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(54) Title: INHALATION FORMULATIONS

(57) Abstract: A metered dose inhalation formulation for once daily administration comprises salmeterol, or a physiologically acceptable salt thereof; and a propellant. A dry powder inhalation formulation for once daily administration comprises salmeterol or a physiologically acceptable salt thereof and a diluent. Also provided is a unit dose inhalation formulation for once daily administration comprising salmeterol or a pharmaceutically acceptable salt, ester of other derivative thereof, wherein the formulation comprises from 25 to 50 mcg of active.

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INHALATION FORMULATIONS.

The present invention relates to salmeterol formulations and to their use in the treatment of the respiratory conditions, including asthma and related disorders.

The pathophysiology of asthma or related disorders involves bronchoconstriction resulting from bronchial smooth muscle spasm and airway inflammation with muscle edema. Treatment of asthma and other related disorders has been known to employ β-2 agonists, also known as β-2 adrenoreceptor agonists. Such β-2 adrenoreceptor agonists are known to provide a bronchodilator effect to patients, resulting in relief from the symptoms of breathlessness. More particularly, β-2 adrenoreceptor agonists have been shown to increase the conductance of potassium channels in airway muscle cells, leading to membrane hyperpolarization and relaxation.

Examples of β-2 adrenoreceptor agonists include terbutaline, salbutamol, lev-albuterol, R, R-formoterol, metaproterol sulfate, pirbuterol acetate, bitolterol mesylate, fenoterol, procaterol, salmeterol, bambuterol hydrochloride, clenbuterol and formoterol. Of these, salmeterol, formoterol and bambuterol hydrochloride are long acting β-2 adrenoreceptor agonists, of which salmeterol has long been approved for the treatment of asthma. The long acting subgroup of β-2 adrenoreceptor agonists act via relaxation of airway smooth muscles and consequent bronchodilation. Drugs of this long acting subgroup may have delayed onset of action, so are used for long-term regular treatment of reversible airways obstruction in asthma and in particular are bronchodilators used for the management of persistent asthma symptoms. Of this group, specifically salmeterol, available as the xinafoate salt, a sympathomimetic amine is a relatively selective long acting β-2 agonist.

Salmeterol xinafoate, which is chemically (±) 4-hydroxy-α^1-[[[6-(4-phenylbutoxy)hexyl]amino] methyl]-1,3-benzenedimethanol, 1-hydroxy-2-naphthalenecarboxylate is used as a bronchodilator for the long term prevention of bronchospasm in patients with reversible obstructive airway disease, including those with symptomatic nocturnal asthma and for the prevention of exercise-induced bronchospasm. Salmeterol is also used as a bronchodilator for long term symptomatic treatment of reversible bronchospasm associated with chronic obstructive disease (COPD), including chronic

bronchitis and emphysema. Salmeterol is used alone or in fixed combination with steroids for the therapy.

Chronic obstructive pulmonary disease (COPD) is a general term encompassing chronic bronchitis, emphysema, and chronic obstructive airways disease. COPD is a chronic slowly progressive disorder characterized by airways obstruction which does not change markedly over several months. Symptoms of COPD, which vary with the severity of the disease, include coughing with or without sputum, and breathlessness (dyspnea) with or without wheezing.

Helium propellant compositions for use with aerosols are discussed in US Patent application No.20030199594 by Larson & Taylor. US Patent application No.20030064097 by Patel et al. discloses solid carriers for improved delivery of hydrophobic active ingredients in pharmaceutical compositions. US Patent application No.20030062042 by Wensley et al. deals with an aerosol generating method for desired particle sizes from molecular to 10 microns and a device for the same. A method and device for delivering a physiologically active compound is discussed in US Patent application No.2003005728 by Lloyd et al. Delivery of aerosols containing small particles through the inhalation route is dealt with in US application No.20030035776 by Hodges et al. US Application No.20030015197 by Hale et al. discloses methods for forming an aerosol for inhalation delivery. Aerosol forming device for use in inhalation therapy is the subject matter of US patent application No.20030015196 by Hodges et al.

Aerosol compositions containing finely divided solid materials and environmentally preferred propellants are discussed in US Pat. 4,352,789 by Thiel et al. WO 9311743 (Glaxo Group Ltd) deals with aerosol formulations for the administration of medicaments by inhalation, in particular pharmaceutical aerosol formulations which comprises particulate medicament selected from the group comprising salmeterol, salbutamol, fluticasone propionate, beclomethasone dipropionate and physiologically acceptable salts and solvates thereof and a fluorocarbon or hydrogen-containing chlorofluorocarbon propellant, which formulation is substantially free of surfactant. A method of treating respiratory disorders which comprises administration by inhalation of an effective amount of a pharmaceutical aerosol formulation as defined is also described.

Patent no. GB2235627 describes the combination of salmeterol or a physiologically acceptable salt thereof and the corticosteroid fluticasone propionate for use in the treatment of asthma and other respiratory disorders via a twice daily dosing regimen. The combination of salmeterol xinafoate and fluticasone propionate is now used clinically in the treatment of asthma. It is indicated for twice daily (b. i. d.) dosing.

Patent no. GB2140800 describes phenethanolamine compounds which are β-2 agonists including salmeterol xinafoate which is used clinically in the treatment of bronchial asthma and related disorders. Salmeterol is used clinically for the treatment of bronchial asthma and related disorders. It is indicated for b. i. d. dosing.

WO 9632150 to Glaxo Wellcome Inc., discloses a metered dose inhaler having part or all of its internal surfaces coated with one or more fluorocarbon polymers, optionally in combination with one or more non-fluorocarbon polymers, for dispensing an inhalation drug formulation comprising salmeterol, or a physiologically acceptable salt thereof, and a fluorocarbon propellant, optionally in combination with one or more other pharmacologically active agents or one or more excipients.

Patent no. US2003125313 describes combinations of salmeterol and budesonide, and their use in the prophylaxis and treatment of respiratory diseases. The amount of salmeterol and budesonide, which is required to achieve a therapeutic effect, varies with the particular compound, the route of administration, the subject under treatment, and the particular disorder or disease being treated. As a monotherapy, salmeterol xinafoate is generally administered to adult humans by aerosol inhalation at a dose of 50 mcg or 100 mcg twice daily.

Therefore, the literature reports the use of salmeterol and its salts thereof for the treatment or prophylaxis of asthma on the basis of a twice-daily regimen.

We have now found that, surprisingly, asthma can be satisfactorily controlled by the use of salmeterol, particularly lower doses of salmeterol, or a physiologically acceptable salt thereof on a once daily basis.

An object of the present invention is to provide a new unit dosage form comprising an effective amount of salmeterol or a physiologically acceptable salt thereof along with pharmaceutically acceptable excipients, for prophylaxis or treatment of mild or moderate asthma, especially persistent asthma, on a once daily basis.

Another object of the present invention is to provide a process for the preparation of a formulation comprising an effective amount of salmeterol or a physiologically acceptable salt thereof, along with pharmaceutically acceptable excipients.

Yet another object of the present invention is to provide a method for prophylaxis or treatment of asthma, which comprises administering an effective amount of a combination of salmeterol or a physiologically acceptable salt thereof, on a once daily basis.

According to the present invention there is provided a daily metered dose inhalation formulation for once daily administration, which formulation comprises salmeterol or a physiologically acceptable salt thereof; and a propellant.

There is also provided a dry powder inhalation formulation for once daily administration, which formulation comprises salmeterol or a physiologically acceptable salt thereof and a diluent.

The present invention also relates to once daily metered dose inhalation formulations comprising the active ingredient, salmeterol or a physiologically acceptable salt thereof; a propellant; a co solvent and optionally a surfactant.

Further, the present invention relates to once daily dry powder inhalation formulations comprising the active ingredient, salmeterol or it's physiologically acceptable salt thereof and a diluent.

The present invention relates to a process for preparation of metered dose inhalation formulations which comprises the steps of weighing the active ingredient in a can; adding cosolvent and for surfactant if required; sonicating the solution (preferably for about 5 minutes); placing a metering valve on the can and crimping (preferably with a vacuum crimpier) and charging propellant through the metering valve.

Further the present invention relates to a process for preparation of dry powder inhalation formulations which comprises the steps of admixing said active ingredient with said lactose and filling said admixture into capsules.

The present invention relates to a method of prophylaxis or treatment of asthma, which comprises administering an effective amount of a combination of salmeterol or a physiologically acceptable salt thereof, on a once daily basis.

The invention also provides a unit dose inhalation formulation for once daily administration comprising salmeterol or a pharmaceutically acceptable salt, ester of other derivative thereof, wherein the formulation comprises from 25 to 50 mcg of active.

Accordingly, the present invention provides a method for prophylaxis or treatment of asthma, which comprises administering an effective amount of salmeterol or a physiologically acceptable salt thereof, such as the xinafoate salt, on a once daily basis. In particular, there is provided a method for prophylaxis or treatment of mild or moderate asthma, especially persistent asthma, which comprises administering an effective amount of salmeterol or a physiologically acceptable salt thereof, such as the xinafoate salt, on a once daily basis.

There are several advantages to once daily treatment. The need for a b. i. d. dosing regimen may discourage effective patient compliance. Once daily dosing offers a more convenient dosing regimen for patients and may lead to improved patient compliance with the dosing regimen. Also, once daily dosing with a combination of salmeterol is particularly suitable for the treatment or prophylaxis of mild or moderate asthma, especially persistent asthma. Treatment may be initiated on the basis of once daily dosing, or may be stepped down from b. i. d. dosing to once daily dosing once a patient's asthma has stabilized. Once asthma stability for a patient has been achieved, it is desirable to titrate to the lowest effective dose to reduce the possibility of any potential side effects. Once daily dosing also allows greater flexibility to physicians in prescribing treatment for persistent asthma. This can be especially important for paediatric patients.

We have also found that lower doses of salmeterol (than are presently given), when given on a once daily basis, can provide a sufficient therapeutic effect, whilst minimizing the potential side effects of higher doses.

In countries where salmeterol is in clinical use, a twice-daily inhalation has been recommended. Studies comparing salmeterol 25, 50 and/or 100 mcg administered by MDI twice daily to patients with mild to severe asthma, have generally detected a dose-related improvement in pulmonary function, subjective criteria and duration of action.

Addition of salmeterol to the regimen of patients with asthma selected for double-blind studies has regularly resulted in a prompt, statistically and clinically significant increase in both morning and evening peak expiratory flow measurements. Most studies have determined bronchodilation for only upto 12 hours after administration of a single dose of salmeterol, with

FEV_1 remaining 15 to 20% above baseline in salmeterol recipients. In a study conducted by us, we compared the bronchodilating effects of salmeterol formulation, delivered using a pressurized metered dose inhaler, by giving single dose administrations, followed by repeated measurements of FEV_1 till FEV_1 becomes less than 15%. The following four treatments were studied in a randomized double blind, double dummy, crossover study: 25 and 50 mcg of salmeterol HFA and 25 and 50 mcg of salmeterol CFC. Mean improvement was 15% in FEV_1 over baseline for over 24 hours.

Various pharmacologically predictable systemic effects are associated with the beta-2-agonists. These include headache, tremor, palpitations, and muscle cramps. In phase III studies, the incidence of these effects was low and did not differ markedly between salmeterol 50 mcg bid and salbutamol 200-400 mcg q.d.s. At higher dose of salmeterol, 100 mcg b.i.d, tremor was more common than in patients receiving placebo or salbutamol q.d.s. Hence it is likely that the adverse events are likely to markedly reduce with 25 mcg once daily or 50 mcg once daily.

The evidence obtained from above mentioned study suggest that salmeterol has a duration of action of 24 hours in asthmatic patients and hence, the recommendations for twice daily dosing seems debatable. The extended duration of action of salmeterol is thought to be related to the binding of salmeterol to a site adjacent to the classic beta-receptor called an exosite, leading to the prolonged long lasting receptor occupancy.

In summary, salmeterol is effective at clinically recommended doses i.e. 25 and 50 mcg and may prove to be beneficial for the treatment of bronchial asthma through their ability to dilate the airways for over 24 hours.

As used herein, the term" once daily" means that a patient's asthma is adequately controlled when the patient takes an effective lower dose of salmeterol or a physiologically acceptable salt thereof, such as the xinafoate salt, once approximately every 24 hours. Preferably, a patient will take an effective dose of the drug at the same time in each 24-hour period.

The amount of salmeterol or a physiologically acceptable salt thereof, such as the xinafoate salt, which is required to achieve a therapeutic effect will vary with the particular salt form, the route of administration, the patient under treatment, and the particular disorder being treated. The drug and/or formulation comprising the same may be administered to an adult by

inhalation at a dose of from 25 mcg to50 mcg per day of salmeterol. The formulation of the invention is preferably administered to an adult by inhalation at a dose of from 25 mcg to 50 mcg of salmeterol, optionally in the form of the xinafoate salt, per day. The total daily dose may be inhaled or administered in one actuation of an inhaler, for example a dry powder inhaler or a metered dose inhaler, or in more than one actuation. Daily doses of about 25 mcg or about 50 mcg are preferred.

Figures 1 and 2 show the FEV_1 curves for subjects receiving a single dose of salmeterol. In the figures, 1 puff translates to 25 mcg of salmeterol. The base line determining the therapeutically effective concentrations of the drug was the 15% base line. The first column of each of the figures describes the first visit of the patient whereas the second column describes the second visit of that particular patient. After the first visit it was seen that the FEV_1 curves for the patient are still above the 15% base line levels and therefore, it was decided to continue the study further. Therefore in figure 1, for the particular subject the study was continued upto 24 hours. And in figure 2, the study for the second visit was continued for upto 48 hours. From both the figures, it is clear that a single dose of salmeterol given once a day provides therapeutically effective concentrations of the drug for over 24 hours.

According to the invention the compositions and methods disclosed herein comprise the use of salmeterol unit dose in a suitable inhalation formulation.

There are quite a few advantages of using inhalers as delivery system such as convenience in use, multiple dose capacity, low dose required for systemic absorption, little or no taste of medication, available for relief and preventive use, can be used by most individuals with suitable added device, etc. hence, by using this route of administration, usage of salmeterol would be controlled in individual patients by reference to asthma and related respiratory disorders.

Hence, according to the present invention, salmeterol may be formulated in any suitable inhalation formulation suitable for delivery of the drug in the respiratory system, including metered dose inhalers and dry powder inhalers.

In a preferred embodiment, the pharmaceutical composition of the invention is an inhaler i.e. it can be a MDI or a DPI. The pharmaceutical products and formulations may conveniently be presented in unit dosage form and may be prepared by methods well known to one of ordinary skill in the art.

Preferably pharmaceutical formulations according to the present invention comprise inhalation formulations to be delivered from pressurized containers with the use of a suitable propellant as the carrier or excipient. Suitable propellants include 1,1,1,2-tetrafluoroethane (HFA 134a) or 1,1,1,2,3,3,3,-heptafluoropropane (HFA 227), or a combination of both, or mono-fluoro trichloromethane and dichloro difluoromethane or chlorofluorocarbons and derivatives thereof, in particular 1,1,1,2-tetrafluoroethane (HFA 134a) or 1,1,1,2,3,3,3-heptafluoropropane (HFA 227), with HFA 1 34a being preferred.

A pharmaceutical inhalation formulation according to the present invention preferably further comprises a polar cosolvent such as C_{2-6} aliphatic alcohols and polyols, for example ethanol, isopropanol and propylene glycol, with ethanol being preferred. Preferably, the concentration of the cosolvent is in the range of about 0.1 to 15 % by weight, of the total formulation.

A formulation according to the present invention may further comprise one or more surfactants. Such surfactants can be included to stabilize the formulations and for lubrication of a valve system. Some of the most commonly used surfactants in inhalation formulations are oils derived from natural sources, such as corn oil, olive oil, cottonseed oil and sunflower seed oil, and also phospholipids such as lecithin. A preferred surfactant for use according to the present invention is oleic acid. The surfactants used in the formulations of the present invention are generally present in the range of about 0.0001% to 0.5%, preferably 0.01 to 0.1% of the therapeutic agents present in the formulations by weight of the therapeutic agents present in the formulations.

A preferred inhalation formulation of this invention is in the form of a suspension or a particulate suspension or a clear solution. In the case of a particulate suspension or a solution, the cosolvent used should have greater polarity than the propellant used. The most commonly used cosolvent is ethanol substantially as hereinbefore described.

Another preferred inhalation formulation of this invention is a dry powder for inhalation. The active ingredient is suitably mixed with a known diluent to prepare the said formulation. The preferred diluent is lactose. The formulation can be filled in blistered cartridges or capsules. Such blistered cartridges and capsules can then be used employing any known inhalation device.

Preferably the therapeutic agent present in inhalation formulations according to the present invention is present at a concentration in the range of about 25 to 50 mcg in the formulation.

There is further provided by the present invention, therefore, a process of preparing a pharmaceutical product substantially as described herein, in which process comprises providing salmeterol preparation for use in the treatment of asthma and related disorders.

The present invention also provides a process of preparing a pharmaceutical formulation substantially as described, which comprises admixing a pharmaceutically acceptable carrier or excipient with salmeterol and functional derivatives thereof.

Pharmaceutical inhalation formulations according to the present invention are particularly suitable for use in DPIs or MDIs. The MDIs substantially as hereinbefore described, utilize a liquefied propellant, as referred to above to expel droplets containing the therapeutic agents employed according to the present invention. Suitably a formulation according to the present invention is filled into an aluminum can through a suitable metering device and typically the can is plastic coated, lacquer-coated or anodized.

A process for preparation of inhalation formulation as claimed in claim 1 comprises the steps of weighing the active ingredient in a plain aluminum can; if required adding the cosolvent and the surfactant; crimping the metering valve and then charging the propellant through the same.

The present invention further discloses a process for preparation of inhalation formulations which comprises the steps of admixing the active ingredient drug with diluent, and using the formulation with the help of any known container used for inhalation.

The present invention will now be further illustrated by the following Examples, which do not limit the scope of the invention in any way.

EXAMPLES

In the following examples the total weight of the propellant-based formulations is 9.6g; for the DPI the total weight is 25mg per capsule.

Example-I

Ingredients	Qty / can
Salmeterol	4.0 mg
HFA134a	Qs.

Example-II

Ingredients	Qty / can
Salmeterol	4.0 mg
Ethanol	1 to 5 %(of formulation)
HFA134a	Qs.

Example-III

Ingredients	Qty / can
Salmeterol	4.0 mg
Ethanol	1 to 5 %(of formulation)
Oleic acid	0.001% to 0.5 % (of salmeterol)
HFA134a	Qs.

Example-IV

Ingredients	Qty / can
Salmeterol	8.0 mg
Ethanol	1 to 5 %(of formulation)
Lecithin	0.001% to 0.5 %
HFA134a	Qs.

Example-V

Ingredients	Qty / can
Salmeterol	8.0 mg
Ethanol	1 to 5 %(of formulation)
Citric acid	0.001% to 0.5%
HFA134a	Qs.

Example-VI

Ingredients	Qty / can
Salmeterol	8.0 mg
Ethanol	1 to 5 %(of formulation)
HFA 134 a	q.s

For the above Examples nos.1- 6, the active ingredient was first weighed in a plain aluminum can (with a capacity to accommodate 120 doses). Ethanol (and the surfactant, if required) was then added and the solution was sonicated for 5 minutes. A metering valve was then placed on the can and crimped with a vacuum crimpier. Propellant 134a was then charged through the metering valve.

Example-VII

Ingredients	Qty / capsule
Salmeterol	26 to 50 mcg
Lactose	q. s.

Procedure:

1. The drug and the diluent (lactose) were admixed.
2. The admixture was then filled in the capsules.
3. The capsules were then used employing any well known inhaler device.

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CLAIMS:

1. A metered dose inhalation formulation for once daily administration, which formulation comprises salmeterol or a physiologically acceptable salt thereof; and a propellant.

2. A dry powder inhalation formulation for once daily administration, which formulation comprises salmeterol or a physiologically acceptable salt thereof and a diluent.

3. An inhalation formulation according to claim 1 or 2, wherein the physiologically acceptable salt is salmeterol xinafoate.

4. An inhalation formulation according to claim 1, 2 or 3 wherein the amount of salmeterol or a physiologically acceptable salt thereof administered is 25 mcg to 50 mcg of the drug.

5. An inhalation formulation according to claim 1, 3 or 4, wherein said propellant is selected from 1,1,1,2-tetrafluoroethane (HFA 134a); 1,1,1,2,3,3,3,-heptafluoropropane (HFA 227) or a combination thereof; mono-fluoro trichloromethane; dichloro difluoromethane; chlorofluorocarbons or derivatives thereof, preferably HFA 134a.

6. An inhalation formulation according to claim 1, 3, 4 or 5 wherein the formulation comprises a co-solvent and a surfactant.

7. An inhalation formulation according to claim 6, wherein the cosolvent is ethanol, isopropanol, or propylene glycol.

8. An inhalation formulation according to claim 7 wherein the amount of cosolvent is from 0.1 to 15% by weight of the total formulation.

9. An inhalation formulation according to claim 6, 7 or 8, wherein the surfactant is oleic acid or lecithin.

10. An inhalation formulation according to any one of claims 6 to 9 wherein the amount of surfactant is in the range of from 0.0001% to 0.5%, preferably from 0.01 to 0.1%, by weight of the therapeutic agents present in the formulation.

11. An inhalation formulation according to claim 2, wherein the diluent is lactose.

12. A process for the preparation of an inhalation formulation according to claim 1 or any of claims 3 to 10, which process comprises the steps of weighing the active ingredient in a can; if required adding the cosolvent and/or the surfactant; crimping the metering valve and then charging the propellant through the valve.

13. A process for the preparation of an inhalation formulation as claimed in claim 2, which process comprises the steps of admixing said active ingredient with said diluent and filling said admixture into a suitable blistered cartridge or a capsule.

14. A method of prophylaxis or treatment of asthma and related disorders, which method comprises administering an effective amount of salmeterol or a physiologically acceptable salt thereof, on a once daily basis.

15. A method according to claim 14 wherein the once daily dose of salmeterol is from 25 to 50 mcg.

16. A unit dose inhalation formulation for once daily administration comprising salmeterol or a pharmaceutically acceptable salt, ester of other derivative thereof, wherein the formulation comprises from 25 to 50 mcg of active.

Fig.1.

	Time	005-01 Dose_I_2P		Time	005-01 Dose_IV_2P					
0 min	0	2.25		0	2.58					
10 min	0.166687	2.9	0.42916667	0.166667	3.2					
20 min	0.333333	3.02	0.49333333	0.333333	3.47	0.555833333				
30 min	0.5	3.25	0.5225	0.5	3.47	0.578333333				
45 min	0.75	3.36	0.82625	0.75	3.62	0.88625				
1 hour	1	3.37	0.84125	1	3.7	0.915				
1.25 hour	1.25	3.5	0.85875	1.25	3.72	0.9275				
1.5 hour	1.5	3.53	0.87875	1.5	3.91	0.95375				
2 hour	2	3.59	1.78	2	4.08	1.9975				
2.5 hour	2.5	3.54	1.8075	2.5	4.07	2.0375				
3 hour	3	3.63	1.8175	3	4.09	2.04				
4 hour	4	4.04	3.835	4	3.78	3.925				
5 hour	5	3.67	3.855	5	3.69	3.725				
6 hour	6	3.67	3.67	6	3.57	3.63				
8 hour	8	3.35	7.02	8	3.54	7.11				
10 hour	10	3.49	6.84	10	3.56	7.1				
12 hour	12	3.36	6.85	12	3.47	7.03				
				14	3.34	6.81				
				16	3.52	6.86				
				20	3.21	13.46				
				24	3.22	12.88				
				32						
				48						
		AUEC0-12	42.325			43.89416667				
		AUEC0-24				83.88416667				
		AUEC0-32								
		AUEC0-48								

AUEC			%
	005-01 Dose_I_2P	005-01 Dose_IV_2P	
0-12	42.33	43.89	103.71
0-24		83.88	
0-32			
0-48			

Dose I
2 Puffs

Dose IV
2 Puffs

Fig.1(Cont.)

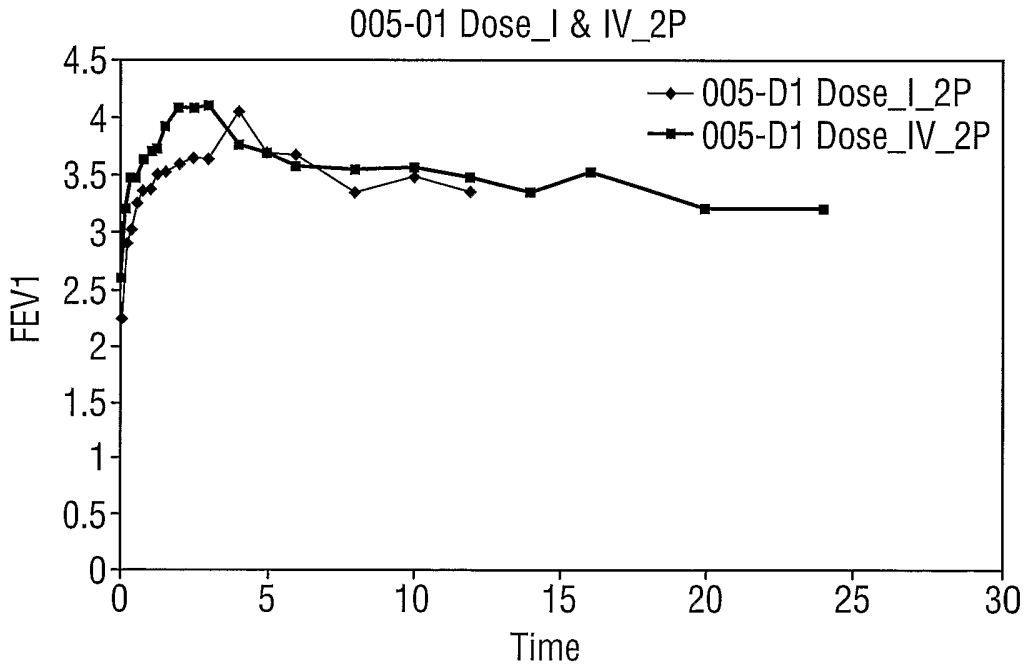
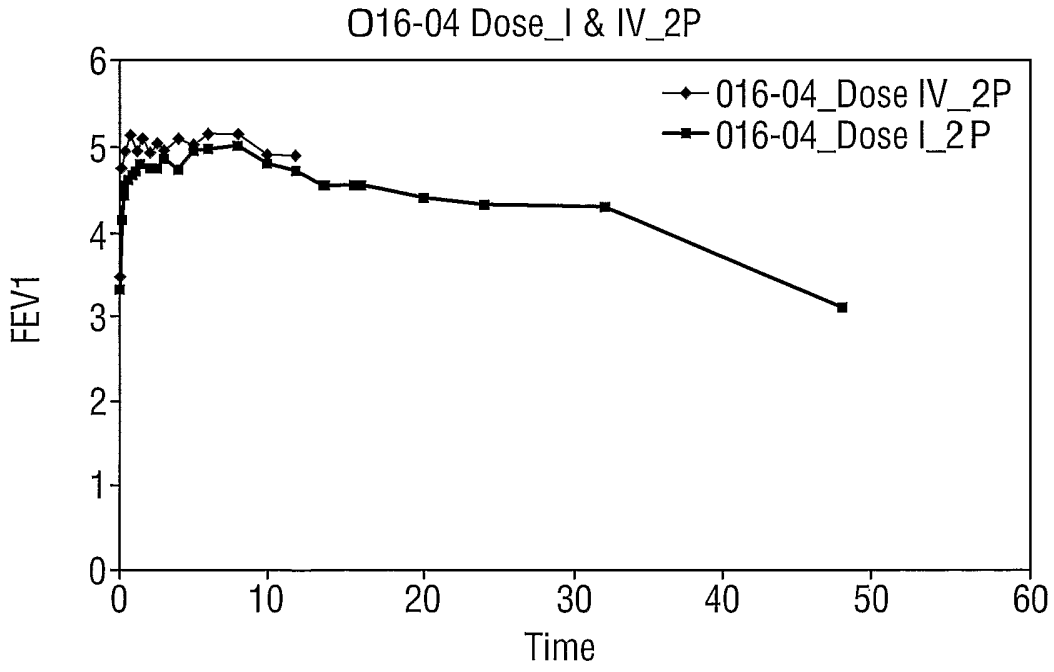

005-01 Dose_I & IV_2P
005-D1 Dose_I_2P
005-D1 Dose_IV_2P
FEV1
Time
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
0
5
10
15
20
25
30

Fig.2.

	Time	016-04_Dose IV_2P		Time	016-04_Dose I_2P			AUEC		%
								016-04 Dose VI_2P	016-04_Dose I_2P	
0 min	0	3.47		0	3.31			0-12 59.99	57.80	98.35
10 min	0.166687	4.73	0.88333333	0.166667	4.14	0.820833333		0-24	111.34	
20 min	0.333333	4.84	0.80583333	0.333333	4.43	0.714185887		0-32	145.74	
30 min	0.5	4.84	0.82333333	0.5	4.57	0.75		0-48	205.02	
45 min	0.75	5.12	1.2575	0.75	4.89	1.1575				
1 hour	1	4.96	1.26	1	4.68	1.17125				
1.25 hour	1.25	4.95	1.23875	1.25	4.77	1.18125				
1.5 hour	1.5	5.08	1.25375	1.5	4.73	1.1875				
2 hour	2	4.92	2.5	2	4.73	2.365				
2.5 hour	2.5	5.02	2.485	2.5	4.72	2.3625				
3 hour	3	4.96	2.495	3	4.86	2.395				
4 hour	4	5.07	5.015	4	4.73	4.795				
5 hour	5	5	5.035	5	4.96	4.845				
6 hour	6	5.14	5.07	6	4.95	4.955				
8 hour	8	5.13	10.27	8	5.01	9.96				
10 hour	10	4.89	10.02	10	4.81	9.82				
12 hour	12	4.89	9.78	12	4.71	9.52				
				14	4.55	9.24				
				16	4.53	9.06				
				20	4.39	17.84				
				24	4.31	17.4				
				32	4.29	34.4				
				48	3.12	59.28				
						57.8				
		AUECO-12	59.5925			111.34				
		AUECO-24				145.74				
		AUECO-32				205.02				
		AUECO-48								
	Dose IV				Dose I					
	2 Puffs				2 Puffs					

Fig.2(Cont.)


O16-04 Dose_I & IV_2P
016-04_Dose IV_2P
016-04_Dose I_2P
FEV1
Time
0
1
2
3
4
5
6
0
10
20
30
40
50
60