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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
19 August 2004 (19.08.2004)

PCT

(10) International Publication Number
WO 2004/069888 A3

(51) International Patent Classification[7]: C08F 293/00, C08L 53/00

(21) International Application Number: PCT/GB2004/000449

(22) International Filing Date: 5 February 2004 (05.02.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
03250730.3 5 February 2003 (05.02.2003) EP

(71) Applicant *(for all designated States except US)*: **BIOCOMPATIBLES UK LIMITED** [GB/GB]; Chapman House, Farnham Business Park, Weydon Lane, Farnham, Surrey GU9 8QL (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **LEWIS, Andrew, Lennard** [GB/GB]; Biocompatibles UK Limited, Chapman House, Farnham Business Park, Weydon Lane, Surrey GU9 8QL (GB). **ARMES, Steven, Peter** [GB/GB]; 16 Farnham Avenue, Keymer House, Hassocks, West Sussex BN6 8NS (GB). **MA, Yinghua** [CN/GB]; 70 Denning Avenue, Croydon CR0 4DF (GB).

(74) Agent: **GILL JENNINGS & EVERY**; Broadgate Hosue, 7 Eldon Street, London EC2M 7LH (GB).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:
— *of inventorship (Rule 4.17(iv)) for US only*

Published:
— *with international search report*

(88) Date of publication of the international search report: 24 March 2005

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2004/069888 A3

(54) Title: BLOCK COPOLYMERS

(57) Abstract: Block copolymers comprise a core block formed of hydrophilic monomers and have pendant zwitterionic groups, and at least two terminal blocks, comprising stimulus-responsive groups. The core block has a degree of polymerisation of at least 100, whilst the terminal blocks have an average degree of polymerisation of at least 20. A solution of polymer in a liquid may be caused to change its characteristics, for instance rheology, upon being subjected to a stimulus such as a change in temperature or pH. Examples comprise core blocks formed of 2-methacryloyloxyethyl-2'-trimethylammonium ethylphosphate inner salt (MPC) and terminal blocks formed of 2-(diisopropylamino)ethyl methacrylate. Upon changing the pH from around 2 to around 8, an aqueous solution of the block copolymer gels, the solution becoming mobile again upon lowering the pH. The effect is due to deprotonation of a quaternary ammonium pendant ion to form a non-ionised group and subsequent protonation to form an ionised group. This changes the hydrophilicity of the terminal blocks and allowing formation of a network of micellar structures when the pendant groups are not ionised and relatively hydrophobic and associated in micelles.

INTERNATIONAL SEARCH REPORT

International Application No
Γ/GB2004/000449

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C08F293/00 C08L53/00

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 7 C08F C08L C07F C09D C09J A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02/28929 A (MA YINGHUA ; WILLIS SEAN LEO (GB); ARMES STEVEN PETER (GB); BIOCOMPATI) 11 April 2002 (2002-04-11) * page 17, line 6-10 ; claims 42,46,47,50,25,65,67 ; page 7, line 23-29, particularly 28-29 ; claims 43-68 ; examples 54-60,19,49-50 ; claims 1,33,34-40 ; page 4, line 4 - page 20, line 10 *	1,2,22
P,X	WO 03/074026 A (BIOCOMPATIBLES UK LTD ; LLOYD ANDREW P (GB); ARMES STEVEN PETER (GB);) 12 September 2003 (2003-09-12) * same applicant, same invention - application priority date not valid ; abstract ; claims 29-36, 1-28 ; page 12, line 12 - page 13, line 6 ; examples *	1,2,22, 25-28

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 August 2004	19 NOV 2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hammond, A

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International Application No
/GB2004/000449

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 03/074090 A (BIOCOMPATIBLES UK LTD ; ARMES STEVEN PETER (GB); LEWIS ANDREW LENNARD) 12 September 2003 (2003-09-12) * same applicant, same invention - application priority date not valid ; page 14, line 8-20, 26-30 ; page 12, line 18-27 ; page 23, line 8-10 ; page 4, line 16 - page 9, line 29 *	1,2,22, 25-28
X	WO 00/71660 A (RHODIA ; PROCTER & GAMBLE (US)) 30 November 2000 (2000-11-30) * claims 1,15 ; page 2, para. 3 ; page 3, para. 6 ; page 4, para. 5-7 ; page 28, para. 3 ; page 33, para. 3 - page 43, para. 3 ; claims 5,6 ; page 2, last para. - page 28, para. 1 * page 4, line 19 - page 20, line 11	1,2,22, 25-28
A	WO 01/27209 A (DAVIES MARTYN CHRISTOPHER ; CLARKE STUART (GB); BIOCOMPATIBLES LTD (GB) 19 April 2001 (2001-04-19) abstract; claims 1-20	1,2,22
A	WO 01/09208 A (REDMAN RICHARD PAUL ; BIOCOMPATIBLES LTD (GB); FREEMAN RICHARD NEIL TE) 8 February 2001 (2001-02-08) abstract; claims 1-23	1,2,22
A	US 6 395 800 B1 (JONES STEPHEN ALISTER ET AL) 28 May 2002 (2002-05-28) * claims 1-29 ; abstract *	1,2,22
A	US 5 441 841 A (LARSON JAMES R ET AL) 15 August 1995 (1995-08-15) * the whole document *	1,2,22
A	WO 01/01957 A (STRATFORD PETER WILLIAM ; TAYLOR ALISTAIR STEWART (GB); ROWAN LEE (GB)) 11 January 2001 (2001-01-11) * claims 1-16 *	1,2,22

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2004/000449

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

As a result of the prior review under R. 40.2(e) PCT, no additional fees are to be refunded.

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☒ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

1,2,22,25-28

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☒ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1,2,22

   A composition comprising a solvent and a block copolymer, in which the block copolymer comprises a hydrophillic core block and at least 2 terminal blocks, each terminal block being stimulus-responsive in which the blocks are each formed at least in part by the polymerisation of ethylenically unsaturated monomers, wherein the average degree of polymerisation of each terminal block is at least 20, characterised in that the core block comprises zwitterionic pendant groups, and has a degree of polymerisation of at least 100.
   For claim 2 the said block copolymer being further specified as an A-B-A structure.

   ---

2. claim: 3

   A composition according to any previous claim, but in which the monomers from which the core block is formed specifically comprise compounds of the general formula, YBX...formula I,
   wherein Y,B, and X are as specifically detailled in application claim 3.

   ---

3. claim: 4

   A composiiton according to claim 3 in which X is further specified as a group of the formula II as described in the lists of application claim 4.

   ---

4. claims: 5-9

   A composition according to any preceding claim, but in which the monomers from which the terminal blocks are formed specifically comprise compounds of the formula VI as described in the lists of application claim 5.

   ---

5. claims: 10-15

   A composition according to any preceding claim in which the monomers from which each terminal block and/or the core blockis formed comprise comonomers specifically selected from compounds of the formula VII as described in the lists of application claim 10.

   ---

6. claim: 16

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

A composition according to any preceding claim in which the solvent is further specified as detailled in claim 16.

---

7. claims: 17-20

A composition according to claim 6 in which the said substituent has a specific pH as detailled in claims 17-20.

---

8. claim: 21

A composition according to any preceding claim which is a gel.

---

9. claim: 23

A composition according to any preceding claim which comprises a biologically active agent.

---

10. claim: 24

A composition according to any preceding claim which comprises an imaging agent as detailled in claim 24.

---

11. claims: 25-28

A method in which a composition according to any claim is subjected to a stimulus to which the stimulus-responsive blocks respond as detailled in application claims 25-28.

---

12. claims: 29-30

A polymerisation process in which core block ethylenically unsaturated monomers comprising zwitterionic monomer are polymerised, and terminal block ethylenically unsaturated monomers are polymerised from the initiation sites on the core block, as described in application claim 29.
For claim 30, the initiation sites are formed at each end of the block and not elsewhere on the core block whereby an A-B-A block copolymer is formed.

---

13. claim: 31

A polymerisation process according to claims 29-30, but in which the core block ethylenically unsaturated monomers comprise compounds of the formula, YBX...formula I.

---

14. claim: 32

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

A polymerisation process according to claim 31, but in which X is further specified as a group of the formula II as described in the lists of application claim 32.

---

15. claims: 33-37

A polymerisation process according to any of claims 29-32, but in which specifically the terminal block ethylenically unsaturated monomers comprise compounds of the formula VI as described in the lists of application claim 33.

---

16. claims: 38-42

A polymerisation process according to any of claims 29-37, but in which each polymerisation step is conducted by controlled radical polymerisation, preferably by atom transfer radical polymerisation.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
/GB2004/000449

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0228929 A	11-04-2002	AU 9209201 A	15-04-2002
		EP 1325046 A1	09-07-2003
		WO 0228929 A1	11-04-2002
		JP 2004510851 T	08-04-2004
		US 2004063881 A1	01-04-2004
WO 03074026 A	12-09-2003	WO 03074026 A1	12-09-2003
WO 03074090 A	12-09-2003	WO 03074090 A2	12-09-2003
WO 0071660 A	30-11-2000	AU 4860000 A	12-12-2000
		EP 1180129 A1	20-02-2002
		WO 0071660 A1	30-11-2000
		US 6528476 B1	04-03-2003
WO 0127209 A	19-04-2001	AT 267854 T	15-06-2004
		AU 7808700 A	23-04-2001
		DE 60011124 D1	01-07-2004
		EP 1228154 A1	07-08-2002
		WO 0127209 A1	19-04-2001
		JP 2003511538 T	25-03-2003
WO 0109208 A	08-02-2001	AT 245667 T	15-08-2003
		AU 4941100 A	19-02-2001
		DE 60004055 D1	28-08-2003
		DE 60004055 T2	15-04-2004
		EP 1189956 A1	27-03-2002
		WO 0109208 A1	08-02-2001
		JP 2003506501 T	18-02-2003
US 6395800 B1	28-05-2002	AT 178927 T	15-04-1999
		AU 674724 B2	09-01-1997
		AU 5711094 A	19-07-1994
		CA 2129905 A1	07-07-1994
		DE 69324480 D1	20-05-1999
		DE 69324480 T2	12-08-1999
		DK 626983 T3	25-10-1999
		EP 0626983 A1	07-12-1994
		ES 2129620 T3	16-06-1999
		WO 9414897 A1	07-07-1994
		JP 7504459 T	18-05-1995
		US 6150432 A	21-11-2000
		US 5712326 A	27-01-1998
US 5441841 A	15-08-1995	NONE	
WO 0101957 A	11-01-2001	AU 4941400 A	22-01-2001
		EP 1180013 A1	20-02-2002
		WO 0101957 A1	11-01-2001
		JP 2003503157 T	28-01-2003