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VASISHT, Niraj [IN/US]; 7006 Almond Green Drive,  
San Antonio, TX 78238 (US).

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(74) Agent: **MORRIS, Paula, D.**; Paula D. Morris & Associates, P.C., 10260 Westheimer, Suite 360, Houston, TX 77042-3728 (US).

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(71) Applicants (*for all designated States except US*): **SOUTHWEST RESEARCH INSTITUTE** [US/US]; 6220 Culebra Road, San Antonio, CA 78238-5166 (US). **NATIONAL AERONAUTICS AND SPACE ADMINISTRATION** [US/US]; Johnson Space Center Office of Patent Council, Mail Code HA 2101, Nasa Road 1, Houston, TX 77058 (US). **UNIVERSITY OF TEXAS SYSTEM** [US/US]; 201 West 7th Street, Austin, TX 78701-2981 (US).

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR), OAPI patent (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*

(72) Inventors; and  
(75) Inventors/Applicants (*for US only*): **PUTCHA, Lakshmi** [US/US]; 1903 Tangle Pines Court, Houston, TX 77062 (US). **MCDONOUGH, Joe** [US/US]; 13070 Adobe Walls Drive, Helotes, TX 78023 (US). **BOLAND, Edward, J.** [US/US]; 257 West Hermine, San Antonio, TX 78212 (US). **DIXON, Hong** [US/US]; 11417 Lago Vista, Helotes, TX 78023 (US). **PERSYN, Joseph, T.** [US/US]; 126 Lakeshore Drive, Lakehills, TX 78063 (US).

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*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.*

(54) Title: CONTROLLED RELEASE COMPOSITIONS AND METHODS FOR USING SAME

(57) Abstract: Pharmaceutical preparations adapted for mucosal delivery of a pharmacologically effective dose of a pharmacologically active agent to a mammal, said pharmaceutical preparation comprising microcapsules adapted to provide controlled release of said pharmacologically effective dose, said microcapsules comprising a shell and a core, said core comprising a quantity of a single enantiomer of said pharmacologically active agent, is selected from the group consisting of antihistamines and anticholinergics.

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# INTERNATIONAL SEARCH REPORT

Interr	Application No
PC1/US	03/02797

**A. CLASSIFICATION OF SUBJECT MATTER**  
 IPC 7 A61K9/50 A61P1/08 A61P37/00 A61K31/54 C07D279/24

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 A61K C07D

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, EMBASE, BIOSIS, CHEM ABS Data, MEDLINE

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	RAMANATHAN RAGHUPATHY ET AL: "Bioavailability of intranasal promethazine dosage forms in dogs." PHARMACOLOGICAL RESEARCH, vol. 38, no. 1, July 1998 (1998-07), pages 35-39, XP002251892 ISSN: 1043-6618 cited in the application	1, 3, 4, 6, 8-19, 22-34, 46, 47, 53, 55-60
Y	the whole document	2, 5, 8-16, 22-28, 32-34

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  <b>5 February 2004</b>	Date of mailing of the international search report  <b>29 MAR 2004</b>
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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  <b>Marttin, E</b>
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INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 03/02797

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>US 5 472 704 A (SANTUS GIANCARLO ET AL) 5 December 1995 (1995-12-05)</p> <p>column 1, line 9 - line 16 column 3, line 40 - line 64 column 5, line 36 - line 61 column 7, line 28 - line 42 claims 1,15</p> <p style="text-align: center;">---</p>	<p>1, 3, 4, 6-8, 10, 11, 26-34, 39-41, 43-46, 53, 55-60</p>
X	<p>EP 0 257 915 A (INNOVATA BIOMED LTD) 2 March 1988 (1988-03-02)</p> <p>claims 1,10 page 2, line 44 page 3, line 21 - line 32 page 3, line 53 - line 56</p> <p style="text-align: center;">---</p>	<p>1, 3, 4, 6-8, 10, 11, 26-34, 46-60</p>
X	<p>WO 99 66904 A (THERATECH INC) 29 December 1999 (1999-12-29)</p> <p>page 5, line 1 page 5, line 24 - line 27 page 8, line 17 page 11, line 3 - line 4; claims 1,5,22,30,33,50; example 1</p> <p style="text-align: center;">---</p>	<p>1, 3, 7-9, 11-18, 22-34, 46-60</p>
X	<p>EP 0 477 135 A (WARNER LAMBERT CO) 25 March 1992 (1992-03-25)</p> <p>page 3, line 2 - line 20 page 4, line 20 - line 22 page 4, line 40 - line 42 page 5, line 6 - line 25; claims 1,3,7,8</p> <p style="text-align: center;">---</p>	<p>1, 3, 7, 8, 11, 26-34, 39-60</p>
X	<p>US 5 192 552 A (JAMBOR GEB HOFFMANN ET AL) 9 March 1993 (1993-03-09)</p> <p>claims 3,4,13; example 6 column 1, paragraph 2</p> <p style="text-align: center;">---</p> <p style="text-align: center;">-/--</p>	<p>1-3, 7-9, 11-16, 22-34, 46-60</p>

## INTERNATIONAL SEARCH REPORT

Intern	Application No
	PCT/US 03/02797

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	<p>WO 93 03029 A (GUIDOTTI &amp; C SPA LABOR) 18 February 1993 (1993-02-18) page 2, line 15 -page 4, line 2</p> <p>page 4, line 24 -page 5, line 2; claims; example 3</p> <p style="text-align: center;">---</p>	<p>61-66, 72-75 2,5, 8-16, 22-28, 32-34</p>
X Y	<p>US 4 097 596 A (BEGANY ALBERT J ET AL) 27 June 1978 (1978-06-27) column 3, line 17 - line 39 column 6, line 17 - line 31; claims 1,5,6,9,14,15; example 5</p> <p style="text-align: center;">---</p>	<p>61-83 84-97</p>
X	<p>US 3 082 210 A (MICHEL JACOB ROBERT ET AL) 19 March 1963 (1963-03-19) column 1, line 9 - line 21 column 1, line 55 - line 63</p> <p style="text-align: center;">---</p>	<p>61-67, 72-75</p>
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X	<p>MADSEN F ET AL: "The protective effect of inhaled levomepromazine (Nozinan) on histamine-induced bronchial constriction." PULMONARY PHARMACOLOGY. ENGLAND JUN 1993, vol. 6, no. 2, June 1993 (1993-06), pages 129-136, XP002269266 ISSN: 0952-0600 page 129, left-hand column, paragraph 1 -right-hand column, line 2 page 135, left-hand column, line 46 - line 52</p> <p style="text-align: center;">---</p>	<p>61-66, 72-75</p>
Y	<p>MABOUDIAN-ESFAHANI M ET AL: "High-performance liquid chromatographic assay of (+/-)-ethopropazine and its enantiomers in rat plasma." JOURNAL OF CHROMATOGRAPHY. B, BIOMEDICAL SCIENCES AND APPLICATIONS. NETHERLANDS 18 SEP 1998, vol. 715, no. 2, 18 September 1998 (1998-09-18), pages 417-423, XP002269267 ISSN: 1387-2273 the whole document</p> <p style="text-align: center;">---</p>	<p>89-97</p>
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## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 03/02797

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>BROCKS D R ET AL: "Disposition of ethopropazine enantiomers in the rat: tissue distribution and plasma protein binding." JOURNAL OF PHARMACY &amp; PHARMACEUTICAL SCIENCES 'ELECTRONIC RESOURCE!': A PUBLICATION OF THE CANADIAN SOCIETY FOR PHARMACEUTICAL SCIENCES, SOCIETE CANADIENNE DES SCIENCES PHARMACEUTIQUES. CANADA 1999 JAN-APR, vol. 2, no. 1, January 1999 (1999-01), pages 23-29, XP002269268 ISSN: 1482-1826 the whole document</p>	89-97
Y	<p>DELNESTE Y ET AL: "Histamine induces IL-6 production by human endothelial cells." CLINICAL AND EXPERIMENTAL IMMUNOLOGY. ENGLAND NOV 1994, vol. 98, no. 2, November 1994 (1994-11), pages 344-349, XP008027267 ISSN: 0009-9104 cited in the application the whole document</p>	84-88
Y	<p>NILSSON J L G ET AL: "Promethazine - Resolution, absolute configuration and direct chromatographic separation of the enantiomers" ACTA PHARMACEUTICA SUECICA 1984 SWEDEN, vol. 21, no. 5, 1984, pages 309-316, XP008027314 cited in the application page 314</p>	89-97
P,X	<p>SINKO, GORAN ET AL: "Separation, conformation in solution and absolute configuration of ethopropazine enantiomers" ENANTIOMER (2002), 7(2-3), 149-156 , March 2002 (2002-03), XP008027264 page 150, right-hand column, paragraph 1</p>	89-97

# INTERNATIONAL SEARCH REPORT

In ternational application No.  
PCT/US 03/02797

## 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:  
  
Although claims 4-6, 8-88 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
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:  
  
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:

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.:
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

## Continuation of Box I.2

Present claims 1-8, 10, 11, 26-60, 84-87 relate to compounds and compositions defined by reference to desirable characteristics or properties, namely antihistamines and anticholinergics. The terms "antihistamines" and "anticholinergics" as used in the present independent claims 1-8 defines the active agent by its pharmacological effect. However, a compound cannot be sufficiently characterised by its pharmacological effect as it is done by expressions like "antihistamines" or "anticholinergics", because it is impossible to know which substances are encompassed in these expressions.

The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds used in the examples, those mentioned in claims 9, 12-25, and those mentioned in the description at pages 10, line 20 - page 11, line 14, page 13, line 7 page 15, line 5, and the concepts of antihistamines and anticholinergics.

The applicant's attention is drawn to the fact that claims, or parts of 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.

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

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

1. Claims: 1,3,4,6-8,9-18 partially,20 partially,  
22-60 partially

- 1.1. Claims: 1,4,8-18 partially, 20 partially,  
22-60 partially

Microcapsules adapted to provide controlled release of an active agent, for mucosal delivery of antihistamines or anticholinergics comprising a shell comprising a release retardant.

- 1.2. Claims: 3,6,7,8-18 partially, 20 partially,  
22-60 partially

Microcapsules adapted to provide controlled release of an active agent, for mucosal delivery of antihistamines or anticholinergics comprising an absorption enhancer.

2. Claims: 2,5,9-18 partially,19,20 partially,21,  
22-60 partially

Microcapsules adapted to provide controlled release of an active agent, for mucosal delivery of antihistamines or anticholinergics comprising a single enantiomer of the active agent.

3. Claims: 61-88

Method for alleviating motion sickness or allergy comprising administering a highest pharmacological activity enantiomer of a phenothiazine.

4. Claims: 89-97

Method for resolving the (+) and (-) enantiomer of ethopropazine.

Please note that all inventions mentioned under item 1, although not necessarily linked by a common inventive concept, could be searched without effort justifying an additional fee.

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 03/02797

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