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(54) **Title**: APPLICATION OF HIGH DOSE COMPOUNDS VIA INHALATION

(57) **Abstract**: This invention concerns the delivery of high doses of active pharmaceutical compounds via inhalation. A pharmaceutical formulation in the form of a powder suitable for inhalation comprises one or more active pharmaceutical ingredients and a mucolytic agent and/or a buffer, wherein the formulation is free of carrier.

APPLICATION OF HIGH DOSE COMPOUNDS VIA INHALATION

Introduction

The present invention relates to a pharmaceutical formulation in the form of a powder suitable for inhalation, to a process for making, and to its use in medicine.

For many years the market of dry powder inhalation (DPI) treatments has been dominated by corticosteroid-based formulations and anticholinergic agents for the treatment of asthma and Chronic Obstructive Pulmonary Disease (COPD). These active pharmaceutical ingredients (APIs) are usually administrated in low quantities, in the micrograms range. Formulation of these agents has employed a strategy whereby the API is blended with carriers, commonly lactose, aiding delivery and dispersion of the API and making it more processable. Examples of such formulations are available in the market.

A growing body of treatments is emerging that requires high dose delivery, well into the milligram range and in some cases tens of milligrams. These emerging treatments include among others antibiotics for the treatment of cystic fibrosis, employing less potent, but perhaps more effective molecules than before. The step change in dosing levels required by these agents means that their effective delivery will require a fundamentally different approach to formulation design. Improvement of existing API/carrier based strategies will not be sufficient. We have appreciated that these new formulations will require higher levels of API concentration, perhaps other substances to promote the penetration of the API to the place where the action is needed, but without active effect, but that they will preferably be carrier-free (or at least carrier reduced) in order to reach the dosing levels required.

Elimination or reductions of carriers imposes new challenges for the efficient dispersion of APIs in a dry powder inhalation system. Appropriate selection of the particle processing technique is extremely important as efficient dispersion requires a particle size

distribution that provides sufficient void space between particles to enhance air permeability and flight properties.

Accurate control of the particle surface morphology is also needed in order that particles in contact with each other during storage can effectively separate once the inhalatory airflow is applied.

US granted patent 6858199 discloses a high efficient method for the delivery of a large therapeutic mass aerosol. This method comprises delivery of at least 50% of the mass of "aerodynamically light" particles having a tap density of less than 0.4 g/cm3, comprising at least 10 milligrams of active agent contained in a receptacle having a volume of at least 0.37 cm^3, which is bigger than the ones at the standard devices. This document teaches that until now to achieve a high delivered dose of active the particles were required to have a very low density and the formulation had to comprise carriers otherwise aggregation would occur. Because of the low density and need of carrier the formulation had to be delivered from a high volume receptacle (equivalent to capsules #2 and bigger).

The combination of an API with other substances such as a mucolytic agent or a buffer may improve the action of the API. As well as the other formulations already referred, formulations combining antibiotics with mucolytic agents usually require the use of a carrier to deliver the formulation (see, for example, WO2012/2080700, GB1242211), which again limits the quantity of API that can be delivered.

Efficiently dosing tens of milligrams of a large concentration of API formulation requires not only a fundamentally different formulation strategy but also a dry powder inhaler capable of holding and efficiently dispersing such a large mass of material.

Brief description of the invention

In accordance with one aspect of the present invention, there is provided a pharmaceutical formulation in the form of a powder suitable for inhalation, which formulation comprises one or more active pharmaceutical ingredients and a mucolytic agent and/or a buffer, wherein the formulation is free of carrier.

In another aspect, the invention provides process for the manufacture of a formulation according to the invention comprising the step of suspending the active pharmaceutical ingredient in a solution of a buffer and/or a mucolytic agent. The powder can then be made therefrom, for example by drying, preferably by spray drying.

In another aspect of the invention, there is provided a method for delivery of a formulation of the invention wherein the formulation is delivered from an inhaler having or being capable of holding a receptacle.

The invention also provides a capsule comprising a formulation according the invention.

Also provided is an inhaler containing a formulation according to the invention.

The invention also provides a blister or blister strip comprising a formulation according to the invention.

In another aspect, the invention provides a pharmaceutical formulation according to the invention for use as a medicament.

This invention presents a high dose powder product suitable for inhalation where an active pharmaceutical ingredient or a mixture of two or more active pharmaceutical ingredients is delivered as a formulation consisting of an active pharmaceutical ingredient or a mixture of two or more active pharmaceutical ingredients and a buffer and/or a mucolytic agent or a buffer that preferably acts as a mucolytic agent where the buffer can control the pH to avoid damage to the lungs and the mucolytic agent facilitates the penetration of the API to the place of treatment.

These formulations are suitable to be delivered by a dry powder inhaler. Dry powder inhalers include reservoir, capsule or blister inhalers or others. The total internal volume of the container should be in any case equal or less than 0.35 cm^3.

Benefits of this invention include the delivery by inhalation of a high dose formulation and including a buffer and/or a mucolytic agent packed in a regular size receptacle with no need of carrier, which leads to a lower amount of powder being delivered and in consequence to less side effects.

By free of carrier, we mean that the formulation of the invention is free of conventional pharmaceutical carriers of the type used as conventional API carriers in dry powder formulations. One conventional carrier is lactose. The formulations of the invention are free, or essentially free, of lactose. The formulations of the invention are also free, or essentially free, of other API carrier compounds.

Detailed description of the invention

This invention presents a carrier free formulation comprising an active pharmaceutical ingredient or a mixture of two or more active pharmaceutical ingredients and a mucolytic agent and/or a buffer. Where a buffer is used without a separate mucolytic agent, it is preferred that the buffer acts as a mucolytic agent.

Preferably, the formulation consists essentially of one or more active pharmaceutical ingredients and a mucolytic agent and/or a buffer.

Preferably, the formulation consists of an active pharmaceutical ingredient or a mixture of two or more active pharmaceutical ingredients and a buffer. Desirably, the buffer itself has mucolytic properties. By mucolytic, we mean an agent which helps dissolve mucous in the respiratory tract.

A particularly preferred formulation of the invention uses a buffer which is a citrate compound, such as sodium citrate.

A preferred formulation of the invention is where the active pharmaceutical ingredient or ingredients is doxycycline or a pharmaceutical acceptable salt thereof.

Thus, a preferred formulation is one which consists essentially of doxycycline or a pharmaceutical acceptable salt thereof and a citrate buffer.

The formulations of the invention are formulated so as to be capable of delivering a high dose of API to a patient. Preferably, the formulation is such that it is capable of delivering a dose of 5mg or more, of the one or more APIs.

The active pharmaceutical ingredient or ingredients can be chosen from any active pharmaceutical ingredients suitable for delivery by inhalation, and examples include compounds such as antibiotics, antivirals, steroids, bronchodilators, anticholinergics, enzymes, hormones, proteins, peptides and analgesics.

The buffer can be any compound suitable for buffering in a DPI formulation, and is preferably a citrate or phosphate salt. Also, the buffer is ideally a mucolytic agent. Sodium citrate is a preferred buffering agent which in addition to its buffering properties has the advantage of acting as a mucolytic agent. Alternatively a mucolytic agent that is not a buffer or a buffer that is not a mucolytic agent can be used. The buffer controls the pH to avoid damage to the lungs. The mucolytic agent facilitates the API penetration into the place of treatment.

The mucolytic agent may be any agent with the required mucolytic activity, and that is suitable for use in a DPI formulation and is compatible with the other components of the formulation. The skilled person will be aware of suitable mucolytic agents which may be used. Examples include acebrophylline, acetylcysteine ,ambroxol, Bromhexine and its derivative brovanexine, carbocisteine, cyclidrol and sobrerol.

The formulation can be used for the treatment of medical conditions in particular pulmonary diseases responsive to antibiotics such as cystic fibrosis and pulmonary bacterial or viral infections. Preferably the active pharmaceutical ingredient is an antibiotic, most preferably doxycycline, tobramycin, amoxylin, vancomycin or phosphomycin or one of their salts or mixtures thereof.

The formulation can be obtained by any suitable particle reduction method that will reduce the particle size of formulation constituents to a particle size suitable for inhalation. The active ingredients are then suspended in a solution of the mucolytic agent, and/or buffer and dried, for example by spray drying.

Also, these high dose formulations because they are delivered directly at the lung by inhalation represent the intake of a lower amount of API than the amount usually given orally to the patient and consequently less adverse side effects are expected.

The formulation can be filled in capsules suitable for a capsule based inhaler, or placed in the cavities of a reservoir inhaler or in the blisters of a blister inhaler or any other container suitable to be used with an inhaler. Independently of the container type, any individual dose will preferably be contained in a volume equal or less than 0.35 cm^3.

The formulation is then delivered by inhalation for the treatment of medical conditions in particular lung diseases such as cystic fibrosis and pulmonary infections, among others.

A process for the manufacture of a formulation according to the invention comprises the step of suspending the active pharmaceutical ingredient in a solution of a buffer and/or a mucolytic agent. The process may then further comprise the step of isolating the formulation as a powder by drying. Preferably, spray drying is used.

In a preferred aspect, the powder after isolation maintains the same polymorphic form and chemical purity, as that before isolation.

The invention includes a method for delivery of a formulation of the invention wherein the formulation is delivered from an inhaler having or being capable of holding a receptacle. The inhaler is preferably a blister, a capsule or a reservoir inhaler. The formulation is delivered to a patient in need of one or more of the APIs, as will be understood.

In the above method, the receptacle preferably has a volume of equal to or less than 0.35 cm^3

In the above method and in the invention generally, the delivered dose is preferably in the milligram range – that is, suitably 1mg or more of API is delivered. More preferably, at least 5 mg or more of API, suitably 10mg or more of API, is delivered.

The invention also provides a capsule comprising a formulation according to the invention. The capsule may be any suitable DPI capsule, as will be clear to those skilled in the art.

The invention also provides an inhaler containing a formulation according to the invention, and this is preferably a dry powder inhaler. Suitable inhalers include a blister inhaler, a capsule inhaler, or a reservoir inhaler.

An inhaler according to the invention preferably delivers an API dose of 5mg or more.

Alternatively, a blister or blister strip comprising a formulation of the invention may be used, as will be understood by those in the art.

The invention includes a pharmaceutical formulation as described herein for use as a medicament. Preferably, a pharmaceutical formulation for use according to the invention delivers an API dose to a patient of 5mg or more. The dose delivered to a patient may be 10mg or more.

The invention includes a pharmaceutical formulation as described herein for use in the treatment of pulmonary diseases, such as cystic fibrosis or a pulmonary infection.

The following examples are included to further illustrate the invention, and do not limit it in any way.

EXAMPLE

To assess the high dose DPI product concept the antibiotic doxycycline monohydrate was used as a model molecule that after formulated was delivered using TwinCaps® (Hovione) inhaler

The formulation strategy employed eliminates the carrier and combines the antibiotic with sodium citrate, a buffer and known mucolytic agent to potentially increase the penetration capability of the antibiotic through the protective mucous layers that protect and inhibit antibiotic activity against *pseudomonas aeruginosa* and other bacteria in the lungs of cystic fibrosis patients.

The model high dose formulation was doxycycline monohydrate (80%), produced by jet-milling, combined with sodium citrate (20%). The sodium citrate was incorporated using spray drying of a doxycycline suspension in a sodium citrate solution.

The resultant powder formulation was filled into TwinCaps® devices at two different trial fill weights of 50mg and 75mg powder in each of the 2 cavities that are smaller than 0.35cm^3. The delivered dose (DD), fine particle dose (FPD) and fine particle fraction (FPF) were then determined using a Fast Screening Impactor (FSI). FPD was classified as the amount of active material less than 5μm.

As observed from the results depicted in the Figure even with formulations comprising 80% doxycycline it is possible to obtain delivered doses greater than 40mg active per cavity and FPD of greater than 20mg active per cavity. The Fine Particle Fractions, a measure of dispersion efficiency, is in the order of 50% and similar for both fill weights.

In previously reported data by Mishra M and Mishra B, *"Formulation optimization and characterization of spray dried microparticles for inhalation delivery of doxycycline hyclate; Yakugaku Zasshi 131(12) 1813-1825.2)* using doxycycline hyclate in a lactose blend formulation, fine particle fractions of a slightly under 50% were achieved.

It was then possible to ensure, a good emited dose and dispersion, as can be seen by the values of FPD and FPF, even without the presence of lactose as carrier agent.

In conclusion the formulation with 80% doxycycline delivered using the TwinCaps® device has demonstrated the ability to deliver more than 40mg of active per dose with a respective Fine Particle Dose greater than 20mg

Description of the figure

Figure 1 shows the results of the DD, and FPD of doxycycline per cavity for the two fill weights analyzed in formulation (1).

Claims

1. A pharmaceutical formulation in the form of a powder suitable for inhalation, which formulation comprises one or more active pharmaceutical ingredients and a mucolytic agent and/or a buffer, wherein the formulation is free of carrier.

2. A formulation according to claim 1 which comprises two active pharmaceutical ingredients.

3. A formulation according to claim 1 or 2 which consists essentially of one or more active pharmaceutical ingredients and a mucolytic agent and/or a buffer.

4. A formulation according to claim 1, 2 or 3 which consists of an active pharmaceutical ingredient or a mixture of two or more active pharmaceutical ingredients and a buffer.

5. A formulation according to any preceding claim wherein the buffer has mucolytic properties.

6. A formulation according to any preceding claim wherein the buffer is a phosphate compound or a citrate compound.

7. A formulation according to claim 6 wherein the buffer is sodium citrate.

8. A formulation according to any preceding claim wherein the active pharmaceutical ingredient or ingredients is an antibiotic.

9. A formulation according to claim 8 wherein the active pharmaceutical ingredient or ingredients is tobramycin, doxycycline or a pharmaceutical acceptable salt thereof.

10. A formulation according to claim 9 wherein the active pharmaceutical ingredient or ingredients is doxycycline or a pharmaceutical acceptable salt thereof.

11. A formulation according to claim 10 which consists of doxycycline a pharmaceutical acceptable salt thereof and a citrate buffer.

12. A process for the manufacture of a formulation according to any preceding claim comprising the step of suspending the active pharmaceutical ingredient or ingredients in a solution of a buffer and/or a mucolytic agent.

13. A process according to claim 12 further comprising the step of isolating the formulation as a powder by drying.

14. A process according to claim 13 wherein the drying comprises spray drying.

15. A process according to claim 14 wherein the powder after isolation maintains the same polymorphic form and chemical purity.

16. A method for delivery of a formulation according to any of claims 1 to 11 wherein the formulation is delivered from an inhaler having or being capable of holding a receptacle.

17. A method for delivery of a formulation according to claim 16 where the inhaler is a blister, a capsule or a reservoir inhaler.

18. A method for delivery of a formulation according to claim 16 wherein the receptacle has a volume of equal to or less than 0.35 cm^3

19. A method for delivery of a formulation according to any one of claims 1 to 11 wherein the delivery dose is 5 mg or more.

20. A capsule comprising a formulation according to any one of claims 1 to 11.

21. An inhaler containing a formulation according to any one of claims 1 to 11.

22. An inhaler according to claim 21 which is a dry powder inhaler.

23. An inhaler according to claim 21 which is a blister inhaler, a capsule inhaler, or a reservoir inhaler.

24. An inhaler according to claim 21, 22, or 23 wherein the inhaler delivers a dose of 5mg or more.

25. A blister or blister strip comprising a formulation according to any one of claims 1 to 11.

26. A pharmaceutical formulation according to any one of claims 1 to 11 for use as a medicament.

27. A pharmaceutical formulation for use according to claim 26 wherein the dose delivered to a patient is 5mg or more.

28. A pharmaceutical formulation for use according to claim 27 wherein the dose delivered to a patient is 10mg or more.

29. A pharmaceutical formulation according to any one of claims 1 to 11 for use in the treatment of pulmonary diseases.

30. A pharmaceutical formulation for use according to claim 29 wherein the pulmonary disease is cystic fibrosis or a pulmonary infection.

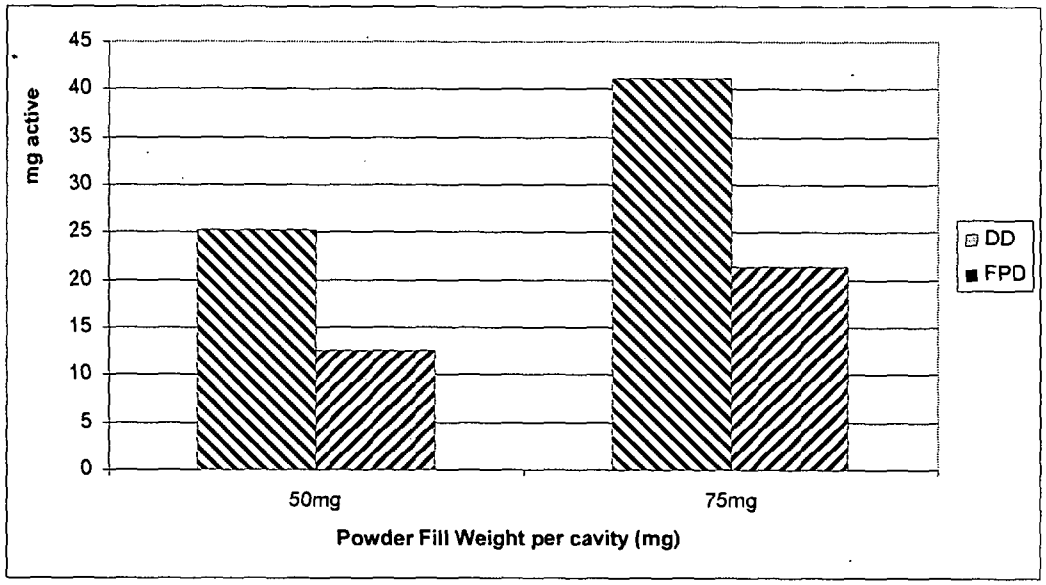

Figure 1 Chart showing Delivered Dose and Fine Particle Dose per cavity for 2 different fill weights of the Doxycycline formulation (1)

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2013/000015

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/00 A61K31/65
ADD.

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)
A61K

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, BIOSIS, EMBASE, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2010/111650 A2 (PULMATRIX INC [US]; CLARKE ROBERT W [US]; BATYCKY RICHARD [US]; HAVA D) 30 September 2010 (2010-09-30) page 3, line 9 - line 11 page 8, line 13 - line 16 page 10, line 3 - line 7 page 17, line 27 - line 31 page 18, line 12 - line 26 table 2 -----	1-30
X	WO 2009/015286 A2 (NEXBIO INC [US]; MALAKHOV MICHAEL [US]; FANG FANG [US]) 29 January 2009 (2009-01-29) page 60, line 20 - line 23 example 17 -----	1-30

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
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INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2013/000015

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2003/113273 A1 (PATTON JOHN S [US] ET AL) 19 June 2003 (2003-06-19) paragraph [0043] claims 1-25	1,3,5-7, 12-28
X	WO 2007/053729 A2 (ADVANCED INHALATION RES INC [US]; BRUSH HENRY [US]; FU FEN-NI [US]; LI) 10 May 2007 (2007-05-10) claims 1-32	1,3,5-7, 12-28

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2013/000015

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