The invention provides a 4-methylbenzenesulphonate salt of the muscarinic antagonist (R)-1-(4-fluorophenethyl)-3-(S)-2-phenyl-2-(piperidin-1-yl)propanoatoxy)-1-azoniabicyclo[2.2.2]octane and its use in therapy, as well as a process for preparing a pharmaceutical composition comprising the salt and its use in therapy.
A Novel 4-Methylbenzenesulphonate Salt and a Process For Preparing a Pharmaceutical Composition Comprising the Salt

The present invention relates to a salt of a muscarinic antagonist and its use in therapy, and a process for preparing a pharmaceutical composition comprising the salt and its use in therapy.

Muscarinic receptors are a G-protein coupled receptor (GPCR) family having five family members M₁, M₂, M₃, M₄ and M₅. Of the five muscarinic subtypes, three (M₁, M₂ and M₃) are known to exert physiological effects on human lung tissue. Parasympathetic nerves are the main pathway for reflex bronchoconstriction in human airways and mediate airway tone by releasing acetylcholine onto muscarinic receptors. Airway tone is increased in patients with respiratory disorders such as asthma and chronic obstructive pulmonary disease (COPD), and for this reason muscarinic receptor antagonists have been developed for use in treating airway diseases. Muscarinic receptor antagonists, often called anticholinergics in clinical practice, have gained widespread acceptance as a first-line therapy for individuals with COPD, and their use has been extensively reviewed in the literature (e.g. Lee et al, Current Opinion in Pharmacology 2001,1, 223-229).

When used to treat respiratory disorders, muscarinic receptor antagonists are typically administered by inhalation. However, when administered by inhalation a significant proportion of the muscarinic receptor antagonist is often absorbed into the systemic circulation resulting in reported side effects such as dry mouth. Additionally, the majority of muscarinic antagonists have a relatively short duration of action requiring that they be administered several times a day. Such a multiple-daily dosing regime is not only inconvenient to the patient but also creates a significant risk of inadequate treatment due to patient non-compliance associated with the frequent repeat dosing schedule. There therefore remains a need for novel compounds that are capable of blocking muscarinic receptors. In particular, a need exists for new muscarinic antagonists that have high potency and reduced systemic side effects when administered by inhalation. Moreover, a need exists for new muscarinic antagonists that exhibit a long duration of action when dosed by inhalation, and which are amenable to either once or twice daily dosing.
In the manufacture of pharmaceutical formulations, it is important that the active compound is in a form in which it can be conveniently handled and processed in order to obtain a commercially-viable manufacturing process. In this regard, the chemical stability and the physical stability of the active compound are important factors. The active compound, and formulations containing it, must be capable of being effectively stored over appreciable periods of time, without exhibiting any significant change in the physico-chemical characteristics (e.g. chemical composition, density, hygroscopicity and solubility) of the active compound.

Furthermore, if the active compound is to be incorporated into a formulation for pulmonary administration (e.g. via inhalation), it is desirable if the active compound can be readily micronised to yield a powder with good flow properties and comprising a high fine crystalline particle fraction (i.e. a fraction in which the active compound particles have a mass median aerodynamic diameter of less than 10 µm (micrometer)). Such a fraction is capable of being carried deep into the lungs leading to faster and increased absorption of the active compound.

International Patent Application WO 2008/075005 describes a novel class of muscarinic antagonist that display high potency to the M3 receptor. One such muscarinic antagonist described in WO 2008/075005 is (R)-1-(4-fluorophenethyl)-3-(((5)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-1-azoniabicyclo[2.2.2]octane bromide.

The preparation of (R)-1-(4-fluorophenethyl)-3-(((5)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-1-azoniabicyclo[2.2.2]octane bromide described in WO 2008/075005 yields a crystalline material. However, on further investigation it was found that (i?)-1-(4-fluorophenethyl)-3-(((5)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-1-azoniabicyclo[2.2.2]octane bromide can exist in more than one physical (polymorphic) form and that the physical form obtained in WO 2008/075005 is not the most thermodynamically stable of those forms. Moreover, attempts to develop a consistent and scaleable method of preparing a single physical form of (i?)-1-(4-fluorophenethyl)-3-(((5)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-1-azoniabicyclo[2.2.2]octane bromide proved unsuccessful.
As such, there is a need for an alternative salt form of (i?)-l-(4-fluorophenethyl)-3-((5)-2-phenyl-2-(piperidin-l-yl)propanoyloxy)-l-azoniabicyclo[2.2.2]octane that may be consistently prepared as a single physical (polymorphic) form and be incorporated into a formulation for pulmonary administration. It has now been found possible to prepare an alternative salt form which has physico-chemical properties that allow it to be formulated into a pharmaceutical composition which is suitable for pulmonary administration.

Thus, in accordance with the present invention, there is provided a salt which is an A-methylbenzenesulphonate salt of (R)-1-(4-fluorophenethyl)-3-((5)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-1-azoniabicyclo[2.2.2]octane.

The salt of the present invention is herein referred to as (i?)-l-(4-fluorophenethyl)-3-((5)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-1-azoniabicyclo[2.2.2]octane A-methylbenzenesulphonate. The name (i?)-l-(4-fluorophenethyl)-3-((5)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-1-azoniabicyclo[2.2.2]octane 4-methylbenzenesulphonate was generated by the IUPAC name program Struct=Name 9.0.7 from CambridgeSoft Corporation and denotes the structure depicted in Figure A. In the present specification this salt may be referred to as the 'tosylate salt'.

Figure A

In an embodiment of the invention, the tosylate salt has crystalline properties and is at least 50% crystalline. In a further embodiment the tosylate salt is at least 60% crystalline; in a still further embodiment at least 70% crystalline and in a yet further embodiment at least 80% crystalline. Crystallinity can be estimated by conventional X-ray diffractometry techniques.
In another embodiment of the invention, the tosylate salt is from 50%, 60%, 70%, 80% or
90% to 95%, 96%, 97%, 98%, ... X-ray powder diffraction peaks (expressed in degrees 2Θ when
using λ = 1.5418): 5.5, 16.6, 17.7, 18.8, 19.4 and 27.9.

In one embodiment, the stoichiometric ratio of cation to anion in the tosylate salt of the
present invention will be approximately 1:1, i.e. in the range of from 1:0.9 to 1:1.1.

An example of a crystalline form of (i?)-l-(4-fluorophenethyl)-3-((5)-2-phenyl-2-(piperidin-
1-yl)propanoyloxy)- 1-azoniabicyclo[2.2.2]octane 4-methylbenzenesulphonate is
crystalline Form A as defined herein below. Thus, in one embodiment the present
invention provides a salt form (Salt Form A) of (R)-1-(4-fluorophenethyl)-3-((5)-2-phenyl-
2-(piperidin- 1-yl)propanoyloxy)- 1-azoniabicyclo[2.2.2]octane 4-methylbenzenesulphonate
which exhibits at least the following characteristic X-ray powder diffraction peaks
(expressed in degrees 2Θ when using λ = 1.5418): 5.5, 16.6 and 18.8.

In a further embodiment, the present invention provides a salt form (Salt Form A) of (R)-l-
(4-fluorophenethyl)-3-((5)-2-phenyl-2-(piperidin- 1-yl)propanoyloxy)- 1-
azoniabicyclo[2.2.2]octane 4-methylbenzenesulphonate which exhibits at least the
following characteristic X-ray powder diffraction peaks (expressed in degrees 2Θ when
using λ = 1.5418): 5.5, 16.6, 17.7 and 18.8.

In a further embodiment, the present invention provides a salt form (Salt Form A) of (R)-l-
(4-fluorophenethyl)-3-((5)-2-phenyl-2-(piperidin- 1-yl)propanoyloxy)- 1-
azoniabicyclo[2.2.2]octane 4-methylbenzenesulphonate which exhibits at least the
following characteristic X-ray powder diffraction peaks (expressed in degrees 2Θ when
using λ = 1.5418): 5.5, 16.6, 17.7, 18.8 and 19.4.

In an embodiment of the invention, the margin of error for X-ray powder diffraction peaks (expressed in degrees 2Θ) is (±0.1°).

Figure 1 shows an X-ray powder diffraction pattern of Salt Form A of (R)-1-(4-fluorophenethyl)-3-((5)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-1-azoniabicyclo[2.2.2]octane 4-methylbenzenesulphonate. The present invention also provides a salt form having an X-ray powder diffraction pattern substantially the same as that shown in Figure 1.

In one embodiment the present invention provides a salt form (Salt Form A) of (R)-1-(4-fluorophenethyl)-3-((5)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-1-azoniabicyclo[2.2.2]octane 4-methylbenzenesulphonate which exhibits at least the following characteristic d-space values:

1. 16.0, 5.3 and 4.7 or
2. 16.0, 5.3, 5.0 and 4.7 or
3. 16.0, 5.3, 5.0, 4.7 and 4.6 or
4. 16.0, 5.3, 5.0, 4.7, 4.6 and 3.2.

In an embodiment of the invention, the tosylate salt is an anhydrate (i.e. a crystalline phase that does not contain water). In an embodiment of the invention, the tosylate salt has a water uptake value of less than 1% as measured by the increase in mass determined by GVS at 80% relative humidity and 25 °C.

An embodiment of the invention provides Salt Form A substantially free of other physical forms. Substantially free of other physical forms means that at least 90% by weight, e.g. 90, 91, 92, 93, 94, 95, 96, 97, 98 or 100% of the tosylate salt is in that physical form.

(R)-1-(4-Fluorophenethyl)-3-((5)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-1-azoniabicyclo[2.2.2]octane 4-methylbenzenesulphonate may be prepared from (R)-1-(A-
fluorophenethyl)-3-((S)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-1-azoniabicyclo[2.2.2]octane bromide using anion exchange techniques. For example, by preparing a solution of (i?-l-(4-fluorophenethyl)-3-((5)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-1-azoniabicyclo[2.2.2]octane bromide in a suitable solvent (e.g. dichloromethane, butanenitrile), mixing said solution with an aqueous solution of sodium 4-methylbenzenesulphonate at a suitable temperature (e.g. 20 to 90°C), and then isolating (R)-1-(4-fluorophenethyl)-3-((S)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-1-azoniabicyclo[2.2.2]octane 4-methylbenzenesulphonate from the mixture. Specific details of preparations (R)-1-(4-fluorophenethyl)-3-((5)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-1-azoniabicyclo[2.2.2]octane 4-methylbenzenesulphonate are described herein below in the examples.

The salt of the invention has activity as a pharmaceutical, in particular as an anticholinergic agent including a muscarinic receptor (M1, M2, and M3) antagonist, in particular a M3 antagonist. Diseases and conditions which may be treated with the salt include:

1. respiratory tract: obstructive diseases of the airways including: asthma, including bronchial, allergic, intrinsic, extrinsic, exercise-induced, drug-induced (including aspirin and NSAID-induced) and dust-induced asthma, both intermittent and persistent and of all severities, and other causes of airway hyper-responsiveness; chronic obstructive pulmonary disease (COPD); bronchitis, including infectious and eosinophilic bronchitis; emphysema; bronchiectasis; cystic fibrosis; sarcoidosis; farmer's lung and related diseases; hypersensitivity pneumonitis; lung fibrosis, including cryptogenic fibrosing alveolitis, idiopathic interstitial pneumonias, fibrosis complicating anti-neoplastic therapy and chronic infection, including tuberculosis and aspergillosis and other fungal infections; complications of lung transplantation; vasculitic and thrombotic disorders of the lung vasculature, and pulmonary hypertension; antitussive activity including treatment of chronic cough associated with inflammatory and secretory conditions of the airways, and iatrogenic cough; acute and chronic rhinitis including rhinitis medicamentosa, and

2. bone and joints: arthritides associated with or including osteoarthritis/osteoarthrosis, both primary and secondary to, for example, congenital hip dysplasia; cervical and lumbar
spondylitis, and low back and neck pain; rheumatoid arthritis and Still’s disease; seronegative spondyloarthropathies including ankylosing spondylitis, psoriatic arthritis, reactive arthritis and undifferentiated spondarthropathy; septic arthritis and other infection-related arthropathies and bone disorders such as tuberculosis, including Potts’ disease and Poncet’s syndrome; acute and chronic crystal-induced synovitis including urate gout, calcium pyrophosphate deposition disease, and calcium apatite related tendon, bursal and synovial inflammation; Behcet’s disease; primary and secondary Sjogren’s syndrome; systemic sclerosis and limited scleroderma; systemic lupus erythematosus, mixed connective tissue disease, and undifferentiated connective tissue disease; inflammatory myopathies including dermatomyositis and polymyositis; polymyalgia rheumatica; juvenile arthritis including idiopathic inflammatory arthritides of whatever joint distribution and associated syndromes, and rheumatic fever and its systemic complications; vasculitides including giant cell arteritis, Takayasu’s arteritis, Churg-Strauss syndrome, polyarteritis nodosa, microscopic polyarteritis, and vasculitides associated with viral infection, hypersensitivity reactions, cryoglobulins, and paraproteins; low back pain; Familial Mediterranean fever, Muckle-Wells syndrome, and Familial Hibernian Fever, Kikuchi disease; drug-induced arthralgias, tendonitis, and myopathies;

3. pain and connective tissue remodelling of musculoskeletal disorders due to injury [for example sports injury] or disease: arthritides (for example rheumatoid arthritis, osteoarthritis, gout or crystal arthropathy), other joint disease (such as intervertebral disc degeneration or temporomandibular joint degeneration), bone remodelling disease (such as osteoporosis, Paget’s disease or osteonecrosis), polychondrititis, scleroderma, mixed connective tissue disorder, spondyloarthropathies or periodontal disease (such as periodontitis);

4. skin: psoriasis, atopic dermatitis, contact dermatitis or other eczematous dermatoses, and delayed-type hypersensitivity reactions; phyto- and photodermatitis; seborrhoeic dermatitis, dermatitis herpetiformis, lichen planus, lichen sclerosus et atrophica, pyoderma gangrenosum, skin sarcoid, discoid lupus erythematosus, pemphigus, pemphigoid, epidermolysis bullosa, urticaria, angioedema, vasculitides, toxic erythemas, cutaneous eosinophilias, alopecia areata, male-pattern baldness, Sweet’s syndrome, Weber-Christian syndrome, erythema multiforme; cellulitis, both infective and non-infective; panniculitis; cutaneous lymphomas, non-melanoma skin cancer and other dysplastic lesions; drug-induced disorders including fixed drug eruptions;
5. **eyes:** blepharitis; conjunctivitis, including perennial and vernal allergic conjunctivitis; iritis; anterior and posterior uveitis; choroiditis; autoimmune; degenerative or inflammatory disorders affecting the retina; ophthalmitis including sympathetic ophthalmitis; sarcoidosis; infections including viral, fungal, and bacterial;

6. **gastrointestinal tract:** glossitis, gingivitis, periodontitis; oesophagitis, including reflux; eosinophilic gastro-enteritis, mastocytosis, Crohn's disease, colitis including ulcerative colitis, proctitis, pruritis ani; coeliac disease, irritable bowel syndrome, and food-related allergies which may have effects remote from the gut (for example migraine, rhinitis or eczema);

7. **abdominal:** hepatitis, including autoimmune, alcoholic and viral; fibrosis and cirrhosis of the liver; cholecystitis; pancreatitis, both acute and chronic;

8. **genitourinary:** nephritis including interstitial and glomerulonephritis; nephrotic syndrome; cystitis including acute and chronic (interstitial) cystitis and Hunner's ulcer; acute and chronic urethritis, prostatitis, epididymitis, oophoritis and salpingitis; vulvovaginitis; Peyronie's disease; erectile dysfunction (both male and female);

9. **allo graft rejection:** acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin or cornea or following blood transfusion; or chronic graft versus host disease;

10. **CNS:** Alzheimer's disease and other dementing disorders including CJD and nvCJD; amyloidosis; multiple sclerosis and other demyelinating syndromes; cerebral atherosclerosis and vasculitis; temporal arteritis; myasthenia gravis; acute and chronic pain (acute, intermittent or persistent, whether of central or peripheral origin) including visceral pain, headache, migraine, trigeminal neuralgia, atypical facial pain, joint and bone pain, pain arising from cancer and tumor invasion, neuropathic pain syndromes including diabetic, post-herpetic, and HIV-associated neuropathies; neurosarcoïdosis; central and peripheral nervous system complications of malignant, infectious or autoimmune processes;

11. other auto-immune and allergic disorders including Hashimoto's thyroiditis, Graves' disease, Addison's disease, diabetes mellitus, idiopathic thrombocytopenic purpura, eosinophilic fasciitis, hyper-IgE syndrome, antiphospholipid syndrome;

12. other disorders with an inflammatory or immunological component; including acquired immune deficiency syndrome (AIDS), leprosy, Sezary syndrome, and paraneoplastic syndromes;
13. **cardiovascular.** atherosclerosis, affecting the coronary and peripheral circulation; pericarditis; myocarditis, inflammatory and auto-immune cardiomyopathies including myocardial sarcoid; ischaemic reperfusion injuries; endocarditis, valvulitis, and aortitis including infective (for example syphilitic); vasculitides; disorders of the proximal and peripheral veins including phlebitis and thrombosis, including deep vein thrombosis and complications of varicose veins;

14. **oncology:** treatment of common cancers including prostate, breast, lung, ovarian, pancreatic, bowel and colon, stomach, skin and brain tumors and malignancies affecting the bone marrow (including the leukaemias) and lymphoproliferative systems, such as Hodgkin's and non-Hodgkin's lymphoma; including the prevention and treatment of metastatic disease and tumour recurrences, and paraneoplastic syndromes; and,

15. **gastrointestinal tract:** Coeliac disease, proctitis, eosinopilic gastro-enteritis, mastocytosis, Crohn's disease, ulcerative colitis, microscopic colitis, indeterminant colitis, irritable bowel disorder, irritable bowel syndrome, non-inflammatory diarrhea, food-related allergies which have effects remote from the gut, e.g., migraine, rhinitis and eczema.

Accordingly, the present invention further provides (i?)-l-(4-fluorophenethyl)-3-((5)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-1-azoniabicyclo[2.2.2]octane A-methylbenzenesulphonate as hereinbefore defined for use in therapy.

In another aspect, the invention provides the use of (i?)-l-(4-fluorophenethyl)-3-((5)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-1-azoniabicyclo[2.2.2]octane A-methylbenzenesulphonate as hereinbefore defined, in the manufacture of a medicament for use in therapy.

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

A further aspect of the invention provides a method of treating a disease state in a mammal suffering from, or at risk of, said disease, which comprises administering to a mammal in need of such treatment a therapeutically effective amount of (i?)-l-(4-fluorophenethyl)-3-
The present invention also provides (i?)-l-(4-fluorophenetyl)-3-((5)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-1-azoniabicyclo[2.2.2]octane 4-methylbenzenesulphonate as hereinbefore defined, in the manufacture of a medicament for treating chronic obstructive pulmonary disease (COPD) (such as irreversible COPD).

The present invention also provides the use of (i?)-l-(4-fluorophenethyl)-3-((5)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-1-azoniabicyclo[2.2.2]octane 4-methylbenzenesulphonate as hereinbefore defined, in the manufacture of a medicament for treating chronic obstructive pulmonary disease (COPD) (such as irreversible COPD).

The present invention also provides (i?)-l-(4-fluorophenethyl)-3-((5)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-1-azoniabicyclo[2.2.2]octane 4-methylbenzenesulphonate as hereinbefore defined, in the manufacture of a medicament for treating asthma.

The present invention further provides a method of treating chronic obstructive pulmonary disease (COPD) (such as irreversible COPD), in a warm-blooded animal, such as man, which comprises administering to a mammal in need of such treatment an effective amount of (R)-1-(4-fluorophenethyl)-3-((S)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-1-azoniabicyclo[2.2.2]octane 4-methylbenzenesulphonate as hereinbefore defined.

In order to use a compound of the invention for the therapeutic treatment of a warm-blooded animal, such as man, said ingredient is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the mode of administration, the treatment desired and the disorder indicated but
typically the daily dose of active ingredient may be in the range from 0.0001 mg/kg to 30 mg/kg.

The salt according to the invention may be used on its own but will generally be administered in the form of a pharmaceutical composition in which the (i?)-l-(4-fluorophenethyl)-3-((S)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-1-azoniabicyclo[2.2.2]octane 4-methylbenzenesulphonate (active ingredient) is in association with a pharmaceutically acceptable adjuvant, diluent or carrier. Conventional procedures for the selection and preparation of suitable pharmaceutical formulations are described in, for example, "Pharmaceuticals - The Science of Dosage Form Designs", M. E. Aulton, Churchill Livingstone, 1988.

Depending on the mode of administration, the pharmaceutical composition may comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.05 to 80 %w, still more preferably from 0.10 to 70 %w, and even more preferably from 0.10 to 50 %w, of active ingredient, all percentages by weight being based on total composition.

The present invention also provides a pharmaceutical composition comprising (i?)-l-(4-fluorophenethyl)-3-((S)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-1-azoniabicyclo[2.2.2]octane 4-methylbenzenesulphonate in association with a pharmaceutically acceptable diluent or carrier.

The invention further provides a process for the preparation of a pharmaceutical composition of the invention which comprises mixing (i?)-l-(4-fluorophenethyl)-3-((S)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-1-azoniabicyclo[2.2.2]octane 4-methylbenzenesulphonate with a pharmaceutically acceptable diluent or carrier.

Pharmaceutical compositions may be administered topically (e.g. to the skin or to the lung and/or airways) in the form, e.g., of creams, solutions, suspensions, heptafluoroalkane (HFA) aerosols and dry powder formulations, for example, formulations in the inhaler device known as Turbuhaler™; or systemically, e.g. by oral administration in the form of tablets, capsules, syrups, powders or granules; or by parenteral administration in the form of solutions or suspensions; or by subcutaneous administration; or by rectal administration in the form of suppositories; or transdermally.
In an embodiment of the present invention, the (i?)-l-(4-fluorophenethyl)-3-((5)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-1-azoniabicyclo[2.2.2]octane 4-methylbenzenesulphonate is incorporated into a formulation for pulmonary administration, i.e. a formulation to be administered by inhalation.

When administered via inhalation the unit dose of the active ingredient may generally be in the range of from 0.1 µg to 10000 µg, 0.1 to 5000 µg, 0.1 to 1000 µg, 0.1 to 500 µg, 0.1 to 200 µg, 0.1 to 200 µg, 0.1 to 100 µg, 0.1 to 50 µg, 5 µg to 5000 µg, 5 to 1000 µg, 5 to 500 µg, 5 to 200 µg, 5 to 100 µg, 5 to 50 µg, 10 to 5000 µg, 10 to 1000 µg, 10 to 500 µg, 10 to 200 µg, 10 to 100 µg, 10 to 50 µg, 20 to 5000 µg, 20 to 1000 µg, 20 to 500 µg, 20 to 200 µg, 20 to 100 µg, 20 to 50 µg, 50 to 5000 µg, 50 to 1000 µg, 50 to 500 µg, 50 to 200 µg, 50 to 100 µg, 100 to 5000 µg, 100 to 1000 µg or 100 to 500 µg.

In formulations to be administered by inhalation, the active ingredient is desirably finely divided, i.e. the particles of active ingredient have a mass median diameter of less 10 µm. In some formulations to be administered by inhalation the finely divided active ingredient may be suspended in a propellant (e.g. a HFA) with the assistance of a dispersant, such as a C8-C20 fatty acid or salt thereof, (for example, oleic acid), a bile salt, a phospholipid, an alkyl saccharide, a perfluorinated or polyethoxylated surfactant, or other pharmaceutically acceptable dispersant. Alternatively, the finely divided compound may be coated by another substance.

In one embodiment of the invention, (i?)-l-(4-fluorophenethyl)-3-((5)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-1-azoniabicyclo[2.2.2]octane 4-methylbenzenesulphonate is administered in a dry powder formulation. Dry powder formulations are used in a dry powder inhaler. The inhaler may be a single or a multi dose inhaler, and may be a breath actuated dry powder inhaler.

In dry powder formulations for administration by inhalation the active ingredient is generally formulated in association with carriers/diluents to facilitate accurate dosing from an inhaler. Examples of carriers/diluents that may be used in dry powder formulations
include for example, a mono-, di- or polysaccharide, and sugars for example, lactose, glucose, raffinose, melezitose, lactitol, maltitol, trehalose, sucrose, mannitol and starch.

One form of dry powdered formulation comprises fine particles of the active ingredient, coarse particles of carrier/diluent, and optionally small and/or fine particles of carrier/diluent. This form of dry powder formulation is known in the art as an Ordered mixture.

The term coarse carrier/diluent refers to carrier/diluent having a mass median diameter of greater than 25 µm; small carrier/diluent refers to carrier/diluent having a mass median diameter in the range of from 10 µm to 25 µm; and fine carrier/diluent refers to carrier/diluent having a mass median diameter of less than 10 µm. In the context of the present invention mass median diameter is measured by a laser diffraction instrument (e.g. a Malvern MasterSizer 2000).

Another form of dry powder formulation is where the fine particles of the drug are mixed with fine and/or small particles of carrier/diluent, and the mixture of particles agglomerated into spheres, which break up during the inhalation procedure e.g. see US 5,551,489. The spheres may be filled into the drug reservoir of a multidose inhaler, for example, that known as Turbuhaler™ in which a dosing unit meters the desired dose which is then inhaled by the patient. With this system the active ingredient, with or without a carrier substance, is delivered to the patient.

The finely divided compound may also be dispensed into hard gelatine capsules or blisters, each containing the desired dose of the active compound.

Finely divided material (e.g. material having a mass median diameter of less than about 10 µm), may be prepared by direct precipitation, spray drying or by a process known in the art as micronisation. Materials may be micronised using known techniques in the art, for example by milling in a spiral jet mill to attain a suitable particle size for inhalation. Material that has been subjected to a micronisation process may be referred to as micronised material.
The suitability of a drug substance for micronisation is dependent upon a number of factors such as its hygroscopicity and its susceptibility to undergo solid-state transformations during mechanical handling. Consequently, obtaining a solid form of a drug substance that may be micronised in a reliable process that is repeatable on a commercially-viable scale can be a significant challenge when developing a formulation to be administered by inhalation. A problem sometimes encountered when micronising a drug substance on a commercial scale is that drug material may adhere to the surfaces of the milling equipment causing deposits of material to build up. This is disadvantageous because it lowers yield, necessitates cumbersome cleaning processes and can lead to large variations in particle size.

With regard to the salt of the present invention, one reliable process of preparing fine particles suitable for use in a formulation for inhalation comprises micronising the active ingredient together with a carrier/diluent. In the context of the present specification such a process may be referred to as a 'co-micronisation process'. It has been found that using a co-micronisation process enables the salt of the present invention to be micronised on a large scale with either no or acceptably low levels of material build up occurring on the surfaces of the mill equipment.

Accordingly, a further aspect of the present invention provides a process of preparing a pharmaceutical composition which comprises (i) preparing a mixture of (R)-l-(4-fluorophenethyl)-3-((5)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-1-azoniabicyclo[2.2.2]octane 4-methylbenzenesulphonate and carrier/diluent, and (ii) micronising the mixture prepared in (i) to yield fine particles of (R)-l-(4-fluorophenethyl)-3-((R)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-1-azoniabicyclo[2.2.2]octane 4-methylbenzenesulphonate and fine particles of carrier/diluent.

The fine particles of carrier/diluent and (R)-l-(4-fluorophenethyl)-3-((5)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-1-azoniabicyclo[2.2.2]octane 4-methylbenzenesulphonate prepared according to the above process may be further processed into dry powder pharmaceutical compositions using techniques known in the art. For example, if additional carrier/diluent is required to reach a desired ratio of active ingredient to carrier/diluent, the mixture may be further mixed with additional carrier/diluent using conventional techniques. Moreover, the flow properties of the micronised mixture of carrier and (R)-l-
(4-fluorophenethyl)-3-((S)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-1-azoniabicyclo[2.2.2]octane 4-methylbenzenesulphonate may be improved by either a controlled agglomeration and spheronisation procedure or by forming an ordered mixture with coarse carrier/diluent.

Accordingly, the present invention further provides a process of preparing a pharmaceutical composition which comprises

(i) preparing a mixture of (i?)-l-(4-fluorophenethyl)-3-((5)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-1-azoniabicyclo[2.2.2]octane 4-methylbenzenesulphonate and carrier/diluent,

(ii) micronising the mixture prepared in (i) to yield fine particles of (i?)-l-(4-fluorophenethyl)-3-((5)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-1-azoniabicyclo[2.2.2]octane 4-methylbenzenesulphonate and fine particles of carrier/diluent,

(iii) optionally adding further pre-micronised carrier/diluent, and

(iv) either subjecting the mixture to agglomerisation and spheronisation, or adding coarse and/or small carrier/diluent.

In one embodiment of the invention, the carrier/diluent is lactose. In another embodiment, the carrier/diluent is lactose monohydrate. In another embodiment of the invention, the fine particles of (R)-1-(4-fluorophenethyl)-3-((5)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-1-azoniabicyclo[2.2.2]octane 4-methylbenzenesulphonate and fine particles of carrier/diluent prepared in step (ii) have a mass median diameter of less than 10 µm. In another embodiment of the invention, the fine particles of (i?)-l-(4-fluorophenethyl)-3-((S)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-1-azoniabicyclo[2.2.2]octane 4-methylbenzenesulphonate and fine particles of carrier/diluent prepared in step (ii) have a mass median diameter of less than 3 µm.

In step (i) the carrier/diluent and (i?)-l-(4-fluorophenethyl)-3-((5)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-1-azoniabicyclo[2.2.2]octane 4-methylbenzenesulphonate may be mixed using any suitable mixing technique, for example in a tumbling mixer.

In the above process the ratio of carrier/diluent to (i?)-l-(4-fluorophenethyl)-3-((5)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-1-azoniabicyclo[2.2.2]octane 4-
methylbenzenesulphonate subjected to micronisation in step (ii) will generally be in the range of from 5:1 to 3:97 by weight.

In one embodiment, the ratio of carrier/diluent to (i?)-l-(4-fluorophenethyl)-3-((S)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-1-azoniabicyclo[2.2.2]octane A-methylbenzenesulphonate subjected to micronisation in step (ii) is in the range of from 5:1 to 4:96 by weight. In a further aspect of this embodiment, the ratio is in the range of from 1:1 to 4:96 by weight. In a yet further aspect, the ratio is in the range 1:5 to 4:96 by weight.

In another embodiment, the ratio of carrier/diluent to (i?)-l-(4-fluorophenethyl)-3-((5)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-1-azoniabicyclo[2.2.2]octane A-methylbenzenesulphonate subjected to micronisation in step (ii) is in the range of from 1:9 to 4:96 by weight. In a further aspect of this embodiment, the ratio is in the range of from 8:92 to 4:96 by weight. In a yet further aspect, the ratio is in the range 6:94 to 4:96 by weight.

In another embodiment, the ratio of carrier/diluent to (i?)-l-(4-fluorophenethyl)-3-((5)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-1-azoniabicyclo[2.2.2]octane A-methylbenzenesulphonate subjected to micronisation in step (ii) is in the range of from 5:1 to 1:10 by weight. In a further aspect of this embodiment, the ratio is in the range 1:2 to 2:1 by weight. In a still further aspect the ratio is approximately 1:1 by weight.

In the above process, the mixture of carrier/diluent and (i?)-l-(4-fluorophenethyl)-3-((5)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-1-azoniabicyclo[2.2.2]octane A-methylbenzenesulphonate may be micronised in any equipment known in the art for micronisation, for example a Spiral Jet mill.

In one embodiment, the co-micronisation is performed at a milling pressure (i.e. pressure in the mill or chamber pressure) in the range of from 3 bar to 8 bar. In a further embodiment, the co-micronisation is performed at a milling pressure in the range of from 4 bar to 7 bar. In another embodiment, the co-micronisation is performed at a milling pressure in the range of from 5 bar to 6.5 bar. In another embodiment, the co-micronisation is performed at a milling pressure in the range of from 3 bar to 6 bar.
When further pre-micronised carrier/diluent is incorporated into the composition as described in optional step (iii) it may be incorporated using conventional techniques known in the art, e.g. in a spiral jet mixer. However, in order to minimise the introduction of amorphous content in the composition, the further pre-micronised carrier/diluent may be conveniently incorporated by mixing at low pressure. In one embodiment of the invention further pre-micronised carrier/diluent is added by mixing at a pressure below 2 bar. In a further embodiment of the invention, further pre-micronised carrier/diluent is added by mixing at a pressure below 1 bar.

When required, agglomerisation and spheronisation may be conducted using techniques known in the art, e.g. as described in WO98/3 135 1.

Optionally, the crystallinity of any amorphous content, possibly introduced during the co-micronisation, may be restored by a conditioning process. Conditioning processes are known in the art may be carried out according to the procedures described in WO 95/05805 or by selecting process parameters such as relative humidity in such a way that the final product when submitted to water vapour gives off heat of less than 1.2 joules per gram for the particles having a mean particle size of less than 10 µm as described in US 5,874,063. In the process of the present invention, a conditioning step may be conveniently performed after the micronisation of a mixture of (i?)-1-(4-fluorophenethyl)-3-((5)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-1-azoniabicyclo[2.2.2]octane A-methylbenzenesulphonate and carrier/diluent in step (ii).

In a further aspect, the present invention provides a pharmaceutical composition obtainable by the co-micronisation process hereinbefore defined.

In another aspect the present invention provides a phramaceutical composition comprising (R)-1-(4-fluorophenethyl)-3-((5)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-1-azoniabicyclo[2.2.2]octane 4-methylbenzenesulphonate and carrier/diluent wherein the ratio of carrier/diluent to (i?)-1-(4-fluorophenethyl)-3-((5)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-1-azoniabicyclo[2.2.2]octane 4-methylbenzenesulphonate is in the range of from 5:1 to 3:97 by weight, and the size of the particles is less than 10 µm.
In a still further aspect, the present invention provides a pharmaceutical composition as hereinbefore defined for treating chronic obstructive pulmonary disease (COPD) (such as irreversible COPD).

In a yet further aspect, the present invention provides a pharmaceutical composition as hereinbefore defined for use in the manufacture of a medicament for treating chronic obstructive pulmonary disease (COPD) (such as irreversible COPD).

In another aspect, the present invention provides a method of treating chronic obstructive pulmonary disease (COPD) (such as irreversible COPD), in a warm-blooded animal, such as man, which comprises administering to a mammal in need of such treatment an effective amount of pharmaceutical composition as hereinbefore defined.

The invention will now be illustrated by the following non-limiting Examples. In the Examples the following Figures are presented:

Figure 1: X-ray powder diffraction pattern of Salt Form A of (R)-1-(4-fluorophenethyl)-3-((S)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-1-azoniabicyclo[2.2.2]octane A-methylbenzenesulphonate.

**Synthesis of (R.M-(4-fluorophenethyl)-3-(YS)-2-phenyl-2-(piperidin-l-yl)propanoyloxy)-1-azoniabicyclo[2.2.2]octane 4-methylbenzenesulphonate.**

*General Experimental Details for Preparations 1 and 2*

Unless otherwise stated all reactions were carried out under an inert atmosphere: reagents and solvents were obtained commercially and used as received; reagent grade solvents
were used. NMR spectra were measured on a Varian Unity Inova spectrometer at a proton frequency of 400 MHz. The MS spectra were measured on an Agilent 1100 MSD G1946D spectrometer.

5 **Preparation 1**

(R)-1-(4-Fluorophenethyl)-3-((5)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-1-azoniabicyclo[2.2.2]octane bromide salt (0.6 g) prepared as described in WO2008/075005 (Example 44) was dissolved in dichloromethane (50 mL) and shaken with a solution of sodium 4-methylbenzenesulfonate (3.1 g) in water (100 mL), in three equal portions (~33 mL). The organic layer was dried over anhydrous sodium sulphate, filtered and evaporated to dryness. The white foam was dissolved in hot acetonitrile (~5 mL) and allowed to cool to RT with stirring for 3 days. A white solid formed which was collected by filtration, washed with cold acetonitrile (~2 mL) and dried in vacuo at 600C for 2 days to yield the product (0.490 g).

m/e M+ 465

1H NMR (400 MHz, d6-DMSO) δ 7.55 (2H, d), 7.47 (2H, d), 7.40-7.31 (4H, m), 7.28 (1H, t), 7.19 (2H, t), 7.11 (2H, d), 5.1-5.08 (1H, m), 3.93-3.83 (1H, m), 3.59-3.50 (1H, m), 3.47-2.35 (4H, m), 3.25-3.14 (2H, m), 2.99-2.90 (2H, m), 2.47-2.31 (4H, m), 2.28 (3H, s), 2.24-2.18 (1H, m), 2.02-1.70 (4H, m), 1.57 (3H, s), 1.56-1.48 (4H, m), 1.48-1.38 (2H, m).

**Preparation 2**

Analytical HPLC and GC Conditions used in Steps a) - g)

Step a) was monitored by HPLC using an Ace phenyl column with standard aqueous/acetonitrile/TFA mobile phase on a gradient, with UV detection at 230 nm. Steps b), c) and d) were monitored by GC using DB-5 capillary column with FID detection and standard oven gradient from 400C to 3000C, with split injection. Steps e), f), g) and h) are monitored by HPLC using C18 phase with standard aqueous/acetonitrile/TFA mobile phase on a gradient, with UV detection at 220 nm. Step e) solvent composition was monitored by GC using a DB-624 capillary column with FID detection and oven gradient from 400C to 2500C, with split injection.
Step e) was monitored for levels of quinuclidinol by GC using an HP-I capillary column with FID detection and oven gradient from 40°C to 300°C, with split injection.

a) Methyl 2-phenylpropanoate

(+/-)-2-Phenylpropionic acid (20.5g) was dissolved in methanol (62mL) in a reaction vessel. Sulfuric acid (98%, 0.82mL) was then charged followed by methanol (20.5mL) as a line rinse. The reaction was then heated to 63°C (±3°C) and stirred at this temperature for up to 4hrs. The reaction was monitored by HPLC analyzing the methyl 2-phenylpropanoate: (+/-)-2-phenylpropionic acid ratio (specification >97:3). Upon completion the reaction mixture was cooled to 23°C (±3°C). Cyclohexane (102mL) was added followed by Na$_2$CO$_3$ (aq) (3.7% wt/wt, 61.5mL). Layers were allowed to separate and the lower aqueous phase discarded. Water (61.5mL) was then charged and the mixture stirred for 10mins before the layers were separated discarding the lower aqueous phase. Cyclohexane (205mL) was then charged to the organic phase. The reaction mixture was then distilled under reduced pressure at 45°C, 150-240mbar removing 180mL solvent. The reaction mixture was then cooled to 23°C (±3°C) yielding methyl 2-phenylpropanoate in a solution in cyclohexane.

b) Methyl 2-bromo-2-phenylpropanoate

Methyl 2-phenylpropanoate in a solution in cyclohexane (prepared in step a) (22.42g; based on 100% yield from step a) was charged to a reaction vessel. Hydrobromic acid (48%, 0.62mL) was then charged followed by cyclohexane (22.4mL) as a line wash. Dibenzoyl peroxide (75%, 2.21g) and N-bromosuccinimide (31.61g) were then charged to the vessel and the reaction heated to 50°C (±3°C) and stirred at this temperature for at least 4hrs. The reaction was monitored by GC analyzing the methyl 2-bromo-2-phenylpropanoate : methyl 2-phenylpropanoate ratio (specification >96:4). Upon completion the reaction mixture was cooled to 20°C (±3°C). The reaction mixture was filtered to remove the solid succinimide by-product, washing the filter cake twice with cyclohexane (22.4mL). The solid by-product was discarded. NaHSO$_3$ (aq) (10%w/w, 81.9mL) was then charged and stirred for 15mins before allowing the phases to separate discarding the lower aqueous phase. Water (81.9mL) was then charged and stirred for 15mins before allowing the phases to separate discarding the lower aqueous phase. 3-
Pentanone (201.9mL) was then charged and the mixture was distilled at 45°C, 150-280mbar removing 210mL of solvent. The reaction mixture was cooled to 23°C (±3°C). 3-Pentanone (10.1mL) was then charged and the solvent composition analyzed by GC (specification <30% cyclohexane) to yield methyl 2-bromo-2-phenylpropanoate in a solution of 3-pentanone.

c) Methyl 2-phenyl-2-piperidin-1-ylpropanoate

Methyl 2-bromo-2-phenylpropanoate in a solution of 3-pentanone (prepared in step b) (33.2g; based on 100% yield from step b) was charged to a reaction vessel followed by piperidine (40.5mL). The reaction was heated to 40°C (±3°C) and held for at least 4hrs. The reaction was monitored by GC analyzing the methyl 2-phenyl-2-piperidin-1-ylpropanoate : methyl 2-bromo-2-phenylpropanoate ratio (specification >97:3). The reaction mixture was then cooled to 23°C (±3°C) and then filtered to remove the piperidine hydrobromide salt by-product, and the filter cake washed with methyl 'butyl ether (66.4mL). The filter cake was discarded. Methyl 'butyl ether (133mL) and hydrogen chloride (2.74M, 172.6mL) were then added and the reaction mixture stirred for 15mins before taking a pH reading to ensure pH <4. The layers were then allowed to separate retaining the lower aqueous phase. Hydrogen chloride (2.74M, 60.4mL) was then added to the organic phase and the mixture stirred for at least 15mins before allowing the phases to separate retaining the lower aqueous phase. The two aqueous phases were then combined, sampled and analyzed by GC to ensure all impurities were <0.5% with the exception of methyl 2-phenyl-3-(piperidin-1-yl)propanoate impurity). The aqueous phase was then charged to a mixture OfNa₂CO₃ (32.29g), water (232mL) and methyl 'butyl ether (332mL). The mixture was stirred for at least 15mins before taking a pH reading to ensure pH >6. The layers were then allowed to separate discarding the lower aqueous phase. Water (66.4mL) was then charged and stirred for 15mins before allowing the phases to separate discarding the lower aqueous phase. Citric acid (0.8wt%, 66.4mL) was then added to the organic phase and the mixture stirred for 15mins before allowing the phases to separate discarding the lower aqueous phase. A second charge of citric acid (0.8wt%, 66.4mL) was then added to the organic phase and the mixture stirred for 15mins before allowing the phases to separate discarding the lower aqueous phase. The organic phase was sampled and analyzed by GC to ensure methyl 2-phenyl-3-(piperidin-1-yl)propanoate impurity was less than 0.5%. The mixture was then distilled at 45°C, 80-220mbar.
removing 265mL solvent. Methanol (332mL) was then charged to the vessel and the mixture again distilled at 45°C, 80-220mbar removing 332mL solvent. The reaction mixture was cooled to 23°C (+3°C) to yield methyl 2-phenyl-2-piperidin-l-ylpropanoate in a solution of methanol. The product was then analyzed by NMR assay and HPLC for purity. 23.8g (at 100w/w%) 70.5% yield, >99.5% HPLC purity.

d) (S)-methyl 2-phenyl-2-(piperidin-l-yl)propanoate

Racemic methyl 2-phenyl-2-piperidin-l-ylpropanoate (prepared in step c) was purified by Simulated Moving Bed (SMB) chromatography to yield methyl (5)-2-phenyl-2-piperidin-1-ylpropanoate. (5)-methyl 2-phenyl-2-(piperidin-l-yl)propanoate was isolated as a 40w/w% solution in toluene. Typical conditions for the SMB purification were as follows:

<table>
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<th>Process Technique</th>
<th>Simulated Moving Bed</th>
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<td>Stationary Phase</td>
<td>Chiralcel OJ 20µm</td>
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<tr>
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</tr>
<tr>
<td>Feed Diluent</td>
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<tr>
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<td>Column Bed Pressure (Bar)</td>
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<tr>
<td>Eluent flowrate (ml/min)</td>
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</tr>
<tr>
<td>Raffinate flowrate (ml/min)</td>
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</tr>
<tr>
<td>Extract flowrate (ml/min)</td>
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</tr>
<tr>
<td>Recycling flowrate (ml/min)</td>
<td>429</td>
</tr>
<tr>
<td>Switch time/period (min)</td>
<td>1.53</td>
</tr>
</tbody>
</table>

e) (S)-((R)-quinuclidin-3-yl) 2-phenyl-2-(piperidin-l-yl)propanoate

(S)-methyl 2-phenyl-2-(piperidin-l-yl)propanoate (prepared in step d) (17.6g as a 40w/w% solution in toluene) was charged to a reaction vessel followed by (i?)-(−)-3-quinuclidinol (9.5g) and toluene (106mL). The mixture was distilled at 60°C, 180-450mbar removing 52mL solvent. A sample was taken and analyzed by HPLC assay (specification 180-
220mg/mL (5)-methyl 2-phenyl-2-(piperidin-l-yl)propanoate. The reaction was then heated to 60°C (±5°C) and potassium tert-pentoxide (25w/w%, 43.12g) was added. The reaction mixture was stirred at 60°C (±5°C) for at least 2hrs and monitored by HPLC analyzing the methyl (5)-methyl 2-phenyl-2-(piperidin-l-yl)propanoate : (S)-((R)-quinuclidin-3-yl) 2-phenyl-2-(piperidin-1-yl)propanoate ratio (specification >95:5) followed by toluene (8.8 mL) as a line rinse. The reaction mixture was cooled to 20°C (±5°C). Butanenitrile (88mL) and water (88mL) were charged and the mixture stirred for 20mins before allowing the phases to separate discarding the lower aqueous phase. Water (88mL) was charged and the mixture stirred for 20mins before allowing the phases to separate discarding the lower aqueous phase. The organic phase was analysed by GC to ensure residual (i?)-(−)-3-quinuclidinol levels were below 0.5%. The organic phase was distilled at 60°C, 100-430mbar removing 142mL of solvent. The reaction was then weighed and analysed by: NMR assay (w/w% of product) and GC (solvent composition) to determine the amount of product in solution and the solvent composition, toluene (18.5mL, 1.05vol) and butanenitrile (52.5mL, 3vol) was then added to the mixture to yield (S)-((R)-quinuclidin-3-yl) 2-phenyl-2-(piperidin-1-yl)propanoate (19.67g, 81% yield) in a 7:3 butanenitrile :toluene solvent composition at 140mg/mL concentration.

\((\text{R})-\text{l-(4-Fluorophenethyl)-3-((S)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-1-azoniabicyclo[2.2.2]octane bromide}

(\text{S}-((\text{iR})-quinuclidin-3-yl) 2-phenyl-2-(piperidin-1-yl)propanoate (prepared in step e) (19.67g as a 140mg/mL solution in butanenitrile :toluene) was charged to a reaction vessel followed by 4-fluorophenethylbromide (13.99g) and butanenitrile (19.7mL). The reaction mixture was heated to 60°C (±5°C) and stirred at this temperature for at least 8hrs. The reaction was monitored by HPLC analyzing the (5)-((i?)-quinuclidin-3-yl) 2-phenyl-2-(piperidin-1-yl)propanoate : product ratio (specification >96:4). The reaction mixture was cooled to 40°C over at least 40mins (0.5°C/min) and then cooled to -5°C over at least 6hrs (0.125°C/min). During the cool no crystallisation had occurred when at 20°C. Therefore the reaction was seeded with a sample of (i?)-1-(4-fluorophenethyl)-3-((S)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-1-azoniabicyclo[2.2.2]octane bromide (25mg - obtainable by methods described in WO 2008/075005 - Form A). After the reaction mixture reached -5°C toluene (39.3mL) was added and the slurry stirred at -5°C for at least 1hr. (\text{R})-\text{l-(4-Fluorophenethyl)-3-((S)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-1-azoniabicyclo[2.2.2]octane bromide}.
azoniabicyclo[2.2.2]octane bromide was then collected by filtration, washing the filtercake with butanenitrile (39.3 mL). The (i?)-l-(4-Fluorophenethyl)-3-((5)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-l-azoniabicyclo[2.2.2]octane bromide product was then dried under vacuum at 45°C. The product was then analysed by HPLC purity and NMR assay. 30g, 96% yield, >99.5% HPLC purity, >99.5w/w% assay.

g) (R)-l-(4-Fluorophenethyl)-3-((S)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-l-azoniabicyclo [2.2.2]octane 4-methylbenzenesulphonate

A solution of sodium p-toluenesulphonate (26.97 g) in water (300 mL; 16.65 moles) was prepared. A 500 mL jacketed vessel was charged with (i?)-l-(4-fluorophenethyl)-3-((5)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-l-azoniabicyclo[2.2.2]octane bromide (15.00 g). Butanenitrile (225 mL) and half of the sodium tosylate solution were added to the reaction vessel. The vessel was then stirred and heated to 35°C. When the vessel contents reached 35°C and were adequately mixed the stirring was stopped and the phases allowed to settle. The lower aqueous phase was removed and discarded. The second half of the sodium tosylate solution was added and the vessel contents heated to 35°C with stirring. When the vessel contents reached 35°C and were adequately mixed the stirring was stopped and the phases allowed to settle. The lower aqueous phase was removed and discarded. Water (75 mL) was added and the mixture heated to 70°C. When the vessel contents reached 70°C and were adequately mixed the stirring was stopped and the phases allowed to settle. The lower aqueous phase was removed and discarded. The hot organic phase was filtered into a clean vessel. The original vessel was washed with butanenitrile (30 mL) and this solvent was added to the filtrate via the filter into the clean vessel. The wet organic solution was distilled in order to azoedry it (120-150mbar - vessel jacket at 80°C). After ca. 60 mL of solvent had been distilled a precipitate was observed; contents were at 48°C. In total, 110 mL of solvent (10 mL water; 100 mL butanenitrile) was collected. At this point the vacuum was released and the vessel contents warmed to 75°C. Acetonitrile (45 mL) was added and the vessel contents re-heated to 75°C (not all material dissolved). More acetonitrile (45 mL) was added and the vessel contents re-heated to 75°C (all material dissolved). The solution was cooled to 5°C over 120 minutes (precipitation started at 65°C). With the vessel contents at 5°C the product was collected by filtration, washed with cold (5°C) butanenitrile (30 mL) and pulled as dry as possible on the filter to give 15.27 g of solid. This solid was left open in a fume cupboard overnight to give (i?)-l-(4-fluorophenethyl)-3-
((S)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-1-azoniabicyclo[2.2.2]octane 4-methylbenzenesulphonate (15.22 g). The ratio of quaternary species to tosylate was determined as 1:1.01 by 400MHz IHNMR using a 30s relaxation delay.

5 h) (R)-l-(4-Fluorophenethyl)-3-((S)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-l-azoniabicyclo [2.2.2]octane 4-methylbenzenesulphonate (Recrystalisation)

(R)-1-(4-Fluorophenethyl)-3-((5)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-1-azoniabicyclo[2.2.2]octane 4-methylbenzenesulphonate (7.50 g) and acetonitrile (90.00 mL) were charged to a vessel. The mixture was heated to 80°C and the resulting solution held at 80°C for 30mins. The mixture was then cooled to 65°C over 20 minutes. The solution was seeded with seed crystals of (5)-1-(4-fluorophenethyl)-3-((5)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-1-azoniabicyclo[2.2.2]octane 4-methylbenzenesulphonate (6mg) and stirred at 65°C for 1 hour. The reaction was then cooled to 5°C over 10 hours and stirred at 5°C for 6 hours. The solid product was then isolated by filtration, washing the filter cake with acetonitrile (15.00 mL). The product was then dried under vacuum at 45°C to yield (i?)-l-(4-fluorophenethyl)-3-((5)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-1-azoniabicyclo[2.2.2]octane 4-methylbenzenesulphonate as a white solid (6.6g).

20 Solid State Analysis of(R)-l-(4-Fluorophenethyl)-3-((S)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-l-azoniabicyclo[2.2.2]octane 4-methylbenzenesulphonate

Instrument Details for Solid State Analysis

- X-Ray Powder Diffraction (XRPD) - PANalytical X'Pert machine in 0 - 0 configuration or a PANalytical Cubix machine in 2θ range 2° to 40° with 100-second exposure per 0.02° increment. The X-rays were generated by a copper long-fine focus tube operated at 45kV and 40mA. The wavelength of the copper X-rays was 1.5418 Å. The Data was collected on zero background holders on which ~ 2mg of the compound was placed. The holder was made from a single crystal of silicon, which had been cut along a non-diffracting plane and then polished on an optically flat finish. The X-rays incident upon this surface were negated by Bragg extinction.

- Differential Scanning Calorimetry (DSC) thermograms were measured using a TA Q100 Differential Scanning Calorimeter, with aluminium pans and pierced lids.
The sample weights varied between 0.5 to 5mg. The procedure was carried out under a flow of nitrogen gas (50mL/min) and the temperature studied from 30 to 230°C at a constant rate of temperature increase of 10°C per minute.

Gravimetric Vapour Sorption (GVS) profiles were measured using a Surface Measurements Systems Dynamic Vapour Sorption DVS-I or a DVS Advantage instrument. The solid sample ca. 1-5mg was placed into a glass vessel and the weight of the sample was recorded during a dual cycle step method (40 to 90 to 0 to 90 to 0% relative humidity (RH), in steps of 10% RH).

A sample of material obtained by Procedure 1 as described herein above was analysed by XRPD (PANalytical X'Pert or Cubix system), GVS and DSC. The melting temperature as determined by DSC was found to be 189°C (onset) (±2°C). GVS determination gave 0.1% weight increase (%w/w) at 80% Relative Humidity (±0.2%).

An XRPD spectrum of (i?)-(4-Fluorophenethyl)-3-((5)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-1-azoniabicyclo[2.2.2]octane 4-methylbenzenesulphonate prepared according to Preparation 1 is presented in Figure 1.

**Alternative preparation of methyl 2-phenyl-2-piperidin-1-ylpropanoate (intermediate C in Preparation 2 described herein above) using methyl 2-phenylacetate as starting material**

**Stage 1:** Methyl 2-bromo-2-phenyl-acetate

Methyl 2-phenylacetate (20.00 g) was dissolved in cyclohexane (120.00 mL). Hydrobromic acid (48%, 0.60mL) was then charged followed by cyclohexane (20mL,) as a line wash. Dibenzoyl Peroxide (75%, 1.61ml) and N-bromosuccinimide (30.81g) was then charged to the vessel followed by cyclohexane (20mL) as a line wash. The reaction was heated to 50°C (±3°C) and stirred at this temperature for at least 4hrs. The reaction was monitored by GC analyzing the methyl 2-bromo-2-phenyl-acetate :methyl 2-phenylacetate ratio, (specification >96:4). Upon completion the reaction was cooled to 20°C (±3°C). The reaction mixture was filtered to removed the solid succinimide by-product, washing the filter cake with cyclohexane (20mL). The solid by-product was discarded. NaHSO₃ (aq) (10%w/w, 73mL) was then charged and stirred for 15mins before allowing the phases to separate discarding the lower aqueous phase. Water (73mL) was
then charged and stirred for 15mins before allowing the phases to separate discarding the lower aqueous phase. 3-pentanone (180mL) was then charged and the mixture was distilled at 50°C, 150-400mbar removing 180mL solvent. The reaction was cooled to 23°C (±3°C). 3-pentanone (90mL) was then charged and the solvent composition analyzed by GC (specification <30% cyclohexane) to yield methyl 2-bromo-2-phenyl-acetate in a solution of 3-pentanone which was telescoped directly into the next stage.

**Stage 2: Methyl 2-phenyl-2-piperidin-ylacetate**

Methyl 2-bromo-2-phenyl-acetate (30.51g, based on 100% yield from stage 1) was charged to the vessel followed by piperidine (39.52mL). The reaction stirred at 20°C (±3°C) and held for at least 1hr. The reaction was monitored by GC analyzing the methyl 2-phenyl-2-(1-piperidyl) acetate : methyl 2-bromo-2-phenyl-acetate ratio, (specification >97:3). The reaction was then filtered to remove the piperidine hydrobromide salt by-product. The filter cake was discarded. Methyl 'butyl ether (183mL) was added to the filtrate, followed by hydrogen chloride (2.74M, 159mL). The mixture was stirred for 15mins before taking a pH reading to ensure pH < 4. The layers were then allowed to separate retaining the lower aqueous phase. Hydrogen chloride (2.74M, 54.9mL) was then added to the organic phase and the mixture stirred for at least 15mins before allowing the phases to separate retaining the lower aqueous phase. The two aqueous phases were then combined and charged to a mixture of Na2CO3 (32.47g), water (213.6mL) and methyl 'butyl ether (305mL). The mixture was stirred for at least 15minutes before taking a pH reading to ensure pH > 6. The layers were then allowed to separate discarding the lower aqueous phase. Water (152.5mL) was then charged and stirred for 15mins before allowing the phases to separate discarding the lower aqueous phase. The organic phase was concentrated under reduced pressure at 40°C (±5°C) to yield methyl 2-phenyl-2-piperidin-ylacetate as an oil. 28.7g, 92% yield.

**Stage 3: Methyl 2-phenyl-2-piperidin-ylpropanoate**

Methyl 2-phenyl-2-piperidin-ylacetate (3g) was dissolved in Tetrahydrofuran (12mL,) and charged to a vessel containing Potassium Hexamethyldisilazide (0.5M solution in toluene, 38.6mL) at -5°C (±3°C) maintaining the temperature below -2°C. Dimethyl Sulfate (1.83mL) was then charged to the reaction maintaining the temperature below -2°C. The reaction was warmed to 20°C (±3°C) and stirred for at least 2hrs. The reaction was monitored by GC analyzing the methyl 2-phenyl-2-(1-piperidyl) propanoate : methyl
2-phenyl-2-(1-piperidyl) acetate ratio (specification >95:5). Water (24mL) was charged to
the reaction and the mixture stirred for at least 5 minutes below allowing the layers to
separate. The aqueous layer was discarded. Aqueous ammonium chloride solution (24mL,
3.98M) was charged and the mixture stirred for 5 minutes. The layers were separated and
the aqueous layer discarded. Water (24mL) was charged and the mixture stirred for
5 minutes before allowing the layers to separate and discarding the aqueous phase. The
organic phase was concentrated under reduced pressure at 40°C (±5°C) to yield methyl 2-
phenyl-2-piperidin-lylpropanoate as an oil. 3.06g, 96% yield.
Co-micronisation of (7g)-l-(4-Fluorophenethyl)-3-(((S)-2-phenyl-2-(piperidin-l-yl)propanoyloxy)-l-azoniabicvclo[2.2.2]octane 4-methylbenzenesulphonate and 10% by weight lactose monohydrate

A mixture of (R)-l-(4-Fluorophenethyl)-3-((S)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-l-azoniabicyclo[2.2.2]octane 4-methylbenzenesulphonate (pre-sieved using a 1 mm sieve) and lactose monohydrate (Respitose SV003 from DMV-Fonterra Excipients - pre-sieved using a 1 mm sieve) was passed through a 1 mm sieve and mechanically mixed in a tumbling mixer at 24 rpm for 15 min. The sieving and mixing procedure was repeated to provide a mixture containing 10% by weight of lactose. The material was then fed into a 205 mm (8") Spiral Jet mill by a screw feeder. The micronisation settings were 7.0 bar inlet pressure and 6.0 bar milling pressure, feeding rate 3.0 Kg/h. After 500g of the mixture had been micronised the mill was inspected and approximately 1g of material was found stuck to the walls of the mill. The amount of material stuck to the walls of the mill was significantly less than that obtained when micronising (i?)-l-(4-fluorophenethyl)-3-((5)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-l-azoniabicyclo[2.2.2]octane A-methylbenzenesulphonate without a diluent/carrier. For example, when (R)-l-(4-fluorophenethyl)-3-((5)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-l-azoniabicyclo[2.2.2]octane 4-methylbenzenesulphonate was micronised with micronisation settings of 5.5 bar inlet pressure, 4.0 bar milling pressure, and a feeding rate of 4.0 Kg/h, after 500g of material was micronised about 9g of material was found stuck to the walls of the mill.

Co-micronisation of (R)-l-(4-Fluorophenethyl)-3-(TS)-2-phenyl-2-(piperidin-l-yl)propanoyloxy)-l-azoniabicvclo[2.2.2]octane 4-methylbenzenesulphonate and 3, 4 and 6 % by weight lactose monohydrate

Mixtures of (R)-l-(4-fluorophenethyl)-3-((5)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-l-azoniabicyclo[2.2.2]octane 4-methylbenzenesulphonate (pre-sieved using a 1 mm sieve) and 3, 4 and 6 % by weight lactose monohydrate (Respitose SV003 from DMV-Fonterra Excipient - pre-sieved using a 1 mm sieve) were passed through a 1 mm sieve and mechanically mixed in a tumbling mixer at 24 rpm for 15 min. The sieving and mixing
procedure was repeated to provide mixtures containing 3, 4 and 6 \% by weight lactose monohydrate.

For each concentration 350g of pre-mixed material was fed into a 205 mm (8") spiral jet mill by a screw feeder at a feeding rate of 3.0Kg/h. On completion of the process the mill was weighed to record the amount of material stuck in the mill. The results of co-micronisation using the mixtures containing 3, 4 and 6 \% by weight lactose monohydrate are presented in Table 1.

**Table 1**

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<th>Amount of lactose (%)</th>
<th>Chamber pressure (bar)</th>
<th>Build up of material in the mill (g)</th>
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\(^a\) Mass Median Diameter of Active Ingredient measured with a laser diffraction instrument (Malvern MasterSizer 2000) using water as dispersion media

\(^b\) The first half of the batch was run at 5.4bar, the second half at 5.7bar

**Preparation of a spheronised mixture comprising co-micronisataio of a 1:1 by weight mixture of (R)-4-(4-fluorophenethyl)-3-((S)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-1-azoniabicyclo[2.2.2]octane 4-methylbenzenesulphonate and lactose monohydrate**

40 g of (R)-1-(4-Fluorophenethyl)-3-((S)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-1-azoniabicyclo[2.2.2]octane 4-methylbenzenesulphonate (pre-sieved using a 0.5 mm sieve) and 40 g lactose monohydrate (Respitose SV003 from DMV-Fonterra Excipients) were passed through 1 mm sieve and mechanically mixed in a tumbling mixer for 15 minutes at 32 rpm. The sieving procedure was repeated to provide a mixture containing 50\% by weight lactose monohydrate. The sieved material was fed into a Spiral Jet mill (diameter 50 mm) by a vibrational feeder. The micronisation settings were 7 bar inlet pressure and 5
bar milling pressure, measured at the wall, feeding rate 3.9 g/min. At the end of the micronisation process the mill was inspected. No build up of material in the mill or abnormal adhesion to surfaces was detected.

To restore the crystallinity of any amorphous content a conditioning process was applied by exposing the micronised powder to 25 °C and 58 % relative humidity for 24 hours. The material was then mixed with additional lactose (4.9 g micronised and conditioned lactose monohydrate per gram of the 1:1 mixture to get a final 100 µg active drug/dose) in a tumbling mixer (Turbula), followed by a mixing step in a modified Spiral jet mill being used at a milling pressure below 2 bar (to avoid formation of amorphous regions in the particles) and with a flow of nitrogen. The mixture was then subjected to a spherisation and agglomeration procedure (conditions as described in US 5,551,489 i.e. i) sieved using a 0.50 mm sieve, ii) rotated in a 240 ml diameter pan for 4 min at 40 rpm, iii) sieved using a 0.50 mm sieve, iv) rotated in a 240 ml diameter pan for 6 min at 40 rpm, and v) sieved using a 0.71 mm sieve). The resulting agglomerated powder was then filled into a dry powder inhaler (a Turbuhaler™ device as used in AstraZeneca’s Symbicort Turbuhaler™ product).

The fine particle fraction (% < 5 µm of delivered dose) of the drug compound (i?)-l-(4-Fluorophenethyl)-3-((5)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-1-azoniabicyclo[2.2.2]octane 4-methylbenzenesulphonate was 67 % when using a Turbuhaler™ inhalation device at 60 l/min.

The mass median aerodynamic diamater (MMAD) for the drug compound (i?)-l-(4-Fluorophenethyl)-3-((S)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-1-azoniabicyclo[2.2.2]octane 4-methylbenzenesulphonate, as measured at 60 l/min using a Next Generation Impactor (Apparatus E in Ph. Eur 2.9.18) equipped with a USP throat, was 1.76 µm.

**Pilot plant scale preparation of a spheronised mixture comprising co-micronisataion of a 95:5 by weight mixture of f/?)-l-f4-fluorophenethyl)-3-ff,S)-2-phenyl-2-fipiperidin-1-yl)propanoyloxy)-l-azoniabicvclo[2.2.2]octane 4-methylbenzenesulphonate and lactose monohydrate**
A mixture of (R)-1-(4-Fluorophenethyl)-3-((5)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-1-azoniabicyclo[2.2.2]octane 4-methylbenzenesulphonate (pre-sieved using a 1 mm sieve) and lactose monohydrate (5 %wt) (Respitose SV003 from DMV-Fonterra Excipients - pre-sieved using a 1 mm sieve) was passed through a 1 mm sieve and mechanically mixed in a tumbling mixer at 24 rpm for 15 min. The sieving and mixing procedure was repeated to provide a mixture containing 5% by weight of lactose. The mixture was then fed into a spiral jet mill 205 mm (8") by a screw feeder. The micronisation settings were 7.2 bar inlet pressure and 5.8 bar milling pressure, measured at the wall, feeding rate 3.0 Kg/h. The co-micronisation procedure was run continuously until 5 Kg of material was obtained. At this time the mill was inspected and only a minor amount of material was found to be stuck to the wall of the mill. The micronised material was sampled during the process and the MMD of the active ingredient measured to be 2.00 µm at the start of the process rising to 2.19 µm at its completion (MMD measured with a laser diffraction instrument (Malvern MasterSizer 2000) using water dispersion media). The content of (R)-1-(4-fluorophenethyl)-3-((5)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-1-azoniabicyclo[2.2.2]octane 4-methylbenzenesulphonate in the micronised material was 92.6 % wt; the reduction in the active ingredient content being attributable to loss of material in the gas stream through the jet mill.

To restore the crystallinity of any amorphous content a conditioning process was applied by exposing the micronised powder to 25 °C and 58 % relative humidity for 24 hour, after which the recrystallisation energy as measured by TAM (Thermal Activity Monitoring) was 0.04 J/g and the MMD of the active ingredient was 2.20 µm (MMD measured with a laser diffraction instrument (Malvern MasterSizer 2000) using water as dispersion media).

The material was then mixed with additional pre-conditioned lactose monohydrate to provide batches with target concentrations of 58 mg/g (batch size 800g) 173 mg/g (batch size 2200g) and 345 mg/g (batch size 800g) of drug substance. The mixing was conducted in a spiral jet mill at a mixing pressure of 0.5 bar and with a flow of nitrogen. 500g of each batch was then subjected to a spheronisation and agglomeration procedure as follows: i) sieved using a 0.50 mm sieve, ii) rotated in a 400 mm granultor for 4 min at 23 rpm, iii) sieved using a 0.50 mm sieve, iv) rotated in a 400 mm granultor for 6 min at 23 rpm, and v) sieved using a 0.80 mm sieve). The resulting spheronised
batches were then filled into a dry powder inhaler (a M3 Turbuhaler™ device as used in AstraZeneca's Symbicort Turbuhaler™ product). The batch concentrations were chosen to provide inhalers with estimated strengths of 100, 300 and 600 µg/dose.

The aerodynamic particle size distribution and delivered dose of (i?)-1-(4-fluorophenethyl)-3-((5)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-1-azoniabicyclo[2.2.2]octane 4-methylbenzenesulphonate from each inhaler was tested using a Next Generation Impactor (NGI) (Apparatus E in Ph. Eur 2.9.18) equipped with a USP throat. The results are given in Table 2. NGI results are based on an average of readings from 3 inhalers (dose 1-5 at 30 %RH and 60 l/min during dose withdrawal).

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<th>Strength µg/dose</th>
<th>Assay mg/g</th>
<th>DD&lt;sub&gt;a&lt;/sub&gt; NGI µg/dose</th>
<th>FPD&lt;sub&gt;b&lt;/sub&gt; NGI µg/dose</th>
<th>FPF&lt;sub&gt;c&lt;/sub&gt; NGI &lt;5 µm %</th>
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<td>64</td>
<td>1.95</td>
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</tbody>
</table>

<sup>a</sup>Delivered dose:  
<sup>b</sup>Fine particle dose  
<sup>c</sup>Fine particle fraction  
<sup>d</sup>Mass median aerodynamic diameter
CLAIMS

1. A salt being (R)-1-(4-fluorophenethyl)-3-((5)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-1-azoniabicyclo[2.2.2]octane 4-methylbenzenesulphonate.

2. A salt according to claim 1, which exhibits at least the following characteristic X-ray powder diffraction peaks (expressed in degrees 2Θ when using λ = 1.5418): 5.5, 16.6 and 18.8.

3. A salt according to claim 2 having an X-ray powder diffraction pattern substantially the same as that shown in Figure 1.

4. A salt according to any one of claims 1 to 3 for treating chronic obstructive pulmonary disease (COPD) (such as irreversible COPD).

5. Use of a salt according to any one of claims 1 to 3 in the manufacture of a medicament for treating chronic obstructive pulmonary disease (COPD) (such as irreversible COPD).

6. A process of preparing a pharmaceutical composition which comprises
   (i) preparing a mixture of (i?)-l-(4-fluorophenethyl)-3-((5)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-1-azoniabicyclo[2.2.2]octane 4-methylbenzenesulphonate and carrier/diluent, and
   (ii) micronising the mixture prepared in (i) to yield fine particles of (i?)-l-(4-fluorophenethyl)-3-((5)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-1-azoniabicyclo[2.2.2]octane 4-methylbenzenesulphonate and fine particles of carrier/diluent.

7. A process according to claim 6 wherein the carrier/diluent is lactose monohydrate.

8. A process according to claim 6 or claim 7 wherein the fine particles of (i?)-l-(4-fluorophenethyl)-3-((5)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-1-azoniabicyclo[2.2.2]octane 4-methylbenzenesulphonate and fine particles of carrier/diluent prepared in step (ii) have a mass median diameter of less than 10 µm.
9. A process according to any one of claims 6 to 8 wherein the ratio of carrier/diluent to (R)-1-(4-fluorophenethyl)-3-((5)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-1-azoniabicyclo[2.2.2]octane 4-methylbenzenesulphonate subjected to micronisation in step (ii) is in the range of from 5:1 to 3.97 by weight.

10. A process according to any one of claims 6 to 9 wherein the ratio of carrier/diluent to (R)-1-(4-fluorophenethyl)-3-((5)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-1-azoniabicyclo[2.2.2]octane 4-methylbenzenesulphonate subjected to micronisation in step (ii) is in the range of from 8:92 to 4:96 by weight.

11. A process of preparing a pharmaceutical composition which comprises preparing a mixture of fine particles of (R)-1-(4-fluorophenethyl)-3-((5)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-1-azoniabicyclo[2.2.2]octane 4-methylbenzenesulphonate and fine particles of carrier/diluent according to the process of any one of claims 6 to 10, optionally adding further micronised carrier/diluent, and either subjecting the mixture to agglomerisation and speheronisation or adding coarse and/or small carrier/diluent.

12. A pharmaceutical composition obtainable by a process according to any one of claims 1 to 11.

13. A pharmaceutical composition according to claim 12 for treating chronic obstructive pulmonary disease (COPD) (such as irreversible COPD).

14. A pharmaceutical composition according to claim 12 for use in the manufacture of a medicament for treating chronic obstructive pulmonary disease (COPD) (such as irreversible COPD).
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

IPC: see extra sheet
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: A61 K, A61 P, C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE, DK, FI, NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, PAJ, WPI data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<th>Category*</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
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<tr>
<td>A</td>
<td>WO 2008075005 A1 (ASTRAZENECA AB ET AL), 26 June 2008 (2008-06-26); page 4, line 20; page 35, line 20; pages 40-42; example 44, page 75</td>
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<td>A</td>
<td>WO 0189491 A1 (ASTRAZENECA AB ET AL), 29 November 2001 (2001-11-29); abstract; page 3, line 1 - page 3, line 16</td>
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<td>WO 20091 54554 A1 (ASTRAZENECA AB ET AL), 23 December 2009 (2009-12-23); example 3, page 29</td>
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Further documents are listed in the continuation of Box C. See patent family annex.

Date of the actual completion of the international search 16-09-2010

Date of mailing of the international search report 17-09-2010

Name and mailing address of the ISA/SE

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Form PCT/ISA/210 (second sheet) (July 2009)
Continuation of: second sheet

International Patent Classification (IPC)

C07D 453/02 (2006.01)
A61K 31/439 (2006.01)
A61K 9/14 (2006.01)
A61K 9/72 (2006.01)
A61P 11/00 (2006.01)

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Cited literature, if any, will be enclosed in paper form.
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