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(57) Abstract

Compositions containing drug– or therapeutic agent–containing solutions and fluorocarbons are disclosed for pulmonary delivery of the drug or therapeutic agent. Suitable fluorocarbons have relatively high vapor pressures or corresponding low boiling points, preferably between about –30° to about 150 °C, and include dodecafluoropentane, dodecafluoroneopentane, perfluorocyclopentane, perfluoro–2–methyl pentane, perfluorohexane, perfluoroheptane, perfluorooctane, perfluorodecalin and isomers and mixtures thereof. Aerosolized emulsions of these fluorocarbons produce fine aerosol particles of ≤ 5 μm and can also provide for improved solubility of the drug or therapeutic agent. The fluorocarbons also have high enough vapor pressures, and are used in small enough amounts, to effectively deliver the drug or therapeutic agent to the lung and then to leave the air spaces of the lungs via evaporation.

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EMULSIONS FOR AEROSOLIZATION AND DRUG DELIVERY

This application claims the benefit of U.S. Provisional Application No. 60/065,003, filed November 10, 1997, which is incorporated herein by reference.

BACKGROUND OF THE INVENTION

1. Field of The Invention

The present invention is directed to compositions suitable for pulmonary drug delivery, more particularly, to compositions containing a fluorocarbon and a drug or a therapeutic agent which can be administered to the lungs of a patient.

2. Description of the Related Art

Effective delivery of drugs and therapeutic agents to the lungs of a patient has long been sought as a simple and convenient means to administer a drug or therapeutic agent to a patient, as compared to other conventional methods such as, for example, oral ingestion, or intravenous or intramuscular injection. In particular, pulmonary aerosols have been considered as such an easy and convenient means for drug delivery.

Dry powders containing drugs or therapeutic agents, or solutions or suspensions containing drugs or therapeutic agents have been considered as pulmonary aerosols. Dry drug powders with fine particle size are produced by mechanical or jet milling processes, then administered to patients using dry powder inhaling devices. Drug solutions or suspensions are administered to patients as aerosols with metered dose inhalers or with spray ultrasonic

nebulizers. One drawback of these methods is that less than 20% of the administered dose is typically delivered to the lungs. Most of the drug or therapeutic agent is either impacted onto the delivery device or lost in the mouth or the back of the throat due to the large size of the drug particles or aerosolized droplets. Aqueous aerosols of drug solutions in particular suffer from large aerosol particle size. Variations in drug solubility also hamper the effectiveness of such aqueous aerosols.

Other methods of delivering drugs or therapeutic agents to the lungs include intratracheal instillation of a drug solution or other delivery agent to the lungs. The disadvantage of intratracheal instillation is that it is quite invasive and requires intubation of the patient, as compared to the ease and non-invasive nature of inhalation of a pulmonary aerosol. U.S. Patent 5,531,219 to Rosenberg, which is hereby incorporated by reference, describes the use of low vapor pressure, oxygenated fluorocarbons, such as perfluorooctylbromide, for delivering a medicament to the lungs. This process includes the steps of: instilling a volume of a fluorocarbon into the lungs, dispersing a microparticulate medicament in a breathable gas to form a gas/medicament dispersion, and introducing the dispersion into the pulmonary air spaces such that the initial fluorocarbon and the gas-dispersed medicament are present simultaneously in the lungs of the patient. The instillation of the fluorocarbon in this process likewise requires intubation of the patient.

For these reasons, pulmonary drug delivery agents which are easy to administer and easily removed from the lungs, are desirable. In

particular, there is a need for pulmonary drug delivery agents that provide for aerosols with reduced particle size for more effective delivery of the drug or therapeutic agent to the lungs. In addition to reduced particle size, reduced surface tension of aerosolized particles would also improve the effectiveness of drug delivery as it would increase surface spreading of the particle upon deposition. In the best case, modifications to, or substitutes for, any known agents would not compromise other beneficial properties of the known agents, such as overall biocompatibility. In all cases, being able to maximize the amount of drug or therapeutic agent effectively administered to the patient while minimizing amount of the delivery agent used would be desirable.

SUMMARY OF THE INVENTION

The present invention meets the above and other needs and is directed to pulmonary drug delivery agents comprising drug- or therapeutic agent-containing solutions and relatively high vapor pressure, low boiling point fluorocarbons, and to methods of their use. The invention is further directed to providing pulmonary aerosols of these formulations having reduced aerosol particle size for improved delivery, reduced surface tension of the aerosolized droplets for better surface spreading properties once deposited, and facilitated exhalation of the delivery agent to minimize the amount of the delivery agent used. Therapeutic agents, drugs or other medicaments or pharmaceutical compositions that can be used in the present invention include, for example, those agents, drugs, medicaments or compositions that are useful for the treatment of cancer, cystic fibrosis, pulmonary infections, neonatal premature lungs, adult respiratory distress syndrome (ARDS), pneumonia, *Pneumocystis carinii* infections, bacterial, fungal and viral infections, diabetes, anemia, hypopituitarism, osteoporosis and cardiovascular diseases and others.

Fluorocarbons effective for use in the present invention have relatively high vapor pressures or corresponding low boiling points. Specifically, those fluorocarbons having a boiling point between about -30° to about 150°C are preferred. In addition, of the high vapor pressure, low boiling point fluorocarbons chemicals used in the invention, those having good biocompatibility are also preferred. Perfluorocarbons are most preferred as a result of their stability. Examples of preferred perfluorocarbons include dodecafluoropentane, dodecafluoroneopentane, perfluorocyclopentane,

perfluoro-2-methyl pentane, perfluorohexane, perfluoroheptane, perfluorooctane, perfluorodecalin and isomers and mixtures thereof. In a most preferred embodiment of the invention, perfluoro-2-methyl pentane, perfluorohexane, perfluorooctane or perfluorodecalin are used, either singly or in mixtures.

The delivery agents of one embodiment of the invention are stable water-in-oil emulsions or microemulsions of an aqueous dispersed phase containing a water-soluble therapeutic agent and a fluorocarbon continuous phase formed of high vapor pressure, low boiling point fluorocarbons effective for use in the invention. These emulsions are stable and capable of being aerosolized and produce fine aerosol particles for effective delivery of the therapeutic agent to the pulmonary system of a patient by inhalation. In another embodiment of the invention, the emulsions or microemulsions can also include one or more fluorosurfactants for further stabilizing the emulsions or microemulsions. In yet another embodiment of the invention, the emulsions or microemulsions include a fluorosurfactant and an additional fluorine-containing cosurfactant. Preferred cosurfactants include partially or fully fluorinated primary n-alcohols and fluorinated acids. The addition of these cosurfactants can significantly increase the volume of water that can be effectively emulsified, thereby allowing for incorporation of larger quantities of water-soluble therapeutic agents for pulmonary delivery.

The invention further provides for methods of delivering a drug or therapeutic agent to the pulmonary system of a patient using formulations of the invention. One such method involves the steps of preparing a stable water-in-oil emulsion or

microemulsion in which a water-soluble therapeutic agent is dissolved in an aqueous continuous phase the emulsion or microemulsion, the oil phase of the emulsion or microemulsion comprising a high vapor pressure, low boiling point fluorocarbon effective for use in the invention. The emulsion or microemulsion is then delivered to the pulmonary system of a patient. The delivery step may be accomplished by aerosolizing the emulsion or microemulsion. Alternatively, the emulsion or microemulsion can be directly instilled into the patient's lungs.

DETAILED DESCRIPTION OF THE FIGURE

FIG. 1 is a diagram showing a system for measuring aerosol particle size.

DETAILED DESCRIPTION OF THE INVENTION

Fluorocarbon bio-compatible chemicals most suitable for use as pulmonary drug delivery agents according to the present invention are relatively high vapor pressure, low boiling point fluorocarbons having a boiling point, under standard temperature and pressure conditions, of between about -30°C to about 150°C. These fluorocarbons have high enough vapor pressures, and are used in small enough amounts, to effectively deliver drugs or therapeutic agents to the lung and then to leave the air spaces of the lungs via evaporation. These chemicals have the further advantage that very soon after they are delivered to the lungs, they have completely evaporated, leaving no residue fluorocarbon to produce toxicity or unwanted pharmaceutical effects and leaving a highly concentrated, highly effective dosage of the active medicament. These fluorocarbons

are further advantageous for use as pulmonary drug delivery agents due to their low surface tension, and low viscosity (relative to aqueous solutions), which enables the agent to penetrate deeply into the lungs for maximum efficiency. The low surface tension of the agent further provides for improved spreading properties of the agent upon deposition on lung surfaces that in turn provide for more effective drug delivery to the lungs. The fluorocarbons can also provide for improved solubility of the drug or therapeutic agents.

In addition, the fluorocarbons of the present invention produce fine aerosol particles of $\leq$ 5 μm, making them highly effective for pulmonary drug delivery. Particle size and particle size ranges are important factors for an effective pulmonary drug delivery agent. The preferred particle size of a delivery agent is between 1-6 μm. Aerosolized particles of such a size are able to penetrate and deposit deep into the lungs or alveoli. Larger particles impact and deposit in the upper respiratory tract whereas particles that are too small can be easily exhaled prior to deposition.

Further, fluorocarbons having higher boiling points than those effective for other applications, such as pulmonary lavage, are effective for drug delivery. This is because the amounts of fluorocarbons used for drug delivery are smaller than the amounts used for lung lavage, yet these fluorocarbons still have vapor pressures high enough to ensure adequate evaporation and excretion of the fluorocarbons from the lung air space after deposition of the drug. Of the selected fluorocarbons, those having higher relative boiling points can enhance deeper pulmonary deposition of the medicament, as such fluorocarbons will not evaporate

as quickly during aerosolization and pulmonary delivery as compared to lower boiling point fluorocarbons.

While perfluorocarbons such as dodecafluoropentane, perfluorohexane (perfluoro-2-methyl pentane), perfluorooctane and perfluorodecalin are the preferred fluorocarbons for use in the invention, other high vapor pressure fluorocarbons which are liquids at room temperature, but which vaporize to a significant extent at body temperature will be useful. The following list, showing boiling points and vapor pressures indicates that, for the preferred fluorocarbon compounds, only those having between one to ten carbon atoms will have the necessary vapor pressure characteristics. The following list contains some of the fluorine-containing compounds that are within the scope of the present invention:

Chemical	M.W.	B.P.	C.Group
Propane, 2-(trifluoromethyl)-1,1,1,3,3,3-hexafluoro	211	12.03	
2-Butene, 3-methyl	68	14.0	1
Methane, disilano	76.25	14.7	11
Ethyl nitrite	75.07	16.0	11
Ethyl amine	45.08	16.6	10
Tungsten hexafluoride	298	17.5	11
2,3-Dimethyl-2-norbornano	140.23	19.0	11
Ethylene, 1,1-dichloro-2, 2-difluoro	133	19.0	3
Methane, bromo fluoro	112.93	19.0	3
1-Butene, 3-methyl	70.13	20.0	1
Borine, trimethyl	55.91	20.0	11
Fluorinert, FC-87 (3M Trade Mark)	Unknown	20.0	3
Cyclopropane, 1,1-dimethyl	70.13	20.6	1
Acetaldehyde	44.05	20.8	7
Acetyl flouride	62.04	20.8	9
Borine, dimethyl, methoxy	71.19	21.0	11
Ethylene, 1,2-dichloro-1,2-difluoro	132.92	21.1	3
Ethylene, dichloro difluoro	132.92	21.1	3
Methane, difluoro-iodo	177.92	21.6	3
Diacetylene	50.08	22.0	1
Propylene, 2-chloro	76.53	22.6	3
Carvone- {d}	150.22	23.0	11
Methane, trichlorofluoro	137.37	23.7	3

1,3-Dioxolane-2-one, 4-methyl	102.09	24.2	1
Methane, dibromo difluoro	209.82	24.5	3
2-Pentanone, 4-amino-4-methyl	115.18	25.0	10
Methane, chloro difluoro nitro	131.47	25.0	3
Propane, heptafluoro-1-nitro	215.03	25.0	3
Cyclopentene, 3-chloro	102.56	25.0	3
1,4-Pentadiene	68.12	26.0	1
1,5-Heptadiyne	92.14	26.0	1
3-Butene-2-one, 4-phenyl {trans}	146.19	26.0	2
Propane, 1,1,2,2,3-Pentafluoro	134.06	26.0	3
2-Butyne	54.09	27.0	1
Ethane, 2,2-dichloro-1,1,1-trifluoro	152.9	27.0	3
Cyclopentene, Octafluoro	211.05	27.0	3
1-Nonene-3-yne	122.21	27.0	1
2-Methyl butane	72.15	27.8	1
Butane, 2-methyl	72.15	27.8	1
Ethane, 1,2-dichlorotrifluoro	152.9	28.0	3
Ether, difluoromethyl 2,2,2-trifluoroethyl	150.05	28.0	3
Cyclopropane, 1,2-dimethyl {trans, l}	70.13	28.0	1
Vinyl ether	70	28.0	6
Cyclopropane, 1,2-dimethyl {trans, dl}	70.13	29.0	1
Toluene, 2,4-diamino	122.17	29.0	2
1-Pentene, perfluoro	250.04	29.0	3
1-Butyne, 3-methyl	68.12	29.5	1
1-Pentene	70.13	30.0	1
1-Pentene, 3,3,4,4,5,5,5-heptafluoro	196	30.0	3
Ethylene, idotrifluoro	207.9	30.0	3
Styrene, 3-fluoro	122.14	30.0	11
1-Pentene, 3-bromo	149.03	30.5	3
Pentane, perfluoro	288.04	30.5	3
Ethane, 1,2-difluoro	66.05	30.7	3
Butane, 3-methyl, 1,1,1-trifluoro	126.12	31.0	3
1-Butene, 2-methyl	70.13	31.2	1
Formic acid, methyl ester	60.05	31.5	9
Methane sulfonyl chloride, trifluoro	168.52	31.6	3
Ethane, 1,1-dichloro-1-fluoro	116.95	32.0	3
Pentane, 1-fluoro	90.14	32.0	3
Acetylene-diido	277.83	32.0	3
Propane, 2-amino	59.11	32.4	10
Butane, 1-fluoro	76.11	32.5	3
Methyl isopropyl ether	74.12	32.5	6
Propylene, 1-chloro	76.53	32.8	3
Butyraldehyde, 2-bromo	151	33.0	3
2-Butene, 2-chloro-1,1,1,4,4,4-hexafluoro	198.5	33.0	3
1,3-Butadiene, 1,2,3-trichloro	157.43	33.0	3
Butene, 2-chloro-1,1,1,4,4,4-hexafluoro	199	33.0	3
bis-(Dimethyl phosphino) amine	137.1	33.5	10
1,3-Butadiene, 2-methyl	68.12	34.0	1
1-Butene-3-yne, 2-methyl	66.1	34.0	1
Isoprene	68..12	34.0	1
Methane, chloro dinitro	140.48	34.0	3
Prethane, dichloro	84.93	40.0	3
Methane, iodo-	141.94	42.4	3
Ethane, 1,1-dichloro	98	57.3	3

perfluoro-2-methyl pentane	338.06	58	3
perfluorohexane	338.06	58	3
perfluoroheptane	388.07	80-82	3
perfluorooctane	438.08	99-100	3
perfluorodecalin	462.10	142	3

M.W. is molecular weight.
B.P. is boiling point.
C. Group is chemical group.

CHEMICAL GROUP DESIGNATION
1 Aliphatic hydrocarbons and/or derivatives
2 Aromatic hydrocarbons and/or derivatives
3 Organic halides and/or derivatives
6 Ethers and/or derivatives
7 Aldehydes and/or derivatives
9 Carboxylic acids and/or derivatives
10 Amines and/of derivatives
11 Miscellaneous

Other fluorine-containing compounds which are suitable for use according to the present invention are disclosed in U.S. Pat. Nos. 5,393,524; 5,409,688; 5,558,094 and 5,558,854 which are co-assigned to Sonus Pharmaceuticals Inc., and are hereby incorporated by reference.

Fluorine-containing emulsions are also contemplated in the present invention, such as a liquid-in-liquid emulsion of the type described in U.S. Patent Application No. 08/148,284 and related U.S. Patents Nos. 5,558,853 and 5,558,855 which are co-assigned to Sonus Pharmaceuticals Inc., and are hereby incorporated by reference. Such emulsions are stable and sterilizable. Fluorocarbons with boiling points from -30°C to 150°C are most effective for forming emulsions for aerosolization and drug delivery according to the present invention. These emulsions also yield aerosols with reduced particle size for improved pulmonary delivery, reduced surface tension of the aerosolized droplets for better surface spreading properties once deposited in the lungs, and facilitated exhalation of the drug carrier

due to the high vapor pressure of the fluorocarbon. These emulsions also provide stability over time, and ease of manufacture, as well as ease of use.

Thus, in one form of the invention, a water soluble medicament can be emulsified in a fluorocarbon continuous phase with the use of a surfactant to form a water-in-oil emulsion or a water-in-oil microemulsion. A water-in-oil emulsion of an aqueous dispersed phase and fluorocarbon continuous phase will yield a liquid composition that is milky-white in color, whereas a water-in-oil microemulsion of an aqueous dispersed phase and a fluorocarbon continuous phase will yield a liquid composition that is bluish in color and translucent. The result is a stable water-in-oil emulsion or microemulsion that can be aerosolized for inhalation or alternatively instilled directly into the tracheobronchial tree for pulmonary delivery of the medicament. The fluorocarbon phase is then exhaled leaving the medicament (as dissolved in the water phase) behind for absorption and/or therapeutic effect. The fluorocarbon phase provides greater density to the aerosolized droplets, which assists in penetrating deeper into the pulmonary tree, and also provides for lower surface tension to give enhanced spreading to the droplets upon deposition.

As an example, a water-in-oil microemulsion according to the present invention is obtained by vortexing water (5-20% v/v) with a low boiling point fluorocarbon (95-80% v/v), preferably perfluoro-2-methyl pentane, perfluorohexane, perfluorooctane or perfluorodecalin, in the presence of a low concentration of a fluorosurfactant (0.1-1.5 w/w) together with an additional fluorine-containing cosurfactant. The addition of a cosurfactant(s) causes a relatively large volume of water (10-20%

v/v) to be efficiently emulsified, producing a bluish, translucent liquid. These water-in-oil microemulsions are the preferred formulations of the invention for aerosolization and drug delivery, due to their homogeneity and thermodynamic stability prior to use. Also, as these water-in-oil microemulsions can incorporate relatively large volumes of water, as compared to other emulsions, these water-in-oil microemulsions have the added advantage being able carry and deliver greater quantities of drug or therapeutic agent solubilized in the aqueous phase.

The fluorosurfactants preferred for use in emulsions of the present invention can be both straight chain and branched chain fluorocarbons. These fluorosurfactants can be, for example, PEG Telomer B, DEA-PAS, FSO 100, FSN 100, FC-171, FC-170C, FC-100, FC-129, FC-120, TBS, FSA, or UR, and are preferably PEG Telomer B, FC-171 or FC-170C due to their non-ionic character and low water solubility. Preferred fluorosurfactants for use as cosurfactants include partially or fully fluorinated primary n-alcohols such as 1H,1H-perfluoro-1-octanol or 1H,1H-perfluoro-1-heptanol, and fluorinated acids such as perfluoro-n-octanoic acid or perfluoro-n-decanoic acid. Most preferably, water-in-oil microemulsions are formed by combining the fluorosurfactant PEG Telomer B with the cosurfactants 1H,1H-perfluoro-1-octanol or 1H,1H-perfluoro-1-heptanol.

The general principles of the present invention will be more fully appreciated by reference to the following non-limiting examples.

Example 1

Preparation of Water-in-Oil Emulsions and Microulsions for Aerosolization and Drug Delivery

A water soluble medicament can be emulsified in a fluorocarbon continuous phase with the use of an appropriate surfactant(s) and dispersed within a water-in-oil emulsion or water-in-oil microemulsion. The resulting mixture can be aerosolized for inhalation or instilled directly into the tracheobronchial tree for pulmonary delivery of the medicament.

Water containing a dissolved, therapeutic agent (i.e., insulin) is emulsified by mixing and sonication in perfluorohexane to contain approximately 0.5% water (w/w). The surfactant used is a fluorosurfactant, PEG Telomer B at a concentration of 0.13% (w/w). The dispersion is then aerosolized and administered via inhalation to the subject for pulmonary delivery of the therapeutic agent.

Surfactants sold under the designation FC-170C and FC-171 (3M, Minn) are also useful as fluorosurfactants in the invention. Water-in-oil emulsions are formed as above with water content less than 0.5%(w/w) and FC-170C or FC-171 fluorosurfactant content less than 0.25%(w/w).

A bluish, translucent water-in-oil microemulsion can be produced that contains 20% water (v/v) with the use of an additional surfactant. The aqueous phase containing medicament is emulsified in perfluoro-2-methyl pentane, perfluorohexane, perfluorooctane, perfluorodecalin or other low boiling fluorocarbon with the use of 2% PEG Telomer B and 1.1% 1H,1H-perfluoro-1-octanol or other biocompatible fluorosurfactant. The resultant

microemulsion is then aerosolized for pulmonary drug delivery.

Examples of other formulations of water-in-oil emulsions and water-in-oil microemulsions are listed in Tables 1-3 below. These formulations were prepared by vortexing water (5-20% v/v) with perfluoro-2-methyl pentane, perfluorohexane, perfluorooctane or perfluorodecalin (80-95% v/v) in the presence of a low concentration of the fluorosurfactant PEG Telomer B (2.0-8.0% w/v) together with the additional fluorine-containing cosurfactant 1H,1H-perfluoro-1-octanol or 1H,1H-perfluoro-1-heptanol (1.0-2.5% w/v).

Table 1

Water-in-oil emulsions and microemulsions

Composition	Emulsion Type
95% PFH (v/v), 5% aqueous (v/v) 2.0% PTB (w/v), 1.1% PFOH (w/v)	water-in-oil microemulsion
90% PFH (v/v), 10% aqueous (v/v) 2% PTB (w/v), 1.1% PFOH (w/v)	water-in-oil emulsion
95% PFD (v/v), 5% aqueous (v/v) 2.0% PTB (w/v), 1.1% PFOH (w/v)	water-in-oil microemulsion
90% PFD (v/v), 10% aqueous (v/v) 2% PTB (w/v), 1.1% PFOH (w/v)	water-in-oil emulsion
80% PFD (v/v), 20% aqueous (v/v) 2% PTB (w/v), 1.1% PFOH (w/v)	water-in-oil microemulsion
95% PFD (v/v), 5% aqueous (v/v) 2.0% PTB (w/v), 1.2% PFOH (w/v)	water-in-oil microemulsion
90% PFD (v/v), 10% aqueous (v/v) 2% PTB (w/v), 1.2% PFOH (w/v)	water-in-oil emulsion

emulsion (milky, white solution)
microemulsion (blue, translucent liquid)
PFH = Perfluorohexane (includes the use of perfluoro-2-methyl pentane)
PFD = Perfluorodecalin
PTB = PEG Telomer B
PFOH = 1H,1H-Perfluoro-1-octanol

Table 2
Water-in Oil Emulsion Formulations
(milky white liquid)

Item Number	Continuous Phase (%, v/v)	Dispersed Phase (%, v/v)	Surfactant (%, w/v)	Cosurfactant (%, w/v)
1	90% PFMP*	10% Water	2% PTB	1.0% PFOH
2	90% Perfluorodecalin	10% Water	2% PTB	1.0% PFOH
3	90% Perflurooctane	10% Water	2% PTB	1.0% PFOH

PFMP = perfluoro-2-methyl pentane (includes the use of perfluorohexane)
PTB = PEG Telomer B
PFOctanol = 1H, 1H-Perfluoro-1-octanol
PFHeptanol = 1H, 1H-Perfluoro-heptanol

Table 3
Water-in Oil Micro-emulsion Formulations
(bluish, translucent liquid)

Continuous Phase (%, v/v)	Dispersed Phase (%, v/v)	Surfactant (%, w/v)	Co-surfactant (%, w/v)
95% PFMP	5% saline solution	2% PTB	1.1% PFOctanol
90% PFMP	10% saline solution	4% PTB	1.5% PFOctanol
80% PFMP	20% saline solution	8% PTB	2.3% PFOctanol
95% Perfluoroctane	5% saline solution	2% PTB	1.1% PFOctanol
90% Perfluoroctane	10% saline solution	4% PTB	1.4% PFOctanol or 1.3% PFHeptanol
80% Perfluoroctane	20% saline solution	8% PTB	2.4% PFOctanol or 2.1% PFHeptanol
95% Perfluoroctane	5% saline solution	2% PTB	1.2% PFOctanol
90% Perfluoroctane	10% saline solution	4% PTB	1.6% PFOctanol
80% Perfluoroctane	20% saline solution	8% PTB	2.5% PFOctanol

PFMP = perfluoro-2-methyl pentane (includes the use of perfluorohexane)
PTB = PEG Telomer B
PFOctanol = 1H, 1H-Perfluoro-1-octanol
PFHeptanol = 1H, 1H-Perfluoro-heptanol

Example 2

Treatments Using Emulsions

The emulsions of Example 1 can also contain other pharmaceuticals or medicaments to treat various conditions. The following are examples for treatments according to the invention:

Adult Respiratory Distress Syndrome: A water-in-oil fluorocarbon emulsion or microemulsion containing a suspension of natural or synthetic lung surfactants containing phospholipids, neutral lipids, fatty acids, and surfactant-associated proteins, and other amphophilic materials to mimic the surface-tension lowering properties of natural lung surfactant.

Premature lungs: A water-in-oil fluorocarbon emulsion or microemulsion containing surfactants containing phospholipids, neutral lipids, fatty acids, and surfactant-associated proteins, licithin, fluorine-containing surfactants and other amphophilic materials to mimic the surface-tension lowering properties of natural lung surfactant.

Cystic Fibrosis: A water-in-oil fluorocarbon emulsion or microemulsion containing recombinant human deoxyribonuclease I stabilized in the aqueous phase with pharmaceutical excipients such as buffers, osmotic agents, viscogens, antioxidants, and the like.

AIDS-associated Pulmonary Infections: For the treatment of the protozoan *Pneumocystis carinii, a* sterile, non-pyrogenic formulation of pentamidine isothionate suspended or emulsified in a low boiling liquid, including dodecafluoropentane, dodecafluoro-

neopentane, perfluorohexane, perfluorocyclopentane, perfluoroheptane, and perfluorooctane.

Pneumonia: Any antibiotic or combination of antibiotics known in the art to be useful for pulmonary infections (bacterial, viral, fungal), dissolved, suspended, or emulsified in or with a chemical selected from the group consisting of dodecafluoropentane, dodecafluoroneopentane, perfluorohexane, perfluorocyclopentane, perfluoroheptane, and perfluorooctane or other low boiling fluorocarbons.

Cancer: Any anti-neoplastic or combination of anti-neoplastics known in the art to be useful for pulmonary cancer, dissolved, suspended, or emulsified in or with a chemical selected from the group consisting of dodecafluoropentane, dodecafluoroneopentane, perfluorohexane, perfluorocyclopentane, perfluoroheptane, and perfluorooctane.

Hormone Delivery: Delivery of hormones such as erythropoietin to treat anemia, insulin to treat diabetes, growth hormone to treat hypopituitarism, calcitonin to treat osteoporosis, and others can be dissolved, suspended, or emulsified in a water-in-oil fluorocarbon emulsion or microemulsion for therapeutic delivery. The continuous phase consists of low boiling fluorocarbons such as dodecafluoropentane, perfluoro-2-methyl pentane, perfluorooctane, perfluorodecalin and the dispersed phase consists of the hormone contained in an aqueous solution.

Infections: Delivery of antimicrobial agents

such as tobramycin and anti-infective agents such as recombinant human granulocyte colony-stimulating factor which is used to prevent infection in cancer patients undergoing certain types of chemotherapy and bone marrow transplants. Following emulsification of the therapeutic agent in aforementioned fluorocarbon emulsions, emulsion is administered via aerosolization and inhalation.

Anti-coagulants: Delivery of anticoagulants or clot reducing agents such as streptokinase or urokinase or others known in the art to be useful for cardiovascular care may be dissolved, suspended or emulsified in or with fluorocarbon containing emulsions or microemulsions such as perfluorohexane, perfluorooctane and perfluorodecalin for administration via inhalation.

Example 3

Aerosolization of Water-in-Oil Emulsions

Aerosolization of the emulsions prepared according to the invention produce aerosolized particles suitable for drug delivery. In this example, water-in-oil emulsions were analyzed to determine particles sizes and particle size ranges upon aerosolization using a Pulsed Doppler Particle Analyzer.

The emulsions of Table 4 were passed through a Di Vilbiss nebulizer, with the probe volume set at 1 cm from the top of the nebulizer mouthpiece. Particle mean diameters ranged from 4.65 to 7.76 μm, as depicted in Table 1 below. Estimated particle ranges are from 1-14 μm. As shown in Table 4, the particle size of the resultant aerosol can be reduced, depending on the ratios of emulsion constituents. The emulsion containing 90%

perfluorodecalin (v/v), 10% water (v/v), and 1.5% PEG Telomer B (w/v) has a particle mean diameter of 5.64 μm, and the emulsion containing 80% perflorodecalin (v/v), 20% water (v/v), and 0.1% PEG Telomer B (w/v) has a mean particle diameter of 4.65 μm. These values are both smaller than the particle mean diameters of either aerosolized water or perfluorodecalin, which are 7.27 μm and 6.91 μm respectively, and allow for deeper penetration of the particles into the lung.

Table 4. 1 cm from Probe Volume to Di Vilbiss Nebulizer

Sample	Estimated Particle Range (μm)	Particle Mean Diameter (μm)
Water	3-11	7.27
PFD	2-11	6.91
6% (w/v) PTB in water	3-11	7.11
90% PFD (v/v) 10% Water (v/v) 1.5% PTB (w/v)	1-10	5.64
75% PFD (v/v) 25% Water (v/v) 1.5% PTB (w/v)	1-12	6.71
99.49% PFD (w/w) 0.38% Water (w/w) 0.13% PTB (w/w)	1-14	7.76
80% PFD (v/v) 20% Water (v/v) 0.1% PTB (w/v)	1-10	4.65

PFD = Perfluorodecalin PFH = Perfluorohexane(s) PTB = PEG Telomer B

Example 4

Aerosolization of Water-in-Oil Microemulsions

The microemulsions according to the invention can be aerosolized to produce aerosol particles suitable for drug delivery under conditions

approximating those found in the lungs. In this example, aerosolized water-in-oil microemulsions were analyzed to determine particle size distributions under conditions simulating delivery to the lungs. Four different formulations were analyzed including a control formulation, a 0.9% saline solution, a 95% PFD formulation, and an 80% PFD formulation. The 95% PFD formulation comprised 95% perfluorodecalin (v/v), 5% water (v/v), 2% PEG Telomer B (w/v) and 1.1% perfluoro-1-octonal (w/v). The 80% PFD formulation comprised 80% perfluorodecalin (v/v), 20% water (v/v), 2.0% PEG Telomer B (w/v), and 1.1% perfluoro-1-octonal (w/v). The control formulation was an aqueous solution containing 2.0% PEG Telomer B (w/v) and 1.1% perfluoro-1-octonal (w/v).

A Hospitec medical nebulizer (Lindebhurst, NY) or a Retec nebulizer (InTox Products, Albuquerque, NM) were used to generate the aerosols. Figure 1 shows the schematic of the experimental setup including the nebulizer, an oral larynx cast, a sample chamber (2.3 L volume, "Lucite" brand material), Aerodynamic Particle Sizer (APS) and its dilutor (TSI, Inc., St. Paul, MN). A humidifier to condition air in the chamber was included producing a relative humidity of 91%. The flow rate to the APS was 5 L/min. Aerosols generated from the nebulizers were delivered through the cast, into the chamber and then to the APS for size measurement.

The APS is a real-time instrument based on time-of-flight principles. Basically, the aerosol is accelerated through a nozzle. Larger particles obtain slower velocities because of inertia. The particle velocity was measured by passing two laser beams near the nozzle exit. The time of a particle passing through the beams was recorded and converted to particle size. The instrument indicates the

particle size distribution in terms of number, surface area, and mass.

Tables 5 and 6 list mean particle sizes of the aerosolized formulations in terms of mass median aerodynamic diameters (MMAD), and respective geometric standard deviations (σ_d). The mean particle size was determined by using the Hospitec and Retec nebulizers to aerosolize the emulsions through an oral larynx cast, in the presence of and in high humidity (91%). The presence of the oral larynx cast, the sample chamber, and high humidity most closely approximates the conditions for pulmonary delivery of an aerosolized emulsion. The 2.3L volume of the sample chamber approximates the inspiratory reserve volume (IRV) of the lungs, which is the added volume of a patient's lungs upon maximum inspiration. This volume thus approximates the volume of air added to the lungs upon deep inhalation. Passing the aerosolized particles through this volume thus simulates the dilution effect for the particles upon administration of the aerosolized formulation to a patient.

The MMADs of the tested particles ranged from 2.6 to 8.1 μm. The aerosol particles produced from the 80% PFD formulation using both nebulizers had considerably smaller MMADs than particles formed from the saline solution (0.9% NaCl). These results indicate that aerosols of the emulsions, due to the smaller size of the particles, would provide deeper penetration into the pulmonary system for improved drug delivery. The smaller size of these particles also indicates that these particles might evaporate more rapidly than aerosol particles produced from other formulations after deposition.

Table 5. Hospitec nebulizer, with oral larynx cast and high humidity.

Name	Temperature (F)	Humidity (%)	Mass distribution	
			MMAD	σ_d
0.9% NaCl	70	91	7.441	2.701
Control A	70	91	3.590	2.305
95% PFD	70	91	8.060	2.571
80% PFD	70	91	4.282	2.439

*With no size distribution assumption

*σ_d is geo. standard deviation

Table 6. Retec nebulizer, with oral larynx cast and high humidity.

Name	Temperature (F)	Humidity (%)	Mass distribution	
			MMAD	σ_d
0.9% NaCl	70	91	7.648	2.562
Control A	70	91	4.213	2.324
95% PFD	60	91	7.862	2.586
80% PFD	68	91	2.563	2.058

*With no size distribution assumption

*σ_d is geo. standard deviation

Example 5:

Incorporation of drug or protein into emulsions

A therapeutic drug or protein can be incorporated into the formulations of the invention without affecting the stability of the formed emulsion. Cromolyn sodium, a drug used in the treatment of asthma, was prepared in an aqueous solution at a concentration of 40 mg/ml. Stable water-in-oil microemulsions were prepared, as discussed above, wherein the microemulsion contained

20%(v/v) of the cromolyn sodium solution as the dispersed phase and 80%(v/v) of either perfluoro-2-methyl pentane or perfluorodecalin as the continuous phase, with 8%(w/v) PEG Telomer B, and 2.0-2.2%(w/v) of 1H,1H-perfluoro-1-octonal or 1H,1H-perfluoroheptanol, as shown in Table 7 below.

Likewise, a stable water-in-oil microemulsion was prepared with a 20%(v/v) solution of bovine serum albumin at a concentration of 100 mg/ml as the dispersed phase and an 80%(v/v) solution of perfluorodecalin as the continuous phase, with 8% PEG Telomer B and 2.5% 1H,1H-perfluoro-1-octonal (Table 7).

Table 7
Microemulsion formulations containing water soluble drug or protein

Item Number	Continuous Phase (%, v/v)	Dispersed Phase (%, v/v)	Surfactant 1 (%, w/v)	Surfactant 2 (%, w/v)
1	80% PFMP	20% solution containing 40 mg/ml Cromolyn Sodium	8% PTB	2.2% PFOctanol or 2.1% PFHeptanol
2	80% Perfluorodecalin	20% solution containing 40 mg/ml Cromolyn Sodium	8% PTB	2.2% PFOctanol or 2.0% PFHeptanol
3	90% Perflurooctane	20% solution containing 100 mg/ml bovine albumin	8% PTB	2.5% PFOctanol

PFMP = perfluoro-2-methyl pentane (includes the use of perfluorohexane)
PTB = PEG Telomer B
PFOctanol = 1H, 1H-Perfluoro-1-octanol
PFHeptanol = 1H, 1H-Perfluoro-heptanol

Although the invention has been described in some respects with reference to specified preferred embodiments thereof, many variations and modifications will be apparent to those skilled in the art.

It is, therefore, the intention that the following claims not be given a restrictive interpretation but should be viewed to encompass such variations and modifications that may be routinely derived from the inventive subject matter disclosed.

We claim:

1. A composition for pulmonary delivery of a water-soluble therapeutic agent comprising:

a stable water-in-oil emulsion or microemulsion comprising:

an aqueous dispersed phase, wherein said therapeutic agent is solubilized in said dispersed phase, and

a continuous phase comprising a high vapor pressure, low boiling point fluorocarbon.

2. The composition of claim 1 wherein said fluorocarbon has a boiling point between -30 °C to 150 °C.

3. The composition of claim 1 wherein said fluorocarbon is selected from the group consisting of dodecafluoropentane, dodecafluoroneopentane, perfluorocyclopentane, perfluoro-2-methylpentane, perfluorohexane, perfluoroheptane, perfluorooctane, and perfluorodecalin.

4. The composition of claim 1 wherein said fluorocarbon is selected from the group consisting of perfluoro-2-methylpentane, perfluorohexane, perfluorooctane, and perfluorodecalin.

5. The composition of claim 1 wherein said emulsion further comprises a fluorosurfactant.

6. The composition of claim 5 wherein said fluorosurfactant is selected from the group consisting of PEG Telomer B, FC-171 and FC-170C.

7. The composition of claim 5 wherein said emulsion further comprises a fluorine-containing cosurfactant.

8. The composition of claim 7 wherein said fluorine-containing cosurfactant is selected from the group consisting of partially fluorinated primary n-alcohols, fully fluorinated primary n-alcohols and fluorinated acids.

9. The composition of claim 7 wherein said fluorine-containing cosurfactant is 1H, 1H-perfluoro-1-octanol or 1H, 1H-perfluoro-1-heptanol.

10. A composition for pulmonary delivery of a water-soluble therapeutic agent comprising:

a stable water-in-oil emulsion or microemulsion comprising:

an aqueous dispersed phase, wherein said therapeutic agent is solubilized in said dispersed phase,

a continuous phase comprising a high vapor pressure, low boiling point fluorocarbon,

a fluorosurfactant, and

a fluorine-containing cosurfactant.

11. The composition of claim 10 wherein:

said fluorocarbon is selected from the group consisting of perfluoro-2-methylpentane, perfluorohexane, perfluorooctane, and perfluorodecalin,

said fluorosurfactant is selected from the group consisting of PEG Telomer B, FC-171 and FC-170C, and

said fluorine-containing cosurfactant is 1H, 1H-perfluoro-1-octanol or 1H, 1H-perfluoro-1-heptanol.

12. A method for delivering a water-soluble therapeutic agent to the pulmonary system of a patient comprising the steps of:

a) emulsifying an aqueous solution of a water-soluble therapeutic agent in a high vapor pressure, low boiling point fluorocarbon to form a stable water-in-oil emulsion or microemulsion, and

b) aerosolizing the emulsion for inhalation by the patient.

13. The method of claim 12 wherein said fluorocarbon is selected from the group consisting of perfluoro-2-methylpentane, perfluorohexane, perfluorooctane, and perfluorodecalin.

14. The method of claim 12 wherein said emulsification step further includes the step of emulsifying a fluorosurfactant to form the oil-in-water emulsion.

15. The method of claim 14 wherein said fluorosurfactant is selected from the group consisting of PEG Telomer B, FC-171 and FC-170C.

16. The method of claim 14 wherein said emulsification step further includes the step of emulsifying a fluorine-containing cosurfactant to form the oil-in-water emulsion.

17. The method of claim 16 wherein said fluorine-containing cosurfactant is selected from the

group consisting of partially fluorinated primary n-alcohols, fully fluorinated primary n-alcohols and fluorinated acids.

18. The method of claim 16 wherein said fluorine-containing cosurfactant is 1H, 1H-perfluoro-1-octanol or 1H, 1H-perfluoro-1-heptanol.

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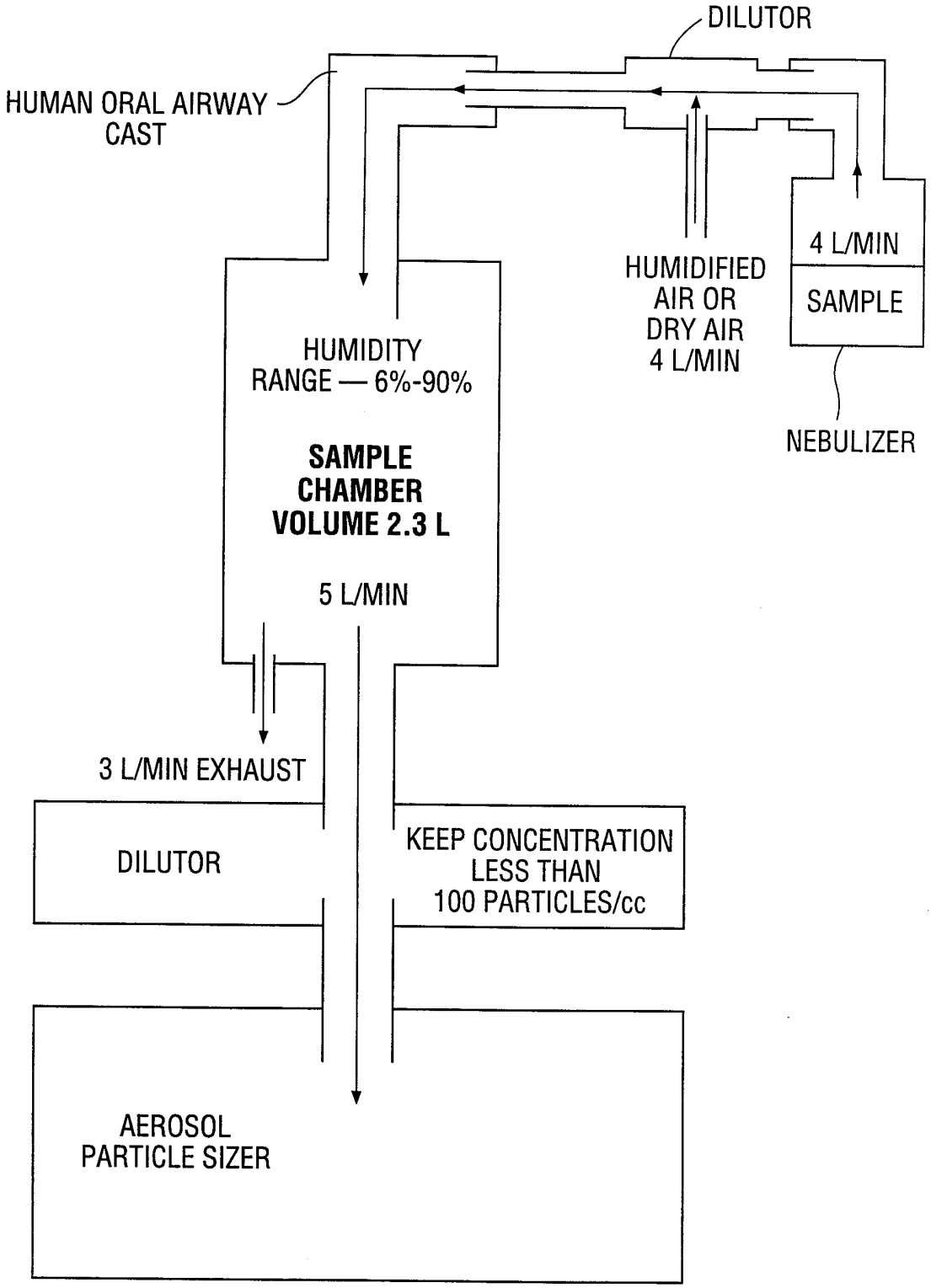
DILUTOR
HUMAN ORAL AIRWAY CAST
HUMIDIFIED AIR OR DRY AIR 4 L/MIN
4 L/MIN
SAMPLE
NEBULIZER
HUMIDITY RANGE — 6%-90%
SAMPLE CHAMBER VOLUME 2.3 L
5 L/MIN
3 L/MIN EXHAUST
DILUTOR
KEEP CONCENTRATION LESS THAN 100 PARTICLES/cc
AEROSOL PARTICLE SIZER

FIG. 1

INTERNATIONAL SEARCH REPORT

:rnational Application No
PCT/US 98/23900

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/00

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.
P,X, Y L	WO 98 16210 A (SONUS PHARMA INC) 23 April 1998 "L": DOCUMENT SO QUOTED FOR ITS' CASTING DOUBT ON THE VALIDITY OF THE CONVENTION-PRIORITY CLAIM see the whole document ---	1-6,18
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A	US 5 340 587 A (MIHALKO PAUL J ET AL) 23 August 1994 see the whole document --- -/--	1-6,18

[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
10 March 1999	16/03/1999

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	Fischer, W

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

INTERNATIONAL SEARCH REPORT

national Application No
PCT/US 98/23900

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	US 4 895 719 A (RADHAKRISHNAN RAMACHANDRAN ET AL) 23 January 1990 see the whole document	1-6,18
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 98/ 23900

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.: 7-17
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

Claims Nos.: 7-17

WHILE IT IS EVIDENT FROM THE THE FILE THAT APPLICANT INTENDED TO SUBMIT A TOTAL OF 18 CLAIMS, PAGES 26 AND 27 (APPEARENTLY COMPRISING CLAIMS 7-16 AND THE BETTER PART OF CLAIM 17 ARE MISSING IN THE SEARCH-FILE AND THEIR WHEREABOUTS COULD NOT BE ASSERTED
BY THE SEARCHEXAMINER WITH REASONABLE EFFORT.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 98/23900

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