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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.

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(54) Title: PHARMACEUTICAL COMPOSITIONS FOR OTIC USE

(57) Abstract: Otic compositions are disclosed. The compositions contain an otic drug and a carrier comprising a low molecular weight compound. The compositions do not drain out of the ear after administration.

PHARMACEUTICAL COMPOSITIONS FOR OTIC USE

BACKGROUND OF THE INVENTION

This invention relates to pharmaceutical compositions. In particular, this invention relates to the use of carriers containing low molecular weight compounds that reversibly change from solid to liquid at approximately 32 - 37 °C in compositions for otic use.

Otic compositions designed for topical application to the external ear are typically aqueous compositions. Such compositions can be formulated as simple aqueous solutions or suspensions. Alternatively, such compositions may be formulated as an oil-in-water emulsion, such as those described in U.S. Patent No. 5,753,269. Still another possibility for use in topical otic compositions is a polymeric ingredient. See, for example, U.S. Patent No. 5,747,061, which describes suspension formulations of the steroid loteprednol etabonate for treating the ear, eye or nose. Gel-forming compositions and gel compositions are also used for delivering otic drugs. See, for example, U.S. Patent No. 6,316,011, which describes certain thermal responsive hydrogels suitable for administering a pharmaceutical agent across otic membranes. See also U.S. Patent No. 6,346,272, which describes thermo-irreversible gel vehicles that may be used to deliver otic drugs, wherein the vehicle contains a polyoxyalkylene polymer and an ionic polysaccharide and the vehicle is a liquid before administration to the body and transform, upon contact with the body, into "a semi-solid gel having a very high viscosity" (Col. 2, line 64 – Col. 3, line 1). The compositions of the '272 patent may be formulated as homogeneous, polyphase systems and, in addition to the polyoxyalkylene polymer and the ionic polysaccharide, optionally contain "such additives as water insoluble high molecular weight fatty acids and alcohols, fixed oils, volatile oils and waxes, mono-, di-, and triglycerides, and synthetic, water insoluble polymers without altering the functionality of the system" (Col. 3, lines 16 – 21).

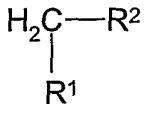
SUMMARY OF THE INVENTION

The present invention provides otic compositions comprising a pharmaceutical drug and a carrier containing one or more low molecular weight compounds. The carrier is a solid or semi-solid at temperatures ≤32 °C, but liquid at temperatures ≥ 37 °C. The compositions reversibly change from solid to liquid at a temperature of 32 – 37 °C.

DETAILED DESCRIPTION OF THE INVENTION

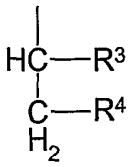
Unless indicated otherwise, all ingredient amounts expressed in percentage terms are presented as % w/w.

The compositions of the present invention comprise an otically acceptable pharmaceutical drug and a carrier comprising one or more compounds having a molecular weight of 150 - 4000, wherein the compounds are of the formula:



(I)

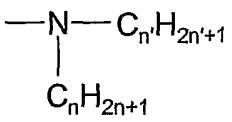
wherein R^1 is -H, -OH, -COOH, $-C_nH_{2n+1-2m}$, $-COOC_nH_{2n+1-2m}$, $-COO(CH_2CH_2O)_nCH_2CH_2OH$, $-CH_2R^3$, or



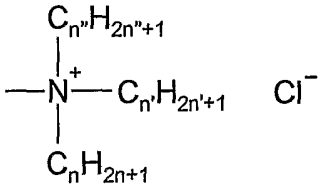
;

R^2, R^3 and R^4 are independently –H, -OH, -COOH, $-C_nH_{2n+1-2m}$, $-OOCC_nH_{2n+1-2m}$, $-COOC_nH_{2n+1-2m}$, $-COO(CH_2CH_2O)_nCH_2CH_2OH$, $-C_nH_{2n+1-2m}COO(CH_2CH_2O)_nCH_2CH_2OH$,

$-OOCC_nH_{2n+1-2m}COOC_{n'}H_{2n'+1-2m'}$, $-COO^-Na^+$, $-COO^-K^+$, $-SO_3H$, $-SO_3^-Na^+$, $-SO_3^-K^+$, $-NH_2$, -Cl,



, or



;

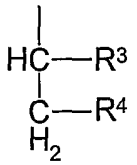
n, n' and n" are independently 0 – 50; and

m, m' and m" are independently 0 – 10.

In a preferred embodiment, the compositions do not contain any polymeric ingredient and the carrier consists essentially of one or more compounds of formula (I). Preferably, the molecular weight of the low molecular weight compounds of formula (I) used in the compositions present invention is ≤2000, and most preferably ≤1000. If the carrier of the present invention contains only one compound of formula (I), then the compound must have a melting point in the range of 32 - 37 °C. If the carrier contains two or more compounds of formula (I), it is only necessary that the mixture of the two or more compounds of formula (I) has a melting point in the range of 32 - 37 °C.

Preferred are the compounds of formula (I) wherein

R^1 is, $-C_nH_{2n+1-2m}$, $-COOC_nH_{2n+1-2m}$, $-COO(CH_2CH_2O)_nCH_2CH_2OH$, $-CH_2R^3$, or



;

R^2, R^3 and R^4 are independently –H, -OH, -COOH, $-C_nH_{2n+1-2m}$,

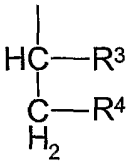
$-OOCC_nH_{2n+1-2m}$, $-COOC_nH_{2n+1-2m}$, $-COO(CH_2CH_2O)_nCH_2CH_2OH$,
$-C_nH_{2n+1-2m}COO(CH_2CH_2O)_nCH_2CH_2OH$, or
$-OOCC_nH_{2n+1-2m}COOC_{n'}H_{2n'+1-2m'}$;

n, n' and n" are independently 0 – 40; and

m, m' and m" are independently 0 – 5.

Most preferred are the compounds of formula (I) wherein

R^1 is



;

R^2, R^3 and R^4 are independently –H, -OH, -COOH, $-C_nH_{2n+1-2m}$, or
$-OOCC_nH_{2n+1-2m}$;

n, n' and n" are independently 0 – 30; and

m, m' and m" are independently 0 – 3.

The compounds of the present invention can be made by methods known in the art and many such compounds are commercially available. For example, commercial suppliers include NuChek Prep (Elysian, Minnesota), Quest International (Hoffman Estates, Illinois), which produces such compounds under the Myvacet® brand, and Gattefossa (Saint-Priest, France), which produces such compounds under the Gelucire®, Suppocire™, Ovucire™, and Monosteol® brands. Suitable compounds include, but are not limited to, the following commercially available products.

propylene glycol mono- and diesters of stearic and palmitic acid (Monosteol®);

glyceryl esters of saturated C_8 – C_{18} saturated fatty acid esters (Gelucire® 33/01);

Suppocire AIM;

Suppocire AM;

Suppocire BM;

Suppocire NAI 25; and

Suppocire NAL

The compositions of the present invention comprise one or more of the compounds of formula (I) in a total concentration of at least 10%, preferably at least 30%, and most preferably at least 50%.

The compositions of the present invention comprise a pharmaceutically effective amount of an otic drug. If necessary or desired, more than one drug can be included in the composition of the present invention. Many types of otic drugs are known, including but not limited to: anti-infective agents including quinolones such as ciprofloxacin, and aminoglycosides such as tobramycin and gentamicin; and non-steroidal and steroidal anti-inflammatory agents, such as suprofen, diclofenac, ketorolac, rimexolone, dexamethasone, hydrocortisone and tetrahydrocortisol. Anti-pain otic drugs are also known, such as those disclosed in U.S. Patent No. 6,174,878. The otic drug may be present in the form of a pharmaceutically acceptable salt. Compositions of the present invention may also include combinations of otic drugs. The total amount of drug contained in the implant compositions of the present invention is preferably not greater than 50%.

In addition to the compound of formula (I) and an otic drug, the compositions of the present invention optionally comprise one or more excipients. Many excipients for pharmaceutical compositions are known. Examples of suitable excipients include, but are not limited to surfactants and other solubilizing agents, preservatives, and stabilizers.

Suitable surfactants include tyloxapol, polysorbate 20, polysorbate 60, and polysorbate 80 surfactants. A preferred surfactant is polysorbate 80.

Suitable stabilizers include chelating agents, such as edetate disodium, and antioxidants, such as ascorbic acid and citric acid.

The compositions may be fashioned into a shape suitable for insertion into the ear. For example, such shapes include, but are not limited to cylindrical, conical and spherical shapes. Alternatively, the compositions may be dropped, injected, deposited, or sprayed into the ear. The compositions of the present invention are administered to the external ear, including the ear canal. In one embodiment, the compositions of the present invention are warmed to a temperature above 35 °C and administered topically into the ear canal as ear drops or injected through a cannula into the ear canal.

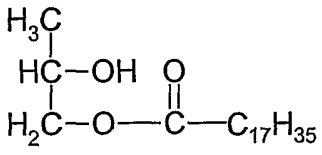
The present invention is also directed toward a method of delivering an otic drug to the ear of a patient wherein the method comprises administering to the ear a composition containing the otic drug and a carrier comprising one or more low molecular weight compounds of formula (I). According to this method, the compositions do not drain out of the ear because they are solid or semi-solid at the temperature of the external ear. On the other hand, the compositions easily allow the drug to diffuse or escape the carrier because the carrier is liquid at 37 °C, the average temperature of the inner ear and it is generally easier for a drug to escape a liquid than a solid.

The following examples are intended to illustrate, but not limit, the present invention.

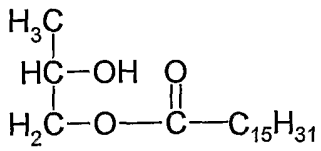
Example 1: Composition containing Dexamethasone

A 95:4:1 (weight basis) composition of Monosteol®, dexamethasone, and polysorbate 80 is heated to melt the Monosteol® and mixed. 1 x 2 mm cylindrical pellets are made by cooling the mixture in a cylindrical mold. Monosteol® contains, according to its manufacturer, no less than 90% total of the following two ingredients:

propylene glycol monostearate ($C_{21}H_{42}O_3$):



propylene glycol monopalmitate ($C_{19}H_{38}O_3$)



Example 2: Composition containing Dexamethasone and Ciprofloxacin

A 82:4:12:2 (weight basis) composition of Monosteol®, dexamethasone, ciprofloxacin hydrochloride and polysorbate 80 is heated to melt the Monosteol® and mixed. 1 x 2 mm cylindrical pellets are made by cooling the mixture in a cylindrical mold.

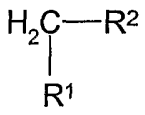
Example 3: Dexamethasone Gelucire® 33/01 Particles

A 95:4:1 (weight basis) composition of dexamethasone, Gelucire® 33/01 and polysorbate 80 is heated to melt the Gelucire® 33/01 and mixed. This mixture is then spray dried to produce particles for incorporation into an otic spray composition.

The invention has been described by reference to certain preferred embodiments; however, it should be understood that it may be embodied in other specific forms or variations thereof without departing from its spirit or essential characteristics. The embodiments described above are therefore considered to be illustrative in all respects and not restrictive, the scope of the invention being indicated by the appended claims rather than by the foregoing description.

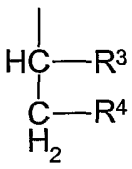
What is claimed is:

1. An otic composition comprising an otic drug and a carrier, wherein the carrier comprises a low molecular weight compound having a molecular weight of 150 – 4000, the carrier reversibly changes from solid to liquid at a temperature of 32 – 37 °C, and the low molecular weight compound has the formula:



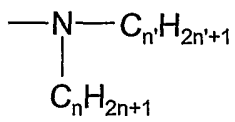
(I)

wherein R^1 is -H, -OH, -COOH, $-C_nH_{2n+1-2m}$, $-COOC_nH_{2n+1-2m}$, $-COO(CH_2CH_2O)_nCH_2CH_2OH$, $-CH_2R^3$, or

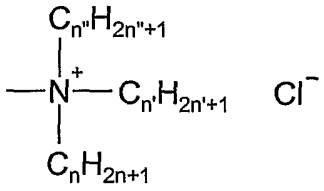


;

R^2, R^3 and R^4 are independently –H, -OH, -COOH, $-C_nH_{2n+1-2m}$, $-OOCC_nH_{2n+1-2m}$, $-COOC_nH_{2n+1-2m}$, $-COO(CH_2CH_2O)_nCH_2CH_2OH$, $-C_nH_{2n+1-2m}COO(CH_2CH_2O)_nCH_2CH_2OH$, $-OOCC_nH_{2n+1-2m}COOC_{n'}H_{2n'+1-2m'}$, $-COO^-Na^+$, $-COO^-K^+$, $-SO_3H$, $-SO_3^-Na^+$, $-SO_3^-K^+$, $-NH_2$, -Cl,



, or



;

n, n' and n" are independently 0 – 50; and

m, m' and m" are independently 0 – 10.

2. The otic composition of Claim 1 wherein the composition does not contain any polymeric ingredient and the carrier consists essentially of one or more low molecular weight compounds of formula (I).

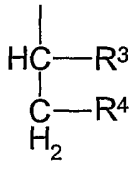
3. The otic composition of Claim 1 wherein the low molecular weight compound of formula (I) has a molecular weight ≤2000.

4. The otic composition of Claim 3 wherein the low molecular weight compound of formula (I) has a molecular weight ≤1000.

5. The otic composition of Claim 1 wherein the carrier contains two or more low molecular weight compounds of formula (I).

6. The otic composition of Claim 1 wherein

R^1 is, $-C_nH_{2n+1-2m}$, $-COOC_nH_{2n+1-2m}$, $-COO(CH_2CH_2O)_nCH_2CH_2OH$, $-CH_2R^3$, or



;

R^2, R^3 and R^4 are independently –H, -OH, -COOH, $-C_nH_{2n+1-2m}$,

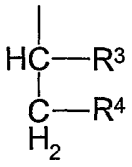
$-OOCC_nH_{2n+1-2m}$, $-COOC_nH_{2n+1-2m}$, $-COO(CH_2CH_2O)_nCH_2CH_2OH$,
$-C_nH_{2n+1-2m}COO(CH_2CH_2O)_nCH_2CH_2OH$, or
$-OOCC_nH_{2n+1-2m}COOC_{n'}H_{2n'+1-2m'}$;

n, n' and n" are independently 0 – 40; and

m, m' and m" are independently 0 – 5.

7. The otic composition of Claim 6 wherein

R^1 is



;

R^2, R^3 and R^4 are independently –H, -OH, -COOH, $-C_nH_{2n+1-2m}$, or
$-OOCC_nH_{2n+1-2m}$;

n, n' and n" are independently 0 – 30; and

m, m' and m" are independently 0 – 3.

8. The otic composition of Claim 1 wherein the total concentration of the low molecular weight compound of formula (I) in the composition is at least 10 % (w/w).

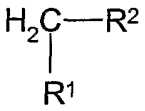
9. The otic composition of Claim 8 wherein the total concentration of the low molecular weight compound of formula (I) in the composition is at least 30 % (w/w).

10. The otic composition of Claim 8 wherein the total concentration of the low molecular weight compound of formula (I) in the composition is at least 50 % (w/w).

11. The otic composition of Claim 1 wherein the otic drug is one or more compounds selected from the group consisting of anti-infective agents;

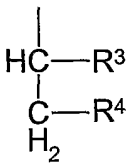
non-steroidal anti-inflammatory agents; steroidal anti-inflammatory agents; and anti-pain agents.

12. A method of delivering an otic drug to the ear comprising the steps of (a) preparing an otic composition comprising the otic drug and a carrier, wherein the carrier comprises a low molecular weight compound having a molecular weight of 150 – 4000, the carrier reversibly changes from solid to liquid at a temperature of 32 – 37 °C, and the low molecular weight compound has the formula:



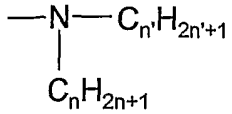
(I)

wherein R^1 is -H, -OH, -COOH, $-C_nH_{2n+1-2m}$, $-COOC_nH_{2n+1-2m}$, $-COO(CH_2CH_2O)_nCH_2CH_2OH$, $-CH_2R^3$, or

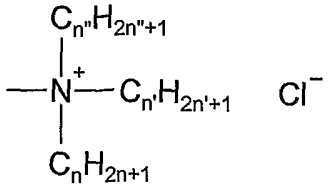


;

R^2, R^3 and R^4 are independently –H, -OH, -COOH, $-C_nH_{2n+1-2m}$, $-OOCC_nH_{2n+1-2m}$, $-COOC_nH_{2n+1-2m}$, $-COO(CH_2CH_2O)_nCH_2CH_2OH$, $-C_nH_{2n+1-2m}COO(CH_2CH_2O)_nCH_2CH_2OH$, $-OOCC_nH_{2n+1-2m}COOC_{n'}H_{2n'+1-2m'}$, $-COO^-Na^+$, $-COO^-K^+$, $-SO_3H$, $-SO_3^-Na^+$, $-SO_3^-K^+$, $-NH_2$, -Cl,



, or



;

n, n' and n" are independently 0 – 50; and

m, m' and m" are independently 0 – 10.

and

(b) inserting the composition prepared in step (a) in the ear.

13. The method of Claim 12 wherein the composition prepared in step (a) is dropped, injected, deposited, or sprayed into the external ear.

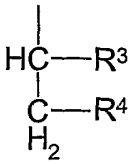
14. The method of Claim 13 wherein the composition prepared in step (a) is warmed to a temperature above 32 °C and administered topically or locally as an ear drop or through a cannula.

15. The method of Claim 12 wherein the composition prepared in step (a) does not contain any polymeric ingredient and the carrier consists essentially of one or more low molecular weight compounds of formula (I).

16. The method of Claim 12 wherein the low molecular weight compound of formula (I) has a molecular weight ≤2000.

17. The method of Claim 12 wherein

R^1 is, $-C_nH_{2n+1-2m}$, $-COOC_nH_{2n+1-2m}$, $-COO(CH_2CH_2O)_nCH_2CH_2OH$, $-CH_2R^3$, or



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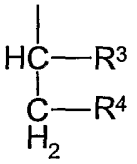
R^2, R^3 and R^4 are independently –H, -OH, -COOH, $-C_nH_{2n+1-2m}$, $-OOCC_nH_{2n+1-2m}$, $-COOC_nH_{2n+1-2m}$, $-COO(CH_2CH_2O)_nCH_2CH_2OH$, $-C_nH_{2n+1-2m}COO(CH_2CH_2O)_nCH_2CH_2OH$, or $-OOCC_nH_{2n+1-2m}COOC_{n'}H_{2n'+1-2m'}$;

n, n' and n" are independently 0 – 40; and

m, m' and m" are independently 0 – 5.

18. The method of Claim 17 wherein

R^1 is



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R^2, R^3 and R^4 are independently –H, -OH, -COOH, $-C_nH_{2n+1-2m}$, or $-OOCC_nH_{2n+1-2m}$;

n, n' and n" are independently 0 – 30; and

m, m' and m" are independently 0 – 3.

19. The method of Claim 12 wherein the total concentration of the low molecular weight compound of formula (I) in the composition prepared in step (a) is at least 10 % (w/w).

20. The method of Claim 12 wherein the otic drug is one or more compounds selected from the group consisting of anti-infective agents; non-steroidal anti-inflammatory agents; steroidal anti-inflammatory agents; and anti-pain agents.

INTERNATIONAL SEARCH REPORT

Inte nal Application No
PCT/US 03/20658

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K47/00 A61K47/14 A61K47/26

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

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, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 279 519 A (BOOTS CO PLC) 24 August 1988 (1988-08-24) page 2, line 28-41 page 3, line 11 - line 14 page 3, line 39 - line 58 examples 3-5 ---	1-20
Y	EP 0 940 138 A (SEIKEN CHEMICAL CO LTD ;YOSHIMIZU KIMIKO (JP)) 8 September 1999 (1999-09-08) page 4, line 32 -page 5, line 36 examples ---	1-20
Y	WO 01 22936 A (ALCON UNIVERSAL LTD ;SINGH ONKAR N (US); BHAGAT HARESH G (US)) 5 April 2001 (2001-04-05) page 2, line 25 -page 4, line 10 examples --- -/--	1-20

[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
24 September 2003	10/10/2003

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	Giménez Miralles, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter ›nal Application No
PCT/US 03/20658

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 00 18388 A (ALCON LAB INC ;CAGLE GERALD (US); STROMAN DAVID W (US); YANNI JOHN) 6 April 2000 (2000-04-06) page 2, line 26 -page 4, line 2 page 9, line 22 - line 27 page 10, line 15 - line 28 examples	1-20
Y	EP 0 420 056 A (VANDEMOORTELE INT NV) 3 April 1991 (1991-04-03) the whole document	1-20

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 12-20 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.

Continuation of Box I.1

Claims Nos.: 12-20

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

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Continuation of Box I.2

Claims Nos.: 1 partially

Present independent claim 1 relates to an extremely large number of possible compounds/compositions, namely otic compositions wherein the carrier is at least one compound of formula (I).

Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds/compositions claimed, namely those wherein the carrier of formula (I) is a propyleneglycol or glyceryl ester of saturated C8-C18 fatty acids, or mixtures thereof, such as i.a. those commercially available under the trade names "Monosteol"(R) or "Gelucire"(R). Other compounds encompassed in formula (I) cannot be considered to be disclosed in the application, because they are not shown to solve the relevant technical problem, namely the provision of otic compositions melting in the temperature range 32-37°C. Furthermore, formula (I) encompasses compouds such as e.g. CH4, CH3OH, acetic acid or glycerol, which obviously do not fall within the required molecular weight range, nor within the required melting point range, and clearly do not solve the relevant technical problem addressed in the application. This fact results in an inconsistency rendering the claims unclear.

Accordingly , 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. 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 compositions wherein the carrier is one of those indicated above, as defined in the description (p.4, l.15 to p.5, l.1) and in the examples.

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

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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.

INTERNATIONAL SEARCH REPORT

national application No.
PCT/US 03/20658

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. [X] Claims Nos.: 12-20
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [X] Claims Nos.: 1 partially
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.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte nal Application No
PCT/US 03/20658

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
EP 0279519	A	24-08-1988	EP	0279519 A1	24-08-1988
			GB	2202741 A	05-10-1988
EP 0940138	A	08-09-1999	AU	733225 B2	10-05-2001
			AU	3358797 A	02-02-1998
			EP	0940138 A1	08-09-1999
			CA	2259433 A1	15-01-1998
			WO	9801113 A1	15-01-1998
			JP	3195756 B2	06-08-2001
			JP	10291961 A	04-11-1998
			KR	2000022433 A	25-04-2000
WO 0122936	A	05-04-2001	AU	7057000 A	30-04-2001
			BR	0014203 A	21-05-2002
			CA	2379605 A1	05-04-2001
			CN	1376054 T	23-10-2002
			EP	1214056 A1	19-06-2002
			JP	2003510263 T	18-03-2003
			TR	200200737 T2	21-08-2002
			WO	0122936 A1	05-04-2001
			US	6284804 B1	04-09-2001
			US	2001034339 A1	25-10-2001
WO 0018388	A	06-04-2000	AU	1310300 A	17-04-2000
			BR	9914109 A	12-06-2001
			CA	2342603 A1	06-04-2000
			EP	1117402 A2	25-07-2001
			JP	2002525319 T	13-08-2002
			WO	0018388 A2	06-04-2000
			US	6509327 B1	21-01-2003
			US	6395746 B1	28-05-2002
			US	2002022629 A1	21-02-2002
EP 0420056	A	03-04-1991	DE	69005960 D1	24-02-1994
			DE	69005960 T2	05-05-1994
			EP	0420056 A2	03-04-1991
			ES	2062242 T3	16-12-1994