PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 3 :		(11) International Publication Number:
A61K 31/54, 45/00; A61L 9/04	A1	WO 83/ 03544
		(43) International Publication Date: 27 October 1983 (27.10.83)

(21) International Application Number: PCT/US83/00484

(22) International Filing Date: 5 April 1983 (05.04.83)

(31) Priority Application Number: 365,539

(32) Priority Date: 5 April 1982 (05.04.82)

(33) Priority Country: US

(71) Applicant: ALCON LABORATORIES, INC. [US/US]; 6201 South Freeway, Fort Worth, TX 76101 (US).

(72) Inventor: YORK, Jr., Billie, Murray ; 3828 Winifred, Fort Worth, TX 76133 (US).

(74) Agents: WATT, Phillip, H. et al.; Fitch, Even, Tabin & Flannery, Room 900, 135 South La Salle Street, Chicago, IL 60603 (US).

(81) Designated States: DK, JP.

Published
With international search report.

(54) Title: PERFLUOROHYDROCARBONS AS VEHICLES FOR ADMINISTERING DRUGS

(57) Abstract

Perfluorohydrocarbons are used as vehicles for administering therapeutic drugs.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	**LI**	Liechtenstein
AU	Australia	**LK**	Sri Lanka
BE	Belgium	**LU**	Luxembourg
BR	Brazil	**MC**	Monaco
CF	Central African Republic	**MG**	Madagascar
CG	Congo	**MR**	Mauritania
CH	Switzerland	**MW**	Malawi
CM	Cameroon	**NL**	Netherlands
DE	Germany, Federal Republic of	**NO**	Norway
DK	Denmark	**RO**	Romania
FI	Finland	**SE**	Sweden
FR	France	**SN**	Senegal
GA	Gabon	**SU**	Soviet Union
GB	United Kingdom	**TD**	Chad
HU	Hungary	**TG**	Togo
JP	Japan	**US**	United States of America
KP	Democratic People's Republic of Korea		

PERFLUOROHYDROCARBONS AS VEHICLES FOR ADMINISTERING DRUGS

This invention relates to compositions for administration of drugs, and, more particularly, this invention relates to compositions containing perfluorohydrocarbon vehicles for drugs for ocular or dermatological application.

Many therapeutic drugs have the disadvantage of being relatively unstable in an aqueous medium. Examples of this category of drugs include cephaloridine, cefamandole, cefamandole nafate, cefazolin, cefoxitin, cephacetrile sodium, cephalexin, cefoperazone sodium, cephaloglycin, cephalosporin C, cephalothin, nafcillin sodium, cephamycins, cephapirin sodium, cephradine, penicillin BT, penicillin N, penicillin O, phenethicillin potassium, pivampicillin, amoxicillin, ampicillin, thienamycin, moxalactam, and cefatoxin.

Many therapeutic drugs are relatively water-insoluble. Examples of this category of drugs include vidarabine, prednisolone, prednisolone acetate, hydrocortisone, hydrocortisone acetate, hydrocortisone valerate, fluorometholone, fluocinolone acetonide, triamcinolone acetonide, dexamethasone, dexamethasone acetate, indomethacin, ibuprofen, and oxyphenbutazone.

Typically, oils or ointments have been used as vehicles for therapeutic drugs which are not stable in an aqueous medium or are relatively insoluble in an aqueous medium. These vehicles often are messy, leave a greasy afterfeel, and are particularly undesirable from a patient's perspective for topical application to the eye. Further, because of their nature, oils and ointments do not readily provide a metered dose to the area of application.

A need exists, therefore, for an improved vehicle for the topical ocular or dermatological application of therapeutic drugs which are

water-unstable, or relatively insoluble in an aqueous medium.

It has been found that perfluorohydrocarbons serve as ideal inert, nontoxic vehicles to provide a metered dose of ocular or dermatological drugs. The perfluorohydrocarbon vehicle is an ideal vehicle to provide a metered dose of ocular or dermatological drugs which are unstable in an aqueous medium.

The perfluorohydrocarbons useful as vehicles are perfluorocycloalkanes, perfluoroalkanes, and perfluorotrialkylamines such as perfluorotripropylamine, perfluorotributylamine, perfluorotripentylamine, and mixtures thereof having a vapor pressure about 1 to about 16 mm Hg. Although the perfluorohydrocarbon may be in the form of an aqueous microemulsion, in the preferred form of the invention, the perfluorohydrocarbon may form the entire vehicle. Specific examples of perfluorohydrocarbons include perfluorodecalin, $C_{10}F_{18}$ which has a vapor pressure of 12.7 mm Hg at 37°C., perfluorotributylamine, $N(CF_2CF_2CF_2CF_3)_3$ which has a vapor pressure of 1.14 mm Hg at 37°C.; perfluoromethyldecalin which has a vapor pressure of 4.8 mm Hg at 37°C.; perfluorocyclohexyldiethylamine which has a vapor pressure of 8.7 mm Hg at 37°C.; perfluoroisopentylpyran which has a vapor pressure of 9.9 mm Hg at 37°C.; perfluorodibutylmethylamine which has a vapor pressure of 16.0 mm Hg at 37°C.; and perfluorobutyltetrahydrofuran. These compounds are known for their use in blood substitutes, are nontoxic, are approved for human systemic use in various countries including the United States, generally are transparent and colorless and leave no stains, are relatively inert, and are easily prepared from commercially available chemicals, or are commercially available.

The inert nature and the vapor pressure of the

fluorohydrocarbons of the invention are an important aspect of the invention. The inert nature of perfluorohydrocarbons permits them to be used by the patient with little or no toxic danger. The vapor pressure of the perfluorohydrocarbons of the invention permits the perfluorohydrocarbon vehicle to vaporize to provide a metered dose of a therapeutic drug, yet in ocular use not cause discomfort to the eye as would be the case with an ointment or cream. Further, the vapor pressure of the perfluorohydrocarbons of the invention do not create messy conditions with nonaqueous ocular or dermatological use which are normally associated with drugs used with nonaqueous vehicles.

The perfluorohydrocarbons of the invention may be used as a vehicle for therapeutic drugs which are not stable or soluble in water. Where therapeutic drugs are not compatible with aqueous vehicles, the drugs may be suspended or emulsified in the perfluorohydrocarbons of the invention. Vaporization of the perfluorohydrocarbons meters the dosage of the therapeutic drug suspended in the perfluorohydrocarbons.

The effective amount of perfluorohydrocarbons used in the invention will depend upon whether the use is ocular or dermatological, the metered dose desired, and the selection as well as strength of the drug to be applied. Generally, an effective amount of perfluorohydrocarbons is provided for ocular use when the ophthalmic composition contains between about 98 percent and about 99.99 percent by weight perfluorohydrocarbons. For dermatological use, generally an effective amount of perfluorohydrocarbons is provided when the composition contains between about 97 percent and about 99.99 percent by weight perfluorohydrocarbons.

The following examples typify the manner by

which the present invention can be practiced. The examples should be construed as illustrative, and not as a limitation upon the overall scope of the invention.

Example I

Sodium cefamandole powder (1.0g supplied by Eli Lilly Co.) is added to perfluorotributylamine (200cc supplied by Pfaltz and Bauer), is manually or mechanically shaken and a uniform 0.5 percent w/v suspension results. On standing, the sodium cefamandole will float to the top of the vehicle; however manual shaking will readily resuspend the sodium cefamandole antibiotic uniformly.

Example II

Indomethacin powder (1.0g) is added to perfluorotributylamine (200cc supplied by Pfaltz and Bauer) and is manually shaken to yield a uniform 0.5 percent w/v suspension. On standing, the indomethacin will float to the top of the vehicle; however, manual shaking will readily resuspend the indomethacin antiinflammatory agent uniformly.

In Vitro Evaluation Of Stability

Sodium cefamandole is stable only for hours at room temperature in aqueous solution. In the perfluorotributylamine vehicle at room temperature, however, sodium cefamandole was found to be chemically stable for five months. Further, after the five months the sodium cefamandole lost no antibacterial activity when evaluated in standard microbiological *in vitro* assays.

In Vivo Evaluation Of Formulation

In a study involving eight groups of six albino rabbits (12 eyes per group), sodium cefamandole as formulated in Example I of the invention was found to be as effective as freshly prepared 0.5 percent w/v aqueous sodium cefamandol in eradicating ocular infection and more effective than 0.5% w/v chloramphenicol ophthalmic

solution, U.S.P., which is a commerically recognized ocular drug product.

The study was conducted as follows:

a) Twenty-four albino rabbits were inoculated in their corneas (48 eyes) with Staphylococcus aureus. At random, six of these inoculated rabbits became treatment Group A, six became treatment Group B, six became treatment Group C, and six became the untreated control Group D.

b) Twenty-four albino rabbits were inoculated in their corneas (48 eyes) with Streptococcus pneumoniae (formerly Diplococcus pneumoniae). At random, six of these inoculated rabbits became treatment Group E, six became treatment Group F, six became treatment Group G, and six untreated became the control Group H.

Groups A and E were treated with an Example I formulation (0.5% w/v) of the sodium cefamandole in perfluorotributylamine. Groups B and F were treated with freshly prepared (0.5% w/v) aqueous sodium cefamandole. Groups C and G were treated with a solution of (0.5% w/v) chloramphenicol ophthalmic solution, U.S.P.

The study was conducted as follows:

Group A was treated with one drop (100 ul) of 0.5% w/v sodium cefamandole in perfluorotributylamine one hour post inoculation and then once an hour thereafter for a total of nine doses. Then the eyes were graded for signs of infection 24 hours thereafter. At that time the eyes were examined with a slit lamp microscope. All eyes were found without signs of infection and all eyes (12) were found to be normal.

Group B was treated with one drop (100 ul) of freshly prepared 0.5% w/v aqueous sodium cefamandole one hour post inoculation and then once an hour thereafter for a total of nine doses. The ocular observations were as that stated for Group A. All eyes were found without

signs of infection at 24 hours. All eyes (12) were found to be normal.

Group C was treated with drops (100 ul each) of 0.5% w/v chloramphenicol ophthalmic solution, U.S.P., as in the protocol of Groups A and B. In this case, the eyes showed signs of infection particularly at 24 hours. Eleven of twelve eyes showed signs of infection.

Group D was untreated and all eyes (12) showed signs of infection at 24 hours.

Group E was treated with one drop (100 ul) of 0.5% w/v sodium cefamandole in perfluorotributylamine one hour post inoculation and then once an hour thereafter for a total of nine doses. Then the eyes were graded for signs of infection at 24, 48 and 72 hours with gross and slit lamp microscopic observation. Most eyes (11/12) were found without signs of infection and normal at 72 hours.

Group F was treated with drops (100 ul each) of 0.5% w/v of sodium cefamandole as in the protocol of Group E. As in the case of Group E most eyes (10/12) were found to be without infection and normal at 72 hours.

Group G was treated with drops (100 ul each) of 0.5% chloramphenicol ophthalmic solution, U.S.P., as in the protocol of Group E. In this case, most eyes (10/12) at 72 hours showed signs of infection.

Group H was untreated and all eyes (12) showed signs of infection at 72 hours.

The conclusion is that sodium cefamandole in trifluorotributylamine is as effective as soluble sodium cefamandole in aqueous vehicle except that the cefamandole is stable for substantially longer periods than water-solubilized sodium cefamandole. In the perfluorotributylamine, the B-lactam ring of cefamandole is not subject to either acid-catalyzed or base-promoted hydrolysis because water is not present to react.

In Vivo Ocular Tolerance Of The
Perfluorotributylamine Vehicle

In one day, multiple (12) topical ocular dose (50 ul drops) regiments of neat perfluorotributylamine vehicle were applied to albino rabbit eyes. There were no detectable untoward ocular side-effects.

It should be understood that while certain preferred embodiments of the present invention have been illustrated and described, various modifications thereof will become apparent to those skilled in the art. Accordingly, the scope of the present invention should be defined by the appended Claims and equivalents thereof.

Various features are set forth in the following claims.

WHAT IS CLAIMED IS:

1. A composition for use in pharmaceutics comprising:

a perfluorohydrocarbon vehicle having a vapor pressure at 37°C. from about 1 to about 16 mm Hg.; and

a therapeutic drug.

2. A composition for topically administering therapeutic drugs comprising:

a perfluorohydrocarbon vehicle having a vapor pressure at 37°C. of from about 1 to about 16 mm Hg.; and a therapeutic drug.

3. A composition as recited in Claims 1 or 2 wherein said perfluorohydrocarbon vehicle comprises a perfluoroalkane.

4. A composition as recited in Claims 1 or 2 wherein said perfluorohydrocarbon vehicle comprises a perfluorocycloalkane.

5. A composition as recited in Claims 1 or 2 wherein said perfluorohydrocarbon vehicle comprises a perfluorotrialkylamine having from 9 to 15 carbon atoms.

6. A composition as recited in Claims 1 or 2 wherein perfluorohydrocarbon vehicle comprises perfluorodecalin.

7. A composition as recited in Claims 1 or 2 wherein said perfluorohydrocarbon vehicle comprises perfluorotributylamine.

8. A composition as recited in Claims 1 or 2 wherein perfluorohydrocarbon vehicle comprises perfluoromethyldecalin.

9. A composition as recited in Claims 1 or 2 wherein said perfluorohydrocarbon vehicle comprises perfluorocyclohexyldiethylamine.

10. A composition are recited in Claims 1 or 2

wherein said perfluorohydrocarbon vehicle is perfluoroisopentylpyran.

11. A composition as recited in Claims 1 or 2 wherein said perfluorohydrocarbon vehicle comprises perfluorodibutylmethylamine.

12. A composition as recited in Claims 1 or 2 wherein perfluorohydrocarbon vehicle comprises perfluorobutyltetrahydrofuran.

13. A method of applying therapeutic drugs comprising administering a composition comprising an effective amount of a therapeutic drug; and a perfluorohydrocarbon vehicle having a vapor pressure at 37°C. from about 1 to about 16 mm Hg.

14. A method as recited in Claim 13 wherein said perfluorohydrocarbon vehicle comprises a perfluoroalkane.

15. A method as recited in Claim 13 wherein said perfluorohydrocarbon vehicle comprises perfluorocycloalkane.

16. A method as recited in Claim 13 wherein said perfluorohydrocarbon vehicle comprises a perfluorotrialkylamine having from 9 to 15 carbon atoms.

17. A method as recited in Claim 13 wherein said perfluorohydrocarbon vehicle comprises perfluorodecalin.

18. A method as recited in Claim 13 wherein said perfluorohydrocarbon vehicle comprises perfluorotributylamine.

19. A method as recited in Claim 13 wherein said perfluorochyrocarbon vehicle comprises perfluoromethyldecalin.

20. A method as recited in Claim 13 wherein said perfluorohydrocarbon vehicle comprises perfluorocyclohexyldiethylamine.

21. A method as reicted in Claim 13 wherein said perfluorohydrocarbon vehicle comprises

perfluoroisopentylpyran.

22. A method as recited in Claim 13 wherein said perfluorohydrocarbon vehicle comprises perfluorodibutylmethylamine.

23. A method as recited in Claim 13 wherein said perfluorohydrocarbon vehicle comprises perfluorobutyltetrahydrofuran.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US83/00484

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [3]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int. Cl.3- A61K - 31/54 A61K-45/00 : U.S. Cl. 424/246, 45, 366
A61L - 9/04 :

II. FIELDS SEARCHED

Minimum Documentation Searched [4]

Classification System	Classification Symbols
U.S.	424/246, 45, 366

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [5]

Lexis Computer Search
Chemical Abstract - perfluorocarbons - 1962-present

III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

Category *	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No. [18]
Y	US,A 3,929,662, published December 30, 1975 Boucher-(See Table II)	1-23
A	US,A 3,282,781, published November 1, 1966 Macek et al.	1-23
Y	Merck, 9th Ed., pp 247-250	1-23
Y	US,A 3,490,923, published January 20, 1970 Eiseman	1,2,4,13&15
A	US,A 4,252,827, published February 24, 1981 Yokoyama et al.	1-23
A	US,A 3,958,014, published May 18, 1976 Watanabe et al.	1-23
A	US,A 2,968,628, published January 17, 1961 Reed	1-23
A	US,A 3,823,091, published July 9, 1974 Samejima et al.	1-23
A	US,A 4,110,474, published August 29, 1978 Lagow et al.	1-23

* Special categories of cited documents: [15]

"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

"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

IV. CERTIFICATION

Date of the Actual Completion of the International Search [2]	Date of Mailing of this International Search Report [2]
13 July 1983	09 AUG 1983
International Searching Authority [1]	Signature of Authorized Officer [20]
ISA/US	

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, 16 with indication, where appropriate, of the relevant passages 17	Relevant to Claim No 18
A	Chemical Abstracts, Vol. 96, issued 1980 Beloyartsev (USSR), Perfluorinated Carbons in Biology and Medicine. Abstract No.74540e	
A	Chemical Abstracts, Vol.96, issued 1980, Koho (Japan), Ointments containing fluorinated organic compounds for improvement of skin respiration. See page 377. Abstract No. 223266z	

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

A	US, A 4,187,252, published February 5, 1980 Lagow et al.	1-23
A	Chemical Abstracts, Vol. 94, 1979 25 June, White (USA) Use of perfluorocarbon as a burn treatment. See page 377, column 1, Abstract No. 145366z	
A	Chemical Abstracts, Vol. 96, issued 1980, Beloyartsev (USSR) Perfluorinated Carbons in Biology and Medicines, See page 406. Abstract No. 91627f	

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [10]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers . . because they relate to subject matter [12] not required to be searched by this Authority, namely:

2. ☐ Claim numbers . . . . . , 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 [13], specifically:

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [11]

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 of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☐ 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 claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.