

Inhaler for moisture sensitive drugs**TECHNICAL FIELD**

The present invention relates to a dry powder inhaler device (DPI), and in particular to a DPI capable of delivering moisture sensitive drugs in humid ambient conditions.

BACKGROUND

The dosing of drugs is carried out in a number of different ways in the medical service today. Within health care there is a rapidly growing interest in the possibility of administering medication drugs as a powder directly to the airways and lungs of a patient by means of an inhaler in order to obtain an effective, quick and user-friendly delivery of such substances. The active substance in dry powder form, suitable for inhalation, needs to be finely divided so that the majority by mass of particles in the powder is between 1 and 5 μm in aerodynamic diameter (AD). Powder particles larger than 5 μm tend not to deposit in the lung, when inhaled, but to stick in the mouth and upper airways where they are medicinally wasted and may even cause adverse side effects.

Because inhalable drugs are attracting a lot of interest today, many new formulations of old and new medicaments are now in development into inhalable dry powders. The objective is to present dry, inhalable powder formulations and have them approved for treatment of local or systemic disorders by means of inhalation to the airways and lungs. However, quite a few of these formulations are very sensitive to humidity. Thus, new demands arise on dry powder inhalers and their ability to maintain acceptable performance in terms of delivered dose mass, dose uniformity and fine particle fraction of the delivered dose when ambient conditions change from the ideal ones, e.g. when administering doses in very humid conditions.

For various reasons many such new dry powder drugs are sensitive to exposure to moisture, not only long term but also extremely short-term

exposure. Inhaling these new drugs using a prior art DPI may provide acceptable dosage performance in normal, dry, ambient conditions, but the dosage performance from the DPI drops dramatically if the inhalation is performed in ambient air of high humidity. This is often the case even if the dose is well protected up to the point of administration by the DPI. The DPI and the method of aerosolizing the powder dose play a big role in this problem. If the drug delivery performance varies depending on ambient conditions, the medical efficacy of the drug will vary uncontrollably too much.

Dose inhalers of prior art often leave the powder dose exposed to the surrounding atmosphere for a long time before the dose is actually delivered. This is due to the inhaler design and the design of the dose container. Barrier properties of the container embodiments are also an issue. Adequate protection must be secured of the fine particle dose of the enclosed medicament during transportation, storing and in-use. Some prior art products make it necessary to open the container and empty the dose into an aerosolizing chamber before the user can begin an inhalation cycle. In some cases the dose may get exposed to a voluntary or involuntary exhalation from the user before a proper inhalation cycle begins. In some inhalers the container is opened by a first action by the user but the act of inhaling from the opened container is delayed uncontrollably, because the user is somehow distracted. Exposing the powder dose to the atmosphere for any reason, including technical shortcomings of the container-inhaler combination, must be kept as short as possible so that the quality of the dose cannot deteriorate before it is inhaled.

The prior art dose inhalers are consequently of limited use with moisture sensitive inhalable medicaments. Efforts have therefore been made to improve the moisture-protecting properties in such dose inhalers. In the powder inhaler devices disclosed in US 3,888,252; US 5,441,060; US 6,098,615 and US 6,715,485 desiccants have included in the inhaler devices. The idea is then to let the desiccants remove moisture from the air drawn into the inhaler device during an applied user suction. As a

consequence, the inlet air that contacts and will carry the dry moisture-sensitive medicament powder has been at least partly dried prior reaching the powder.

5 However, the included desiccants in these prior art inhalers have limited useful life which is often shorter than the service life of the dry powder inhaler device. Thus, the drying and moisture-capturing effect of the desiccant will decline to unacceptable low levels after a limited use time. This in turn will reduce the total service life of the inhaler device unless the
10 user is forced to remove the used desiccant from the inhaler device and replace it with fresh desiccant, which might be a complex or even impossible operation depending on the actual inhaler design.

SUMMARY

15 Thus, there is a need for a more efficient usage of a desiccant material in a dry powder inhaler device to thereby exploit the full service life of the inhaler device without the need of premature discarding of the inhaler device due to shortage of desiccant action.

20 It is a general object of the present invention to provide a more efficient usage of desiccant action in a dry powder inhaler device.

It is another object of the present invention to increase the service life of a dry powder inhaler device equipped with desiccant material.

25 The present invention discloses a dry powder inhaler device having an air inlet system provided in the inhaler body and a mouthpiece. A first channel structure of the inhaler defines a first airflow channel inside the inhaler device. This first airflow channel is provided for connection between the
30 mouthpiece, or a suction nozzle of the mouthpiece, and an air inlet of the inlet system. In addition, the first airflow channel has or passes a dose entrainment region, at which dry powder of a dry powder medicament dose is entrained and carried by air flowing through the first airflow channel. A desiccant structure is provided in the inhaler for housing a desiccant

material. This desiccant material is in connection with the first flow channel downstream of the air inlet but upstream of the dose entrainment region. For example, the first airflow channel may pass through the desiccant material in the desiccant structure.

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A second channel structure of the inhaler device defines a second flow channel. This flow channel is provided for connection between the mouthpiece or nozzle and an air inlet of the inlet system. This second airflow channel bypasses the desiccant material. Thus, air flowing through the
10 second airflow channel is not dried by the desiccant material.

A flow channel switch arrangement is arranged for switching, in use of the inhaler device, between the first airflow channel and the second airflow channel during a suction action applied to the mouthpiece. This applied
15 suction action will induce an airflow from the air inlet system through an airflow channel selected by the switch arrangement and to the mouthpiece.

Thus, when the switch arrangement selects usage of the first airflow channel, ambient air entering this channel will first be dried by the desiccant
20 material. The so-obtained (at least partly) dried air then passes the dose entrainment region, where the airflow will entrain and carry dry powder of the dose through the nozzle and mouthpiece and to the airways of a user or to a dose powder analyzing equipment. However, when the switch arrangement selects the second airflow channel, ambient air entering the
25 second channel will not contact the desiccant material before entering the nozzle and mouthpiece, optionally first passing the dose entrainment region.

The first airflow channel will, according to the present invention, be employed and selected by the switch arrangement during the dose delivering
30 part of an inhalation procedure. It is only during this short period of time of the inhalation procedure that there is a need for air drying. Consequently, when substantially all dry powder has been entrained by the dry air passing through the first flow channel and left the inhaler, the switch arrangement switches to the second airflow channel. Thus, during the remainder part of

the inhalation procedure, non-dried air will be drawn and flow through the second airflow channel. This allows for an efficient usage of the desiccant material since inhaled air is only dried during the short period of the inhalation procedure when the dry powder is actually delivered. For the remaining major part, the desiccant material is bypassed to save the drying effect of the material.

The invention offers the following advantages:

Efficient usage of desiccant material in a dry powder inhaler device;

Allows for full exploitation of the service life of a dry powder inhaler device;

Reduces the need for large quantities of desiccant material; and

Provides a simple solution for providing multiple internal airflow channels and switching between the channels during operation.

Other advantages offered by the present invention will be appreciated upon reading of the below description of the embodiments of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention, together with further objects and advantages thereof, may best be understood by referring to the following detailed description taken together with the accompanying drawings, in which:

FIG. 1 illustrates a diagram of relative humidity and temperature for air having passed through a desiccant material;

FIG. 2A illustrates a top view of a preferred embodiment of an inhaler device;

FIG. 2B illustrates a side view of the preferred embodiment of the inhaler device with a movable protective cover in a closed position;

FIG. 2C illustrates a side view of the preferred embodiment of the inhaler device with the movable protective cover in an opened position and a movable slide in an outer position;

5 FIG. 2D illustrates a side view of the preferred embodiment of the inhaler device with the movable protective cover in the opened position and the movable slide in an inner position; and

FIG. 3 is a flow diagram illustrating a method of operating a dry powder inhaler device according to the present invention.
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DESCRIPTION OF THE INVENTION

Throughout the drawings, the same reference characters will be used for corresponding or similar elements.

15 The present invention discloses a novel type of dry powder inhaler device (DPI), which is suitable for all types of dry powder drug formulations, but particularly advantageous for moisture sensitive dry powders. By introducing a desiccant material into one or more of the airflow channels of
20 the inhaler device, the inventors have surprisingly found that it is possible to reduce the relative humidity of the flowing air before the air stream reaches the dry powder dose. The dose may be pre-metered and introduced into the device e.g. in a tight blister or capsule, which is opened just before delivery to an inhaling user. Alternatively, the dose may also be metered from a bulk
25 store inside the inhaler device prior to delivery by inhalation. Regardless of what type of DPI is preferred, the novel use of desiccant in the upstream air channels of a DPI, according to the present invention, provides a major potential for improvement in the drug delivery performance of the inhaler device in high humidity conditions. Surprisingly, the disclosed invention can
30 thus be put to use in most DPI types. It may thus be possible to boost the performance of well-proven inhaler devices and make them into inhaler candidates for the moisture sensitive drug formulations, which are at the root of the inhalation problem that this invention tries to solve.

A use of desiccant materials in inhalers is known in the art, but the use is intended mainly for keeping internal parts dry, especially if powder is available from a bulk source. Desiccants are often kept out of the air channel in prior art devices in order not to create loss of air pressure during inhalation, which is crucial to the drug delivery efficacy of most prior art devices. Those prior art documents identified in the background section are marred by considerable shortcomings in terms of reducing the service time of the inhaler due to too large reduced air drying effect of the desiccant material or, to combat this problem, requiring a large quantity of desiccant material.

The present invention relates in a first aspect to a dry powder inhaler device that allows for an efficient usage of a desiccant material to be housed within the inhaler body. Thus, the desiccant material is typically employed for drying the flowing air stream during the actual dose delivery period of an inhalation procedure. The inventors have realized that the actual dose delivery only lasts for a portion of the total inhalation time. In a real inhalation procedure, the inhalation lasts for up to about four to five seconds or more. However, the entrainment of the dose in the inhalation air stream and, thus, the delivery of the dose to the airways of an inhaling user typically lasts for less than one second. Thus, several seconds of inhalation are preferably used to push the dose into the lung and to let the particles of the dose sediment onto the mucous membrane. It is not necessary to let the air following on the release of the dose pass through the desiccant material whereby the air would be dried, since the dose, after its release, is already in the airways of the user. Therefore, there is a need for drying the input air stream only during about one second of dose delivery but not during the remaining and/or preceding seconds of the total inhalation procedure. The present invention provides a more efficient usage of the desiccant material by drying the input air stream during the powder entrainment and dose delivery part of the inhalation but then bypassing the desiccant material for the remainder part of the inhalation. As a consequence, the drying action of the desiccant material is utilized only when needed and not when the dose already has been delivered.

The dry powder inhaler device of the present invention comprises a mouthpiece onto which a suction action is applied in operation or use (of the inhaler device) during an inhalation procedure. It is anticipated by the present invention that this suction action most often is applied by a user inhaling through the mouthpiece. However, the dry powder inhaler device of the invention can also be used with other suction sources, such as a suction inducing device used in a test laboratory.

The inhaler device also comprises an air inlet system consisting of one or more air inlets in the inhaler body. In a first embodiment, the inhaler device has a single air inlet. However, in a second embodiment, at least two such air inlets are provided in the inhaler body, possibly adjacent each other or at separate positions in the inhaler body. It is anticipated by the present invention that the at least one air inlet of the inlet system may be equipped with an air filter or membrane preventing ingress of small particles present in the ambient air into the internal space of the inhaler device.

In clear contrast to the prior art inhaler devices, the inhaler of the invention comprises (internal) channel structures defining multiple, i.e. at least two, different airflow channels for connection between the mouthpiece and the air inlet system. Usage of multiple inner airflow channels allows bypassing the desiccant material when no further drying of the air stream entering the air inlet system is required.

In a typical implementation, the dry powder inhaler device comprises a first channel structure defining at least a first airflow channel for connection between the mouthpiece and at least one air inlet of the inlet system. This first airflow channel also has a dose entrainment region at which a powder dose inserted into or provided in the inhaler device is entrained by an air stream flowing through the first airflow channel. This typically implies that the first airflow channel passes the position or region in the inhaler device at which the dose is provided and should be entrained and captured by the induced air stream. This entrainment region can be a dedicated position

inside the inhaler body. However, in the case the mouthpiece or a container carrying the dose is movable, the entrainment region can be an area or movement path over which inhaled air will pass the dose and entrain the medicament powder of the dose.

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The dose entrainment region can therefore be regarded as the location or area inside the inhaler device where a dose of a dose container or metering receptacle comes in contact with an air stream passing through the at least one first airflow channel defined by the first channel structure of the inhaler device.

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As was described in the foregoing, the at least one first airflow channel is adapted for connection between the mouthpiece and the air inlet system. In an implementation, this means that the input of the first airflow channel is in connection with at least one air inlet of the inlet system and an output of the first channel is in connection with the mouthpiece or a nozzle connected to the mouthpiece. However, the present invention is not limited to such an implementation. The first channel structure can comprise movable parts so that the input (output) opening of the first airflow channel is initially not connected to an air inlet of the inlet system (mouthpiece). This implies that no free first airflow channel connecting the mouthpiece with the air inlet system defined by the first channel structure is present inside the inhaler body. However, by moving internal parts of the inhaler body, the elements of the first channel structure together form and define the first airflow channel connecting the mouthpiece with the air inlet system.

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The inhaler device also comprises a desiccant structure for housing a desiccant material. This desiccant structure can be an internal space of the inhaler device into which a container, cartridge or other element comprising the desiccant material is to be inserted. In such a case, the desiccant carrying cartridge can be removably arranged inside the inhaler device and removed after use, possibly to be replaced by a cartridge containing fresh desiccant material. This desiccant structure is arranged inside the dry powder inhaler device so that, in operation, the desiccant material housed

therein is in air connection with the first airflow channel. Furthermore, the desiccant material is in connection with the first airflow channel downstream of the air inlet system but upstream of the above-described dose entrainment region. This positioning of the desiccant material inside the inhaler device makes sure that an air stream entering the first airflow channel through the inlet system will be dried by the desiccant material before the air stream comes into contact with and entrains medicament powder at the dose entrainment region. As a consequence, inhaled air carrying the medicament powder past the mouthpiece will be dried prior to contacting with the powder.

This desiccant material arrangement can be realized by filling, at least partly, the first air channel of the inhaler device with desiccant material to preferably last the specified in-use period (service life) of the inhaler device, even if the device is used in harsh and very humid conditions. In many parts of the world, people and potential users find themselves in hot and humid climates, where ambient relative humidity may be as high as 75 % Rh or higher. Of course, a safe treatment of human disorders based on inhaled medicaments must provide stable, predictable drug delivery to all users in foreseeable situations of usage, including humid ambient conditions. In-process drying of the flowing inhalation air every time the user inhales a dose of a dry powder drug is an effective method of improving and securing the level of performance from a dry powder inhaler, i.e. performance in terms of high, stable, medical efficacy of the drug, even in very humid conditions of use.

In clear contrast to the prior art inhaler device, the inhaler of the invention also comprises a second channel structure defining at least one second internal airflow channel for connection between the mouthpiece and the air inlet system. In consistency with the first air channel described above, the input and output openings of the second airflow channel can be connected to the air inlet system and the mouthpiece, respectively. Alternatively, at least one of the input and output openings can be caused to become

connected to the air inlet system or the mouthpiece through the movement of at least one element of the second channel structure.

In contrast to the first channel structure and the first airflow channel, the second airflow channel defined by the second channel structure bypasses the desiccant material in the desiccant structure, and optionally the dose entrainment region. This means that an air stream flowing from the air inlet through the second airflow channel and the mouthpiece will bypass (not contact) the desiccant material. As a consequence, no drying of the air flowing through the second airflow channel is performed.

The inhaler device also comprises an airflow channel switch arrangement for switching in operation between the first and second airflow channel during a suction applied to the mouthpiece. This allows for induction of an airflow from the air inlet system through an airflow channel selected by the switch arrangement and to the mouthpiece. If the switch arrangement selects the first airflow channel to be currently employed, the induced airflow will additionally pass or contact the desiccant material and become dried before it entrains medicament powder from a dose bed at the dose entrainment region. However, if the switch arrangement selects the second airflow channel to be currently employed, the induced airflow will not pass or contact the desiccant material and may optionally also bypass the dose bed at the entrainment region before reaching the mouthpiece.

The switch arrangement therefore allows usage of the first airflow channel when medicament powder on a dose bed is entrained by the airflow through the first channel and then switching to the second airflow channel once substantially all powder has been delivered through the mouthpiece to thereby save the drying action of the desiccant material.

In a preferred implementation and during an inhalation procedure, the first airflow channel is first open and selected by the switch arrangement for enabling initial drying of the air stream entering the air inlet system and entrainment of the dose by the dried air stream. Thereafter, once

substantially all medicament powder has become entrained by the air stream and delivered, the switch arrangement switches to the second airflow channel. This means that air will flow through the second airflow channel and not the first airflow channel through the remainder of the inhalation procedure.

Alternatively, the second airflow channel is first active and selected by the switch arrangement until a sufficient inhalation pressure has been reached. At this point in the inhalation procedure, the switch arrangement switches from the second channel to the first airflow channel for providing air stream drying and dose delivery. Thereafter, the switch arrangement switches back to the second airflow channel so that no drying of the inhaled air is performed during the last portion of the inhalation procedure.

The channel switch arrangement may be arranged in the inhaler device for switching in operation of the inhaler device from the first airflow channel to the second airflow channel during the applied suction action once a pre-determined time has elapsed from application of the suction action. For example, when about one or two seconds has elapsed from initiation of an inhalation, the switch arrangement switches to the second airflow channel since during this about one to two seconds substantially all medicament powder has been entrained and carried by the dried air stream through the first airflow channel. In this case, the timing of channel switch operation can be realized by usage of a latched spring arrangement that moves a channel obstruction from the second airflow channel to the first airflow channel or removes an obstruction in the second airflow channel and adds an obstruction to the first airflow channel. This latched spring arrangement can be triggered once a threshold inhalation pressure is reached or once the inhalation pressure declines below a threshold level.

In a preferred implementation, the inhaler device comprises a slide for carrying and inserting a dose container into the inhaler body. The movement of this slide into the inhaler device can be connected to the operation of the switch arrangement. Thus, when the slide is in an outer position to receive a

new dose container, the first airflow channel can be open in the inhaler device. However, somewhere during the movement of the slide and the container into the inhaler body, the first channel becomes obstructed while the second channel is opened. In such a case, the slide can constitute a part of the switch arrangement of the invention or the slide can be connected to an element of the switch arrangement.

It is anticipated by the present invention that the first channel structure can define more than one airflow channel that connects the air inlet system with the mouthpiece and is in contact with the dose entrainment region and the desiccant material. Correspondingly, the second channel structure can define more than one airflow channel that connects the air inlet system with the mouthpiece but bypasses the desiccant material.

In a further embodiment of the invention, the inhaler device is provided with means to open and close the air inlet system and preferably the mouthpiece opening of the device such that the inlet system opens to let inhalation air enter the device when the dose is about to be administered. A suction effort made by a user or a suction generating equipment generates airflow into at least one first airflow channel of the inhaler device, such that the airflow is first directed onto a desiccant material placed in connection with the first channel(s). The flowing air passes, at least partly, through the desiccant material, where moisture in the air is adsorbed and/or absorbed by the desiccant before the dried air stream hits the dose container or aerosolization chamber (dose entrainment region) where the dose to be sucked up is located.

Fortunately, it is not necessary to remove all moisture from the incoming air, because most dry powder drugs do not deteriorate chemically or physically in a linear proportion to relative humidity. Generally, dry powders show an unlinear, typically exponential deterioration rate with increasing relative humidity. Thus, it is only meaningful to remove the excess moisture over a certain Rh-value, whereby the relative humidity (Rh) of the air having passed through the desiccant material is reduced below a certain, safe threshold

value of relative humidity given as % Rh, such that short-term deterioration of the powder dose by the remaining moisture in the air stream is prevented. If a desiccant material tends to reduce the humidity in the streaming air more than necessary, i.e. significantly below the safe threshold value, it may be advantageous to use at least one third airflow channel in parallel with the first, desiccant-holding channel. Alternatively, the above described second airflow channel can be used parallel with the first channel during a portion of the inhalation procedure. The airflows through the first and the second/third channels are preferably mixed with each other downstream of the desiccant material in the inhaler device in order to present an averaged relative humidity of the combined airflow below the critical threshold value of relative humidity. A correct humidity of the mixed airflow may be achieved by adjusting the airflow resistance of the second or third airflow channel, such that the proportion of humid, non-dried airflow mixed and combined with the dried airflow results in a desired relative humidity below the safe threshold value of the flowing air that further downstream releases and aerosolizes the dose. This arrangement of air channels having desiccant material and those without desiccant will extend the lifetime of the desiccant even further without risking deterioration of the dose delivery performance.

Short-term deterioration of dry, medicament powders is generally not determined by chemical degradation, but is rather more physical in nature. Humidity in the surrounding air may be very quickly adsorbed by the powder particles. Depending on the degree of hydrophobia or hydrophilia of the powder this process of adsorption of moisture from the air is more or less rapid and more or less pronounced. Some powder formulations tend to act as drying agents, i.e. gaining weight extremely fast by water adsorption or absorption in humid air. Thus, it is important to study the water sorption isotherm for a powder formulation before deciding which DPI is best suited to use for administration of doses thereof. For instance, water on the surface of small, inhalable particles may be harmless up to a point where the number of water droplets on a particle have increased so that the droplets connect to water droplets on neighboring particles, whereby particle agglomerates form that are held together by strong inter-particle forces.

Such agglomerates are very difficult to de-aggregate by the DPI. Keeping the humidity in the air below a critical point for the particular medicament powder is thus important, as soon as the dose is being exposed to air before the dose is released and entrained into inhalation air. What relative humidity
5 in air is critical to drug delivery performance depends largely on the powder and the formulation, but typically the threshold value, not to be exceeded, is in a range from 40 to 70 % Rh.

According to the invention, it is normally not necessary to dry the inhalation
10 air beyond the critical point, as discussed above, for the combination of a selected inhaler device and the powder dose, which is going to be inhaled. Thus, a desiccant material should be selected, which adsorbs water from air predominantly at and above the critical relative humidity, i.e. x % Rh, where x is a decimal number preferably between e.g. 40 and 75. The selected
15 desiccant material is thus preferably much less active below this threshold x . A successful selection of desiccant material in this respect means that less desiccant are needed in the inhaler device compared to another desiccant, which adsorbs water at lower relative humidity. Such a desiccant will be saturated before the selected preferred one, given the same number of doses
20 and ambient conditions, thereby requiring more desiccant to compensate for the tendency to adsorb more water than strictly necessary. Furthermore, the less desiccant mass that is used means less pressure loss over the desiccant material, which in turn means that more suction power is available for the job of releasing and de-aggregating the powder in the dose. Typically,
25 pressure loss across the desiccant may be 2 – 20 % of the applied suction pressure during inhalation, the particular application sets what may be an acceptable value. The resulting air speed through the desiccant should be low, preferably not higher than 2-3 m/s, more preferably below 1 m/s to allow the air enough duration of stay for the desiccant to adsorb as much
30 water molecules from the air as possible within a specification framework.

In a further aspect of the invention, active inhalers including the ones using so called spacers also benefit from the disclosure. Active inhaler devices often use pressurized, ambient air to aerosolize the dose before it is inhaled.

Some devices use a spacer, i.e. a large receiver, into which the aerosolized dose is taken as a dust cloud. Normally, a user pumps up the pressure in a reservoir chamber prior to an inhalation. The pressurized air is then let out through an outlet inside the device, such as a valve, and the air is directed
5 onto the dose with high air speed, which releases the dose and the aerosolized dose is then inhaled either directly or indirectly through a spacer arrangement. Advantageously, the desiccant material in this case is arranged at the air inlet, such that the ambient air being pumped into the reservoir chamber is first dried by the desiccant. The pressurized air in the
10 chamber will be reduced in relative humidity when let out onto the dose, which improves the performance of the inhaler device regarding sensitive drugs.

In this case, at least two airflow channels are present in the inhaler device
15 from the air inlet system via the reservoir chamber and to the mouthpiece. For example, two input airflow channels can be used for pumping in air into the reservoir chamber. In such a case, at least one of these channels, the first airflow channel, passes the desiccant material before reaching the chamber. However, at least one of the channels, the second airflow channel,
20 bypasses the desiccant material before reaching the chamber. This solution allows for a correct selection of humidity of the pressurized air provided in the reservoir chamber.

Desiccants suitable for use in the present application are typically but non-
25 exclusively silica gels (SiO_2), activated alumina (Al_2O_3), molecular sieves and clays. Each material has advantages and disadvantages. For example, silica gels generally have a quick response time, which is very suitable for dynamic applications, typical of inhaler applications as described in the foregoing. Silica gels also have a high adsorption capacity (saturation approximately at
30 35 % weight increase) and high efficacy in relative humidity between 40 and 80 % Rh, which is perhaps the most interesting humidity range for inhaler applications. Activated alumina, on the other hand, have a higher adsorption capacity (saturation approximately at 42 % weight increase) but are slower in the response to dynamic conditions. Molecular sieves have less adsorption

capacity than aforementioned types, but they are generally very good at adsorption in low relative humidity, e.g. below 40 % Rh. Of course, in any particular application for the present invention, it may be desirable to combine different desiccants in order to combine the best qualities from different types or from differently acting desiccants of the same type to meet the requirements in the particular case.

Figure 1 illustrates a test of the invention in a diagram showing how temperature (curve B) and relative humidity (curve A) of the inhaled air after a silica gel desiccant varies over a long time and several hundred of simulated inhalations, when the inhaler device is used in ambient conditions of 25 °C/75 %Rh. As can be seen the inhaled air is much reduced in humidity over the whole test period.

In a non-limiting, illustrative embodiment of the present invention a silica gel is used adapted for adsorbing humidity in excess of 65 % Rh. The amount of silica gel is selected with regard to the size and volume of first air channel in the inhaler device, the number of doses of a selected medicament formulation that the device is specified to deliver, which typically is between 100 and 500 off. Typically, the amount of gel necessary to provide safe and consistent drug delivery performance for the full in-use time of the device is in a range from 2 to 20 g dry mass. Preferably, a type of gel is selected, which comprises dust-free, spherical, biologically acceptable particles, which do not change in size or disintegrate when saturated. Crushed gel particles, common in the industry, should be avoided, because they have a wide range of particle sizes and present much more of a problem from a regulatory aspect, because of the potential risk of emitting dust particles into the inhalation air. Of course, in any embodiment of the invention, i.e. having desiccants in the first air channels of an inhaler device, adequate filter protection or the like should be implemented to eliminate the risk of inhaling unwanted dust particles, even if they are not harmful as such.

In yet a non-limiting, illustrative embodiment of the present invention a so-called monolith extruded from e.g. silica gel, clay or zeolite is used, said

monolith presenting a honeycomb structure, similar to an automotive catalytic converter, e.g. formed to physically suit a space in the first air channel of a selected inhaler device. The honeycomb structure makes the active surface extremely large per weight of the material used, which may be
5 advantageously used in the inhaler device application.

In a further aspect of the invention, the inhaler device is closed when not in use, such that ambient air is prevented, as far as possible, to enter the device. The desiccant material is thereby preserved and not consumed
10 unnecessarily. The desiccant is predominantly in use only during a portion of the time for inhalation of doses. The inhaler device is therefore preferably provided with means to close the air inlet, such as a flap or valve, behind which the desiccant material is located. Optionally, also the mouthpiece may be closed when not in use. If all exterior ports of the inhaler device are closed
15 after use, the internal surfaces and the internal air volume of the first airflow channel will be dried out while the device is closed. Later, when the inhaler device is opened in preparation for use shortly before delivery of a next dose, the initial air being inhaled by the user is dry, which is a further advantage of the present invention.

20 This embodiment of the invention is very suitable for different types of inhaler devices, particularly for those using blisters or capsules containing a metered dose, where the dose container is first opened inside the device in an opening operation to be followed in a next step by an act of inhalation.
25 Since the internal inhaler space in this case is filled with dry air, the effect of an interval of dose exposure to the internal air of the device is negligible.

In yet a further aspect of the invention, the desiccant material is filled in a cartridge or carrier adapted for insertion into the desiccant structure that is
30 in contact with the first airflow channel of the inhaler device. The cartridge may then be removed and discarded and a new one inserted either at regular intervals or the cartridge may be regenerated by the user of the inhaler device and used again, e.g. if the inhaler is intended for a long life of administering a large number of doses before scrapping. The cartridge may

signal by color change, for instance, or by a dose counter or other signaling means when the cartridge is due to be exchanged or regenerated by the user.

5 In a different embodiment of the invention, such as in the case of an inhaler administering pre-metered single or combined doses of medicaments from dose containers, such as blisters or capsules, desiccant material is integrated in the container as either an added component or integrated in the container material as such. The airflow is forced by the channel structure defining the first airflow channel of the inhaler device to pass
10 through the desiccant material, before the air reaches into the dose container to release the dose, whereby the air is dried before releasing the dose. In this case it is possible to exclude all or part of the desiccant material otherwise necessary to be incorporated into the device itself. In this embodiment, the desiccant structure forms part of the internal structure of
15 the inhaler device that is used for receiving the dose container.

In a preferred embodiment of the present invention the user pushes a slide carrying the dose in a sealed container into the inhaler body during an interval of between 0.1 and 5 s, although preferably between 0.2 and 2 s.
20 The slide is thus manually pushed with a generally constant speed using a relatively light force at the same time as he or she inhales through a mouthpiece of the inhaler. The motion of the slide brings the container seal foil into contact with an opener inside the inhaler device. The opener slits the foil and folds it away from the enclosed dose. This action makes the dose
25 available to a suction nozzle connected to the mouthpiece, such that the stream of air entering the inhaler flows initially through first airflow channel and contacts the desiccant material, at least partly, and then into the inlet aperture of the suction nozzle at high speed at this point. The dose is thereby released, aerosolized and de-aggregated gradually while the dose
30 container is being carried past the foil opener at the same time as the dose is carried past the suction nozzle by the user operated slide.

Optionally but preferably, the slide is locked by a catch in its first, container loading position so that the slide cannot move when the user exerts force on

the slide. The catch lets go of the slide when the user also applies a certain minimum suction effort to the mouthpiece of the inhaler. Then, a flap or similar arrangement known in the art opens for air to be sucked in through first airflow channel and the desiccant, at least in part. The user can now
5 push the slide and dose container into the inhaler body while inhaling, whereby the dose gets delivered in the process of pushing and inhaling. Optionally, the flap itself, or additional means for controlling opening and closing of air inlets, lets air on the way to the dose pass through the desiccant material placed in the first airflow channel during the motion of
10 the slide. The flap or additional means closes the air inlet of the first airflow channel holding the desiccant material when the slide is brought fully home into the inhaler body or nearly fully home. At, or near, this home position the slide is used to divert the inlet airflow so that incoming air bypasses the desiccant material for the remaining interval of the inhalation effort by
15 passing through the second airflow channel. This therefore reduces the consumption of the desiccant material, thereby extending the useful lifetime of the desiccant. The inhaler according to this particular embodiment comprises flaps or valves that are controlled by the slide to open and close for air at correct moments of a user's inhalation.

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Figs. 2A to 2D illustrate a preferred embodiment of an inhaler device **1** according to the present invention comprising multiple airflow channels **50**, **60**, **70**. When the inhaler device **1** is to be employed for an inhalation, a user removes a preferred protective mouthpiece cap **16** and air inlet cover **17**, if
25 provided. In the figures, these two protective entities **16**, **17** are connected to each other and rotatably fixed to the inhaler body **10** by means of a hinge arrangement. A slide **13** is movably provided in the inhaler device **1** and can be released from a position inside the inhaler body **10** by the user into a dose loading position (see Fig. 2C). At this position, a dose container **14** can be
30 inserted in the slide **13**, which is adapted to receiving the dose container **14**. When the slide **13** is released and extends out of the inhaler housing **10**, airflow opening means **30** connected to the slide **13** opens an air flap or valve **24** on the downstream, outlet side of a first airflow channel **50**. This

airflow channel **50** passes a desiccant structure **40** that is, in use, filled with a calculated amount of a desiccant material **45**. The opening means **30** may also optionally open an air flap or valve **25** of an optionally third airflow channel **70**. Furthermore, an optional breath-actuation device (not illustrated) in the inhaler **1** may control opening of an air inlet flap **21**, **23** to the first and third channels **50**, **70**. When a suction action is applied to the mouthpiece **11**, the slide **13** is simultaneously pushed into (see indicated arrow) the inhaler body **10** and air begins to flow through the opened first airflow channel **50** and optionally the third airflow channel **70**, whereby at least some air flows through the desiccant material **45** on the way to a dose entrainment region **19**, where the dose in the container **14** is provided. The container **14** typically comprises a sealing foil that protects the dose from ingress of moisture, preferably up to the point of delivery. This sealing foil is being opened simultaneously by the pushing action using a knife arrangement **15** arranged in the inhaler device **1**. The airflows through the first airflow channel **50** and optionally the third channel **70** are mixed inside the inhaler body **10** before the mixed airflow reaches the dose in the dose container **14** at the dose entrainment region **19**. When the slide **13** is completely pushed home into the inhaler **1**, or when the slide **13** is almost completely home, the airflow opening means **30** connected to the slide **13** closes the air outlet flap or valves **24**, **25**. As the slide **13** is pushed home into the inhaler **1**, a flap **32** of the opening means **30** connected to the slide **13** opens an inlet **22** of a second airflow channel **60** that bypasses the desiccant material **45** so that the inhalation can continue undisturbed with small changes in airflow resistance until the inhalation is complete. Naturally, the air through channel **60** is not being dried, which is not necessary, since the dose has already been delivered through a nozzle **12** connected to the mouthpiece **11**. In this manner, the desiccant material **45** is only used to dry the influx of air when the dose is being aerosolized, thereby using the desiccant material **45** as efficiently as possible. As the skilled artisan will realize, the slide **13** may be moved in and/or out of the inhaler body **10** by user force or by e.g. spring loading or hydraulic, pneumatic or electrical power means. Combinations of user force and other

sources of power may also be used in order to control the operation of the inhaler **1**, according to the invention, which operation solutions are within the scope of the present invention.

- 5 In another embodiment of the invention, similar to the disclosure in Figs. 2A to 2D, the slide **13** may be replaced by a carrier of a multitude of dose containers, which may be exchangeable in the inhaler or individually integrated with the inhaler.
- 10 In the Figs. 2A to 2D, the inhaler body **10** together with the desiccant structure **40**, an airflow guide **18** provided in the desiccant structure **40**, the slide **13** and elements **30**, **31**, **32** forming the airflow channel switch and the nozzle **12** constitute the structure that defines the first airflow channel **50** inside the inhaler device **1**. The airflow through this first channel **50** first
- 15 passes an air inlet **21** of the inlet system, see Fig. 2C. The air is directed through the desiccant structure **40** and the desiccant material **45** provided therein by the inner walls of the desiccant structure **40** and the air guide **18**. The dried air then exits the desiccant material through an air outlet **24** and may optionally be mixed by non-dried air coming through the optional third
- 20 airflow channel **70** before the air passes through an opening **31** in the opening means **30**. The air will then impinge on the dose in the dose entrainment region **19** and carry the medicament powder of the dose through the nozzle **12** and mouthpiece **11** and out of the inhaler device **1**.
- 25 Correspondingly, the second channel structure defining the second airflow channel **60** constitutes the inhaler body **10**, the airflow channel switch elements **30**, **32**, the slide **13** and the nozzle **12**. As is clearly seen in Fig. 2D, this second airflow channel **60** bypasses the desiccant material **45** in the desiccant structure **40**.

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The airflow channel switch of the invention constitutes, in Figs. 2A to 2D, the opening means **30** with its opening **31** and the flap **32** connected to the opening means. Correspondingly, the air inlet system comprises the air inlet

21 of the first channel **50**, the air inlet **22** of the second channel **60** and optionally the air inlet **23** of the optional third channel **70**.

The desiccant structure **40** comprises an air guide **26** for guiding air from an air inlet **23** to an air outlet **25** of the structure **40**. This air guide **26** isolates air flowing through the guide **26** from the desiccant material **45**. As a consequence, air passing through the guide **26** will not be dried by the desiccant **45**. This air guide **26** forms part of a channel structure defining the third airflow channel **70** together with the inhaler body **10**, slide **13** and the elements **30**, **31**, **32** of the switching arrangement.

In a particular aspect of the invention a dry powder inhaler device is provided. This inhaler device comprises an air inlet system comprising at least one air inlet and a mouthpiece connected to a suction nozzle. A first or primary airflow channel is present in the inhaler and connects an air inlet of the inlet system with the suction nozzle. This primary airflow channel passes a desiccant material that is arrangeable in the inhaler device. This causes drying of ambient air entering the air inlet and flowing through the primary airflow channel before reaching a dose entrainment region in connection with an inlet end of the suction nozzle. A second or bypass channel is also present in the inhaler and connects an air inlet of the inlet system with the suction nozzle. This bypass channel bypasses the desiccant material so that ambient air entering the air inlet and flows through the bypass channel is not dried when entering the suction nozzle. A flow channel switch arrangement is provided in the inhaler device for switching airflow between the primary channel and the bypass channel during an act of inhalation. When suction is applied to the mouthpiece an airflow is induced from an air inlet through a airflow channel selected by the switch arrangement and to the mouthpiece.

Fig. 3 illustrates a flow diagram of operating a dry powder inhaler device according to the present invention. In a first optional step S1, a desiccant material is inserted into a desiccant structure, unless already provided

therein. In a next optional step S2, a dose container carrying a dry powder medicament dose is inserted into the inhaler device, e.g. by means of a slide arrangement. However, if the dose is already provided inside the inhaler device, such as metered from an internal multi-dose store, this optional step S2 can be omitted. A suction action is thereafter applied in step S3 to the mouthpiece of the inhaler device. This suction action draws ambient air through an air inlet system via a first airflow channel past the desiccant material and up to a dose entrainment region. At this region, the dried air entrains the dry powder of the dose and carries the dose through a suction nozzle and the mouthpiece to the lungs of an inhaler user or to a dose analyzing equipment. During this operation or use of the inhaler device, when suction is provided to the mouthpiece, a switch arrangement switches between the first airflow channel to a second airflow channel that bypasses the desiccant material. This means that non-dried air will pass through the second airflow channel and exit the inhaler device through the mouthpiece for the remainder of the inhalation procedure. The method then ends.

In a further preferred embodiment of the present invention, a selected, sealed dose container, optionally comprising more doses than one, is inserted in a DPI as described in US 6,422,236, which document is incorporated herein by reference. A container is opened and the enclosed, metered dose is immediately sucked up by an applied, user-initiated suction during a single inhalation effort, whereby the delivered fine particle dose by weight amounts to at least 30 %, preferably at least 50 % and most preferably at least 70 % or more of the active pharmaceutical ingredient(s) of the metered dose, even in specified humid ambient conditions. The present invention is advantageously applied to such a sealed container and inhaler arrangement, whereby retention of powder in the container is minimized and not exceeding 20 %, preferably not exceeding 10 % and most preferably not exceeding 5 % of the active pharmaceutical ingredient(s) of the metered dose by mass, even in specified humid ambient conditions.

An inhaler providing delivery of a dose during the course of a single inhalation from a sealed dose container constitutes an inhaler, which would

benefit from the present invention, for improving the delivery of a moisture sensitive dry powder medicament formulation. An Air-razor method as described in US 6,840,239 and an Air-razor device as described in US 6,892,727, which documents are incorporated herein by reference, are preferably applied in the inhaler to efficiently and gradually aerosolize the dose when delivered to the user.

The present invention is suitable for many kinds of dry powder drug formulations and powders produced by different methods and processes, e.g. spray-drying, freeze-drying, super critical crystallization, jet milling and other types of micronization. Formulations may contain one or more pure active pharmacologic ingredients (API's) or a formulation may comprise pure API's and excipients, in mixtures of powders or ingredients integrated into particles.

As used herein, the phrases "selected from the group consisting of," "chosen from," and the like include mixtures of the specified materials.

All references, patents, applications, tests, standards, documents, publications, brochures, texts, articles, instructions, etc. mentioned herein are incorporated herein by reference. Where a numerical limit or range is stated, the endpoints are included. Also, all values and sub-ranges within a numerical limit or range are specifically included as if explicitly written out.

What has been said in the foregoing is by example only and many variations to the disclosed embodiments may be obvious to a person of ordinary skill in the art, without departing from the scope of the invention as defined in the appended claims.

CLAIMS

1. A dry powder inhaler device (1) comprising:

an air inlet system (21, 22, 23);

a mouthpiece (11);

5 a first channel structure (10, 13, 18, 30, 31, 32, 40) defining a first airflow channel (50) for connection between said mouthpiece (11) and said air inlet system (21, 22, 23) and having a dose entrainment region (19);

a desiccant structure (40) for housing a desiccant material (45) in connection with said first airflow channel (50) downstream of said air inlet system (21, 22, 23) but upstream of said dose entrainment region (19),

10 **characterized by:**

a second channel structure (10, 13, 30, 31) defining a second airflow channel (60) for connection between said mouthpiece (11) and said air inlet system (21, 22, 23); and

15 an airflow channel switch arrangement (30, 31, 32) for switching, in operation, between said first airflow channel (50) and said second airflow channel (60) during a suction action applied to said mouthpiece (11) thereby inducing an airflow from said air inlet system (21, 22, 23), through an airflow channel selected by said airflow channel switch arrangement (30, 31, 20 32), and to said mouthpiece (11).

2. The inhaler device according to claim 1, **characterized in** that said second air flow channel (60) bypasses said desiccant material (45) housed in said desiccant structure (40).

25 3. The inhaler device according to claim 1 or 2, **characterized in** that said airflow channel switch arrangement (30, 31, 32) is arranged for switching, in operation, from said first airflow channel (50) to said second airflow channel (60) during said applied suction action.

30 4. The inhaler device according to any of the claims 1 to 3, **characterized in** that said dose entrainment region (19) is constructed for receiving, in operation, a dry powder medicament dose in order to enable said airflow to

entrain dry powder of said dry powder medicament dose provided said first airflow channel (50) is selected by said airflow channel switch arrangement (30, 31, 32).

5 5. The inhaler device according to claim 4, **characterized in** that said airflow channel switch arrangement (30, 31, 32) is arranged for switching, in operation, from said first airflow channel (50) to said second airflow channel (60) during said applied suction action once substantially all of said dry powder has been entrained by said airflow.

10 6. The inhaler device according to any of the claims 1 to 5, **characterized in** that said airflow channel switch arrangement (30, 31, 32) is arranged for switching, in operation, from said first airflow channel (50) to said second airflow channel (60) during said applied suction action once a pre-
15 determined time has elapsed from application of said suction action.

7. The inhaler device according to any of the claims 1 to 6, **characterized by** a movable slide (13) being movable between a dose loading position and a dose releasing position, said airflow channel switch arrangement (30, 31, 32)
20 is arranged for switching, in operation, from said first airflow channel (50) to said second airflow channel (60) during said applied suction action once said movable slide (13) has reached said dose releasing position.

8. The inhaler device according to any of the claims 1 to 7, **characterized by** a third channel structure (10, 13, 26, 30, 31, 32) defining a third airflow
25 channel (70) for connection between said mouthpiece (11) and said air inlet system (21, 22, 23), said first airflow channel (50) and said third airflow channel (70) partly overlapping enabling mixing of an induced airflow through said first airflow channel (50) and an induced airflow through said
30 third airflow channel (70) upstream of said dose entrainment region (19).

9. The inhaler device according to claim 8, **characterized in** that said third airflow channel (70) bypasses said desiccant material (45).

10. The inhaler device according to any of the claims 1 to 9, **characterized by** a movable slide (13) having a dose receiving region and being movable between a dose loading position in which said dose receiving region is accessible outside of a body (10) of said inhaler device (1) and a dose releasing position in which said dose receiving region at least partly overlaps with said dose entrainment region (19), said airflow channel switch arrangement (30, 31, 32) being connected to said movable slide (13).
11. The inhaler device according to any of the claims 1 to 10, **characterized in** that said desiccant structure (40) having an air outlet (24) through which said first airflow channel (50) passes, and said airflow channel switch arrangement (30, 31, 32) comprises:
- an outlet closing element (30) movable between an open position spaced apart from said air outlet (24) and a closed position connected to and closing said air outlet (24); and
 - an inlet closing flap (32) connected to said outlet closing element (30), said inlet closing flap (32) being connected to and closing an air inlet (22) of said air inlet system (21, 22, 23) connected to said second airflow channel (60) when said outlet closing element (30) is in said open position and said closing flap (32) being spaced apart from said air inlet (22) when said outlet closing element (30) is in said closed position.
12. The inhaler device according to any of the claims 1 to 11, **characterized in** that said desiccant material (45) is filled in a cartridge removably arrangeable in said desiccant structure (40).
13. The inhaler device according to any of the claims 1 to 12, **characterized in** that said desiccant material (45) housed in said desiccant structure (40) having a mass selected to provide a minimum air drying for a time period corresponding to a service life of said inhaler device (1).

14. The inhaler device according to claim 13, **characterized in** that said mass of said desiccant material (45) is in a range of from about 2 g to about 50 g.

5 15. The inhaler device according to claim 13 or 14, **characterized in** that said service life of said inhaler device (1) corresponds to delivery of a number of doses between 100 and 500.

10 16. The inhaler device according to any of the claims 1 to 15, **characterized by** a closure element (16, 17) for closing said mouthpiece (11) and said air inlet system (21, 22, 23) to isolate said desiccant material (45) housed in said desiccant structure (40) from ambient air outside of said inhaler device (1).

15 17. The inhaler device according to any of the claims 1 to 16, **characterized in** that said desiccant material (45) having an air drying property to adsorb and/or absorb moisture from ambient air predominantly at and above a critical relative humidity in a range from about 40 % to about 75 %.

20 18. The inhaler device according to any of the claims 1 to 17, **characterized in** that said desiccant material (45) is selected from a group of materials consisting of silica, SiO_2 , gels; activated alumina, Al_2O_3 ; molecular sieves; and clays.

25 19. A method of operating a dry powder inhaler device (1) comprising a first channel structure (10, 13, 18, 30, 31, 32, 40) defining a first airflow channel (50) for connection between a mouthpiece (11) and an air inlet system (21, 22, 23) and having a dose entrainment region (19), and a desiccant structure (40) for housing a desiccant material (45) in connection with said first airflow
30 channel (50) downstream of said air inlet system (21, 22, 23) but upstream of said dose entrainment region (19), said method **characterized by:**

switching, during a suction action applied to said mouthpiece (11), between said first airflow channel (50) and a second airflow channel (60) for

connection between said mouthpiece (11) and said air inlet system (21, 22, 23) and being defined by a second channel structure (10, 13, 30, 31) to induce an airflow from said air inlet system (21, 22, 23), through a selected airflow channel, and to said mouthpiece (11).

5

20. The method according to claim 19, **characterized in** that said switching step comprises switching, during said applied suction action, from said first airflow channel (50) to said second airflow channel (60).

10 21. The method according to claim 19 or 20, **characterized by:**

receiving, in operation, a dry powder medicament dose in said dose entrainment region (19) to enable said airflow to entrain dry powder of said dry powder medicament dose when said first airflow channel (50) is selected.

15 22. The method according to claim 21, **characterized in** that said switching step comprises switching, during said applied suction action, from said first airflow channel (50) to said second airflow channel (60) once substantially all of said dry powder has been entrained by said airflow.

20 23. The method according to any of the claims 19 to 22, **characterized in** that said switching step comprises switching, during said applied suction action, from said first airflow channel (50) to said second airflow channel (60) once a pre-determined time has elapsed from application of said suction action.

25

24. The method according to any of the claims 19 to 23, **characterized in** that said inhaler device (1) comprises a movable slide (13) having a dose receiving region for receiving a dose container (14), said method comprising the further step of:

30 moving said movable slide (13) from a dose loading position in which said dose receiving region is accessible outside of a body (10) of said inhaler device (1) and a dose releasing position in which said dose receiving region at least partly overlaps with said dose entrainment region (19), said switching step being triggered by the movement of said movable slide (13).

25. The method according to any of the claims 19 to 24, **characterized in** that said desiccant structure (40) having an air outlet (24) through which said first airflow channel (50) passes, and said switching step comprises the
5 step of:

moving an outlet closing element (30) between an open position spaced apart from said air outlet (24) and a closed position connected to and closing said air outlet (24); and

10 moving an inlet closing flap (32) connected to said outlet closing element (30) between said open position in which said inlet closing flap (32) is connected to and closes an air inlet (22) of said air inlet system (21, 22, 23) connected to said second airflow channel (60) and said closed position in which said closing flap (32) is spaced apart from said air inlet (22).

15 26. The method according to any of the claims 19 to 25, **characterized by:**
inserting a removable cartridge comprising said desiccant material (45) into said desiccant structure (40).

20 27. The method according to any of the claims 19 to 26, **characterized by:**
selecting a mass of said desiccant material (40) to provide a minimum air drying for a time period corresponding to a service life of said inhaler device (1).

25 28. The method according to claim 27, **characterized in** that said selecting step comprises:
selecting said mass of said desiccant material (40) to be in a range from about 2 g to about 50 g.

30 29. The method according to any of the claims 19 to 28, **characterized by:**
closing said mouthpiece (11) and said air inlet system (21, 22, 23) when said inhaler device (1) is not needed, such that said desiccant material (45) is not subjected to ambient air and humidity between releases of doses.