



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 49/00	A3	(11) International Publication Number: WO 98/04292 (43) International Publication Date: 5 February 1998 (05.02.98)
(21) International Application Number: PCT/US97/03007 (22) International Filing Date: 27 February 1997 (27.02.97) (30) Priority Data: 08/681,710 29 July 1996 (29.07.96) US (71) Applicant: ACUSPHERE, INC. [US/US]; 38 Sidney Street, Cambridge, MA 02139 (US). (72) Inventors: BERNSTEIN, Howard; Apartment 2B, 929 Massachusetts Avenue, Cambridge, MA 02139 (US). STRAUB, Julie, Ann; 16 Plato Terrace, Winchester, MA 01890 (US). BRUSH, Henry, T.; 911 Broadway, Somerville, MA 02144 (US). CHURCH, Charles, C.; 38 Hancock Street, Arlington, MA 02174 (US). (74) Agents: PABST, Patrea, L. et al.; Amall Golden & Gregory, 2800 One Atlantic Center, 1201 West Peachtree Street, Atlanta, GA 30309-3450 (US).		(81) Designated States: AU, BR, CA, CN, CZ, HU, IL, JP, KR, NO, NZ, PL, RU, SG, SK, VN, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i> (88) Date of publication of the international search report: 14 May 1998 (14.05.98)
(54) Title: POLYMER-LIPID MICROENCAPSULATED GASES FOR USE AS IMAGING AGENTS		
(57) Abstract It has been discovered that the incorporation of gases, especially fluorinated gases such as perfluorocarbons, into microparticles formed from the combination of a natural or synthetic polymer and lipid have significantly enhanced echogenicity as compared with microparticles not including the lipid. Compounds other than lipids which are hydrophobic and limit the penetration and/or uptake of water into the microparticles can also be incorporated into the microparticles to enhance echogenicity. In the preferred embodiment, the polymers are synthetic biodegradable polymers. The microparticles are manufactured with a diameter suitable for the targeted tissue to be imaged, for example, with a diameter of between 0.5 and 8 microns for intravascular administration, and a diameter of between 0.5 and 5 mm for oral administration for imaging of the gastrointestinal tract or other lumens. Preferred polymers are polyhydroxy acids such as polylactic acid-co-glycolic acid, most preferably conjugated to polyethylene glycol or other materials inhibiting uptake by the reticuloendothelial system (RES). The most preferred lipids are phospholipids, preferably dipalmitoylphosphatidylcholine (DPPC), distearoylphosphatidylcholine (DSPC), diarachidoylphosphatidylcholine (DAPC), dibehenoylphosphatidylcholine (DBPC), ditricosanoylphosphatidylcholine, dilignoceroylphosphatidylcholine (DLPC), incorporated at a ratio of between 0.01-30 (w lipid/w polymer), most preferably between 0.1-10 (w lipid/w polymer). Microparticles for imaging using other detectable agents can be similarly manufactured.		

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INTERNATIONAL SEARCH REPORT

Internal Application No
PCT/US 97/03007

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K49/00

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 6 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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 92 18164 A (DELTA BIOTECHNOLOGY LTD) 29 October 1992 cited in the application	1-30
Y	see page 9, line 5 - line 11 see page 7, line 25 - page 8, line 27 see page 9, line 13 - line 24; claims 1,18 ---	1-30
A	WO 95 03356 A (MASSACHUSETTS INST TECHNOLOGY ;DOMB ABRAHAM J (IL); GREF RUXANDRA) 2 February 1995 cited in the application see page 9, line 27 - line 34; claims 1,37 see abstract, line 8-line 9 ---	1-30
E	WO 97 32609 A (ACUSPHERE INC) 12 September 1997 see claims; examples --- -/--	1

Further documents are listed in the continuation of box C. Patent family members are listed in annex.

° Special categories of cited documents :

<p>*A* document defining the general state of the art which is not considered to be of particular relevance</p> <p>*E* earlier document but published on or after the international filing date</p> <p>*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)</p> <p>*O* document referring to an oral disclosure, use, exhibition or other means</p> <p>*P* document published prior to the international filing date but later than the priority date claimed</p>	<p>*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</p> <p>*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</p> <p>*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.</p> <p>*Z* document member of the same patent family</p>
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Date of the actual completion of the international search <p style="text-align: center;">29 January 1998</p>	Date of mailing of the international search report <p style="text-align: center;">1 1. 03. 98</p>
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Name and mailing address of the ISA 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	Authorized officer <p style="text-align: center;">Berte, M</p>
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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 97/03007

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 18420 A (BRACCO RESEARCH SA) 20 June 1996 see claims 1,9,15,16,18,19 ---	1-30
P,Y	WO 96 40275 A (MARSDEN JOHN CHRISTOPHER ;NYCOMED IMAGING AS (NO); DUGSTAD HARALD) 19 December 1996 see page 3, line 6 - line 35 see page 4, line 12 - line 28; claims 1,3,4,11-13 -----	1-30

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 97/03007

Box I Observations where certain claims were found unsearchable (Continuation of item 1 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.: 1-30
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:
See extra sheet FURTHER INFORMATION PCT/ISA/210

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 II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

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

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.:

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.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/ US 97/03007

FURTHER INFORMATION CONTINUED FROM PCT/ISA/

In view of the large number of compounds which are designed by the compounds mentioned in the claims, the search had to be restricted for economic reasons. The search was limited to the compounds for which pharmacological data was given and/or the compounds mentioned in the claims or examples, and the general idea underlying the invention.
(See guidelines, Part B, Chapter III, Paragraph 3.6)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 97/03007

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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