPIA HYDROPHILIC POLYMER

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 849 841 A (ANDREAS MUHLEBACH ET AL) 15 DECEMBER 1998 See columns 1-4; columns 6-9; claims 1-33.	1-11
A	DERWENT JPAT ONLINE ABSTRACT NO. 99-267075/23 JP 11 080274 A (MENICON CO LTD) 26 MARCH 1999 See abstract.	1-11
A	US 5 814 680 A (SUGURU IMAFUKU ET AL) 29 SEPTEMBER 1998 See columns 1-5; claims 1-7.	1-11

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

• Special categories of cited documents:	
"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E" earlier application or patent but published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search
18 August 2000Date of mailing of the international search report
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/AU00/00916

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report				Patent Family Member			
US	5 849 841	WO	9624075	AT	178414	AU	46205/96
		DE	69601924	EP	807270	IL	116899
		ZA	9600824				
US	5 814 680	WO	9625962	AU	46767/96	BR	9606822
		CA	2207010	CN	1175905	EP	811393
		JP	8224295	NZ	301359		

END OF ANNEX

親水的生物化學合成物

公開一個親水(乙烯方面)的不飽和大單體：由包括了一些含有氫氣根或氨基功能組織(而當中一些可以於其後的反應中產生進行甲基丙烯-乙烯的不飽和作用)的附加可聚合單體的附加聚合作用來造成。此大單體可以透過其聚合作用以在原位置形成眼內晶體。