



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification⁶ : A61K 9/127, 49/00</p>	<p>A3</p>	<p>(11) International Publication Number: WO 99/36104</p> <p>(43) International Publication Date: 22 July 1999 (22.07.99)</p>
<p>(21) International Application Number: PCT/US99/00747</p> <p>(22) International Filing Date: 14 January 1999 (14.01.99)</p> <p>(30) Priority Data: 60/071,332 14 January 1998 (14.01.98) US</p> <p>(71) Applicant: DU PONT PHARMACEUTICALS COMPANY [US/US]; 974 Centre Road, WR-1ST18, Wilmington, DE 19807 (US).</p> <p>(72) Inventors: HUI, Poh, K.; 45 Wareland Road, Wellesley, MA 02181 (US). BISHOP, John, E.; 878 Townsend Road, Groton, MA 01450 (US). MADRIGAL, Eleodoro, S., Jr.; Apartment 12, 14B Strawberry Hill Road, Acton, MA 01720 (US).</p> <p>(74) Agent: O'BRIEN, Maureen, P.; Du Pont Pharmaceuticals Company, Legal Patent Records Center, 1007 Market Street, Wilmington, DE 19898 (US).</p>		<p>(81) Designated States: AU, BR, CA, CN, CZ, EE, HU, IL, JP, KR, LT, LV, MX, NO, NZ, PL, RO, SG, SI, SK, UA, VN, 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).</p> <p>Published <i>With international search report.</i></p> <p>(88) Date of publication of the international search report: 13 January 2000 (13.01.00)</p>
<p>(54) Title: PREPARATION OF A LIPID BLEND AND A PHOSPHOLIPID SUSPENSION CONTAINING THE LIPID BLEND, AND CONTRAST AGENTS BASED ON THESE</p> <p>(57) Abstract</p> <p>The present invention describes processes for the preparation of a lipid blend and a uniform filterable phospholipid suspension containing the lipid blend, such suspension being useful as an ultrasound contrast agent.</p>		

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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER IPC 6 A61K9/127 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				
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Y	US 5 637 289 A (KLAVENESS JO ET AL) 10 June 1997 (1997-06-10) example 5 ---	1-28, 36-44		
Y, X	WO 95 32006 A (IMARX PHARMACEUTICAL CORP) 30 November 1995 (1995-11-30) --- examples 1-3 ---	1-28 36-44		
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<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C.				
<input checked="" type="checkbox"/> Patent family members are listed in annex.				
° Special categories of cited documents :				
<table style="width: 100%; border: none;"> <tr> <td style="width: 50%; border: none; vertical-align: top;"> "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 </td> <td style="width: 50%; border: none; vertical-align: top;"> "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 </td> </tr> </table>			"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
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Date of the actual completion of the international search <p style="text-align: center; font-size: 1.2em;">12 August 1999</p>		Date of mailing of the international search report <p style="text-align: center; font-size: 1.2em;">01.09.99</p>		
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; font-size: 1.2em;">Dullaart, A</p>		

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X	example 1 ---	36-44
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X	abstract page 110, left-hand column page 113; figure 4 page 117 ---	36-44
A	MARUYAMA KAZUO ET AL.: "Prolonged circulation time in vivo of large unilamellar liposomes composed of distearoyl phosphatidylcholine and cholesterol containing amphipathic poly(ethylene glycol)." BIOCHIMICA ET BIOPHYSICA ACTA, 1992, VOL. 1128, PAGES 44-49, XP002101582 table 1 figures 1-3 ---	1-28, 36-44
A	BEDU-ADDO FK ET AL: "Effects of polyethyleneglycol chain length and phospholipid acyl chain composition on the interaction of polyethyleneglycol-phospholipid conjugates with phospholipid: implications in liposomal drug delivery." PHARM RES, MAY 1996, VOL. 13, NO. 5, PAGE(S) 710-717, XP002101583 paragraph 'RESULTS! --- -/--	1-28, 36-44

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A,P	BELSITO S. ET AL: "Sterically stabilized liposomes of DPPC/DPPE-PEG:2000. A spin label ESR and spectrophotometric study" BIOPHYSICAL CHEMISTRY, 5-10-1998, VOL. 75, NO. 1, PAGE(S) 33-43, XP002101584 figure 1	1-28, 36-44
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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.: 1-44 in part
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 FURTHER INFORMATION sheet 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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. Claims: 1-23 in part, and 36-44

The process for preparing a phospholipid suspension as described in claims 1-23, and the phospholipid suspension thus obtained.

2. Claims: 1-23 in part, and 24-28

The process for preparing a perfluorocarbon-containing contrast agent according to these claims.

3. Claims: 29-35

The process for the prepreparation of a lipid blend according to these claims.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-44 in part

In view of the large number of compositions, which are defined by the general definition in the claims, the search had to be restricted for economic reasons. The search was limited to the compositions for which pharmacological data was given and/or the compositions mentioned in the claims, and to the general idea underlying the application (see guidelines, Chapter III, paragraph 2.3).

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

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information on patent family members

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