# Dry powder inhaler with an adherence / compliance monitor

## Technical Field of the Invention

The present invention relates to an inhaler for dry powders containing an active substance for inhalation. In particular, the invention relates to an inhaler and a module for monitoring a patient's adherence and / or compliance.

## Background to the Invention

Dry powder inhalers (DPIs) provide an attractive method for administering medicaments, for example to treat local diseases of the airway or to deliver drugs to the bloodstream via the lungs. The medicament is commonly provided as individual doses, such as a strip having a plurality of blisters. The dose is typically dispensed by the user opening a cap or cover to access a mouthpiece, then operating an actuator, such as a button or lever to release the powder and finally inhaling through the mouthpiece. In some inhalers (known as "open-inhale-close" inhalers) the cover itself is the actuator, so that there is no separate actuating lever or button. The inhalers usually have vents to allow air to flow in and a dose counter which displays the number of doses that have been used, or that remain to be used.

The efficacy of treatment is dependent on the patient using the inhaler correctly and as prescribed. Consequently, there is increasing interest in monitoring patient adherence (i.e. whether the patient takes the prescribed number of doses per day, e.g. once or twice daily) and compliance (i.e. whether the patient uses their inhaler correctly, e.g. if they inhale sufficiently strongly to entrain the powder and disperse it into particles that reach the lung).

DPIs typically contain a month's supply of medication. Since adherence / compliance monitors usually contain expensive sensors, electronics etc., they are often provided as separate add-on modules which detachably couple to the inhaler. Thus, when the medication in the inhaler has been used up, the monitor can be detached and then re-attached to a new inhaler.

However, the monitor must not interfere with the operation of the inhaler. For example, to ensure proper actuation of the inhaler and successful dose delivery, the motion of the cover and actuator (if present) must be uninterrupted. Moreover, the air vents and dose counter must be unobstructed. These constraints limit the possible locations for attaching the monitor to the inhaler. Typically therefore, the monitor must fit onto a part that the user holds during operation. For example, WO 2016 / 111633 and WO 2014 / 204511 disclose detachable adherence monitors for specific dry powder inhalers. However, the presence of the monitor affects how and where the patient holds the inhaler while operating it, which results in a different user interface compared to the inhaler on its own. This can be confusing for some patients, and could result in patients choosing to remove the monitor. Moreover, because of these constraints, it may not be straightforward to attach and detach the monitor.

**Brief description of the invention**

The present invention addresses this problem and, in a first aspect, provides a dry powder inhaler having a housing and a cover which is pivotable relative to the housing from a closed position to an open position in order to expose a mouthpiece, wherein the inhaler is designed for use with a monitor having one or more sensors, wherein the housing has one or more formations for attaching the monitor to the inhaler and wherein, when the cover is in the open position, it at least partially covers the formations. Thus, in the open position, the cover at least partially covers the location in which the monitor is mounted. In other words, when the monitor is mounted onto the inhaler and the cover is fully opened, the cover at least partially covers the monitor.

In a second aspect, the invention provides a monitor designed to be used with the inhaler of the first aspect, the monitor having a sensor and formations for attaching the monitor to the inhaler, so that when the monitor is mounted onto the inhaler and the cover is fully opened, the cover at least partially covers the monitor.

The invention has the advantage that the patient does not need to touch the monitor when using the inhaler. In fact, the patient is discouraged or prevented from touching the monitor when the cover is in the open position for inhalation, because the monitor at least partially is

situated under the cover. The cover thereby protects the monitor, for example from inadvertent removal and accidental damage. The formations on the housing are preferably accessible when the cover is in the closed position.

The formations on the housing and the monitor perform the function of positioning the monitor on, and attaching the monitor to the inhaler. The formations may be mechanical, for example one or more clip connections, such as pegs or clips on the monitor and corresponding holes or slots on the inhaler, or vice versa. In one embodiment, the housing of the inhaler has one or more clips which are accessible when the cover is in the closed position and at least partially covered by the cover when it is the open position. The formations may facilitate attachment of the monitor to the inhaler by one or more screws. The monitor could also be positioned on and / or attached to the inhaler by magnets.

In a preferred embodiment, the monitor is detachably mountable onto the inhaler.

The sensor may be an optical sensor, for determining the position and / or direction of motion of the cover. The inside of the cover may have markings designed to be read by the monitor in order to determine the position and / or direction of motion of the cover. The sensor may be configured to read the markings so that the monitor can determine the position and / or direction of motion of the cover. Alternatively, the inside of the cover may have one or more cams designed to operate switches on the monitor for determining the position and / or direction of motion of the cover.

In one embodiment, the opening motion of the cover has two stages: in the first stage, moving the cover from the closed position to an intermediate position causes a blister strip to be advanced; and in the second stage, moving the cover from the intermediate position to the open position causes a piercer to pierce an aligned blister.

The monitor may have an inner face that matches the shape of the housing of the inhaler on which it is designed to be mounted and an outer face which corresponds to the curve defined by the rotation of the cover.

The monitor may have a sensor, preferably an optical sensor, for reading a code on the blister strip. The optical sensor may be configured to read the code so that the monitor can determine the position and / or direction of motion of the blister strip.

The monitor may determine the position and / or direction of motion of the blister strip during the first stage of the opening movement of the cover by means of the sensor that reads the code on the blister strip, and determine the position and / or direction of motion of the cover during the second stage by means of the sensor that reads the markings on the inside of the cover. Alternatively, the monitor may have switches on its outer side which are operated by the cams on the inside of the cover of the inhaler, and the monitor may be configured to determine the position and / or direction of motion of the cover in both the first and the second stages of the opening movement of the cover based on the states of the switches.

The monitor may additionally have a pressure sensor for sensing a patient's inhalation on the mouthpiece.

The monitor may have a controller and memory for processing and / or storing information from the sensor(s) and communication means for transmitting information to an external device, such as a computer or smartphone.

In a third aspect, the invention provides a combination of the inhaler of the first aspect and monitor of the second aspect, such as a kit comprising the inhaler and the monitor. Preferably the monitor is mounted onto the inhaler.

**Brief Description of the Figures**

The invention will now be further described with reference to the Figures, wherein:

Figure 1A shows a prior art adherence monitor for the Handihaler® inhaler.

Figure 1B shows the monitor of Figure 1A in place on the Handihaler®.

Figure 2A shows a prior art adherence monitor for the Ellipta® inhaler.

Figure 2B shows the monitor of Figure 2A in place on the Ellipta®.

Figure 3A shows a prior art adherence monitor for the Diskus® inhaler.

Figure 3B shows the monitor of Figure 3A in place on the Diskus®.

Figure 4A shows an inhaler and a monitor according to the invention, with the cover in the closed position, so that the mouthpiece is covered.

Figure 4B shows the inhaler of Figure 4A with the cover in the open position so that the mouthpiece is exposed and the monitor is covered.

Figure 4C shows the inhaler of Figure 4A with the monitor removed and the cover open.

Figures 4D and 4E show the monitor removed from the inhaler.

Figure 5A shows a second embodiment of the monitor that has switches on its outer side.

Figure 5B shows a second embodiment of the mouthpiece cover that has cams on its inside that actuate the switches.

**Detailed Description of the Invention**

In the context of dry powder inhalers, the term "adherence" is normally used to refer to whether the patient takes the prescribed number of doses per day, e.g. once or twice daily. The term "compliance" is normally used to refer to whether the patient uses their inhaler correctly, e.g. if they inhale sufficiently strongly to entrain the powder and disperse it into particles that reach the lung. Consequently, a monitor may be designed to measure adherence and / or compliance, according to the type of sensors that it uses, and how they are configured. In the present application, the term "monitor" therefore refers to a module having one or more sensors that is designed to measure and capture information relating to adherence and / or compliance. However, the monitor does not perform any of the functions associated with dosing the medication, such as a piercing or opening blisters / capsules, de-agglomerating the powder or providing a breath-actuation mechanism. The inhaler therefore operates to dispense powder whether the monitor is present or not.

WO 2016 / 111633 discloses detachable adherence monitors which have been retrospectively designed for specific dry powder inhalers, namely the Handihaler® and the Ellipta®, shown in Figures 1 and 2 respectively. WO 2014 / 204511 discloses adherence monitors for the Diskus® dry powder inhaler, shown in Figure 3. Figures 1A, 2A, 3A show the monitors **100, 200, 300** alone; Figures 1B, 2B, 3B show them attached to the inhaler **110, 210, 310 i**n each case.

To attach the monitor **100** to the Handihaler® **110**, the user has to slide the inhaler into the monitor at an angle, with the actuator button **130** first, so that the top edge of the inhaler fits under a retaining catch. Then outward pressure is applied to the monitor so that further retaining catches flex and allow the inhaler to fit into the monitor. The cover and mouthpiece may then be pivoted open to insert a capsule containing the powder. Then the actuator button **130** is pressed to pierce the capsule. The monitor has a switch **140** which is activated when the cover is opened / closed and a timer which records the time between opening and closing of the cap. If this time is in a defined range (such as between 3 and 10 seconds), then inhalation is deemed to have taken place.

The monitor **200** is attached to the Ellipta® inhaler **210** by an interference fit. The monitor has a switch **240** which is activated when the cover is opened / closed and a timer which records the time between opening and closing of the cap. It also has transparent sections **250** so that the label on the inhaler is not hidden. To operate the inhaler, the cover **220** is pivoted, which exposes the mouthpiece and also actuates the blister indexing and opening mechanism. The monitor may also have an acoustic sensor for detecting actuation or inhalation.

The monitor **300 f**or the Diskus® inhaler **310**, may be configured as a clip that fits over the top and bottom portions of the inhaler. To operate the inhaler, the cover **320** is opened, then the actuator lever **330** is pressed. The monitor has motion sensors which determine whether or not the motion is characteristic of typical inhaler use. The monitor also has a temperature sensor **340** which can detect the presence of the patient's mouth at the mouthpiece.

In each case, since the monitors must not interfere with the cover or the actuator button / lever, they are designed to fit onto the other part of the inhalers, i.e. the part that the user holds during operation. Consequently, the patient must hold the monitor while operating the inhaler, resulting in a different user experience compared to the inhaler on its own. Moreover, the fact that the patent holds the monitor during inhalation can lead to inadvertent removal of the monitor or accidental damage to it.

An inhaler and monitor of the invention are shown in Figure 4. Figure 4A shows the inhaler with a monitor attached, and with the mouthpiece cover in the closed position. Figure 4B

shows the inhaler with the mouthpiece cover in the open position so that the mouthpiece is visible and so that the monitor is covered. Figure 4C shows the inhaler with the monitor removed and with the mouthpiece cover in the open position. Figures 4D and 4E show the monitor detached from the inhaler.

The inhaler shown in Figure 4 is an "open-inhale-close" inhaler of the type described in WO13/175177, which has a gear mechanism that selectively couples the mouthpiece cover to a blister strip indexing mechanism and also to a piercer. Moving the cover from the closed position to an intermediate position (the first stage of opening) causes the indexing mechanism to advance the blister strip. Then, once an unused blister is in position beneath the piercer, the indexing mechanism is disengaged. Moving the mouthpiece cover from the intermediate position to the fully open position (the second stage) causes the piercer to pierce the aligned blister. The user then inhales through the mouthpiece, which aerosolizes the powder in the pierced blister. However, the invention is not limited to this type of inhaler, and for example, could equally be used with an inhaler which has a passive mouthpiece cover, and a separate actuating lever, as described for example in WO13/175176, or with an inhaler which has a blister disk instead of a blister strip.

The inhaler of the invention preferably has a strip of blisters containing powdered medicament, and a mechanism for advancing the blister strip and for opening the blisters which is operated by an actuator. The opening mechanism is suitably a piercer which is mounted on the underside of the mouthpiece. The actuator drives the indexing mechanism to move a blister into alignment with the piercer and then moves the mouthpiece relative to the housing so that the piercer pierces the aligned blister. The actuator may be a lever which causes indexing of the blister strip and piercing of the blisters. Preferably however, the actuator is formed as part of, or is connected to, the cover, so that rotation of the cover causes indexing of the blister strip and piercing of the blisters. The inhaler may be configured to index and pierce one blister on each actuation. Alternatively, it may index and pierce two (or more) blisters on each actuation. For example, it may deliver two (or more) different formulations or medicaments simultaneously.

The inhaler **1** shown in Figure 4 is constructed from two shell parts **2, 3** which are joined together to form a housing that contains a blister strip. A detachable monitor **40** is attached to one side of the inhaler. A mouthpiece cover **4** is mounted onto the housing. The cover **4** can be rotated through approximately 100° from the closed position (Figure 4A) in which it covers and protects a mouthpiece, to a fully open position (Figure 4B), in which the mouthpiece **5** is exposed so that the user can inhale a dose of medicament.

Once the monitor has been attached to the inhaler, the user does not need to touch it. When the cover is in the closed position, the monitor is located on a part of the inhaler which the patient does not hold when opening the cover (if the inhaler was held in this area, the patient's fingers would obstruct the opening movement of the cover). Consequently, the user interface is exactly the same as when the monitor is not present. Moreover, when the cover is in the open position for inhalation, the monitor is situated under the cover, so that it is protected from accidental damage or inadvertent removal.

The inner face of the monitor matches the shape of the housing of the inhaler on which it is mounted. The outer face is designed to correspond to the curve defined by the rotation of cover. In other words, it is shaped as an arc of a circle centred on the axis of rotation of the cover, with a radius which is slightly less than the radius of the internal surface of the cover. Thus, when the cover is opened there is a small clearance gap (about 0.5 – 1mm) between the internal surface of the cover and outer face of the monitor. This maximises the volume of the monitor within the constraint that it must fit under the cover. By appearing as a continuation of the curve of the cover, the outer face also provides a visual cue to aid the user in mounting the monitor in the correct position.

Figure 4C shows the inhaler with the monitor having been removed. An orifice **11** is visible in the wall **12** of the housing where the monitor was attached; its purpose is described below. A slot **13** for mounting the monitor is also visible. There is a second slot located towards the bottom of the wall **12**, but this is not visible in Figure 4C because it is hidden by the cover **4**.

The monitor has an external optical sensor **44** located in a recess on its outer side, shown in Figure 4D. This sensor is used to determine whether the mouthpiece cover has been fully

opened. The cover has markings (e.g. moulded or embossed) on its internal surface which are read by the external optical sensor during the second stage of opening. Hence the monitor can determine whether the cover has been fully opened so that the blister was pierced, or whether actuation was aborted before piercing. This provides a further advantage for "open-inhale-close" inhalers: having the monitor located underneath the cover (when it is in the open position) provides a simple way of determining whether the patient has actually actuated the inhaler, or whether they have only partly opened the cover, and then closed it again. Two such sensors may be used, in combination with a two-part code on the inside of the cover. This allows the monitor to distinguish between four states, so that the direction of motion of the cover can be determined, as well as its position.

The inside face of the monitor (i.e. the side which abuts the inhaler when the monitor is attached) is shown in Figure 4E. The monitor **40** has two clips **41** which fit into the corresponding slots **13** in the housing (only one of which is visible in Figure 4C), and thereby hold the monitor in place when attached to the inhaler. The monitor has a pressure sensor **42**, which is is located in a recess on the inside face. The pressure sensor abuts the orifice **11**, which leads via a channel in the housing to the mouthpiece. The monitor can thereby measure the pressure in the mouthpiece to detect the user's inhalation. The monitor also has three internal optical sensors **46** (for example photomicrosensors). These read a code on the blister strip (for example, a printed bar code), so that the number of doses that have been dispensed or that remain to be dispensed can be determined.

The monitor may be supplied separately from the inhaler, so that one monitor may be used with many different inhalers. The clips and slots allow the monitor to be detachably mounted on the inhaler by an interference fit. Alternatively, the monitor may be fixedly attached to the inhaler, in which case the clips can be welded onto the slots, e.g. by ultrasonic welding.

The position of the cover during the first stage of opening may be monitored by means of the optical sensors **46** on the inner side of the monitor which detect the motion of the code on the blister strip. Monitoring is handed over to the external optical sensor for the second stage in which the blister strip does not move. The external optical sensor is switched on shortly before the indexing mechanism is disengaged, at which point the cover has pivoted far

enough to cover the outer optical sensor. This saves battery power because the external optical sensor is only switched on when needed. It also prevents false readings, which could otherwise occur e.g. if the user puts their fingers over the outer sensor.

In another embodiment, shown in Figures 5A and 5B, the monitor does not have an external optical sensor, but instead has two switches **81, 82**. The inside of the cover has two corresponding cams **91, 92** which come into or out of contact with the switches as the cover is opened causing the switches to change state. Each cam causes two changes of state in each switch, so there are eight changes of switch state as the cover is fully opened. This provides two complete cycles of quadrature logic, which allow the monitor to determine the direction of motion of the cover (opening or closing). The switches and cams are arranged so that each change of switch state occurs at a different opening angle spanning both the first and second stages of the opening / closing motion. The monitor counts the changes in switch state and determines the position of the cover from the known angles at which the changes occur. Consequently, there is no need to use the motion of the blister strip to determine the position of the cover during the first stage of opening. Nonetheless, the monitor may have internal optical sensors for reading a code on the blister strip so that the monitor can determine the dose number. The cams and switches allow the monitor to determine whether the cover has been fully opened so that the blister was pierced, or whether actuation was aborted before piercing. The monitor may also have a pressure sensor for detecting inhalation.

This embodiment has the advantage that, due to the close fit between the inside of the cover and the outside of the monitor at all opening angles, the arrangement of cams and switches is simple to implement. Moreover, the power consumption of the monitor is reduced for two reasons. Firstly, there is no need for an external optical sensor. Secondly, the monitor can be switched on, or woken up from a sleep state, whenever one of the switches changes state. This avoids the need for the monitor to be permanently switched on.

The monitor may have a controller and memory (e.g. a suitable microprocessor) which are configured to process and/or store information read from the sensors relating to patient's usage of the inhaler. The monitor may also include communication means to transmit adherence / compliance information (e.g. via bluetooth) to an external device, such as a

computer or smartphone. The information may then be displayed to the patient and / or a medical professional, by means of suitable software, for example a smartphone app. The information may additionally or alternatively be stored on the monitor for subsequent interrogation, or wirelessly transmitted to, for example, an online health platform.

The medicament is suitable for administration by inhalation, for example for the treatment of a respiratory disease. It may include one of more of the following classes of pharmaceutically active material: anticholinergics, adenosine A2A receptor agonists, β2-agonists, calcium blockers, IL-13 inhibitors, phosphodiesterase-4-inhibitors, kinase inhibitors, steroids, CXCR2, proteins, peptides, immunoglobulins such as Anti-IG-E, nucleic acids in particular DNA and RNA, monoclonal antibodies, small molecule inhibitors and leukotriene B4 antagonists. The medicament may include excipients, such as fine excipients and / or carrier particles (for example lactose), and / or additives (such as magnesium stearate, phospholipid or leucine).

Suitable β2-agonists include albuterol (salbutamol), preferably albuterol sulfate; carmoterol, preferably carmoterol hydrochloride; fenoterol; formoterol; milveterol, preferably milveterol hydrochloride; metaproterenol, preferably metaproterenol sulfate; olodaterol; procaterol; salmeterol, preferably salmeterol xinafoate; carmoterol; terbutaline, preferably terbutaline sulphate; vilanterol, preferably vilanterol trifenatate or indacaterol, preferably indacaterol maleate.

Suitable steroids include budesonide; beclamethasone, preferably beclomethasone dipropionate; ciclesonide; fluticasone, preferably fluticasone furoate; mometasone, preferably mometasone furoate. In one aspect, the method comprises jet milling mometasone, preferably mometasone furoate in the presence of a liquid aerosol.

Suitable anticholinergics include: aclidinium, preferably aclidinium bromide; glycopyrronium, preferably glycopyrronium bromide; ipratropium, preferably ipratropium bromide; oxitropium, preferably oxitropium bromide; tiotropium, preferably tiotropium bromide; umeclidinium, preferably umeclidinium bromide; Darotropium bromide; or tarafenacin.

The active material may include double or triple combinations such as salmeterol xinafoate and fluticasone propionate; budesonide and formoterol fumarate dihydrate glycopyrrolate and indacaterol maleate; glycopyrrolate, indacaterol maleate and mometasone furoate; fluticasone furoate and vilanterol; vilanterol and umclidinium bromide; fluticasone furoate, vilanterol and umclidinium bromide.

**Claims**

1. A dry powder inhaler having a housing and a cover which is pivotable relative to the housing from a closed position to an open position in order to expose a mouthpiece, wherein the inhaler is designed for use with a monitor having one or more sensors, wherein the housing has one or more formations for mounting the monitor onto the inhaler, and wherein when the cover is in the open position, it at least partially covers the formations.

2. A dry powder inhaler according to claim 1 wherein the formations on the housing are accessible when the cover is in the closed position.

3. A dry powder inhaler according to claim 1 or claim 2 wherein the one or more formations are clip connections.

4. A dry powder inhaler according to any of claims 1 to 3 wherein the formations are adapted for detachably mounting the monitor onto the inhaler.

5. A dry powder inhaler according to any of claims 1 to 4 wherein the inside of the cover has one or more cams designed to operate switches on the monitor for determining the position and / or direction of motion of the cover.

6. A dry powder inhaler according to any of claims 1 to 5 wherein:
   - in a first stage, moving the cover from the closed position to an intermediate position causes a blister strip to be advanced;
   - in a second stage, moving the cover from the intermediate position to the open position causes a piercer to pierce an aligned blister.

7. A monitor designed to be used with an inhaler according to any of claims 1 to 6, the monitor having a sensor and one or more formations for mounting the monitor onto the inhaler, so that when the monitor is mounted onto the inhaler and the cover is in the open position, the cover at least partially covers the monitor.

8. A monitor according to claim 7 wherein the one or more formations are clip connections which are configured to connect with corresponding clip connections on the inhaler.

9. A monitor according to claim 7 or claim 8 which is detachably mountable onto the inhaler.

10. A monitor according to any of claims 7 to 9 which has an inner face that matches the shape of the housing of the inhaler on which it is to be mounted and an outer face which corresponds to the curve defined by the rotation of the cover.

11. A monitor according to any of claims 7 to 10 which is designed to be used with an inhaler according to claim 6, wherein the sensor is an optical sensor for reading a code on the blister strip.

12. A monitor according to any of claims 7 to 11 designed to be used with an inhaler according to claim 5, wherein the monitor has switches on its outer side which are operated by the cams and wherein the monitor is configured to determine the position and / or direction of motion of the cover based on the states of the switches.

13. A monitor according to any of claims 7 to 12 which further comprises a pressure sensor for sensing a patient's inhalation on the mouthpiece.

14. A monitor according to any of claims 7 to 13 which further comprises a controller and memory for processing and / or storing information from the sensor(s) and communication means for transmitting information to an external device.

15. A dry powder inhaler according to any of claims 1 to 6 and a monitor according to any of claims 7 to 14.