Title: AEROSOL PRODUCTION USING A FRANGIBLE DIAPHRAGM

Abstract: There is described a method of producing an aerosol which comprises placing a dispersible material adjacent to a first surface of a frangible diaphragm, applying a pressure differential across the diaphragm so that the pressure on the first side of the diaphragm adjacent to the dispersible material is less than that on the second side of the diaphragm distal to the material such that when the diaphragm ruptures the released pressure acts to disperse the material away from the diaphragm.

Published:
— *with international search report*
AEROSOL PRODUCTION USING A FRANGIBLE DIAPHRAGM

This invention relates to a novel form of diaphragm and to devices comprising the novel diaphragm.

It is well established that asthma and other respiratory diseases can be treated with medicaments administered by inhalation. Such medicaments may be administered in the form of a dry powder with the use of a dry powder inhaler (DPI) or in the form of a solution or suspension with the use of a pressurised metered dose inhaler (MDI). A particular problem encountered with MDI's is that considerable coordination is required for the patient to actuate the pressurised aerosol, thus dispensing the medicament, and inhaling at the correct moment. The problem is exacerbated by the fact that many patients being administered such medicaments are often children or the elderly.

Furthermore, it is common practice to use a holding chamber, such that an aerosolised medicament is dispensed from an inhaler and the medicament is momentarily held in the chamber before the patient inhales. One disadvantage of such holding chambers is that, due to, inter alia, electrostatic charges, agglomeration of the aerosolised particles may occur and/or particles may be attached to the surfaces of the chamber.

Our co-pending patent application No. PCT/GB01/03578 describes a method of generating an aerosol by use of a resiliently flexible diaphragm valve member.

US Patent No 5,349,947 describes a powder inhaler which comprises pillows or a blister type contained which, in use, is compressed between an anvil and piston, such that when the pillow is compressed the pillow is explosively ruptured, causing the gas and medicament encased in the pillow to escape at very high speed.
However, on disadvantage with such an inhaler system is that, inter alia, prior to rupture of the pillow, the compression of the gas within the pillow may also lead to compression of the medicament powder within the pillow.

However, we have now found that a frangible diaphragm is especially suitable for generating a powder and air mixture, e.g. an aerosol, and which overcomes the aforementioned disadvantage of the prior art. Therefore, such a frangible diaphragm especially finds utility in a medicament delivery device, such as an inhaler, e.g. a dry powder inhaler (DPI) and may be suited to the delivery of a medicament into, for example, a holding chamber.

Thus according to the invention we provide a method of producing an aerosol which comprises placing a dispersible material adjacent to a first surface of a frangible diaphragm, applying a pressure differential across the diaphragm so that the pressure on the first side of the diaphragm adjacent to the dispersible material is less than that on the second side of the diaphragm distal to the material such that when the diaphragm ruptures the released pressure acts to disperse the material away from the diaphragm.

Although the dispersible material should be adjacent the frangible diaphragm in order to overcome the disadvantages of the prior art, the material should be remote from the frangible diaphragm.

In the method of the invention the frangible diaphragm should have only minimal fluid, e.g. gas permeability, thus enabling a pressure to be built against the second surface of the diaphragm. The diaphragm therefore preferentially comprises a substantially non-gas permeable material. Such a substantially non-gas permeable material may be a plastics material or a metal foil, e.g. aluminium foil.
Thus in a yet further embodiment of the invention we provide an aerosol delivery device comprising a frangible diaphragm and means for placing a dispersible material adjacent to a first surface of the diaphragm.

In the delivery device of the invention the frangibly closed end preferably comprises a frangible diaphragm as hereinbefore described.

The means for delivering the material, e.g. a powder material, may comprise conventionally known means. Such means preferentially comprises a metering member. Thus the means may comprise a bulk powder reservoir in conjunction with a metering member. Alternatively, the means may comprise a metering member with a predetermined amount of powder material. In the most preferred embodiment of the invention the powder delivery means comprises a spool housed in a spool carrier. Each spool is provided with a flange at each end. The flanges forming a tight slidable fit within the body of the spool carrier. The space left between the body of the spool and the spool carrier is filled with an appropriate power material. Such spools are described, for example, in International Patent Application No. WO/93/16748 (PCT/GB93/00335).

The system of the invention has utility in a variety of areas, including, for example, medicament delivery devices, such as inhalers; air fresheners or any other devices which rely upon an aerosol generation and especially a powder aerosol. Thus the system of the present invention is especially suited for use in conjunction with an inhaler, including an MDI, a DPI, an insufflator and a nebuliser.

By the term inhaler used herein, it is intended to mean any of the aforementioned devices. In a preferred embodiment, the inhaler of the invention comprises a DPI.

Thus according to the invention we provide a delivery system as hereinbefore described wherein the powder material is a medicament optionally including carrier material.
Thus, according to a yet further feature of the invention we provide a medicament delivery device which comprises a medicament reservoir, a metering mechanism and a medicament outlet characterised in that the delivery device is provided with a frangible diaphragm as hereinbefore described and with means for creating a pressure differential across the diaphragm.

The medicament reservoir may be a bulk reservoir, in which a separate metering mechanism is provided. Such an arrangement is described in International Patent application No. WO 92/00771, which is incorporated herein by reference. Alternatively, if the medicament reservoir comprises unit dosage means, then the medicament reservoir and metering mechanism may comprise a single unit. Such an arrangement is described in European Patent No. 664 239, which is also incorporated herein by reference.

In an especially preferred embodiment of the invention the medicament delivery device is an inhaler.

In a preferred embodiment the medicament delivery means is adapted to be positioned adjacent to the frangible diaphragm. In use, a predetermined amount of medicament may be housed in a delivery unit, such as a spool carrier and thus the medicament is exposed when the metering mechanism is actuated. Pressure may be introduced by an increase in pressure on the surface of the diaphragm remote from the medicament delivery member. Alternatively, a vacuum may be applied to the first surface of the diaphragm. When the pressure vacuum reaches a predetermined level, the diaphragm breaks allowing a rush of air to flow through the diaphragm towards the outlet and mixing with the medicament.

In a further alternative embodiment the medicament may be positioned such that it rests on the frangible diaphragm.
The change in pressure may be mechanically or electromechanically actuated. However, in an alternative embodiment the increase in pressure may be actuated manually, for example, by the use of a flexible portion of the inhaler. The pressure may be introduced by an increase in pressure on the non-dispensing surface of the frangible member or, alternatively, by a decrease in pressure on the dispensing surface of the frangible member, e.g. when a patient inhales.

The actuation of the metering mechanism and the breaking of the frangible diaphragm may occur simultaneously separately or sequentially.

In the most preferred embodiment the inhaler of the invention may be provided with a holding chamber. This may be a holding chamber which is conventionally known *per se*. Alternatively it may be an electrically charged holding chamber such as is described in our co-pending applications Nos. GB 0010742.5 and GB 001743.2.

In addition, the inhaler of the invention may optionally include a conventionally known breath actuated mechanism.

The particle size of the medicament may be varied depending, *inter alia*, on the type of aerosol being formed. In the case of a dry powder medicament, the particle size of the medicament, and the carrier, if one is present, may be varied. The nature of the carrier may also be varied. Thus, the particle size of the medicament may be substantially between 1 and 100 μm. That is, at least 90% w/w of the medicament should have a particle size of between 1 and 100 μm. The preferred particle size may also depend upon the nature of the medicament being delivered. Thus, for example, for the treatment of respiratory disorders a particle size of 4 to 8 μm may be preferred, e.g. 6 μm. However, for the delivery of systematically active medicaments a smaller particle size may be desirable, for example from 1 to 5 μm, e.g. 3 μm.

In a dry powder formulation a variety of carriers may be used. Certain carriers may be mentioned, by way of example only, such as sugars, e.g. dextran, mannitol and
lactose, for example α-lactose monohydrate. The particle size of the carrier may be across a wide range, between 0.1 and 500 μm, preferably between 1 and 200 μm, more preferably between 1 and 100 μm and especially between 1 and 20 μm. Alternatively, the carrier may itself comprise a mixture of fine and coarse particles.

A method of treating a patient with a respiratory disorder which comprises administering a therapeutically effective amount of a medicament using an inhaler according to either of claims 14 or 18.

According to a further feature of the invention we provide a method of drug delivery to a patient which comprises administering a medicament to a patient suffering a respiratory disorder which comprises administering a therapeutically effective amount of a medicament using an inhaler as hereinbefore described.

The inhaler of the invention is advantageous in that, inter alia, it enables the delivery of dispersions of finely divided forms of medicament and avoids some if the disadvantageous of agglomeration experienced with some known DPIs.

A variety of medicaments may be administered by using the inhaler of the invention, such medicaments may have a systemic or non-systemic activity on the patient. Such medicaments are generally (but not limiting) antibiotics, bronchodilators or other anti-asthma drugs. Such medicaments include, but are not limited to β₂-agonists, e.g. fenoterol, formoterol, pirbuterol, reproterol, rimiterol, salbutamol, salmeterol and terbutaline; non-selective beta-stimulants such as isoprenaline; xanthine bronchodilators, e.g. theophylline, aminophylline and choline theophyllinate; anticholinergics, e.g. ipratropium bromide; mast cell stabilisers, e.g. sodium cromoglycate and ketotifen; bronchial anti-inflammatory agents, e.g. nedocromil sodium; and steroids, e.g. beclomethasone dipropionate, fluticasone, budesonide and flunisolide; and combinations thereof.

Specific combinations of medicaments which may be mentioned include combinations of steroids, such as, beclomethasone dipropionate, fluticasone,
budesonide and flunisolide; and combinations of to β₂-agonists, such as, formoterol
and salmeterol. It is also within the scope of this invention to include combinations
of one or more of the aforementioned steroids with one or more of the
aforementioned β₂-agonists.

Thus, according to a yet further feature of the invention we provide a method of
treating a patient with a respiratory disorder which comprises administering a
therapeutically effective amount of a medicament using an inhaler as hereinbefore
described.

Further medicaments which may be mentioned include systemically active materials,
such as, proteinaceous compounds and/or macromolecules, for example, leuprolide
and alpha interferon; growth factors, anticoagulants, immunomodulators, cytokines,
nucleic acids, hormones, such as insulin human growth hormone and parathyroid
hormone.

We also provide the use of an aerosol delivery device of the invention in the
manufacture of an medicament delivery device as hereinbefore described.

It is within the scope of this invention to include combinations of any of the
aforementioned medicaments.

The invention will now be described by way of example only and with reference to
the accompanying drawings, in which Figure 1 is a perspective cutaway
representation of a cartridge of the invention with the medicament dispensing
member in the open position; and

Figure 2 is a perspective, cut away, representation of the invention in the dispensing
position.
With reference to Figures 1 and 2 a cartridge (1) comprises an open and (2) and a closed end (3). The closed end (3) is provided with a frangible diaphragm (4) comprising a first surface (5) and a second surface (6). The second surface (6) is positioned adjacent a pressure delivery conduit (7) whilst the first surface (5) is positioned adjacent a medicament delivery member (8). The medicament delivery member (8) comprises a spool (9) and a spool carrier (10) and is preferentially remote from the first surface (5) of the diaphragm (4). The spool (9) is provided with flanges (11 and 12) at either end and holds a cake of medicament (13).

The cartridge (1) is provided with a spool rest (14).

In use the spool is ejected from the spool counter (10) exposing the cake of medicament (13). One flange (11) of the spool (9) rests in the spool rest (14). Pressure is applied to the second surface (6) of the frangible diaphragm (4). When the pressure reached a critical point the diaphragm (4) breaks allowing a rush of air through the cartridge (1). The rush of air deagglomerates the medicament cake (13) and creates a powder aerosol which can be inhaled by a patient.
CLAIMS

1. A method of producing an aerosol which comprises placing a dispersible material adjacent to a first surface of a frangible diaphragm, applying a pressure differential across the diaphragm so that the pressure on the first side of the diaphragm adjacent to the dispersible material is less than that on the second side of the diaphragm distal to the material such that when the diaphragm ruptures the released pressure acts to disperse the material away from the diaphragm.

2. A method according to claim 1 characterised in that the dispersible material is remote from the tangible diaphragm.

3. A method according to claim 1 characterised in that the application of the pressure differential comprises applying an increased pressure to the second surface of the diaphragm.

4. A method according to claim 1 characterised in that the dispersible material is placed against the first surface of the frangible diaphragm.

5. An aerosol delivery device comprising a frangible diaphragm and means for placing a dispersible material adjacent to a first surface of the diaphragm.

6. An aerosol delivery device according to claim 5 characterised in that the device comprises means for placing a dispersible material remote from the first surface of the diaphragm.

7. An aerosol delivery device according to claim 5 characterised in that means is provided for applying a pressure differential.
8. An aerosol delivery device according to claim 5 characterised in that the diaphragm comprises a substantially non-gas permeable material.

9. An aerosol delivery device according to claim 8 characterised in that the substantially non-gas permeable material comprises a metal foil.

10. An aerosol delivery device according to claim 5 characterised in that the device comprises a chamber provided with an open end, a frangibly closed end and means for delivering the material into the chamber.

11. An aerosol delivery device according to claim 5 characterised in that the means for placing a disperseable material adjacent the diaphragm includes a metering member.

12. An aerosol delivery device according to claim 11 characterised in that the means for placing a disperseable material adjacent the diaphragm comprises a bulk powder reservoir in conjunction with a metering member.

13. An aerosol delivery device according to claim 11 characterised in that the means for placing a disperseable material adjacent the diaphragm comprises a metering member with a predetermined amount of powder material.

14. An aerosol delivery device according to claim 13 characterised in that the means for placing a disperseable material adjacent the diaphragm comprises a spool housed in a spool carrier.

15. A medicament delivery device which includes an aerosol delivery device according to claim 5.

16. A medicament delivery device according to claim 15 characterised in that the device is an inhaler.
17. A medicament delivery device according to claim 16 characterised in that the inhaler is an MDI.

18. A medicament delivery device according to claim 17 characterised in that the material is a medicament including a carrier material.

19. A medicament delivery device according to claim 15 characterised in that the device comprises a medicament reservoir, a metering mechanism and a medicament outlet and an aerosol delivery device according to claim 5.

20. A medicament delivery device according to claim 19 characterised in that the device is an inhaler.

21. A medicament delivery device according to claim 15 characterised in that the pressure differential is created mechanically or is electromechanically actuated.

22. A medicament delivery device according to claim 15 characterised in that the pressure differential is created manually.

23. A medicament delivery device according to claim 15 characterised in that the actuation of the metering mechanism and the breaking of the frangible diaphragm occurs simultaneously.

24. A medicament delivery device according to claim 15 characterised in that the device is provided with a holding chamber.

25. A medicament delivery device according to claim 24 characterised in that the holding chamber is an electrically charged holding chamber.
26. A medicament delivery device according to claim 25 characterised in that the holding chamber is one described in co-pending application No. PCT/GB01/01993.

27. A medicament delivery device according to claim 15 characterised in that the particle size of the medicament is substantially between 1 and 100 μm.

28. A method of delivering a medicament to a patient which comprises administering a therapeutically effective amount of a medicament using a medicament delivery device according to claim 15.

29. A method of treating a patient with a respiratory disorder which comprises administering a therapeutically effective amount of a medicament using an inhaler according to claim 16.

30. A method of treating a patient with a systemic disorder which comprises administering a therapeutically effective amount of a medicament using an inhaler according to claim 16.

31. The use of an aerosol delivery device according to claim 5 in the manufacture of a medicament delivery device according to claim 15.

32. A method or an aerosol delivery device substantially as described with reference to the accompanying examples and drawings.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61M15/00 B05B11/06

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 7 A61M B05B

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 practical, search terms used)
EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>CH 518 744 A (CIBA GEIGY AG) 15 February 1972 (1972-02-15) column 2, line 37 -column 3, line 2; figure 7</td>
<td>1-22, 24, 25, 27, 31</td>
</tr>
<tr>
<td>X</td>
<td>US 5 215 221 A (DIRKSING ROBERT S) 1 June 1993 (1993-06-01) column 3, line 20 - line 49; figures</td>
<td>1, 3-5, 7, 8, 10-13, 15-18, 21, 22, 27, 31</td>
</tr>
<tr>
<td>A</td>
<td>WO 93 16748 A (INNOVATA BIOMED LTD) 2 September 1993 (1993-09-02) cited in the application abstract</td>
<td>11-14</td>
</tr>
</tbody>
</table>

Further documents are listed in the continuation of box C.

Patent family members are listed in 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 document but published on or after the international filing date
  *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
  *O* document referring to an oral disclosure, use, exhibition or other means
  *P* document published prior to the international filing date but later than the priority date claimed

*"" 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
*"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
*"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
*"A" document member of the same patent family

Date of the actual completion of the international search
11 January 2002

Date of mailing of the international search report
18/01/2002

Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2060, Tx. 31 651 spo nl
Fax (+31-70) 340-3916

Authorized officer
Lakkis, A
<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>P,X</td>
<td>WO 01 00263 A (INHALE THERAPEUTIC SYST)</td>
<td>1-22, 24, 25, 27, 31</td>
</tr>
<tr>
<td></td>
<td>4 January 2001 (2001-01-04)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>page 18, line 25 - line 29</td>
<td></td>
</tr>
<tr>
<td></td>
<td>page 29, line 7 - line 9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>figures 4, 38</td>
<td></td>
</tr>
</tbody>
</table>

Form PCT/ISA/210 (continuation of second sheet) (July 1992)
<table>
<thead>
<tr>
<th>Patent document cited in search report</th>
<th>Publication date</th>
<th>Patent family member(s)</th>
<th>Publication date</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH 518744</td>
<td>15-02-1972</td>
<td>NONE</td>
<td></td>
</tr>
</tbody>
</table>