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[Continued on next page]

(54) Title: BIODEGRADABLE COPOLYMERS, FORMING AND USING SAME

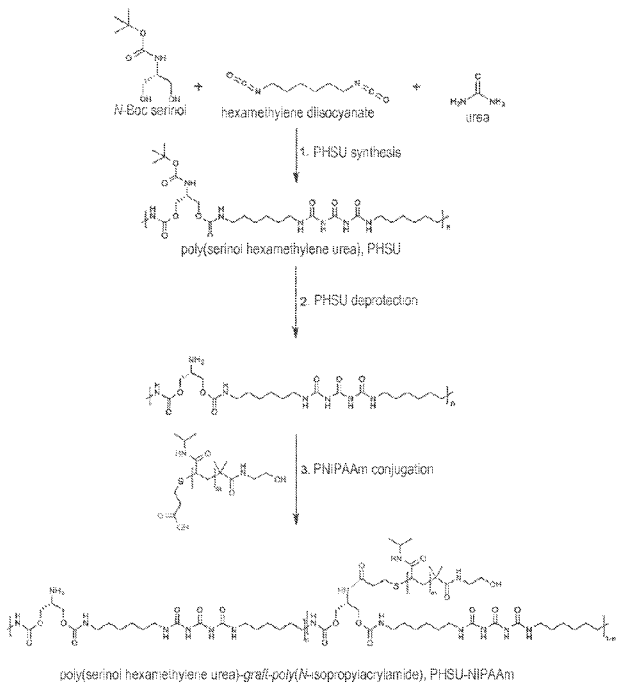

FIG. 11

(57) Abstract: Therapeutic agent delivery systems, which include a thermally-sensitive copolymer and optionally a therapeutic agent, are disclosed. The copolymer is water soluble and biodegradable and, in accordance with exemplary embodiments, includes hydrophobic and hydrophilic portions. The systems may include supplemental compounds, such as polymeric nanoparticles, micelle compounds, or a combination thereof, to further provide sustained release of the therapeutic agent.

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TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

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INTERNATIONAL SEARCH REPORT

International application No.
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A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 38/42, 47/30, 47/34, 47/48; C08G 18/83 (2014.01)
CPC - A61K 9/107, 47/34, 47/48, 9/0019, 9/0024; C08L 101/16; C08G 81/00, 18/83
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(8): A61K 38/42, 47/30, 47/34, 47/48; C08G 18/83 (2014.01)
CPC: A61K 9/107, 47/34, 47/48, 9/0019, 9/0024; C08L 101/16; C08G 81/00, 18/83; USPC: 424/78.17, 427, 428, 484, 486; 525/453, 54.1

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 practicable, search terms used)
MicroPatent (US-G, US-A, EP-A, EP-B, WO, JP-bib, DE-C,B, DE-A, DE-T, DE-U, GB-A, FR-A); ProQuest; IP.com; Google/Google Scholar; Key Words: drug*, therapeut*, deliver*, sustain*, release, reverse thermal gel*, thermal sensitive, phase transition, micell*, copolymer*, amphiphilic, hydrophobic, hydrophilic, block*, segment*, encapsult*, bond*, backbone, graft*, *hexamethylene*, *serinol

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y -- A	US 2011/0182813 A1 (HELLER, J et al.) 28 July 2011; abstract; paragraphs [0021], [0029], [0034]-[0035], [0049]-[0050], [0059], [0062], [0065]-[0066], [0068]-[0069], [0077], [0079], [0081], [0083]; figure 1; example 12; claim 3	1, 3-28, 29/1, 29/3-28, 30/1, 30/3-28, 31/30/1, 31/30/3-28, 32/30/1, 32/30/3-28, 33/30/1, 33/30/3-28, 34/1, 34/3-28 --- 2, 29/2, 30/2, 31/30/2, 32/30/2, 33/30/2, 34/2
Y -- A	WO 2011/109732 A2 (FRIBERG, TR et al.) 09 September 2011; page 3, lines 25-27, 30-32; page 14, lines 15-17; page 15, lines 9-12; page 20, lines 14-16, 25-27; figures 1, 5; claims 1, 30-31, 34	1, 3-28, 29/1, 29/3-28, 30/1, 30/3-28, 31/30/1, 31/30/3-28, 32/30/1, 32/30/3-28, 33/30/1, 33/30/3-28, 34/1, 34/3-28 --- 2, 29/2, 30/2, 31/30/2, 32/30/2, 33/30/2, 34/2
Y	US 6,100,338 A (AKASHI, M et al.) 08 August 2000; column 6, lines 1-5; column 16, lines 60-63; column 18, lines 40-45	6, 11, 29/6, 29/11, 30/6, 30/11, 31/30/6, 31/30/11, 32/30/6, 32/30/11, 33/30/6, 33/30/11, 34/6, 34/11

☒ Further documents are listed in the continuation of Box C. ☐

* 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 application or patent 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
01 August 2014 (01.08.2014)	03 APR 2015
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US14/36446

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 6,841,617 B2 (JEONG, BM et al.) 11 January 2005; abstract; column 6, lines 10-14	21-22, 29/21-22, 30/21-22, 31/30/21-22, 32/30/21-22, 33/30/21-22, 34/21-22
Y	US 2005/0089545 A1 (KUWANO, M et al.) 28 April 2005; abstract; claim 5	32/30/1, 32/30/3-28, 33/30/1, 33/30/3-28
Y	WO 2010/088548 A1 (DE JUAN JR, E et al.) 05 August 2010; abstract; paragraph [0012]	34/1, 34/3-28
A	Park, D et al. A Functionalizable Reverse Thermal Gel Based on a Polyurethane/PEG Block Copolymer. Biomaterials. January 2011, Vol. 32, No. 3, abstract, ISSN: 0142-9612	2, 29/2, 30/2, 31/30/2, 32/30/2, 33/30/2, 34/2
A	US 5,702,717 A (CHA, Y et al.) 30 December 1997; entire document	1-28, 29/1-28, 30/1-28, 31/30/1-28, 32/30/1-28, 33/30/1-28, 34/1-28
A	US 8,309,623 B2 (YU, YJ et al.) 13 November 2012; entire document	1-28, 29/1-28, 30/1-28, 31/30/1-28, 32/30/1-28, 33/30/1-28, 34/1-28

INTERNATIONAL SEARCH REPORT

International application No.
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Box No. 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 No. 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:

-Continued from 1. (ii):

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I: Claims 1-34 are directed toward therapeutic agent delivery systems.
Group II: Claims 35-37 are directed toward method of fabricating micelles.
Group III: Claims 38-41 are directed toward a reverse thermal gel.
Group IV: Claims 42-47 are directed toward method of forming a copolymer.

-***-Continued Within the Next Extra Sheet-***-

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 additional fees, this Authority did not invite payment of additional fees.

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.:

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.:
Claims 1-34

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

-***-Continued From Box III Above: Observations where unity of invention is lacking-***-

Claims 36-37 are objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 6 because claims 36-37 are indefinite for the following reason: Claims 36-37, which depend from claim 29, lack antecedent basis in claim 29. For purposes of this examination, and for purposes of determining unity of invention, Claims 36-37 are interpreted to depend from Claim 35, where antecedent basis is provided.

The inventions listed as Groups I-IV do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the special technical features of Group I include a therapeutic agent delivery system, the system comprising copolymer having thermally sensitive molecules, hydrophobic segments and hydrophilic segments, or a combination thereof; a compound selected from the group consisting of one or more nanoparticles, micelles, liposome systems, or a combination thereof, the compound distributed within the reverse thermal gel composition; and a first therapeutic agent at least partially encapsulated in or bound to the compound, wherein the system is configured to provide sustained release of the first therapeutic agent for a period of greater than 3 months, which are not present in Groups II-IV; the special technical features of Group II include a method of fabricating micelles, the method comprising the steps of: dissolving a polymer amenable to micelle formation in a suitable solvent such as DMSO; additionally dissolving one or more therapeutic agents in the solvent with the polymer; adding a volume of this solution to a greater volume of water such that an emulsion is formed; passing this emulsion through a filter membrane with a defined pore structure; and removing the starting solvent, which are not present in Groups I and III-IV;
the special technical features of Group III include a reverse thermal gel comprising one or more of poly[hexamethylene-alt-(serinol; urea)]-graft-poly(N-isopropylacrylamide) and poly(ethylene oxide)-block-poly(hexamethylene-alt-serinol)-block-poly(ethylene oxide), which are not present in Groups I-II and IV; the special technical features of Group IV include a method of forming a copolymer, the method comprising the steps of: forming a molecule having a lower critical solution temperature above a body temperature; forming a polymer; and forming a copolymer comprising the molecule and the polymer, wherein the lower critical solution temperature of the copolymer is below the body temperature, which are not present in Groups I-III.

The common technical features of Groups I-IV are a copolymer with reverse thermal gelling properties, amenable to micelle formation; and one or more therapeutic agents.

These common technical features are disclosed by US 6,316,011 B1 to Ron, et al. (hereinafter 'Ron'). Ron discloses a copolymer with reverse thermal gelling properties (a reverse thermally viscosifying (gelling) polymer, which is a linear block copolymer capable of reversible gelation upon temperature change; column 5, lines 26-42; claim 11), amenable to micelle formation (at least one block of the copolymer comprises a poloxamer having a hydrophobic region and a hydrophilic region effective to form micelles in solution in response to a change in temperature; claim 11); and one or more therapeutic agents (the composition comprising an active agent which imparts a pharmaceutical effect (therapeutic agent); claim 11).

Since the common technical features are previously disclosed by Ron, these common features are not special and so Groups I-IV lack unity.