(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
15 September 2016 (15.09.2016)

WIPO | PCT

(10) International Publication Number
WO 2016/142708 A2

(51) International Patent Classification:
A61K 9/127 (2006.01) *A61K 31/00* (2006.01)
A61K 9/19 (2006.01)

(21) International Application Number:
PCT/GB2016/050645

(22) International Filing Date:
9 March 2016 (09.03.2016)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
770/MUM/2015 10 March 2015 (10.03.2015) IN

(71) Applicant: **CIPLA LIMITED** [IN/IN]; Cipla House Peninsula Business Park, Ganpatrao Kadam Marg, Lower Parel, Mumbai 400 013 (IN).

(71) Applicant *(for MW only)*: **KING, Lawrence** [GB/GB]; 10 Old Bailey, London EC4M 7NG (GB).

(72) Inventors: **MALHOTRA, Geena**; 3403 Springs Island City Centre, Next to Wadala Telephone Exchange, G.D Ambedkar Marg, Dadar (East), Mumbai 400014 (IN). **RAUT, Preeti**; A - 502, Anant Tejpal Scheme, Road No.5, Ville Parle (East), Maharashtra, Mumbai 400 057 (IN).

(74) Agent: **A.A. THORNTON & CO.**; 10 Old Bailey, London EC4M 7NG (GB).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

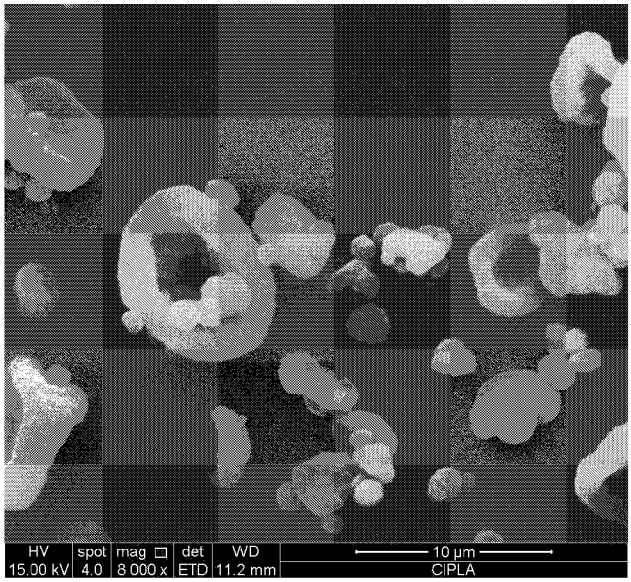
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

(54) Title: PHARMACEUTICAL COMPOSITION

Fig. 1



(57) Abstract: The present invention provides a pharmaceutical composition comprising lipid microparticles comprising a lipid layer and at least one active pharmaceutical ingredient, wherein the at least one active pharmaceutical ingredient is adsorbed on the lipid microparticle. The present invention also provides a process for preparing the lipid microparticles and the associated pharmaceutical compositions. The pharmaceutical composition may be used in the treatment and/or prophylaxis of lung disease.

WO 2016/142708 A2

PHARMACEUTICAL COMPOSITION

FIELD OF THE INVENTION:

The present invention relates to pharmaceutical compositions comprising lipid microparticles of active pharmaceutical ingredients. The present invention also relates to a process for preparing such lipid microparticles and pharmaceutical compositions.

BACKGROUND AND PRIOR ART:

Liposomes have found wide applications in the therapeutic as well as diagnostic sectors. Liposomes are lipid (generally phospholipid) vesicles composed of at least one lipid bilayer enclosing/encapsulating one or more aqueous compartments (vacuole) in which drugs and other substances might be included.

Liposomal systems have proved to be effective through the intravenous, oral and intramuscular route of administration wherein the concerns regarding toxicity, bioavailability and release rate of the drugs can be addressed. They have been investigated as a vehicle for sustained-release therapy in the treatment of systemic diseases and lung disease by delivering therapeutic agents to the alveolar surface.

Pulmonary delivery of these liposomes is an alternative system of drug administration to the conventional systems of drug administration used in pulmonary disorders. Such pulmonary liposomes offer protection against drug metabolism in the pulmonary tissues. Also, use of such liposomes achieves sustained or prolonged release of drugs in the lungs.

It is known, however, that stability problems may be encountered with liposomes when stored as aqueous dispersions due to the mechanisms of hydrolysis of ester bonds and/or oxidation of unsaturated acyl chains of the lipids. These long-term instability problems arising due to the physicochemical changes in liposomal dispersions could result in leakage of the encapsulated drug. Such stability issues with liposomal dispersions have been overcome by using liposomes in dry powder formulations.

The pulmonary delivery of such dry powder formulations comprising liposomes is an alternative system of drug administration as compared to the conventional dry powder inhalers.

Fluticasone Propionate Liposomes for Pulmonary Delivery, M. S. Nagarsenkar *et al*, Indian Journal of Pharmaceutical Sciences, November - December 2009, 709-711. This article concludes that liposomal dispersions with 25% cholesterol and 50% cholesterol exhibited more than 90% of Fluticasone Propionate entrapment.

Lectin-functionalized liposomes for pulmonary drug delivery: effect of nebulization on stability and bioadhesion, Abu-Dahab R *et al*, Eur J Pharm Sci. 2001 Aug;14(1):37-46. This article mentions that the incorporation of cholesterol enhanced the stability of the liposomes during nebulization.

A Dry Powder Formulation of Liposome-Encapsulated Recombinant Secretory Leukocyte Protease Inhibitor (rSLPI) for Inhalation: Preparation and Characterization, Aileen Gibbons *et al*, AAPS PharmSciTech, Vol. 11, No. 3, September 2010, 1411-1421. This article discloses preparation of 1,2-dioleoyl-sn-glycero-3-[phosphor-L-serine] (DOPS)/Cholesterol liposomes by the conventional thin film hydration procedure and concludes that the liposome powder was more physically stable in terms of retaining liposome size stability after storage at room temperature for 5 months.

Development of Liposomal Amphotericin B Dry Powder Inhaler Formulation, Drug Delivery, Shah SP *el al* 2004, Vol. 11, No. 4: Pages 247-253. This article discloses that liposomes were prepared by the reverse phase evaporation technique. The drug lipid ratio was 1:10 with a membrane composition of hydrogenated soya phosphatidylcholine and cholesterol.

Liposomal Amikacin Dry Powder Inhaler: Effect of Fines on In Vitro Performance, Shrenik P. Shah *et al*, AAPS PharmSciTech 2004; 5 (4) Article 65, 107-113. This article discloses that liposomes were prepared by the modified reverse phase evaporation (REV) technique using cholesterol.

Liposomal tobramycin against pulmonary infections of Pseudomonas aeruginosa: a pharmacokinetic and efficacy study following single and multiple intratracheal administrations in rats, J. F. Marier *et al*, Journal of Antimicrobial Chemotherapy (2003) 52, 247–252. This article discloses that liposomes were prepared by using dipalmitoylphosphatidylcholine (DPPC) and dimyristoylphosphatidylglycerol (DMPG).

WO2014141069 discloses dry powder formulations, wherein the formulations contain a uniform blend of a first spray-dried powder and a second spray-dried powder. The first spray-dried powder contains spray-dried particles of a therapeutically active ingredient dispersed in/contained within a pharmaceutically acceptable hydrophobic excipient. The second spray-dried powder contains spray-dried particles formed from a pharmaceutically acceptable hydrophobic excipient but are substantially free of any therapeutically active ingredient.

WO 01/85137 discloses metal-ion lipid powdered pharmaceutical microparticle compositions for drug delivery and associated methods of use. WO 01/85137 teaches of the formation of a lipid-metal ion complex matrix that incorporates the drug or active agent to be delivered. The stable powdered metal ion-lipid pharmaceutical compositions have a glass transition temperature of at least 20^{O}C above the recommended storage temperature for drugs and exhibit improved stability and dispersability over the shelf-life of the composition.

There are a number of prior art documents which disclose lipid based pharmaceutical compositions comprising active pharmaceutical ingredients. However, there still arises a need to develop such lipid containing formulations with enhanced therapeutic efficacy and stability.

OBJECT OF THE INVENTION:

An object of the invention is to provide novel and improved lipid based pharmaceutical compositions.

A further object of the present invention is to provide stable lipid based pharmaceutical compositions comprising active pharmaceutical ingredients.

Another object of the present invention is to provide lipid based pharmaceutical compositions with enhanced delivery.

Another object of the present invention is to provide lipid based pharmaceutical compositions which enable patient compliance.

Yet another object of the present invention is to provide lipid based pharmaceutical compositions with reduced dose.

Another object of the present invention is to provide inhalable lipid based pharmaceutical compositions with increased bioavailability.

Yet another object of the present invention is to provide a process for preparing lipid based pharmaceutical compositions comprising active pharmaceutical ingredients and one or more pharmaceutically acceptable excipients.

SUMMARY OF THE INVENTION:

According to one aspect of the present invention, there is provided a lipid microparticle comprising a lipid layer and at least one active pharmaceutical ingredient, wherein the at least one active pharmaceutical ingredient is adsorbed on the lipid microparticle.

According to another aspect of the present invention, there is provided a process of preparing lipid microparticles which process comprises preparing an aqueous liposomal suspension of small unilamellar vesicles (SUV); adding one or more active pharmaceutical ingredients to the aqueous liposomal suspension; and spray drying the aqueous liposomal suspension to form lipid microparticles.

According to a further aspect of the present invention, there is provided a pharmaceutical composition comprising lipid microparticles and an associated process for their preparation.

According to a further aspect of the present invention, there is provided the use of lipid microparticles in the manufacture of a medicament for the treatment and/or prophylaxis of lung disease.

According to a further aspect of the present invention, there is provided a method of treatment and/or prophylaxis of lung disease comprising administering a therapeutically effective amount of a lipid microparticles to a patient in need thereof.

According to a further aspect of the present invention, there is provided lipid microparticles for use in the treatment and/or prophylaxis of lung disease.

According to a further aspect of the present invention, there is provided lipid microparticles substantially as herein described with reference to the examples.

According to a further aspect of the present invention, there is provided a process substantially as herein described with reference to the examples.

BRIEF DESCRIPTION OF THE DRAWINGS:

Figure 1 is a Scanning Electron Microscopy (SEM) image (x8000 magnification) of lipid microparticles of the present invention.
Figure 2 a Scanning Electron Microscopy (SEM) image (x4000 magnification) of lipid microparticles of the present invention.
Figure 3 is a Scanning Electron Microscopy (SEM) image (x2000 magnification) of lipid microparticles of the present invention.

DETAILED DESCRIPTION OF THE INVENTION:

Liposomes are lipid (generally phospholipid) vesicles composed of at least one lipid bilayer completely enclosing/encapsulating/surrounding one or more aqueous compartments (vacuoles).

The bilayer(s) is composed of two lipid monolayers having a hydrophobic "tail" region and a hydrophilic "head" region. The structure of the membrane bilayer is such that the hydrophobic (nonpolar) "tails" of the lipid monolayers orient toward the center of the bilayer while the hydrophilic "heads" orient towards the aqueous phase.

They can be unilamellar vesicles (possessing a single membrane bilayer) or multilamellar vesicles possessing multiple membrane bilayers.

On the basis of their size and number of bilayers, liposomes are classified in the art into one of three categories –

(1) Multilamellar vesicles (MLV) – comprised of more than one bilayer and having a size of from about 100nm to about 20 microns.
(2) Large unilamellar vesicles (LUV) – comprised of a single bilayer and having a size of from about 0.1 to about 1 micron.
(3) Small unilamellar vesicles (SUV) – comprised of a single bilayer and having a size of from about 20 to about 100nm.

Used herein the term "size" of a particle refers to the D_{50} diameter of that particle, when measured by conventional means such as laser light diffraction (LLD).

Generally, liposomes include natural and/or synthetic phospholipids which constitute the two major structural components of most biological membranes of liposomes. However, the bilayers may also contain other constituents such as cholesterol, hydrophilic polymer conjugated lipids and water. These constituents may be dissolved or incorporated into or in between the bilayer(s).

Liposomes can encapsulate water-soluble drugs and other water soluble substances in their aqueous (central) compartments and lipid soluble drugs and other lipid soluble substances within the lipid bilayer membrane itself, in between the bilayers.

Cholesterol is largely used to improve the membranous bilayer characteristics of the liposome. It improves the membrane fluidity, bilayer stability and reduces the permeability of water soluble molecules through the membrane. Cholesterol increases both the rigidity and the degree of order of the lipid layer in the fluid phase of lipids. The bilayer rigidity dictates whether large diameter liposomes can be deformed and eventually pass through relatively narrow pores.

As per the prior art, the use of cholesterol is typically preferred in the preparation of liposomes, as its use increases the rigidity of the lipid bilayer and liposome. Liposomes which are prepared in the absence of cholesterol result in non-rigid liposomes.

However, the inventors of the present invention have unexpectedly found that small unilamellar liposomes (unilamellar liposomes comprised of a single bilayer and the liposomes having a size of from about 20 to about 100nm) which are prepared without using cholesterol can be easily fused to form lipid microparticles using spray drying which result in lipid microparticles that exhibit low

density and good aerodynamic properties in addition to high stability. Such active pharmaceutical ingredient comprising lipid microparticles ultimately give rise to better deep lung deposition of the active pharmaceutical ingredients.

Within the context of the present invention, lipid microparticles (lipid microparticle compositions) are microparticles comprised of at least one active pharmaceutical ingredient and a lipid layer, wherein the at least one active pharmaceutical ingredient is adsorbed on the lipid microparticle.

Adsorption is the binding of molecules/substances to a surface. It may encompass physical adsorption, involving Van der Waals forces of attraction between the solid adsorbent and the adsorbate molecules, or chemical adsorption which involves the chemical bonding of the surface of the adsorbent with the adsorbate.

Within the context of the present invention, the adsorbent is the lipid microparticle (preferably the outermost surface of the lipid layer) and the adsorbate is the active pharmaceutical ingredient.

The lipid microparticles of the present invention are lipid microparticles comprised of a lipid layer and at least one active pharmaceutical ingredient adsorbed on the lipid microparticle. Preferably the lipid microparticles are hollow particles, that is they comprise a hollow core/compartment. Within the context of the present invention, microparticles are considered particles with any dimension (for example diameter) in the micrometer (µm) range, for example from about 1 µm to about 100 µm. Preferably the lipid microparticles (preferably hollow particles) have an average particle size, for example a D_{50} diameter, of from about 1 µm to about 10 µm, more preferably from about 1µm to about 4 µm, when measured by conventional means such as LLD.

The hollow core/compartment may be considered a central void or an internal void space. This hollow core is preferably completely surrounded/encompassed/enclosed by the lipid layer. In other words, the lipid layer defines an internal void/core. As such, the lipid microparticle of the present invention could be considered comprised of an outer lipid shell and an inner hollow core. The hollow nature of the lipid microparticle of the present invention can be characterized by any known technique in the art, such as scanning electron microscopy.

The active pharmaceutical ingredient(s) is adsorbed on the lipid microparticle, i.e., it is not encapsulated/enclosed in the core. Further, it is preferable that the lipid layer is not a lipid bilayer. The lipid microparticle of the present invention may not be a liposome.

The lipid layer is a layer comprising at least one lipid. The layer has two surfaces, an outermost surface and an innermost surface, which innermost surface faces the hollow core. The outermost surface of the lipid layer is the outermost surface of the lipid microparticle.

Preferably, the active pharmaceutical ingredient(s) is adsorbed on a surface of the lipid microparticle, more preferably an outermost surface or innermost surface of the lipid layer.

The lipid microparticle may be spherical in shape or irregular in shape, that is the microparticle may deviate from that of a perfect sphere, such as it may be indented, deformed or collapsed. It may be shaped like a biconcave disc, which may be hollow.

Preferably the lipid layer (lipid shell) of the microparticle is not porous. More preferably it is completely (100%) not porous. The lipid layer (lipid shell) may not comprise voids, pores, holes or perforations.

The density of the lipid microparticles of the present invention is preferably from about 0.05 to about 0.5 g/cm^3, about 0.07 to about 0.3 g/cm^3, more preferably about 0.09 to about 0.2 g/cm^3.

The lipid layer (i.e. the layer comprising at least one lipid) may further comprise additional components. It is preferred that the lipid layer does not comprise cholesterol.

Suitable additional components are metal ions and/or saccharides. It is preferred that the lipid layer further comprises at least one metal ion (preferably in the form of a metal compound or a salt). The metal ion may form a lipid-metal ion complex, that is the lipid layer may be a lipid-metal ion complex matrix. The saccharide may be incorporated in this matrix.

Suitable metal ions for use in the present invention may be selected from lanthanides, transition metals, alkali metals, alkaline earth metals, non-toxic metal ions or any metal ion at non-toxic levels from groups IIa, IIIb and all metals from atomic numbers 21-30; 39-48, 57-80 and 89-106 and

mixtures thereof. It is also within the scope of the present invention to use a metal containing ion such as $V0^{+2}$. Preferred metal ions are calcium, sodium, magnesium, aluminum, zinc, iron, lithium and any mixtures thereof. More preferably, the metal ion is an alkali metal ion or an alkaline earth metal ion, most preferably sodium or calcium.

The metal ion is preferably in the form of a salt. Suitable salts are alkaline earth metal salts or alkali metal salts, preferably calcium chloride, magnesium chloride and sodium chloride, most preferably sodium chloride or calcium chloride.

Any saccharide in the art is suitable for use in the present invention. Preferably the saccharide is a disaccharide. Suitable disaccharides are sucrose, cellobiose, lactose, maltose, chitobiose, trehalose and any combination thereof. Particularly preferred disaccharides are lactose or trehalose, most preferably trehalose.

Preferably the saccharide is included in the lipid microparticle in an amount of from about 3 to about 25%, more preferably about 4 to about 20%, most preferably about 4 to about 15%, wherein the percentage is in reference to the total weight of lipid, saccharide, metal ion (preferably metal ion salt) and active pharmaceutical ingredient used.

The inventors have also unexpectedly found that utilizing a metal ion in combination with a saccharide in a lipid comprising microparticle increases the lipid's glass transition temperature (T_g) significantly. This increase in T_g is larger than when a metal ion is used alone with the lipid to increase the T_g of the lipid. For example, the presence of a saccharide (preferably a disaccharide, more preferably trehalose) raises the T_g of a lipid microparticle comprising a metal ion (preferably in the form of a metal ion-lipid complex) at least about $20^{O}C$ above that of the same lipid microparticle without the saccharide.

More specifically, the inventors unexpectedly found that a lipid layer comprising a lipid and calcium chloride, preferably in the form of a calcium-lipid complex, had a T_g of from about 90-$95^{O}C$, whereas when trehalose was added to the same lipid layer of the microparticle, that T_g was increased to about 115-$120^{O}C$.

The use of a metal ion in combination with a saccharide will also result in the lipid microparticle maintaining its structural state/morphology. In other words, an amorphous lipid microparticle will not convert partly or wholly to a crystalline lipid microparticle (it will remain amorphous). Accordingly, it is preferable that the lipid microparticle of the present invention is amorphous. These amorphous lipid microparticles would result in improved absorption in the body (for example, deep lung deposition) and improved stability within the formulation.

Further the use of a saccharide, preferably trehalose, has the added advantage of providing a final spray dried powder of lipid microparticles which is free flowing and thus is in a respirable form. As such, the use of a saccharide (such as lactose or trehalose) is particularly advantageous for inhalable formulations.

Physicochemical properties and design of the composition are the prime factors that affect the efficacy of any drug delivery systems. Apart from these factors, stability of the composition is of utmost importance as well.

Dry powder inhalation (DPI) compositions can overcome the instability problems that are associated with the conventional liposomal dispersions as well as exhibit better stability, ease of administration and patient compliance. Liposomal dry powder formulations are capable of delivering defined doses of drugs, represent promising tools for pulmonary drug administration, such as selective localization of drug, reduced local and systemic toxicities, increased patient compliance and high dose loading.

The inventors of the present invention have designed alternative and advantageous lipid containing compositions comprising lipid microparticles, which preferably have hollow cores, having lesser density and modified particle morphology which ultimately contribute to the improved efficacy of the compositions. These lipid containing compositions would be particularly advantageous in inhalable compositions.

The lipid microparticles of the present invention have at least one active pharmaceutical ingredient adsorbed on the lipid microparticle.

The term "active pharmaceutical ingredient(s)' (API(s)) is used in its broad and usual sense to mean the active ingredient of a pharmaceutical product (also known as an active ingredient, therapeutically active ingredient, therapeutic agent, active agent, drug, drug substance). This term also encompasses the API's pharmaceutically acceptable derivatives such as salts, solvates, hydrates, enantiomers, esters, polymorphs, prodrugs or complexes. Examples of suitable categories of APIs for use in the present invention include corticosteroids, anticholinergic agents, β2 agonists, antituberculosis drugs, antipsychotics, cessation drugs, biomolecules, monoclonal antibodies, anti-HIV drugs, antidiabetic drugs, antibiotics, anti-inflammatories, antihistamines, decongestants, anti-tussive drug substances, antifungal agents, antihelminthics, anxiolytics, calcium antagonists, antacids, antianemics, antiepileptic, cough relief agents, antivirals, and prostacyclin analogs. Preferred categories of APIs for use in the present invention are anticholinergic agents, corticosteroids and β2 agonists.

Suitable active pharmaceutical ingredients for use in the present invention include tiotropium, oxitropium, flutropium, ipratropium, otilonium, umeclidinium, darotropium, darifenacin, aclidinium, glycopyrronium, dexpirronium, trospium, prednisolone, prednisone, flunisolide, beclomethasone, triamcinolone, budesonide, R budesonide, butixocort, flunisolide, rofleponide, terbutaline, fluticasone furoate, fluticasone propionate, fluticasone valrate, levosalbutamol, salbutamol (albuterol), salmeterol, carmoterol, pirbuterol, clenbuterol, etanterol, fenoterol, flerbuterol, indacaterol, olodaterol, bambuterol, bitolterol, metaproterenol, milveterol, naminterol, pirbuterol, procaterol, reproterol, salmefamol, vilanterol, abediterol, formoterol, arformoterol, salmeterol, mometasone, ciclesonide, rofleponide, dexamethasone, betamethasone, amikacin, tobramycin, ciprofloxacin, pirfenidone, nintedanib, isoniazid, rifampicin, pyrazinamide, ethambutol, streptomycin, kanamycin, amikacin, capreomycin, levofloxacin, moxifloxacin, ofloxacin, chlorpromazine, haloperidol, pimozide, trifluoperazine, sulpiride, lurasidone, olanzapine, quetiapine, aripiprazole, risperidone, ziprasidone, asenapine, cariprazine, brexpiprazole, pimavanserin, sitagliptin, Vildagliptin, metformin, ketoconazole, Posaconazole, Selexipag, varenicline, bupropion, insulin, omalizumab, denosumab, efavirenz, tenofovir, atazanavir, pseudoephedrine, phenylephirine, acetylcysteine, guaifenesin, primaquine, pregabalin, diltiazem, nifedipine, omeprazole, rabeprazole, Epoetin alpha, clonazepam, lorazepam, *per se* and also their pharmaceutically acceptable salts, pharmaceutically acceptable solvates, pharmaceutically acceptable hydrates, pharmaceutically acceptable enantiomers, pharmaceutically acceptable esters, pharmaceutically acceptable polymorphs, pharmaceutically acceptable prodrugs,

pharmaceutically acceptable complexes. Particularly preferred APIs for use in the present invention are albuterol, glycopyronium (for example albuterol sulphate and glycopyrronium bromide), salmeterol, fluticasone, budesonide, formoterol and any combination thereof. The present invention also encompasses any combination of the above suitable APIs.

These suitable active pharmaceutical ingredients may be crystalline, amorphous or any mixture thereof.

In a broad sense, lipids suitable for use in the present invention include any of those known in the art. Preferably the lipids are phospholipids, that is the lipid layer of the lipid microparticles of the present invention are preferably phospholipid layers, that is the layer is comprised of a phospholipid(s).

Other lipids including glycolipids, ganglioside GM1, sphingomyelin, phosphatidic acid, cardiolipin; lipids bearing polymer chains such as polyethylene glycol, chitin, hyaluronic acid, or polyvinylpyrrolidone; lipids bearing sulfonated mono-, di-, and polysaccharides; fatty acids such as palmitic acid, stearic acid, and oleic acid; cholesterol, cholesterol esters, and cholesterol hemisuccinate may also be used in accordance with the present invention.

Suitable natural, synthetic and semi- synthetic phospholipids that may be employed in the formation of the lipid microparticle compositions of the present invention include, but are not limited to, dipalmitoylphosphatidylcholine (DPPC), dioleoylphosphatidylcholine (DOPC), dimyristoylphosphatidylcholine (DMPC), dimyristoylphosphatidylglycerol (DMPG), dipalmitoylphosphatidylglycerol (DPPG), distearoylphosphatidylcholine (DSPC), distearoylphosphatidylglycerol (DSPG), dioleylphosphatidylethanolamine (DOPE), mixed phospholipids like palmitoylstearoylphosphatidylcholine (PSPC) and palmitoylstearoylphosphatidylglycerol (PSPG), triacylglycerol, diacylglycerol, seranide, sphingosine, sphingomyelin and single acylated phospholipids like mono-oleoyl-phosphatidylethanolamine (MOPE), tocopherols, steroids, fatty acids, glycoproteins such as albumin, negatively-charged lipids and cationic lipids and the like or combinations thereof. Phosholipids include egg phosphatidylcholine (EPC), egg phosphatidylglycerol (EPG), egg phosphatidylinositol (EPI), egg phosphatidylserine (EPS), phosphatidylethanolamine (EPE), and egg phosphatidic acid (EPA); the soya counterparts, soy phosphatidylcholine (SPC); SPG, SPS,

SPI, SPE, and SPA; the hydrogenated egg and soya counterparts (e.g., HEPC, HSPC), other phospholipids made up of ester linkages of fatty acids in the 2 and 3 of glycerol positions containing chains of 12 to 26 carbon atoms and different head groups in the 1 position of glycerol that include choline, glycerol, inositol, serine, ethanolamine, as well as the corresponding phosphatidic acids or combinations thereof. The preferred phospholipids for use in the present invention are DSPC and DPPC or combination thereof.

It is preferred that the drug to lipid weight ratio in the final (spray dried) lipid microparticle is about, 0.001 to 10, 0.002 to 5.0, 0.005 to 5.0, 0.005 to 2.0, More preferably, the drug:lipid ratio is about 0.002 to 0.2 (which lipid microparticle is particularly suitable for dry powder inhalers) or 0.005 to 5.0 (which lipid microparticle is particularly suitable for metered dose inhalers).

It is further preferred that the percentage of active pharmaceutical ingredient used in the present invention is from about 0.2 to about 90%, about 0.2 to about 50%, about 0.2 to about 25%, more preferably about 0.2 to about 12%, or about 1% to about 12%, wherein the percentage is in reference to the total weight of active pharmaceutical ingredient, lipid and metal ion salt used.

In a particularly preferred embodiment of the present invention, there is provided a hollow, amorphous lipid microparticle comprising a lipid layer and an active pharmaceutical ingredient(s), wherein the lipid layer comprises a saccharide and a lipid-metal ion complex and wherein the active pharmaceutical ingredient is adsorbed on the lipid microparticle.

The present invention also provides a first process for preparing lipid microparticles of the present invention which process comprises –

(a) Preparing an aqueous liposomal suspension of unilamellar vesicles (small unilamellar vesicles):
(b) Adding one or more active pharmaceutical ingredient(s) to the aqueous liposomal suspension; and
(c) Spray drying the aqueous liposomal suspension to form lipid microparticles.

The preparation of the aqueous liposomal suspension of unilamellar vesicles may involve the preparation of multilamellar lipid vesicles by any process known in the art such as, but not limited to, reverse phase evaporation, lipid film hydration, rehydration dehydration of vesicles, ethanol

injection or ether injection. Preferably lipid film hydration is used to form the multilamellar lipid vesicles.

Accordingly, the preparation of the liposomal suspension of (small) unilamellar vesicles may comprise dissolving (and preferably mixing) a suitable lipid in a suitable solvent, preferably an organic solvent.

Suitable solvents include, but are not limited to, chloroform, methanol, ethanol and any mixtures thereof. The preferred solvent is chloroform or a methanol:chloroform mixture.

Preferably, the lipid content in the solvent is from about 0.5% to about 10%, about 1% to about 5% or about 2% to about 5%, more preferably about 2% or about 3%, most preferably about 2% (wt/vol %).

The solvent is then evaporated to form a lipid film. Suitable techniques in the art may be used, such as evaporation using a dry nitrogen/rotary evaporation. The film may then be dried to remove residual solvent by for example placing the film in a vacuum pump overnight.

The lipid film is then hydrated with an aqueous solution to form multilamellar vesicles. As a result, the aqueous solution is entrapped within the lipid bilayer membrane of the multilamellar liposomes.

During hydration the lipid content in the solvent is from about 1% to about 15%, about 1% to about 10%, or about 2% to about 6%, more preferably about 2% to about 4%.

Preferably the aqueous solution comprises water. Suitable aqueous solutions preferably comprise a metal ion in the form of a metal compound or a salt.

Suitable metal ions may be selected from lanthanides, transition metals, alkaline earth metals, alkali metals, non-toxic metal ions or any metal ion at non-toxic levels from groups IIa, IIIb and all metals from atomic numbers 21-30; 39-48, 57-80 and 89-106 and mixtures thereof. It is also within the scope of the present invention to use a metal containing ion such as $V0^{+2}$. Preferred metal ions are calcium, magnesium, aluminum, zinc iron, lithium and any mixtures thereof. It is also possible

to use organic ions or compounds that form dehydrating complexes with phospholipids. Most preferably, the metal ion is calcium or sodium.

The metal ion is preferably in the form of a salt. Suitable preferred salts are alkaline earth metal salts or alkali metal salts, for example calcium chloride, magnesium chloride and sodium chloride. As such, suitable aqueous solutions for hydration comprise a salt such as calcium chloride, magnesium chloride or sodium chloride. Most preferably the aqueous solution comprises calcium chloride (for example calcium chloride dihydrate) or sodium chloride.

This hydration is carried out above the gel-liquid transition temp of the lipid for a suitable period of time, for example 1-2 hours, while agitating.

The size of the multilamellar lipid vesicles may then be reduced (the multilamellar vesicles may be nanosized, that is formed into nano sized unilamellar vesicles) by any process known in the art to form an aqueous liposomal suspension of (small) unilamellar vesicles.

Used herein the term “nano” refers to dimensions of about 50-500nm. For example, nano-sized vesicles means a vesicle that has an average diameter (D_{50}) from about 100 to about 300nm, when measured by conventional means such as LLD.

Suitable processes in the art for reducing the size of the multilamellar lipid vesicles to small unilamellar vesicles include, but are not limited to, extrusion, sonication or homogenization milling, precipitation and homogenization, high pressure homogenization, spray-freeze drying, supercritical fluid technology, double emulsion/solvent evaporation, PRINT (Particle replication in non-wetting templates), thermal condensation, ultrasonication or spray drying. Preferably the mutilamellar lipid vesicles are reduced (nanosized) to small unilamellar vesicles by extrusion or high pressure homogenization, most preferably high pressure homogenization.

Accordingly, it is preferred that the liposomal suspension of unilamellar vesicles is obtained by lipid film hydration with the particle (the mutilamellar lipid vesicles) size further reduced by extrusion or high pressure homogenization.

The active pharmaceutical ingredient(s) is then added to the aqueous liposomal suspension. The active pharmaceutical ingredient(s) is added to the aqueous liposomal suspension in an aqueous or non-aqueous solvent, depending on the solubility of the active pharmaceutical ingredient. Suitable aqueous solvents include water and suitable non-aqueous solvents include alcohols such as methanol and ethanol.

The aqueous solution preferably further comprises a saccharide. Any saccharide in the art is suitable for use in the present invention. Preferably the saccharide is a disaccharide. Suitable disaccharides are sucrose, cellobiose, lactose, maltose, chitobiose, trehalose and any combination thereof. Particularly preferred disaccharides are trehalose (for example trehalose monohydrate) or lactose (for example lactose monohydrate), most preferably trehalose.

If more than one active is used then each separate active is dissolved in its suitable solvent and then added separately to the liposomal suspension.

This feed stock for spray drying can be any solution, course suspension, slurry, or paste that may be atomized by spray drying. It is preferred that the feed stock does not comprise an emulsion, reverse emulsion, microemulsion, or multiple emulsion. Accordingly, it is preferred that the lipid microparticles of the present invention are not spray dried from such emulsions. Also, it is preferred that the aqueous suspension is not an oil-in-water emulsion.

The aqueous liposomal suspension comprising the active pharmaceutical ingredient(s) (the feed stock) is then spray dried (using for example a mini spray drier)) to form lipid microparticles using standard conditions. Preferably the inlet temperature is from about 90-150^{O}C, more preferably about 100-130^{O}C and the outlet temperature is about 60-70^{O}C. The spray drying results in the liposomes (the SUVs) completely fusing together to form the lipid microparticles of the present invention. The entrapped/encapsulated aqueous solution is evaporated leading to fusion of the bilayer of the unilamellar liposomes to preferably form hollow lipid microparticles which are preferably completely amorphous.

The final lipid microparticles are in the form of a powder (a spray dried powder comprising lipid microparticles). The density of the powder comprising the lipid microparticles of the present

invention is preferably from about 0.05 to about 0.5 g/cm^3, about 0.07 to about 0.3 g/cm^3, more preferably from about 0.09 to about 0.2 g/cm^3.

The process of spray drying the feed stock may result in the active pharmaceutical ingredient(s) remaining in an amorphous state, changing to an amorphous state or becoming more amorphous in nature. In other words, the active pharmaceutical ingredient(s) comprised in the final lipid microparticle may be amorphous. In a preferred embodiment, the active pharmaceutical ingredient(s) added to the aqueous liposomal suspension is crystalline and the same active pharmaceutical ingredient(s) when adsorbed is amorphous.

Amorphous solids do not give a definitive x-ray diffraction pattern (XRD). In addition, amorphous solids do not give rise to a specific melting point and tend to liquefy at some point beyond the glass transition temperature.

The active pharmaceutical ingredient(s) comprised in the lipid microparticle of the present invention and/or the lipid microparticle of the present invention is preferably amorphous, that is essentially or substantially free of crystallinity. The API(s) and/or lipid microparticle may be at least about 50% amorphous, 60%, 70%, 80%, 90%, 95%, 96%, 97%, 98%, or about 99% amorphous. Most preferably the active pharmaceutical ingredient(s) and/or lipid microparticle of the present invention is about 100% amorphous, wherein the percentage is in reference to the total percentage of crystalline and amorphous forms of that API.

It is also within the scope of this invention for the active pharmaceutical ingredient(s) to be added before the reduction in size of the multilamellar lipid vesicles to small unilamellar vesicles (i.e. before the production of the aqueous liposomal suspension). This is particularly suitable if the active is soluble in water. The addition of the active(s) can be with the lipid into the solvent.

Accordingly, the present invention also provides a second alternative process for preparing lipid microparticles of the present invention which process comprises –

(a) Preparing an aqueous liposomal suspension of unilamellar vesicles (small unilamellar vesicles) which liposomal suspension also comprises at least one active pharmaceutical ingredient: and
(b) Spray drying the aqueous liposomal suspension to form lipid microparticles.

The preparation of the liposomal suspension of (small) unilamellar vesicles may comprise dissolving (and preferably mixing) a suitable lipid and at least one active pharmaceutical ingredient in a suitable solvent, preferably an organic solvent. In other words, the active pharmaceutical ingredient (s) is added with the lipid to a suitable solvent.

The solvent is then evaporated to form a lipid film and the lipid film is subsequently hydrated to form multilamellar lipid vesicles.

The size of the multilamellar lipid vesicles may then be reduced by any process known in the art (for example homogenization) to form an aqueous liposomal suspension of (small) unilamellar vesicles. This liposomal suspension would already contain the active pharmaceutical ingredient.

The liposomal suspension is then spray dried.

The addition of the active(s) before the preparation of the liposomal suspension is particularly suitable for salmeterol, fluticasone, budesonide, tiotropium, formoterol and any combination thereof.

All of the features discussed above with regard to the first process for preparing the lipid microparticles of the present invention (for example, suitable solvents, amounts, process conditions) are also suitable features of this second alternative process of the present invention.

Whether the lipid microparticles are prepared from the first or second process, the lipid microparticles of the present invention may then be formulated for use. Suitable uses may be, (but are not limited to) respiratory, pulmonary, otic, anal, optic, vaginal, intramuscular, intravenous, intratracheal, intracuticular, intraperitoneal, nasal, pharyngeal, sinal, subcutaneous, extradural, intracisternal, intrapleural and intrathecal delivery. Preferably the use is in an inhalable composition.

There is thus provided a process for preparing a pharmaceutical composition wherein the process comprises preparing the lipid microparticles as described herein and then further mixing these lipid

microparticles with at least one pharmaceutically acceptable excipient to provide the pharmaceutical (preferably inhalable) composition.

Suitable excipients include, but are not limited to, diluents, binders, water soluble polymers, water insoluble polymers, sweeteners, flavors, fillers, disintegrants, surfactants, glidants, lubricants and any combination thereof.

Any known method in the art can be used to mix the excipients with the lipid microparticles.

Accordingly, the present invention also provides a pharmaceutical composition (preferably an inhalable pharmaceutical composition) comprising lipid microparticles of the present invention. Preferably an inhalable pharmaceutical composition is formulated for use in an inhalable dry powder formulation (DPI) or metered dose inhaler (MDI). Preferably, the inhalable pharmaceutical composition further comprises at least one pharmaceutically acceptable excipient. It may further comprise additional active pharmaceutical ingredients.

The inhalable pharmaceutical composition may be filled/encapsulated in capsules, cartridges, blisters or contained within a reservoir in a single-dose or multi-dose dry powder inhalation device.

The pharmaceutical composition of the present invention may also be formulated for use in solid oral dosage forms such as, but not limited to, powders, granules, pellets, tablets, sprinkles and capsules; liquid oral dosage forms such as but not limited to syrups, suspensions, dispersions, and emulsions; and injectable preparations such as but not limited to solutions, dispersions, and freeze dried compositions. Formulations may be in the form of immediate release, delayed release or modified release.

In a preferred embodiment, there is provided a process for preparing an inhalable pharmaceutical composition comprising lipid microparticles which process comprises dissolving a lipid in an organic solvent, evaporating the organic solvent to form a lipid film, hydrating such lipid film with an aqueous solution to form multilamellar vesicles. Such multilamellar vesicles are nanosized to form the small unilamellar vesicles followed by the addition of the active pharmaceutical ingredients in the aqueous lipid microparticle suspension of the small unilamellar vesicles to form a feed stock (preparation to be spray dried). The lipid microparticle suspension is spray dried to produce hollow

particles comprising the active pharmaceutical ingredients. The inhalable pharmaceutical composition, may then be filled in capsules, cartridges and/or blisters.

In a further preferred embodiment, there is provided a process for preparing lipid microparticles which process comprises:

(a) dissolving a lipid in an organic solvent,

(b) evaporating the organic solvent to form a lipid film,

(c) hydrating the lipid film with an aqueous solution comprising an alkaline earth metal salt or an alkali metal salt to form multilamellar vesicles,

(d) nanosizing the multilamellar vesicles to form small unilamellar vesicles in an aqueous liposomal suspension,

(e) adding one or more active pharmaceutical ingredients and a saccharide to the aqueous liposomal suspension to form a feed stock,

(f) spray drying the feed stock to produce hollow, amorphous lipid microparticles with the active pharmaceutical ingredient(s) adsorbed on the microparticles.

In a further preferred embodiment, there is provided a process for preparing lipid microparticles which process comprises:

(a) dissolving a lipid and at least one active pharmaceutical ingredient in an organic solvent,

(b) evaporating the organic solvent to form a lipid film,

(c) hydrating the lipid film with an aqueous solution comprising an alkaline earth metal salt or an alkali metal salt to form multilamellar vesicles,

(d) nanosizing the multilamellar vesicles to form small unilamellar vesicles in an aqueous liposomal suspension,

(e) adding a saccharide to the aqueous liposomal suspension to form a feed stock,

(f) spray drying the feed stock to produce hollow amorphous lipid microparticles with the active pharmaceutical ingredient(s) adsorbed on the microparticles.

Preferably, the processes of the present invention result in one spray-dried lipid microparticle powder that is used in one single inhalable pharmaceutical composition.

It will further be appreciated that the lipid microparticles of the present invention may, if desired, comprise a combination of two or more active pharmaceutical ingredients.

The present invention also provides a delivery system comprising an inhaler and an inhalable pharmaceutical composition as described herein.

The present invention also provides a method of treatment and/or prophylaxis of lung disease which method comprises administering a therapeutically effective amount of lipid microparticles as described herein (or inhalable pharmaceutical composition comprising lipid microparticles as described herein) to a patient in need thereof.

The present invention also provides the use of lipid microparticles as described herein (or inhalable pharmaceutical composition comprising lipid microparticles as described herein) in the manufacture of a medicament for the treatment and/or prophylaxis of lung disease.

The present invention also provides lipid microparticles as described herein (or inhalable pharmaceutical composition comprising lipid microparticles as described herein) for use in the treatment and/or prophylaxis of lung disease.

The term “lung disease” is any disease or disorder where lung function is impaired which diseases include, but are not limited, to Asthma, Chronic Obstructive Pulmonary Disease, Cystic Fibrosis, Influenza, Pneumonia, Lung Cancer, Pulmonary emboli, Pulmonary Arterial Hypertension, Tuberculosis, Respiratory Distress Syndrome and Bronchopulmonary Dysplasia, Respiratory Syncytial Virus, Sarcoidosis, lymphangioleiomyomatosis.

The present invention also provides lipid microparticles (or pharmaceutical composition comprising lipid microparticles) substantially as herein described with reference to the examples.

The present invention also provides a process substantially as herein described with reference to the examples.

The following examples are for the purpose of illustration of the invention only and are not intended in any way to limit the scope of the present invention.

Example 1: Preparation of a pharmaceutical composition comprising lipid microparticles of glycopyrronium bromide

Sr. No.	Ingredients	Quantity
1.	DSPC	2.0 g
2.	Glycopyronium bromide	0.005 g

Process -

1) DSPC was dissolved in chloroform which was evaporated to form a dried lipid film.
2) The film obtained in step (1) was further hydrated to form multilamellar vesicles.
3) The multilamellar vesicles obtained in step (2) were nanosized to form an aqueous liposomal suspension of unilamellar vesicles.
4) Glycopyronium bromide was added to the aqueous liposomal suspension of unilamellar vesicles obtained in step (3).
5) The liposomal suspension obtained in step (4) was spray dried to form lipid microparticles.
6) The spray dried powder obtained in step (5) was filled in capsules and/or cartridges.

Example 2: Preparation of a pharmaceutical composition comprising lipid microparticles of albuterol sulphate

Sr. No.	Ingredients	Quantity
1.	DSPC	2.0 g
2.	Albuterol sulphate	0.02 g

Process –

1) DSPC was dissolved in chloroform which was evaporated to form a dried lipid film.
2) The film obtained in step (1) was further hydrated to form multilamellar vesicles.
3) The multilamellar vesicles obtained in step (2) were nanosized to form an aqueous liposomal suspension of unilamellar vesicles.

4) Albuterol sulphate was added to the aqueous liposomal suspension of unilamellar vesicles obtained in step (3)

5) The liposomal suspension obtained in step (4) was spray dried to form lipid microparticles.

6) The spray dried powder obtained in step (5) was filled in capsules and/or cartridges.

Example 3: Preparation of a pharmaceutical composition comprising lipid microparticles of glycopyrronium bromide

Sr. No.	Ingredients	Quantity
1.	DSPC	4.0 g
2.	Glycopyronium bromide	0.05g
3.	Calcium chloride dihydrate	0.22g
4.	Purified water	200ml

Process –

1) DSPC was dissolved in chloroform which was evaporated to form a dried lipid film.

2) Calcium chloride was dissolved in water.

3) The film obtained in step (1) was further hydrated using step (2) solution to form multilamellar vesicles.

4) Glycopyrronium bromide was added to the aqueous liposomal suspension of multilamellar vesicles obtained in step (3).

5) The multilamellar vesicles of step (4) were nanosized to form an aqueous liposomal suspension of unilamellar vesicles.

6) The liposomal suspension obtained in step (5) was spray dried to form lipid microparticles.

7) The spray dried powder obtained in step (6) was filled in capsules and/or cartridges.

Example 4: Preparation of a pharmaceutical composition comprising lipid microparticles of glycopyrronium bromide

Sr. No.	Ingredients	Quantity
1.	DSPC	4.0 g
2.	Glycopyronium bromide	0.05g

3.	Calcium chloride dihydrate	0.22g
4.	Trehalose monohydrate	0.20
5.	Purified water	200ml

Process –

1) DSPC was dissolved in chloroform which was evaporated to form a dried lipid film.
2) Calcium chloride was dissolved in water.
3) The film obtained in step (1) was further hydrated using step (2) solution to form multilamellar vesicles.
4) Glycopyrronium bromide and trehalose were added to the aqueous liposomal suspension of multilamellar vesicles obtained in step (3).
5) The multilamellar vesicles of step (4) were nanosized to form an aqueous liposomal suspension of unilamellar vesicles.
6) The liposomal suspension obtained in step (5) was spray dried to form lipid microparticles.
7) The spray dried powder obtained in step (6) was filled in capsules and/or cartridges.

Example 5: Preparation of a pharmaceutical composition comprising lipid microparticles of glycopyrronium bromide

Sr. No.	Ingredients	Quantity
1.	DSPC	4.0 g
2.	Glycopyronium bromide	0.05g
3.	Sodium chloride	0.16
4.	Purified water	200ml

Process –

1) DSPC was dissolved in chloroform which was evaporated to form a dried lipid film.
2) Sodium chloride was dissolved in water.
3) The film obtained in step (1) was further hydrated using step (2) solution to form multilamellar vesicles.

4) Glycopyrronium bromide was added to the aqueous liposomal suspension of multilamellar vesicles obtained in step (3).

5) The multilamellar vesicles of step (4) were nanosized to form an aqueous liposomal suspension of unilamellar vesicles.

6) The liposomal suspension obtained in step (5) was spray dried to form lipid microparticles.

7) The spray dried powder obtained in step (6) was filled in capsules and/or cartridges.

Example 6: Preparation of a pharmaceutical composition comprising lipid microparticles of glycopyrronium bromide

Sr. No.	Ingredients	Quantity
1.	DSPC	4.0 g
2.	Glycopyronium bromide	0.05g
3.	Sodium chloride dihydrate	0.16
4.	Trehalose monohydrate	0.20
5.	Purified water	200ml

Process –

1) DSPC was dissolved in chloroform which was evaporated to form a dried lipid film.

2) Sodium chloride was dissolved in water.

3) The film obtained in step (1) was further hydrated using step (2) solution to form multilamellar vesicles.

4) Glycopyrronium bromide and trehalose were added to the aqueous liposomal suspension of multilamellar vesicles obtained in step (3).

5) The multilamellar vesicles of step (4) were nanosized to form an aqueous liposomal suspension of unilamellar vesicles.

6) The liposomal suspension obtained in step (5) was spray dried to form lipid microparticles.

7) The spray dried powder obtained in step (6) was filled in capsules and/or cartridges.

Example 7: Preparation of a pharmaceutical composition comprising lipid microparticles of glycopyrronium bromide

Sr. No.	Ingredients	Quantity
1.	DSPC	6.0 g
2.	Glycopyronium bromide	0.08g
3.	Calcium chloride dihydrate	0.32g
4.	Purified water	300ml

Process –

1) DSPC was dissolved in chloroform which was evaporated to form a dried lipid film.

2) Calcium chloride was dissolved in water.

3) The film obtained in step (1) was further hydrated using step (2) solution to form multilamellar vesicles.

4) Glycopyrronium bromide was added to the aqueous liposomal suspension of multilamellar vesicles obtained in step (3).

5) The multilamellar vesicles of step (4) were nanosized to form an aqueous liposomal suspension of unilamellar vesicles.

6) The liposomal suspension obtained in step (5) was spray dried to form lipid microparticles.

7) The spray dried powder obtained in step (6) was filled in capsules and/or cartridges.

Example 8: Preparation of a pharmaceutical composition comprising lipid microparticles of glycopyrronium bromide

Sr. No.	Ingredients	Quantity
1.	DSPC	6.0 g
2.	Glycopyronium bromide	0.08g
3.	Calcium chloride dihydrate	0.32g
4	Lactose Monohydrate	0.31g
5.	Purified water	300ml

Process –

1) DSPC was dissolved in chloroform which was evaporated to form a dried lipid film.

2) Calcium chloride was dissolved in water.

3) The film obtained in step (1) was further hydrated using step (2) solution to form multilamellar vesicles.

4) Glycopyrronium bromide and lactose monohydrate was added to the aqueous liposomal suspension of multilamellar vesicles obtained in step (3).

5) The multilamellar vesicles of step (4) were nanosized to form an aqueous liposomal suspension of unilamellar vesicles.

6) The liposomal suspension obtained in step (5) was spray dried to form lipid microparticles.

7) The spray dried powder obtained in step (6) was filled in capsules and/or cartridges.

Example 9: Preparation of pharmaceutical compositions comprising lipid microparticles of salmeterol and fluticasone

Ingredients	Quantity [g]	Quantity [g]	Quantity [g]
Salmeterol	0.07	0.07	0.07
Fluticasone	0.1	0.25	0.5
DSPC	4.0	4.0	4.0
$CaCl_2$	0.22	0.22	0.22
Trehalose	0.60	0.45	0.20
Total	5.0	5.0	5.0

Process –

1) DSPC was dissolved in chloroform which was evaporated to form a dried lipid film.

2) Calcium chloride was dissolved in water.

3) The film obtained in step (1) was further hydrated using step (2) solution to form multilamellar vesicles.

4) The multilamellar vesicles of step (3) were nanosized to form an aqueous liposomal suspension of unilamellar vesicles.

5) Salmeterol and Fluticasone along with trehalose were added to the aqueous liposomal suspension obtained in step (4).

6) The liposomal suspension obtained in step (5) was spray dried to form lipid microparticles.

7) The spray dried powder obtained in step (6) was filled in capsules and/or cartridges.

Example 10: Preparation of pharmaceutical compositions comprising lipid microparticles of salmeterol and fluticasone

Ingredients	Quantity [g]	Quantity [g]	Quantity [g]
Salmeterol	0.07	0.07	0.07
Fluticasone	0.1	0.25	0.5
DSPC	4.0	4.0	4.0
$CaCl_2$	0.22	0.22	0.22
Trehalose	0.60	0.45	0.20
Total	5.0	5.0	5.0

Process –

1) DSPC along with both the drugs was dissolved in chloroform which was evaporated to form a dried lipid film.

2) Calcium chloride was dissolved in water.

3) The film obtained in step (1) was further hydrated using step (2) solution to form multilamellar vesicles.

4) The multilamellar vesicles of step (3) were nanosized to form an aqueous liposomal suspension of unilamellar vesicles.

5) Trehalose was added to the aqueous liposomal suspension obtained in step (4).

6) The liposomal suspension obtained in step (5) was spray dried to form lipid microparticles.

7) The spray dried powder obtained in step (6) was filled in capsules and/or cartridges.

Example 11: Preparation of pharmaceutical compositions comprising lipid microparticles of budesonide and formoterol

Ingredients	Quantity [g]	Quantity [g]
Budesonide	2.18	4.36
Formoterol	0.127	0.12

DSPC	4.0	4.0
$CaCl_2$	0.22	0.22
Trehalose	0.68	0.68
Total	7.2	9.4

Process –

1) DSPC was dissolved in chloroform which was evaporated to form a dried lipid film.

2) Calcium chloride was dissolved in water.

3) The film obtained in step (1) was further hydrated using step (2) solution to form multilamellar vesicles.

4) The multilamellar vesicles of step (3) were nanosized to form an aqueous liposomal suspension of unilamellar vesicles.

5) Micronized Budesonide and Formoterol along with trehalose were added to the aqueous liposomal suspension obtained in step (4).

6) The liposomal suspension obtained in step (5) was spray dried to form lipid microparticles.

7) The spray dried powder obtained in step (6) was filled in capsules and/or cartridges.

Example 12: Preparation of pharmaceutical compositions comprising lipid microparticles of budesonide and formoterol

Ingredients	Quantity [g]	Quantity [g]
Budesonide	0.09	0.18
Formoterol	0.005	0.005
DSPC	4.0	4.0
$CaCl_2$	0.22	0.22
Trehalose	0.68	0.59
Total	5.0	5.0

Process –

1) DSPC along with both the drugs was dissolved in chloroform which was evaporated to form a dried lipid film.

2) Calcium chloride was dissolved in water.

3) The film obtained in step (1) was further hydrated using step (2) solution to form multilamellar vesicles.

4) The multilamellar vesicles of step (3) were nanosized to form an aqueous liposomal suspension of unilamellar vesicles.

5) Trehalose was added to the aqueous liposomal suspension obtained in step (4).

6) The liposomal suspension obtained in step (5) was spray dried to form lipid microparticles.

7) The spray dried powder obtained in step (6) was filled in capsules and/or cartridges.

It will be readily apparent to one skilled in the art that varying substitutions and modifications may be made to the invention disclosed herein without departing from the spirit of the invention. Thus, it should be understood that although the present invention has been specifically disclosed by the preferred embodiments and optional features, modification and variation of the concepts herein disclosed may be resorted to by those skilled in the art, and such modifications and variations are considered to be falling within the scope of the invention.

It is to be understood that the phraseology and terminology used herein is for the purpose of description and should not be regarded as limiting. The use of “including,” “comprising,” or “having” and variations thereof herein is meant to encompass the items listed thereafter and equivalents thereof as well as additional items.

It must be noted that, as used in this specification and the appended claims, the singular forms "a," "an" and "the" include plural references unless the context clearly dictates otherwise. Thus, for example, reference to "an excipient" includes a single excipient as well as two or more different excipients, and the like.

CLAIMS:

1. A lipid microparticle comprising a lipid layer and at least one active pharmaceutical ingredient, wherein the at least one active pharmaceutical ingredient is adsorbed on the lipid microparticle.

2. The lipid microparticle according to claim 1, wherein the at least one active pharmaceutical ingredient is in the form of a pharmaceutically acceptable derivative thereof.

3. The lipid microparticle according to claim 1 or 2, wherein the pharmaceutically acceptable derivative is a salt, solvate, hydrate, enantiomer, ester, polymorph, prodrug or complex.

4. The lipid microparticle according to any preceding claim, wherein the at least one active pharmaceutical ingredient is crystalline, amorphous or a mixture thereof.

5. The lipid microparticle according to any preceding claim, wherein the at least active pharmaceutical ingredient is a corticosteroid, anticholinergic agent, β_2 agonist, or antibiotic.

6. The lipid microparticle according to any preceding claim, wherein the at least one active pharmaceutical ingredient is selected from tiotropium, oxitropium, flutropium, ipratropium, otilonium, umeclidinium, darotropium, darifenacin, aclidinium, glycopyrronium, dexpirronium, trospium, prednisolone, prednisone, flunisolide, beclomethasone, triamcinolone, budesonide, R budesonide, butixocort, flunisolide, rofleponide, terbutaline, fluticasone furoate, fluticasone propionate, fluticasone valrate, levosalbutamol, salbutamol, salmeterol, carmoterol, pirbuterol, clenbuterol, etanterol, fenoterol, flerbuterol, indacaterol, olodaterol, bambuterol, bitolterol, metaproterenol, milveterol, naminterol, pirbuterol, procaterol, reproterol, salmefamol, vilanterol, abediterol, formoterol, arformoterol, salmeterol, mometasone, ciclesonide, rofleponide, dexamethasone, betamethasone, amikacin, tobramycin, ciprofloxacin, pirfenidone, nintedanib or any combination thereof.

7. The lipid microparticle according to any preceding claim, wherein the lipid layer is a phospholipid layer.

8. The lipid microparticle according to any preceding claim, wherein the phospholipid is distearoylphosphatidylcholine (DSPC) or dipalmitoylphosphatidylcholine (DPPC).

9. The lipid microparticle according to any preceding claim, wherein the lipid microparticle is hollow.

10. The lipid microparticle according to any preceding claim, wherein the lipid layer is not porous.

11. The lipid microparticle according to any preceding claim, wherein the lipid layer does not comprise cholesterol.

12. The lipid microparticle according to any preceding claim, wherein the lipid microparticle is a spray dried lipid microparticle.

13. The lipid microparticle according to any preceding claim, wherein the lipid layer comprises a metal ion.

14. The lipid microparticle according to claim 13, wherein the metal ion is an alkali metal ion or alkaline earth metal ion, preferably sodium or calcium.

15. The lipid microparticle according to any preceding claim, wherein the lipid layer further comprises a saccharide, preferably a disaccharide.

16. The lipid microparticle according to claim 15, wherein the disaccharide is trehalose.

17. A process for preparing lipid microparticles as defined in any one of claims 1 to 16, which process comprises:

(a) preparing an aqueous liposomal suspension of small unilamellar vesicles (SUV);

(b) adding one or more active pharmaceutical ingredients to the aqueous liposomal suspension; and

(c) spray drying the aqueous liposomal suspension of step (b) to form lipid microparticles.

18. The process according to claim 17, wherein step (a) comprises dissolving a lipid in a solvent and then evaporating the solvent to form a lipid film.

19. The process according to claim 18, wherein the solvent is chloroform.

20. The process according to claim 17 or 18, wherein step (a) further comprises hydrating the lipid film with an aqueous solution.

21. The process according to claim 20, wherein the aqueous solution comprises a salt.

22. The process according to claim 21, wherein the salt is an alkaline earth metal salt or an alkali metal salt.

23. The process according to claim 22, wherein the salt is an alkaline earth metal salt and is calcium chloride or is an alkali earth metal salt and is sodium chloride.

24. The process according to any one of claims 17 to 23, wherein a saccharide is added with the at least one active pharmaceutical ingredient to the aqueous suspension in step (b).

25. The process according to claim 24, wherein the saccharide is a disaccharide.

26. The process according to claim 25, wherein the disaccharide is trehalose.

27. A pharmaceutical composition comprising lipid microparticles as defined in any one of claims 1 to 16.

28. The pharmaceutical composition according to claim 27, which is an inhalable formulation and formulated for use in a dry powder inhaler (DPI), or metered dose inhaler (MDI).

29. The pharmaceutical composition according to 28, claim formulated for use as a dry powder inhalation formulation.

30. The pharmaceutical composition according to any one of claims 27 to 29, further comprising at least one pharmaceutically acceptable excipient.

31. The pharmaceutical composition according to any one of claims 27 to 30, wherein the composition is encapsulated in capsules, cartridges, or is encapsulated in blisters, or is contained within a reservoir in a single-dose or multi-dose dry powder inhalation device.

32. A process for preparing the pharmaceutical composition as defined in any one of claims 27 to 31, wherein the process comprises the process as defined in any one of claims 17 to 26 and further comprises mixing the lipid microparticles with at least one pharmaceutically acceptable excipient to provide the pharmaceutical composition.

33. Use of a lipid microparticle according to any one of claims 1 to 16 in the manufacture of a medicament for the treatment and/or prophylaxis of lung disease.

34. A method of treatment and/or prophylaxis of lung disease comprising administering a therapeutically effective amount of a lipid microparticle according to any one of claims 1 to 16 to a patient in need thereof.

35. A lipid microparticle as defined in any one of claims 1 to 16 for use in the treatment and/or prophylaxis of lung disease.

36. A lipid microparticle substantially as herein described with reference to the examples.

37. A process substantially as herein described with reference to the examples.

Fig. 1/3

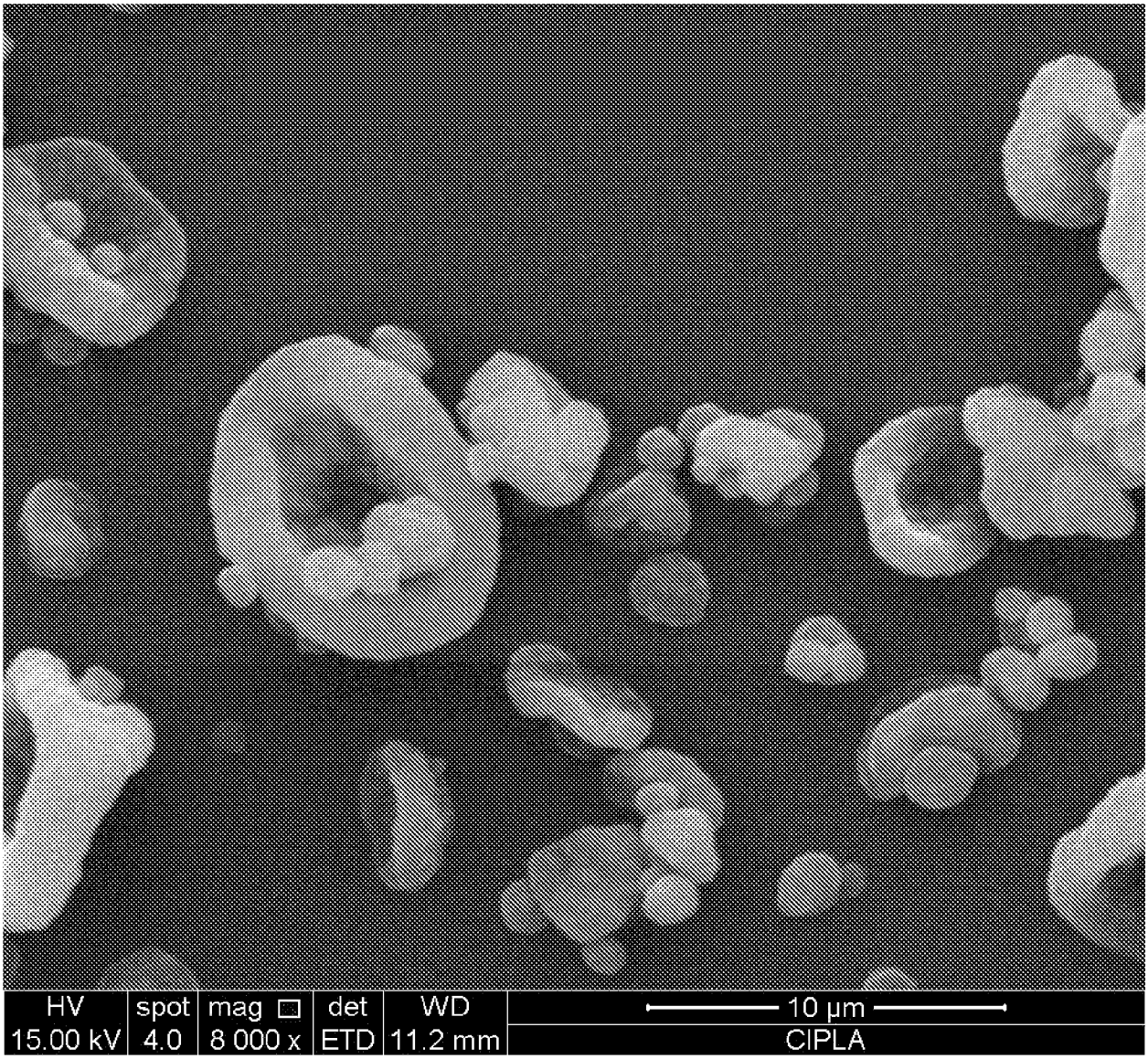


Fig. 2/3

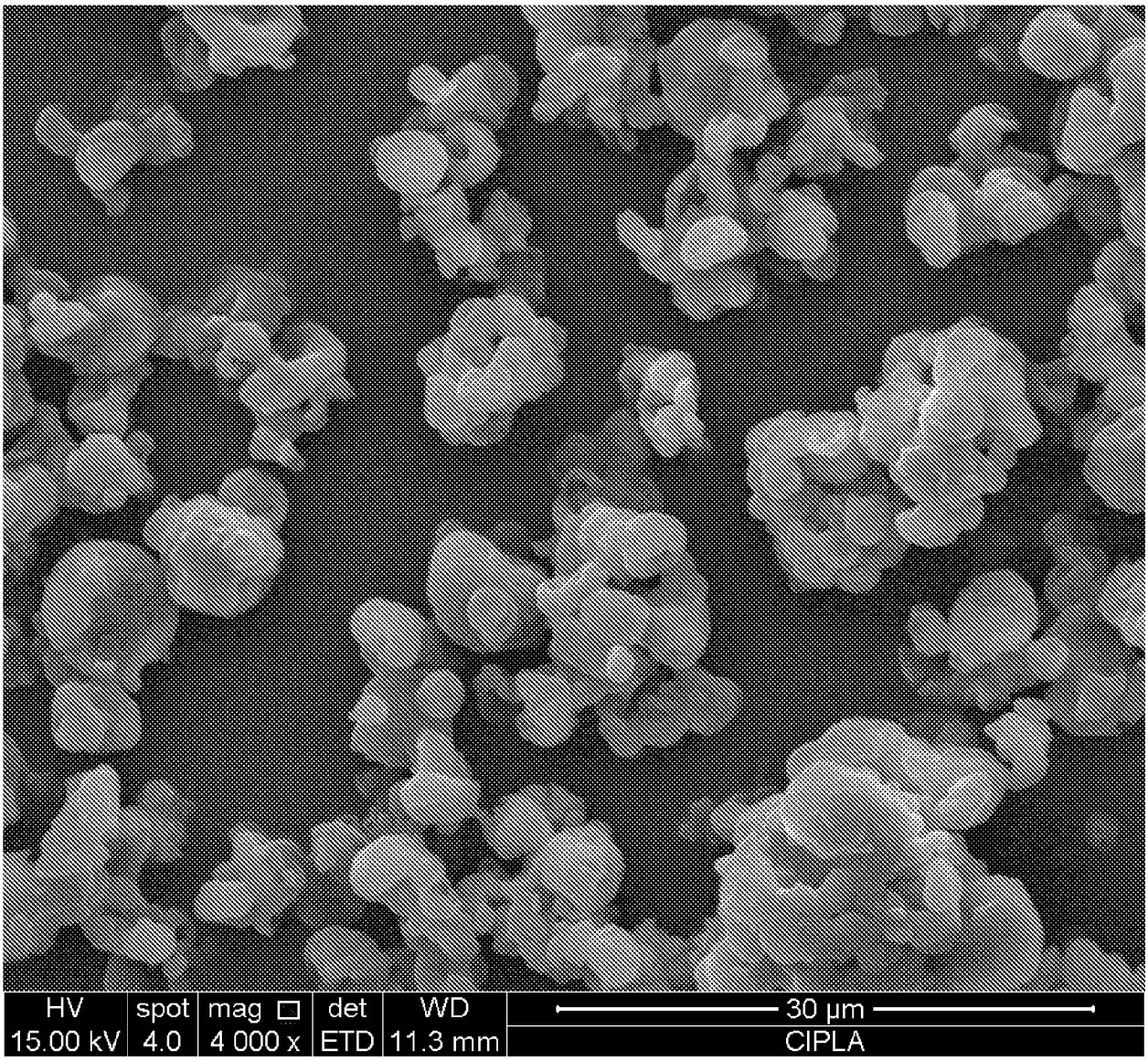


Fig. 3/3