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Radhakrishnan et al.

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[54] **METHOD AND APPARATUS FOR ADMINISTERING DEHYDRATED LIPOSOMES BY INHALATION**

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[21] Appl. No.: **22,937**

[22] Filed: **Mar. 6, 1987**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 737,221, May 22, 1985, abandoned, and Ser. No. 860,528, May 7, 1986, abandoned, and Ser. No. 937,609, Dec. 3, 1986.

[51] **Int. Cl.**[4] **A61K 31/35;** A61K 9/14; A61K 9/48; A61K 9/68

[52] **U.S. Cl.** **424/45;** 514/958; 514/959; 604/140

[58] **Field of Search** 424/45, 46; 514/956, 514/958, 964, 965

[56] **References Cited**

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[57] **ABSTRACT**

A system and method for administering a drug, at a selected dose, via the respiratory tract. Spray-dried liposome particles containing the selected dose of the entrapped drug are released into the air in aerosolized form, either by entrainment in an air or propellant stream, or by release from a pressurized can containing a suspension of the liposomes in a fluorchlorocarbon solvent.

18 Claims, 1 Drawing Sheet

fig. 1A

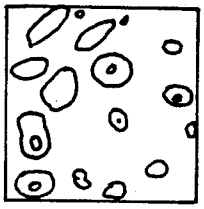


fig. 1B

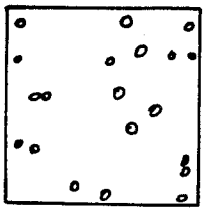


fig. 2A

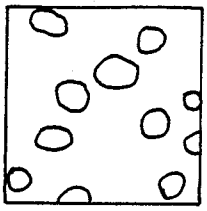


fig. 2B

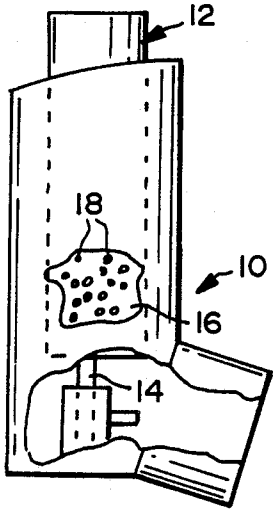
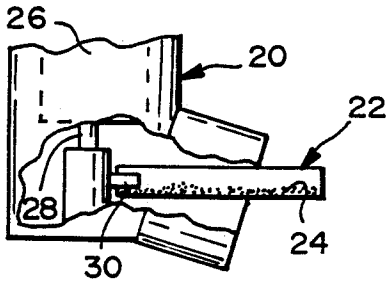


fig. 3

fig. 4



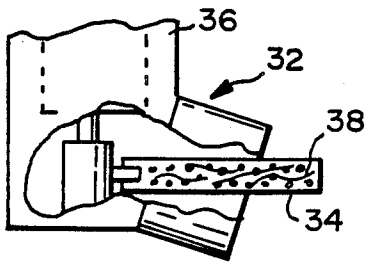


fig. 5

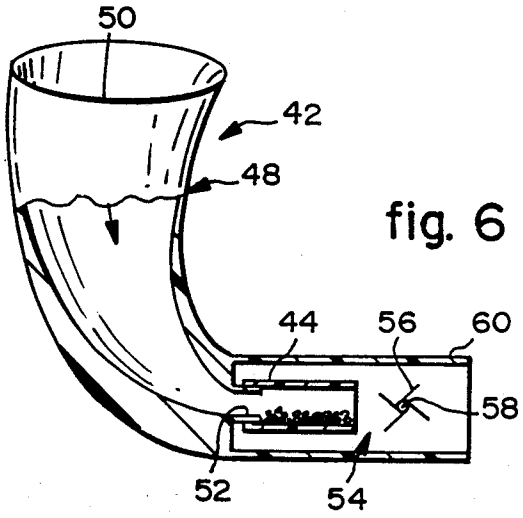


fig. 6

METHOD AND APPARATUS FOR ADMINISTERING DEHYDRATED LIPOSOMES BY INHALATION

This application is a continuation-in-part of U.S. patent applications for "Liposome Inhalation Method and System", Ser. No. 737,221, filed May 22, 1985, now abandoned "Liposome Concentrate and Method", Ser. No. 860,528, filed May 7, 1986, now abandoned and "Liposome Inhalation Method and System", Ser. No. 937,609, filed Dec. 3, 1986 currently pending.

FIELD OF THE INVENTION

The present invention relates to drug delivery by inhalation, and, in particular, to an improved system and method for delivering liposomes containing a metered drug dose via inhalation.

REFERENCES

The following references are incorporated herein by corresponding number:

1. Hollenbeck, R. G., et al, in "Pharmaceutics and Pharmacy Practice" (Banker, G. S., et al, eds), J. P. Lippincott, Philadelphia (1982), pp. 344–358.
2. Szoka, F., Jr., et al, *Ann Rev Biophys Bioeng* (1980), 9: 467.
3. Szoka, F., Jr., et al, *Proc Natl Acad Sci* (USA) (1978) 75: 4194.
4. Hollenbeck, R. G., op cit. pp. 382–391.

BACKGROUND AND SUMMARY

Inhalation provides an effective means for delivering a variety of drugs, including nasal decongestants, drugs useful in the treatment of asthma and other bronchial and pulmonary conditions (1). One advantage of inhalation in treating nasal, bronchial, and pulmonary conditions is the ability to deliver the drug directly to the site of drug action. A related advantage is the rapid onset of the therapeutic effect, compared with other routes of administration, such as intramuscular and oral routes. For drugs which are susceptible to breakdown in the gastrointestinal tract, or which otherwise cannot be administered orally, inhalation may be preferred for a variety of reasons over intravenous or intramuscular injection. Other drugs, such as nitroglycerin, whose primary drug action is systemic, can also be delivered efficiently by inhalation.

Several methods for delivering drugs via inhalation are known. In one, the drug is dissolved in a suitable solvent which can be aerosolized to form a small-particle mist. The drug solution may be aerosolized by pneumatic or ultrasonic nebulizer, or, more conveniently, by means of a self-contained nebulizer containing a pressurized, fluorocarbon propellant. Inhalation of the aerosol mist, i.e., drawing the mist from the mouth or nose into the respiratory tract, acts to deposit the drug-containing aerosol particles on various sites of the respiratory tract, including the upper nasopharyngeal region, the tracheobronchial region, and the pulmonary region. In the latter region, the drug has the opportunity for rapid absorption into the bloodstream for systemic action.

Also well known in the prior art are inhalation systems in which a drug is administered in particulate form, either as a dry powder or as a micronized suspension in a suitable carrier solvent system. Typically the drug is a water-soluble compound which is suspended in micronized form in a fluorocarbon-type propellant solvent. Following aerosolization, most of the propellant solvent is lost through flash evaporation and replaced by moisture in the respiratory tract, leading to the deposition of hydrated micronized particles.

Both types of inhalation systems mentioned above are based on delivery of the drug in a free form to sites in the respiratory tract. As such, the drug is rapidly utilized and, in the case of pulmonary deposition, taken up systemically at the site of deposition. Because of this rapid drug uptake and utilization, the drug effect may be relatively short-lived, requiring frequent dosing. A related problem is the limited amount of drug that can be administered safely at each dosing, particularly where the drug has unwanted systemic side effects. This problem is illustrated by a number of β_2-adrenergic agonist type brochodilators which also produce marked tachycardia. Even at relatively low doses of these drugs, the stimulatory effect of the drug on the heart and other side effects, such as dizziness and insomnia, are a nuisance to the patient. Additionally, micronized particles may irritate the respiratory tract.

More recently, liposome inhalation systems for administering a drug to the respiratory tract in liposome-entrapped form have been proposed. UK patent application GB 2,145,107A describes an aerosol device which brings aqueous and organic-solvent phase solutions together under pressure, and passes the mixture through a nozzle to form aerosolized liposomes. EPO patent application 0,158,441 discloses liposome formation, in aerosol form, from a water/lipid/ethanol mixture. In PCT application WO 86/01714, it is proposed to spray lipid droplets in a volatile liquid carrier, with liposome formation occurring upon contact of the droplets with a moist aqueous surface. UK patent application GB 2,170,815 describes a system in which an aqueous solution is emulsified in a lipid-containing propellant solvent, then sprayed through an atomizing nozzle to form lipid-coated droplets which can form liposomes upon contact with a moist surface. All of these approaches are characterized by "in situ" liposome formation, i.e., liposome formation at the spray valve or on contact with the moist surface of the lungs. As such, the concentration and size of the liposomes formed, and the percentage of drug entrapment in the liposomes, will vary from one dose delivery to another, depending upon temperature and humidity conditions, the extent of solvent mixing, and the total and relative amounts of solvent components present in the system. Thus each of these systems would be difficult to adapt for metered dose delivery, in which a reproducible amount of liposome-encapsulated drug is needed.

SUMMARY OF THE INVENTION

Co-pending patent application for "Liposome Inhalation Method and System" Ser. No. 737,221, filed May 22, 1985, now abandoned, discloses a lipsome-based aerosol system for delivering a drug, at a controlled release rate, via the respiratory tract. The invention is based on two discoveries: First, that rapid systemic uptake of drugs from the site of administration in the respiratory tract can be eliminated or greatly reduced by administering the drug in a predominantly liposome-encapsulated form. Secondly, it was found that the rate of release of a water-soluble drug from a drug/liposome composition delivered to the respiratory tract can be modulated according to the acyl-chain composition of the phospholipids making up the liposomes. As a rule,

slower drug release rates correlate with longer in vitro drug efflux half lives in serum. The liposome aerosol compositions used in these studies were prepared under conditions in which the drug was predominantly in liposome-encapsulated form, and the liposome suspensions were delivered in metered dose form from a fixed-volume nebulizer.

Co-owned patent application for "Liposome Concentrate and Method", Ser. No. 860,528, filed Apr. 22, 1986, now abandoned addresses another aspect of effective drug delivery in a liposome-based inhalation system: that of delivering a water-soluble, liposome-permeable drug in predominantly encapsulated form, from a dilute aqueous liposome suspension. The method of the invention involves preparing and storing a liposome/-drug suspension initially in paste form, then diluting the paste to a concentration suitable for aerosolizing.

Co-owned U.S. patent application Ser. No. 937,607, filed Dec. 3, 1986, currently pending additionally showed that administration of the β_2-agonist metaproteranol sulfate (MPS) in liposomal form via inhalation reduced initial plasma levels of the drug more than about 8 fold with respect to free drug, and that plasma levels remained substantially constant over a two hour period, compared with a rapid drop in plasma levels of the drug administered by inhalation in free form. At the levels of MPS which were studied, the percent protection against bronchoconstriction provided by the drug was about the same for both free drug and liposomal-entrapped drug.

It was further discovered, according to the teaching of co-owned patent application for "Liposome Bronchodilator System and Method", Ser. No. 022,669, filed Mar. 6, 1987, that β_2-adrenoreceptor agonists, when administered in liposome-entrapped form at a therapeutic drug dose (i.e., minimum dose required for optimal or near-optimal short-term therapeutic effect), produce significantly greater bronchodilation, over an extended time period, than is produced by the the same amount of β_2-agonist delivered to the respiratory tract in a free-drug aerosol form.

The inventions mentioned above show that liposome drug delivery by inhalation provides advantages of (a) reduced side effects due to rapid systemic drug uptake, (b) improved therapeutic action over an extended period, and (c) the ability to modulate rate of drug release from the target site.

The present invention is concerned with a self-contained apparatus, or system and method for delivering a selected amount of drug, efficiently and reproducibly, in liposome encapsulated form. The apparatus of the invention includes liposome particles which have been formed by spray drying a dilute aqueous suspension of the liposomes. The particles formed (a) have a fine particle size, (b) retain the majority of their originally encapsulated material, and (c) are stable, in a preferred formulation, when suspended in a fluorochlorocarbon solvent. The particles are preferably formed, according to one method of the invention, by forming the liposomes from partially or totally saturated phospholipid components and drying the liposomes in a stream of heated gas whose temperature does not degrade the lipid components or structural integrity of the liposomes.

The apparatus further includes a self-contained delivery device for producing an airborne suspension of the liposome particles containing a metered dose of drug, in liposome-entrapped form. In one embodiment, the liposomes are contained in a suspension of a pressurized fluorochlorocarbon solvent in a metered-dose spray device designed to release a selected volume of the suspension in aerosolized form.

In a second embodiment, the liposomes and a metered amount of the liposome-entrapped drug are contained in individual packets. The delivery device may be a propellant spray device designed to release a stream of aerosolized propellant particles through the packet, to entrain the liposomes in the stream. Alternatively, the delivery device may be a flow-through air chamber designed to support a liposome packet such that the liposomes are entrained in a stream of air drawn through the chamber.

These and other objects and features of the present invention will be more fully understood when the following detailed description of the invention is read in conjunction with the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGS. **1A** and **1B** are renderings of light micrographs of spray dried liposomes which have been suspended in a propellant solvent and sprayed onto a dry (**1A**) or moist (**1B**) slide;

FIGS. **2A** and **2B** are renderings of light micrographs of liposomes, as in FIGS. **1A** and **1B**, respectively, but where the liposomes were spray dried from a 5% lactose solution;

FIG. **3** is a side cutaway view of a liposome delivery apparatus according to one embodiment of the invention, in which spray-dried liposomes are delivered from a suspension in a pressurized propellant;

FIG. **4** is a side cutaway view of a liposome delivery apparatus constructed according to another embodiment of the invention, in which spray-dried liposomes are contained in a cylindrical packet, for entrainment in an aerosol stream produced by a self-contained propellant device;

FIG. **5** is a side cutaway view of a liposome delivery apparatus like the one shown in FIG. **4**, except where the liposomes are supported loosely on a porous matrix in a packet, for entrainment in an aerosol stream produced by a self-contained propellant device; and

FIG. **6** is a side cutaway view of a liposome delivery apparatus constructed according to a third embodiment of the invention, in which spray-dried liposomes are contained in a capsule-like packet, and the packet is supported in the air passageway of a delivery device, for entrainment of the liposomes in a stream of air drawn through the passageway.

DETAILED DESCRIPTION OF THE INVENTION

I. Spray-Dried Liposome Particles

This section discusses methods for preparing spray dried liposomes having desired properties in the inhalation system of the invention. The most important of these properties are (a) high drug entrapment, (b) selected pharmacokinetic behavior when delivered to the respiratory tract, (c) ability to form fine particle sizes on spray drying, and (d) stability on storage in dehydrated or propellant suspension form. Section IA below discusses lipid composition factors which are important to drug release rates, most compatible with spray drying, and give greatest storage stability. Sections IB describes several methods for forming lipsomes containing en-

trapped water-soluble or lipid-soluble drugs. Spray drying methods are discussed in Section IC.

A. Liposome Components

The effect of liposome lipid components on the rate of drug release in the respiratory tract has been reported in the above-cited co-pending patent applications. Briefly, studies on in vitro drug release rates, as a function of lipid composition in the liposomes, showed that liposomes whose phospholipid components contain longer and/or more saturated acyl chain moieties have longer drug-release half lives. The drug-release rates ranged from less than about 0.5 hour for soy phosphatidylcholine (SPC) to nearly ten days for a mixture of distearoyl PC/distearoyl phosphatidyl glycerol (DSPC/DSPG). The most significant increases in drug release rates were observed when the liposomes contained a significant proportion of lipids whose transition temperature (T_c) are above the temperature at which the efflux half lives are measured, e.g., 37+ C.

Studies on the effect of lipid charge on drug release rates indicated that the addition of a negatively charged lipid, such as phosphatidyl glycerol (PG), at a mole ratio of about 10%, produces a slight to moderate increase in efflux half life. The lipid-charge effect is dependent somewhat on the degree of saturation and chain length in the charged and uncharged lipids used in forming the liposomes, with the charge effect producing a greater increase in drug efflux half life where the liposomes are formed of predominantly shorter and/or unsaturated lipids, and producing less effect in the case of longer-chain and/or saturated lipids. The effect of sterol components, such as cholesterol, was relatively minor, and generally followed the known fluidizing effect of sterol on liposomal membranes. That is, in relatively fluid membranes, where sterol increase membrane rigidity, drug-release half lives were increased, and in more rigid membranes, where sterol have a fluidizing effect, drug release half lives were decreased.

Another important consideration in the choice of lipid components is the phase transition temperature of the lipids, which may be greater than the temperature of heated gases used in drying the liposomes such that the drug is retained in liposomes on drying. Most efficient drying temperatures are at least about 37° C., and preferably between about 40°–50° C., although higher temperatures are also possible. Table 1 below gives the transition temperatures and acyl chain composition for a number of different liposome lipid components.

As can be appreciated from the table, liposomes can be formulated with mixtures of relatively low and relatively high phase transition temperature components, to achieve an overall phase transition temperature in the 37° to 50° C. range. Alternatively, partially hydrogenated lipid components, such as PHPC, are suitable when used in combination with other components. The transition temperature of liposomes formed with the selected lipid components can be determined conventionally by differential scanning calorimetry (2).

TABLE 1

Some Properties of Phospholipids Used in Liposomes

Lipid	Abbrev.	Charge	Tc (°C.)	Ref.
Egg phosphatidylcholine	EPC	0	−15 to −7	109
Dilaurylolylphosphatidylcholine (C12:0)	DLPC	0	−1.8	122
Dimyristoylphosphatidylcholine (C14:0)	DMPC	0	23	109
Dipalmitoylphosphatidylcholine (C16:0)	DPPC	0	41	109
Distearoylphosphatidylcholine (C18:0)	DSPC	0	55	109.1
1-Myristoyl-2-palmitoylphosphatidyl-choline (C14:0.16:0)	MPPC	0	27	97
1-Palmitoyl-2-myristoyl phosphatidyl-choline (C16:0.14:0)	PMPC	0	35	97
1-Palmitoyl-2-stearoyl phosphatidyl-choline (C16:0.18:0)	PSPC	0	44	97
1-Stearoyl-2-palmitoyl phosphatidyl-choline (C18:0.16:0)	SPPC	0	47	97
Dioleoylphosphatidylcholine (C18:1)	DOPC	0	−22	109
Dilaurylolylphosphatidylglycerol	DLPG	−1	4	46
Dimyristoylphosphatidylglycerol	DMPG	−1	23	158
Dipalmitoylphosphatidylglycerol	DPPG	−1	41	86
Distearoylphosphatidylglycerol	DSPG	−1	55	153
Dioleoylphosphatidylglycerol	DSPG	−1	−18	46
Dimyristoyl phosphatidic acid	DMPA	−1	51	86
Dimyristoyl phosphatidic acid	DMPA	−2	45	153
Dipalmitoyl phosphatidic acid	DPPA	−1	67	153
Dipalmitoyl phosphatidic acid	DPPA	−2	58	153
Dimyristoyl phosphatidylethanolamine	DMPE	—	50	153
Dipalmitoyl phosphatidylethanolamine	DPPE	—	60	203
Dimyristoyl phosphatidylserine	DMPS	—	38	203
Dipalmitoyl phosphatidylserine	DPPS	—	51	120
Brain phosphatidylserine	PS	—	6–8°	86
Brain sphingomyelin	BSP	0	32	191
Dipalmitoyl sphingomyelin	DPSP	0	41	18
Distearoyl sphingomyelin	DSSP	0	57	42

Other lipid components, including PG, and cholesterol, can be included. In general, cholesterol has a fluidizing effect in liposomes containing predominantly saturated phospholipid components, and thus is expected to lower phase transition temperature slightly. The effect of added PG or other phospholipid components will, of course, depend largely on the acyl chain composition of the lipids.

The liposomes may also be formulated to include various types of drug-protective or lipid-protective agents, such as the antioxidant α-tocopherol, which is typically included at a mole ratio of between about 0.1–2 mole percent.

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