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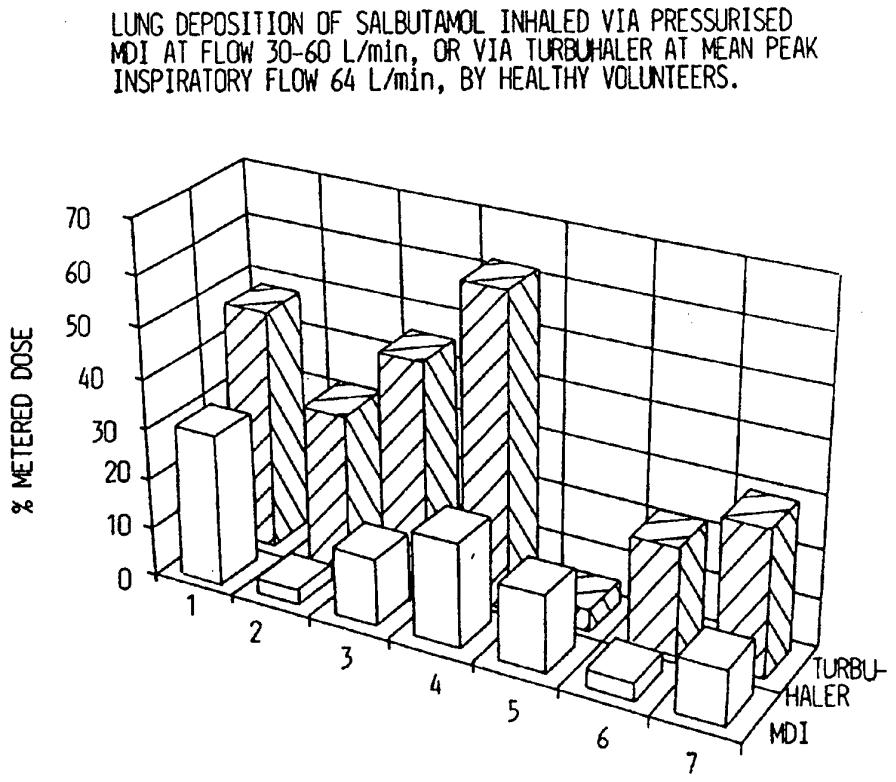
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(54) Title: SYSTEM FOR DISPENSING PHARMACEUTICALLY ACTIVE COMPOUNDS



(57) **Abstract**

The use of an inhaler having the capacity to dispense a high proportion of pharmaceutical substance in inhalable powder particles of up to 10 microns in diameter permits the use of a lower metered dose of the pharmaceutical substance as compared with the metered dose required when a conventional MDI is used.

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SYSTEM FOR DISPENSING PHARMACEUTICALLY ACTIVE COMPOUNDS

This invention relates to a system comprising a dry powder inhaler and a pharmaceutical substance, for dispensing clinically effective doses of pharmaceutically active compounds such as β-2 agonists, corticosteroids, anti-cholinergic and other pharmaceutically active compounds for local or systemic treatment of diseases which have the potential for treatment with inhalable drugs.

Background of the Invention

Inhalable drugs are commonly used in the treatment of disease of the airways and lungs such as rhinitis, asthma, and chronic bronchitis. As examples of such drugs may be mentioned β2-adrenoreceptor agonists such as salbutamol, terbutaline, rimiterol, fenoterol, reproterol, adrenaline, pirbuterol, isoprenaline, orciprenaline, bitolterol, salmeterol, formoterol, clenbuterol procaterol, broxaterol, picumeterol, TA-2005, mabuterol and the like, and their pharmacologically acceptable esters and salts; anticholinergic bronchodilators such as ipratropium bromide and the like; glucocorsticosteroids such as betamethasone, fluticasone, budesonide, tipredane, dexamethasone, betamethasone, fluocinolone, triamcinolone, mometasone, D-5519 and the like, and their pharmacologically acceptable esters and salts; anti-allergic drugs such as sodium cromoglycate and nedocromil sodium; expectorants; mucolytics; antihistamines; cyclooxygenas inhibitors; leukotriene synthesis inhibitors; leukotriene antagonists, PLA2 inhibitors, PAF antagonists and prophylactics of asthma. In addition to these, a wide range of systemically acting drugs may be administered via the respiratory tract. As examples of these may be mentioned antiarrhythmic drugs, tranquilisers, cardiac glycosides, hormones, anti-hypertensive drugs, antidiabetic- antiparasitic- and anticancer- drugs, sedatives and analgesic drugs, antibiotics, antirheumatic drugs, immunotherapies, antifungal and antihypotension drugs, vaccines, antiviral drugs, proteins, peptides, vitamins and

others, such as cell surface receptor blockers.

Inhalable drugs are commonly administered using a metered dose inhaler (MDI) or using a dry powder inhaler (DPI). The MDI, in which the drug is dissolved or suspended in a liquid propellant mixture (sometimes including small amounts of a volatile organic or inorganic solvent) is hitherto the more widely used device and functions by dispensing drug upon activation, by the patient, of a dosage in coordination with inhalation. The DPI, in which the drug is present as a dry powder, frequently together with a carrier, dispenses drug by means of the particle cloud generated by the airflow obtained upon patient inhalation.

The aim of both the MDI and the DPI is to deposit a clinically effective amount of active compound in the lungs. By "clinically effective amount of active compound" is meant that amount of active compound which is required in order to effect a response.

If handled correctly, MDI's and many DPI's deliver pharmaceuticals to the active site in approximately the same efficiency; however the amount of active substance which reaches the lungs in each case is only in the region of 10% of the amount in the metered dose. In order therefore to ensure a clinically effective amount of active compound in the lungs, this metered dose must necessarily contain a much larger than clinically effective amount of active compound. The active compound which does not reach the lungs is lost mainly in the apparatus and gastrointestinal tract. This is disadvantageous, since loss of active substance in the apparatus is costly and may reduce efficiency further, by for example clogging the mouthpiece or inhalation channel. More significant for the patient, loss in the gastrointestinal tract can trigger or accentuate side effects, which are associated with the use of any effective pharmaceutical. In the case of bronchodilators for example, possible side effects commonly include tremor and increased heart rate, and irritation of the hyperreactive airways of many sufferers of airway disease.

There has come onto the market new types of dry powder inhalers which are able to facilitate the dispensation of pharmaceutical substance in which a high proportion of the dispensed particles are of diameter up to 10 microns. It is conventional practice that powders are prepared prior to loading into an inhaler, into primary particles with as many as possible of these particles having a diameter of up to 10 microns. However the nature of such fine powder causes larger agglomerates to be formed, in high proportion, and only a small percentage of the particles which are actually dispensed from the inhaler exist in the primary particle diameter range.

The first of the above said new dry powder inhalers to come onto the market was a unique, multi-dose breath-actuated dry powder inhaler as is described in European Patents numbers 0 237 507 and 69 715 and known by the trade mark "TURBUHALER". It features deagglomeration means which function by disrupting the particle agglomerates to give a higher proportion of particles in the primary particle diameter range of up to 10 microns. It has generally been thought (see for example Bogaard et al in "Pharmatherapeutica", Vol.5, No.6, 1989) that this new inhaler has efficiency only comparable to a prior art dry powder inhaler (and therefore also to an MDI). Recommended dosages have therefore been of the same order as those recommended with an MDI.

The Invention

It is an aim of the present invention to provide for lower dispensing doses of pharmaceutical substance to be used, with the result that wastage and side-effects are minimalised.

We have now most surprisingly found that the use of an inhaler such as the breath-actuated dry powder inhaler of the type described in EP 0 237 507 and EP 69,715 and known by the trademark TURBUHALER, permits the use of a lower dose than

a MDI, in the dispensation of a clinically effective dose of active compound for administration by inhalation and that consequently, the use of such an inhaler as above can reduce the side-effects associated with drug administration.

After the TURBUHALER inhaler have come other dry powder inhalers which are also able to dispense a high proportion of pharmaceutically active compound in particles of up to 10 microns. As an example of these may be mentioned the breath-actuated dry powder inhaler which is described in patent applications WO 92/04069 and WO 93/17728, and which is known by the trademark "MONOHALER". Such inhalers are also able to be used in the present invention.

According to this invention therefore, there is provided a system comprising a dry powder inhaler and a metered dose of an inhalable pharmaceutically active compound in powder form, for dispensing a clinically effective dose of the inhalable pharmaceutically active compound, comprising a dry powder inhaler having the capacity to dispense at least 40% of the metered dose of pharmaceutically active compound in inhalable particles of up to 10 microns in diameter, and the said metered dose of pharmaceutically active compound comprising primary particles of which at least 80% have a diameter of up to 10 microns, which metered dose is in an amount which is not more than 70% by weight of the metered dose which when used with a MDI is equally clinically effective.

Preferably the dry powder inhaler used in the present invention is a breath-actuated dry powder inhaler.

Preferably at least 90% of the primary particles have a diameter of up to 10 microns.

The advantage of a lower metered dose in accordance with the present invention is

reflected in greater lung deposition if equal doses of pharmaceutically active compound are used in a dry powder inhaler such as for use in the present invention and in a conventional MDI.

Preferably the metered dose of pharmaceutically active compound for use in the present invention is not more than 50%, more preferably not more than 40%, of the metered dose which when used with an MDI is equally clinically effective.

Preferably at least 50% of particles which are dispensed in accordance with the present invention have a diameter of up to 5 microns when dispensed.

Preferably, the dry powder inhaler of the present invention is one of the breath-actuated dry powder inhalers referred to hereinabove which are known by the trademarks TURBUHALER and MONOHALER.

The pharmaceutically active compound of the present invention may if desired be contained in a pharmaceutical formulation containing commonly used additives such as diluents and/or carrier substances which are generally non-toxic and chemically inert to the pharmaceutically active compound. For example a carbohydrate such as lactose, glucose, fructose, galactose, trehalose, sucrose maltose zylitol, myoinositol, dextrane, starch and the like or a hydrate thereof, and especially lactose, mannitol or myoinositol, or an amino acid such as alanine, betaine and the like, or any additive which will impart a desired property such as taste or a physiochemical or pharmaceutical property, may be employed. However, it is stressed that the pharmaceutical active compound for use in the present invention requires no additive and may advantageously be used in its pure form.

Therefore the pharmaceutically active compound of the present invention is contained in a pharmaceutical formulation in powder form containing the pharmaceutically active compound alone or in combination with appropriate

additives, and may be used as the powder or be contained in a capsule or loaded on an elongate carrier such as a tape, web or belt wherein it is used in conjuction with an appropriate inhaler which dispenses the desired powder particles.

An inhaler will only dispense the desired powder particles if the pharmaceutically active compound itself is in a form suitable for yielding particles in the desired size range. Therefore it is essential that the pharmaceutically active compound for use in the present invention is in the form of a powder comprising particles of which at least 80%, and preferably at least 90%, are of diameter less than 10 microns, or in the form of agglomerates of such particles. Such powder may be obtained in conventional manner, if necessary.

Any inhalable pharmaceutically active compound which has adequate physicochemical pharmaceutical and powder characteristics, as recognised in the art and including for example suitable particle size, agglomerability, deagglomerability, flowability, melting point, crystallinity and hygroscopicity is suitable for use in the present invention. As examples of these may be mentioned β2-adrenoreceptor agonists such as salbutamol, terbutaline, rimiterol, fenoterol, reproterol, adrenaline, pirbuterol, isoprenaline, orciprenaline, bitolterol, salmeterol, formoterol, clenbuterol,procaterol, broxaterol, picumeterol, TA-2005, mabuterol and the like, and their pharmacologically acceptable esters and salts; anticholinergic bronchodilators such as ipratropium bromide and the like; glucocorsticosteroids such as betamethasone, fluticasone, budesonide, tipredane, dexamethasone, betamethasone, fluocinolone, triamcinolone, mometasone, D-5519 and the like, and their pharmacologically acceptable esters and salts; anti-allergic drugs such as sodium cromoglycate and nedocromil sodium; expectorants; mucolytics; antihistamines; cyclooxygenas inhibitors; leukotriene synthesis inhibitors; leukotriene antagonists, PLA2 inhibitors, PAF antagonists and prophylactics of asthma, and antiarrhythmic drugs, tranquilisers, cardiac glycosides, hormones, anti-hypertensive drugs, antidiabetic- antiparasitic- and anticancer- drugs, sedatives and

analgesic drugs, antibiotics, antirheumatic drugs, immunotherapies, antifungal and antihypotension drugs, vaccines, antiviral drugs, proteins, peptides, vitamins and others, such as cell surface receptor blockers.

The present invention is especially useful when the pharmaceutically active compound is a β-2 agonist such as terbutaline, salbutamol, formoterol, budesonide or their salts or hydrates or a mixture of any of the said β-2 agonists or their salts or hydrates with carbohydrate, especially lactose, mannitol or myoinositol, or any of the following mixtures: ipratropium bromide and lactose, formoterol and budesonide, ipratropium bromide and budesonide, terbutaline and sodium cromoglycate, terbutaline and budesonide.

Since drugs targetted at the same disease are commonly not equipotent, the dispensing dose and of course the clinically effective amount of active compound referred to will be different for different drugs. For example, the β-2 agonist salbutamol is generally accepted as being more potent than the β-2 agonist terbutaline sulphate, 0.1 mg of salbutamol generally being regarded as equipotent to 0.25 mg of terbutaline sulphate. In any assessment of efficiency therefore, equipotent doses of pharmaceutically active compounds should be directly compared. Recommended MDI doses of many common inhalable drugs are well known. In accordance with the present invention, these recommended doses can be reduced. For example, the metered dose of salbutamol, budesonide and terbutaline may be reduced by a factor of two in accordance with the present invention.

In the dispensing of a clinically effective dose, more than one metered dose may be required, depending on the patient, disease, and drug profile.

The present invention also provides the use of a dry powder inhaler having the capacity to dispense at least 40 % of the metered dose of pharmaceutically active compound in inhalable particles of up to 10 microns in diameter, the metered dose

of pharmaceutically active compound in powder form comprising primary particles of which at least 80% have a diameter of up to 10 microns, which metered dose is not more than 70% (by weight), and preferably not more than 50% by weight, of the metered dose which when used in a MDI is equally clinically effective, in the administration to a patient of a clinically effective amount of an inhalable drug.

Further the present invention provides an improved method of administering a clinically effective amount of a pharmaceutically active compound, comprising using a dry powder inhaler having the capacity to dispense at least 40 % of the metered dose of pharmaceutically active compound in inhalable particles of up to 10 microns in diameter, and a metered dose of pharmaceutically active compound in powder form comprising primary particles of which at least 80% have a diameter of up to 10 microns, which metered dose is not more than 70% (by weight), and preferably not more than 50% by weight, of the metered dose which when used in a MDI is equally clinically effective.

Yet further this invention provides a method for the treatment of diseases which are treatable with inhalable drugs, comprising administering to a patient suffering therefrom a clinically effective amount of pharmaceutically active compound, using a dry powder inhaler having the capacity to dispense at least 40 % of the metered dose of pharmaceutically active compound in inhalable particles of up to 10 microns in diameter, and a metered dose of pharmaceutically active compound in powder form comprising primary particles of which at least 80% have a diameter of up to 10 microns, which metered dose is not more than 70% (by weight), and preferably not more than 50% by weight, of the metered dose which when used in a MDI is equally clinically effective.

The invention will now be illustrated by Examples which are intended to illustrate but not to limit the scope of the invention.

Examples

Particle size analysis: TURBUHALER v MDI

In vitro studies have shown that the delivery of budesonide by Turbuhaler at inspiratory flows of 60 litres/minute leads to a greater proportion of fine particles than the delivery by an MDI. The measurements were performed with a four-stage (>13, 7-13-, 4-7 and 1-4 microns) cascade impactor, which operates at a flow rate of 60 litres/minute. Five separate of each device were tested. The results are presented in Figure 1.

Example 1 - Budesonide: TURBUHALER v MDI

In order to determine the absolute systemic availability and the amount deposited and absorbed in the lung of budesonide after inhalation via Turbuhaler and via an MDI, 24 healthy subjects were given budesonide 1 mg as five inhalations of 200 microns via Turbuhaler or MDI, and 0.5 mg intravenously, on separate study days. Budesonide levels were determined in plasma by a LC-MS method. The amount of budesonide absorbed in the lung was calculated on the assumption of an availability of swallowed budesonide of 13%. Furthermore, absorption in the lung was calculated in 13 of the subjects after inhalation with concominant oral dosing of charcoal to prevent absorption of budesonide from the gastrointestinal tract. There was good conformity between the two modes of calculation.

From Turbuhaler, the absolute systemic availability of budesonide, as a geometric mean, was 38%. For the MDI, this figure was 28%. CMAX and TMAX were 3.6 nmol/l and 0.3 hours with Turbuhaler, and 2.3 nmol/l and 0.5 hours with the MDI. The amount of budesonide deposited and absorbed in the lung as a geometric mean was 32% (16%-59%) for Turbuhaler and 15% (3%-47%) for the MDI. This shows a lung deposition of budesonide from Turbuhaler which is less variable and twice

that from an MDI, and demonstrates that a lower metered dosage may be used when Turbuhaler is employed.

Example 2 - Terbutaline: TURBUHALER v MDI

Eight healthy volunteers were administered terbutaline sulphate tagged with (99m)Tc from Turbuhaler or MDI on two separate days at least 48 hours apart in randomised cross-over fashion. In order to deposit approximately 10MBq (99m)Tc in the body on each study day, four doses of terbutaline sulphate (total 1 mg) were given by MDI and two doses of terbutaline sulphate (total 1 mg) were given by Turbuhaler, Administration of radioactive aerosol was performed with the inhaler connected in series with a Vitalograph MDI-compact spirometer (Vitalograph Ltd, UK) modified for measuring inhalation flows. An average inhalation flow rate of 30 l/min was aimed at for the MDI and a peak inhalation flow rate of 60 l/min was aimed at for Turbuhaler. These flow rates are believed to be optimal with respect to drug delivery to the lungs for the two devices. After inhalation the volunteers were instructed to hold their breath for 10 seconds before exhaling through an exhalation filter (Pall Ultipor, UK) that retains terbutaline inhaled into, but not deposited in, the lungs. The MDI was actuated by an investigator during the course of inhalation. Lung function tests were performed before and after inhalation of the labelled terbutaline to ensure that no deterioration in lung function had occured. Immediately after inhalation of a study drug, a posterior view of the lungs, an anterior view of the lungs and a lateral view of the oropharynx were taken by gamma camera (General Electric Maxicamera) connected on line to a Nodecrest computer system. Gamma radiation from the mouthpiece and exhalation filter was also measured. All images were stored on magnetic tape for subsequent data analysis. From these measurements the fraction of the metered dose into the lungs could be determined. The measurements, when adjusted to take account of an observed mismatch between the distributions of unlabelled drug, labelled drug and radiolabel for Turbuhaler, gave a mean value of 29.3% for total lung

deposition (Turbuhaler), compared with 16.7% for a MDI. These figures indicate the possiblity of using a lower metered dose when Turbuhaler is employed.

Example 3 - Salbutamol: TURBUHALER v MDI

The relative efficacy of cumulative doses (100 micrograms up to 1600 micrograms) of salbutamol in Turbuhaler and "Ventolin" (salbutamol) in a MDI was compared in 12 patients with reversible obstructive airway disease. The results are indicated in Figures 2 and 3 and show that salbutamol delivery is more efficient from Turbuhaler. Therefore the metered dose can be lower for the same clinical effect.

Example 3A - Salbutamol: Particle Distribution

The absolute pulmonary deposition of salbutamol inhaled via Turbuhaler and a MDI was investigated. Salbutamol was mixed with lactose in order to achieve lower dosing without affecting the dosing accuracy. Individual data from 7 healthy volunteers indicated a difference in deposition favouring Turbuhaler. The results are presented in Figure 4.

Example 4 - Budesonide: MONOHALER

Particle size distribution from Monohaler has been found to be comparable with Turbuhaler particle size distribution. This would indicate that Monohaler also has high efficiency at least compared with a MDI, and the advantage of lower dosing requirements can be expected.

CLAIMS

1. A system comprising a dry powder inhaler and metered dose of a pharmaceutically active compound in powder form, for dispensing a clinically effective dose of an inhalable pharmaceutically active compound, comprising a dry powder inhaler having the capacity to dispense at least 40% of the metered dose of the pharmaceutically active compound in inhalable particles of up to 10 microns in diameter, and the said metered dose of pharmaceutically active compound comprising primary particles of which at least 80% have a diameter of up to 10 microns, which metered dose is in an amount which is not more than 70% by weight of the metered dose which when used in an MDI is equally clinically effective.

2. A system according to claim 1, in which the dry powder inhaler is a breath-actuated dry powder inhaler.

3. A system according to claim 1 or 2, in which at least 90% of said primary particles have a diameter of up to 10 microns.

4. A system according to claim 1, 2 or 3, in which the metered dose of the pharmaceutically active compound is not more than 50% of the metered dose which when used with an MDI is equally effective.

5. A system according to any of claims 1 to 4, in which the inhaler is the breath-actuated dry powder inhaler known by the trademark TURBUHALER.

6. A system according to any of claims 1 to 4, in which the inhaler is the breath-actuated dry powder inhaler known by the trademark MONOHALER.

7. A system according to any preceding claim, in which the

pharmaceutically active compound comprises a β-2 agonist.

8. A system according to any preceding claim, in which the pharmaceutically active compound is terbutaline, salbutamol, formoterol, budesonide, or a salt or hydrate of any of these, or a mixture of any or these or their salts of their hydrates with a carbohydrate.

9. A system according to claim 8, in which the carbohydrate is lactose, mannitol or myoinositol.

10. The use of a dry powder inhaler having the capacity to dispense at least 40% of the metered dose of pharmaceutically active compound in inhalable particles of up to 10 microns in diameter, and a metered dose of pharmaceutically active compound in powder form comprising primary particles of which at least 80% have a diameter of up to 10 microns, which meterd dose is not more than 70% by weight of the metered dose which when used with an MDI is equally clinically effective, in the administration to a patient of a clinically effective amount of an inhalable drug.

11. A method for the treatment of diseases which are treatable with inhalable drugs, comprising administering to a patient suffering therefrom a clinically effective amount of pharmaceutically active compound, by using a dry powder inhaler having the capacity to dispense at least 40% of the metered dose of pharmaceutically active compound in inhalable particles of up to 10 microns in diameter, and a metered dose of pharmaceutically active compound in powder form comprising primary particles of which at least 80% have a diameter of up to 10 microns, which metered dose is not more than 70% by weight of the dispensing dose which when used with an MDI is equally clinically effective.

12. A method of administering an inhalable drug, comprising using a dry powder inhaler having the capacity to dispense at least 40% of the metered dose of pharmaceutically active compound in inhalable particles of up to 10 microns in diameter, and a metered dose of pharmaceutically active compound in powder form comprising primary particles of which at least 80% have a diameter of up to 10 microns, which metered dose is not more than 70% by weight of the dispensing dose which when used with an MDI is equally clinically effective.

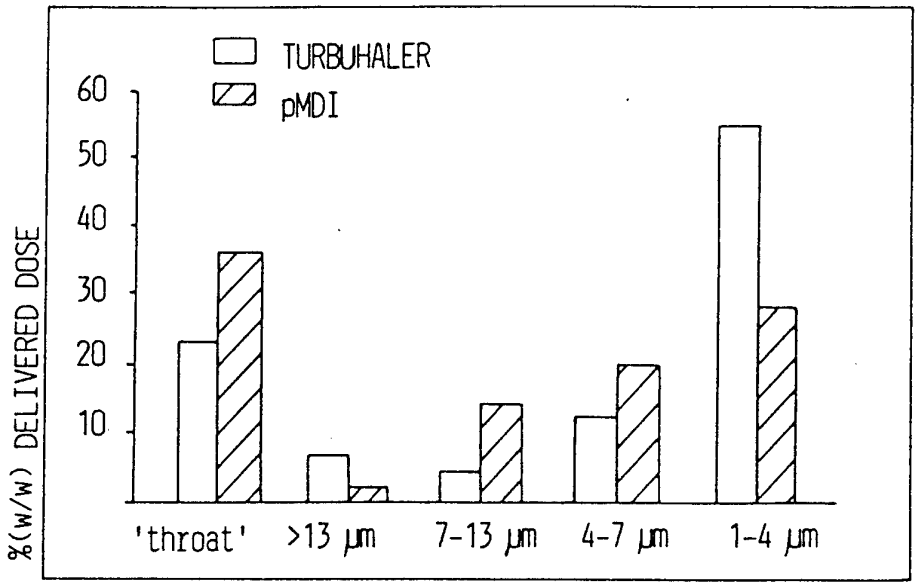


FIG.1

LUNG DEPOSITION OF SALBUTAMOL INHALED VIA PRESSURISED MDI AT FLOW 30-60 L/min, OR VIA TURBUHALER AT MEAN PEAK INSPIRATORY FLOW 64 L/min, BY HEALTHY VOLUNTEERS.

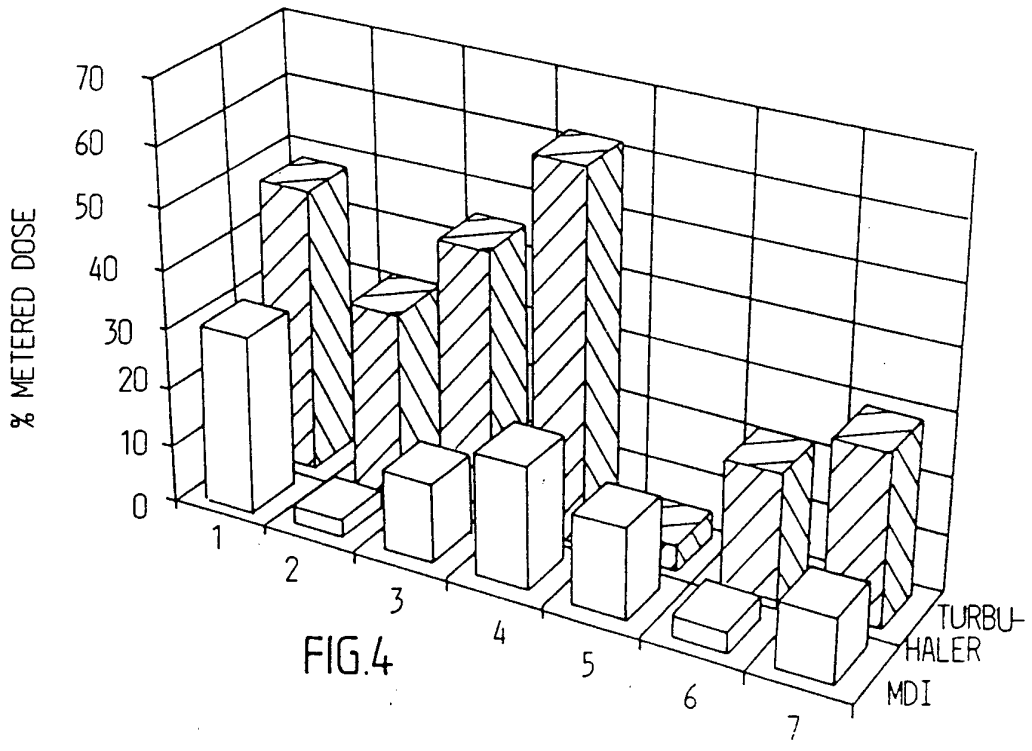


FIG.4

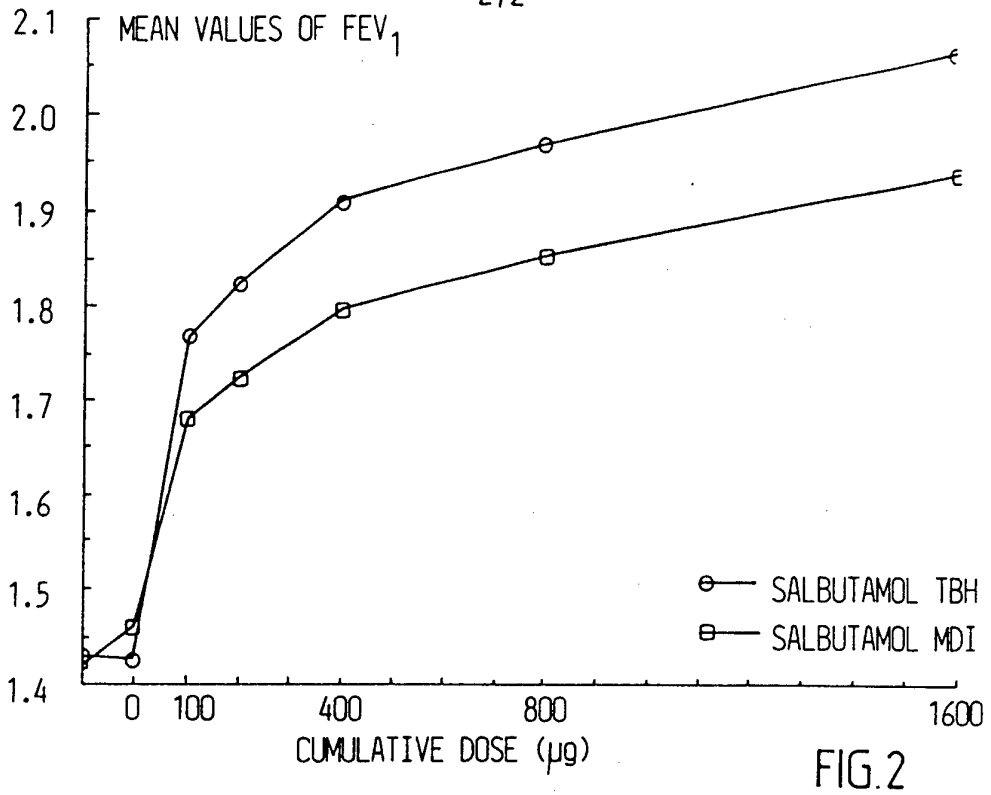


FIG.2

MEAN VALUES OF FORCED EXPIRATORY VOLUME IN ONE SECOND, FEV_1(L), BEFORE DOSING AFTER CUMULATIVE DOSES OF SALBUTAMOL (µg) INHALED VIA TURBUHALER® AND □ PRESSURISED MDI.

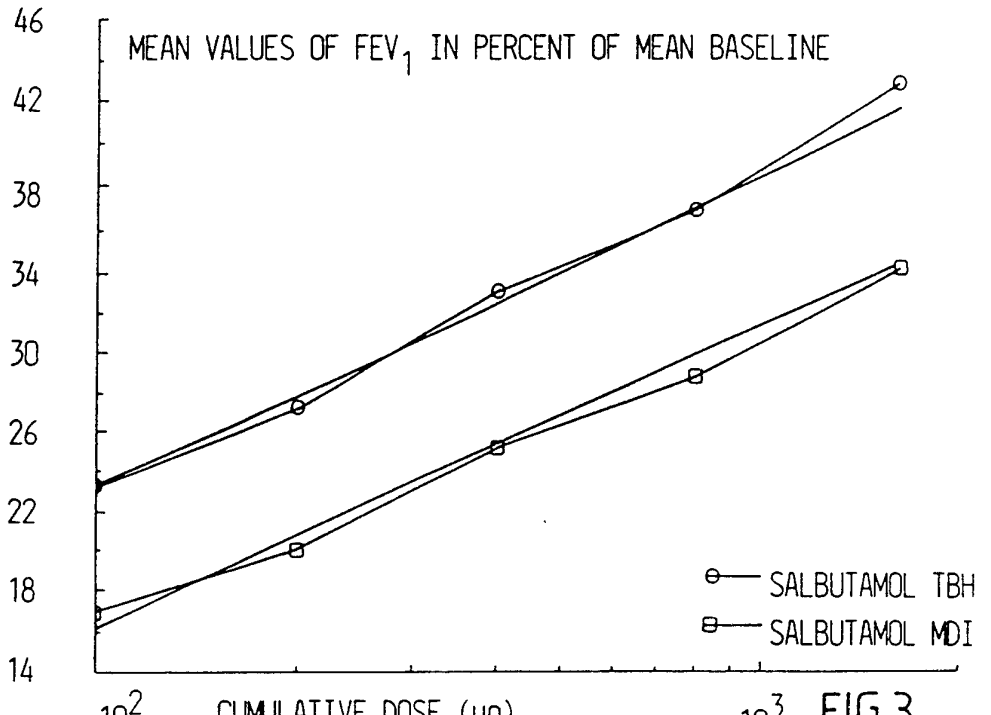


FIG.3

MEAN VALUES OF FORCED EXPIRATORY VOLUME IN ONE SECOND, FEV_1(L), IN PERCENT OF MEAN BASELINE AFTER CUMULATIVE DOSES OF SALBUTAMOL (µg) INHALED VIA TURBUHALER® AND □ AND PRESSURISED MDI.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 93/01053

A. CLASSIFICATION OF SUBJECT MATTER

IPC5: A61K 9/72, A61K 31/135
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)

IPC5: A61K

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)

CA, EMBASE, MEDLINE, WPI, WPIL, CLAIMS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO, A1, 9311746 (BOEHRINGER INGELHEIM INTERNATIONAL GMBH ET AL.), 24 June 1993 (24.06.93), see page 1, line 8 - page 4, line 12, claims --	1-10
X	Chemical Abstracts, Volume 107, No 22, 30 November 1987 (30.11.87), (Columbus, Ohio, USA), Vidgren M.T. et al., "Respiratory tract deposition of technetium-99m-labeled drug particles administred via a dry powder inhaler", page 442, THE ABSTRACT No 205053u, Int. J. Pharm. 1987, 39 (1-2), 101-105 --	1-9

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

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"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
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Date of the actual completion of the international search	Date of mailing of the international search report
24 March 1994	25 -03- 1994
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Anneli Jönsson Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 93/01053

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Dialog Information Services, file 155, Medline, dialog acc.no. 05633599, Kim C.S. et al: "Size aspects of metered-dose inhaler aerosols", Am Rev Respir Dis, Jul 1985, 132 (1) p137-42 --	1-9
A	Chemical Abstracts, Volume 117, No 18, 2 November 1992 (02.11.92), (Columbus, Ohio, USA), Borgstrom Lars et al., "Pulmonary deposition of inhaled terbutaline: comparison of scanning gamma camera and urinary excretion methods", page 433, THE ABSTRACT No 178194p, J. Pharm. Sci. 1992, 81 (8), 753-755 --	1-9
A	Chemical Abstracts, volume 110, no. 16, 17 April 1989, (17.04.89), (Columbus, Ohio, USA), Paronen P et al., "Drug particle deposition in respiratory tract after delivery from the dry powder inhaler", page 399, THE ABSTRACT No 141403k, Proc. - Eur. Congr. Biopharm. Pharmacokinet., 3rd 1987, 1, 357-65 --	1-9

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 93/01053

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 10-12
because they relate to subject matter not required to be searched by this Authority, namely:

See PCT Rule 39.1(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

26/02/94

International application No.
PCT/SE 93/01053

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A1- 9311746	24/06/93	AU-A- 3085492	19/07/93
		DE-A- 4140689	17/06/93