Dry Powder Inhaler

TECHNICAL FIELD

The present invention relates to a dry powder inhaler device for metered dry powder medicament doses, and particularly to a single dose inhaler relying on a user providing a necessary action and force in order to deliver a selected dose made available in the inhaler.

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. Because the efficacy of inhaled doses often are much higher than e.g. orally administered capsules, the inhalation doses need only be a fraction of the medicament powder mass in an oral capsule. Thus, there is an increasing demand for medicament compositions and small and exact inhalation doses of dry powder with low relative standard deviation (RSD). The doses should be available in different sizes, such that they can be easily selected by a user and administered by a dry powder inhaler device.

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.

In WO 02/00280 A2 and US 6,655,381 B2, an inhaler comprising a magazine holding a rigid unitary magazine including a plurality of integral reservoirs is described. Each reservoir will hold a pre-metered dose of dry powder sealed with a foil.

In WO 03/66470 A1, GB 02 385 020 A, and WO 03/15857 A1 an inhaler using compartments to hold the pharmaceutical formulation is described. The compartments have a first and a second face that will be sealed with a foil. A separate part inside each compartment is designed to rupture the foil before inhalation and the documents discuss weakening special sections in the foil to make the opening easier and more reliable.

In WO 01/30430 A1 a dosage unit for dry powder medicaments is described. The dosage unit is possible to incorporate into a dry powder inhaler such as the one described in WO 02/00279, the dosage unit having a slidable chamber in a sleeve and an openable closure member possible to fit into the dry powder inhaler device. The dosage unit is described to have a cover of substantially the same diameter as the sleeve or being of a frangible material. A separate part inside the device will then push the cover open or rupture the frangible material.

In US 2002/0033176 A1 a dry powder medicament inhalator is described, which is possible to load with a medicament cartridge. The inhalator uses an inhalation activated flow-diverting means for triggering the delivery of the medicament using a lancet to penetrate the medicament cartridge.

Metered dose inhalers of prior art, as in the above examples, often leave the powder dose exposed to the surrounding atmosphere for a long time. This depends on the inhaler design and the design of the dose container. Barrier properties of the container embodiments are not discussed, leaving the question unanswered of how adequate protection is secured of the fine particle dose of the enclosed medicament during transportation, storing and in-use.

Thus, there is a need for improved dry powder medicament doses loaded in high integrity dose containers adapted for insertion into dry powder inhalers guaranteeing consistent high quality administration of such doses.

SUMMARY

The present invention discloses a manually operated dry powder inhaler device (DPI) that relies totally on power provided by a user for delivering dry powder medication doses. The device is capable of delivering an enclosed dose directly from a medicament container, inserted into the DPI. Dose delivery is manually activated by a user of the inhaler device. A method is also disclosed for delivering a dry powder medicament dose directly from a sealed dose container to a user of a DPI. A seal sealing the dose container is optionally opened concurrently with a release of the dose and aerosolization of the powder into the inhalation airstream.

An objective of the present invention is that the dose container, when made available in a DPI, is not to be opened until a user starts to inhale through the DPI, thereby exerting a suction power exceeding a set minimum pressure before the dose container is opened. In a particular embodiment a sealing foil is opened in a relative motion of an opener vis-à-vis the container, where the speed of motion is controlled by the user.

Another objective of the present invention is that the speed of the air stream into the DPI resulting from the inhalation is built up to exceed a set, minimum speed before the air stream is directed to the powder in the dose.

In a particular aspect of the invention the sealing foil being opened is folded away from the dose, whereby a suction nozzle gets free access to all of the powder in the dose during the inhalation.

In still another aspect of the present invention a dry powder inhaler device is disclosed, which is adapted to receiving a dose container with an enclosed metered dose. The container is opened by an opener when at least a minimum suction has been applied to the device and the powder in the enclosed dose of the container is sucked up by a suction nozzle when a minimum speed of the air flow into the nozzle has been exceeded.

The present device is set forth by the independent claim 1 and the dependent claims 2 to 8.

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 side view of an embodiment of the invention, and

FIG. 2 illustrates a top view of the embodiment of the invention.

DESCRIPTION OF THE INVENTION

The present invention discloses a novel type of manually operated, dry powder inhaler device (DPI) accepting a dose container enclosing a metered dry powder dose. The disclosed inhaler device is a single dose inhaler relying on the power of a user for delivering dry powder doses of medicaments. The inhaler device has a movable slide, which is intended to be loaded with a replaceable dose container in a first action by a user. In a second action the user inserts the dose container into the inhaler body by pushing the slide into the body by hand force. When the dose in the dose container has been delivered by the DPI, the slide is brought out of the inhaler body in a third action, at a convenient point in time. The user then removes the spent container and either pushes the now empty slide again into the inhaler body or loads a new dose container into the slide in preparation of a new dose delivery. In this manner a new container with a new dose may be administered by the user of the DPI on an as-needed basis. Preferably, the dose is kept intact by a high barrier seal, which effectively seals the container from ingress of foreign matter, especially moisture, until the container is opened in direct connection with inhalation of the enclosed dose.

In a particular embodiment of the present invention the user pushes the slide into the inhaler body 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 container seal is thereby brought into contact with an opener that slits the foil and folds it away from the enclosed dose. This action makes the dose available to a suction nozzle, such that the stream of air entering the inhaler flows into the inlet aperture of the suction nozzle at high speed. The dose is thereby released, aerosolized and de-aggregated gradually while the container is being carried past the container opener and the suction nozzle by the user operated slide.

In another particular embodiment of the present invention the speed of the slide motion while pushed by the user is prevented from becoming too high by a damping mechanism, such that an increase in user driving force is met with an increased opposing force.

Preferably, the slide is locked by a catch in its first, loading position so that it cannot move when the user exerts a low to moderate force on the slide, i.e. not until the user also applies a certain minimum suction effort to the mouthpiece of the inhaler. Then, a flap or similar arrangement opens for air to be sucked in and at the same time releases the catch holding the slide so that the user can begin to push the slide and dose container into the inhaler body, whereby the dose gets delivered gradually.

A particular embodiment of the present invention comprises an overriding rescue mechanism, which is activated when the user exerts a high force on the slide, i.e. a force considerably higher than the normal low to moderate force, whereby the catch releases the slide and the flap opens even if no or too low suction is present at the mouthpiece. In a panic situation, therefore, the user can still get a reasonable dosage even if he or she cannot synchronize the pushing and the suction perfectly.

In Figure 1 and 2 reference numbers **10 – 14** of the drawings, like numbers indicate like elements throughout the several views of the embodiment of an inhaler device as illustrated, presented here as a non-limiting example.

Figure 1 illustrates a side view of an embodiment of the invention, where **10** designates the inhaler body, **11** designates the mouthpiece, **12** designates the slide and **13** designates the end of the slide, where the user exerts a force by the hand to push the slide into the inhaler body.

Figure 2 illustrates a top view of the embodiment, also indicating the position **14** for a loaded dose container.

In a particular embodiment of the present invention a container and an enclosed dose are loaded into a DPI for a later user initiated dose delivery concurrent with a simultaneous opening of the container.

Another particular embodiment of the present invention comprises a slitting element, an opener, which slits the seal from a point of penetration at a first end of the dose container to a point of exit at a second end of the dose container. Thus, the point of penetration of the seal is not necessarily the same as the point of exit.

In a further preferred embodiment of the present invention, a selected, sealed dose container inserted in a DPI is opened and the enclosed, metered dose is sucked up by a suction nozzle during a single inhalation, 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.

Another preferred embodiment of the present invention is a sealed dose container and inhaler, which, when the dose container is being opened and powder is being sucked up by a nozzle, present consistent airflow conditions and equal dose accessibility for the airflow into the suction nozzle during a dose delivery sequence.

Another particular embodiment of the present invention is a sealed container and inhaler arrangement, where the seal is slit open and folded away from

the dose, such that the dose is efficiently aerosolized into a suction nozzle, provided at least a minimum of suction power is applied to the nozzle, 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.

According to the present invention a dry powder inhaler device is disclosed, which arranges dose containers, if more than one, for a user initiated administration and delivery of one or more metered dose per inhalation. In one embodiment of the invention one dose container at a time is arranged by the inhaler for delivery of the enclosed, metered dose in a single inhalation by a user. The design of the inhaler controls how dose containers are to be inserted into the inhaler and the number of dose containers, which may be inserted and used before it becomes necessary to provide a new set of dose containers. Another embodiment requires that at least one dose container is first mounted onto a container carrier, which is then loaded into the inhaler.

Obvious areas of therapy where the present invention is advantageously applied include asthma, COPD and pain, but other examples of therapy areas, not limiting the scope of the invention, are non-exclusively:

Disorders of the alimentary tract or the digestive system
Disorders of the cardiovascular system
Disorders of the endocrine system
Disorders of the respiratory system
Genital or sexual disorders
Disorders of the muscular or neuromuscular system
Disorders of the nervous system
Psychosomatic disorders
Anti-infectives
Allergic disorders
Protective or antinoxious agents

The present invention may be used for delivering single medicaments or combinations of medicaments in combined doses in a single delivery by an inhalation route. The invention offers an opportunity to improve the quality of treatment, lower the cost and improve quality of life for users, should the invention be applied in therapy.

Non-limiting examples of suitable medicaments in dry powder form, which are eminently suitable for delivery of dosages by the present invention - whether in pure or diluted formulations, in single preparations or in combination with other active substances - are insulin, sumatriptan, fluticasone, formoterol and tiotropium to name but a few.

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.

"Dry" as used herein means that the, e.g., walls of the container are constructed from selected materials and/or materials treated such that the walls, especially the inside wall surface of the container, cannot release water that may affect the medication powder in the dose such that the fine particle dose (FPD) is reduced. As a logical consequence, container construction and materials should not be in need of processes suggested in the German publication DE 101 26 924 A 1 (US2003070679). As an example, gelatin is not a dry material and even after a special drying process gelatin still contains water. Generally, “dry” means the medicament FPD is not affected by the concerned material.

"High barrier seal" means a dry packaging construction or material or combinations of materials. A high barrier seal represents a high barrier

against moisture and other foreign matter, and the seal itself is 'dry', i.e. it cannot give off measurable amounts of water to the load of powder. A high barrier seal may for instance be made up of one or more layers of materials, i.e. technical polymers, aluminum or other metals, glass, silicon oxides etc that together constitute the high barrier seal. If the high barrier seal is a foil a 50 µm PCTFE/PVC pharmaceutical foil is a particularly useful high barrier foil. For longer in-use stability, metal foils like aluminum foils from Alcan Packaging Lawson Mardon Singen GmbH is a preferred choice.

A "high barrier container" is a mechanical construction made to harbour and enclose a dose of e.g. tiotropium. The high barrier container is built using high barrier seals constituting the walls of the container. The term "container" is used in this document to describe a high barrier container, characterized by having a bottom suitable for receiving a metered dose of a dry powder, either by volumetric or electrodynamic filling methods, and further characterized in being sealed by a foil, which may be slit open by a opener such that the enclosed dose may be accessed by a suction nozzle.

"Directly loaded" means that the metered dose is loaded directly into the high barrier container, i.e. without first filling the dose into e.g. a gelatin capsule, and then enclosing one or more of the primary containers (capsules) in a secondary package made of a high barrier seal material.

The high barrier containers to be loaded with medicament doses are preferably made out of aluminum foils approved to be in direct contact with pharmaceutical products. Aluminum foils that work properly in these aspects generally are composed of technical polymers laminated with aluminum foil to give the foil the correct mechanical properties to avoid cracking of the aluminum during forming. Sealing of the formed containers is normally done by using a thinner cover foil of pure aluminum or laminated aluminum and polymer. The container and cover foils are then sealed together using at least one of several possible methods, for instance:

using a heat sealing lacquer, through pressure and heat;

using heat and pressure to fuse the materials together;

ultrasonic welding of the materials in contact.

The sealed container of the invention that is directly loaded with a formulation of a medicament comprises a flat or curved dose bed, e.g. a formed cavity in aluminum foil or a molded cavity in a polymer material, using a high barrier seal foil against ingress of moisture and other foreign matter, e.g. of aluminum or a combination of aluminum and polymer materials. The sealed, dry, high barrier container may form a part of an inhaler device or it may form a part of a separate item intended for insertion into an inhaler device for administration of doses. The sealed container may e.g. have the following data, as a non-limiting example:

- Container internal volume: 100 mm^3
- Effective diffusion area: 46 mm^2
- Diffusion constant: 0.044 g/m^2 for 24 hours at 23 °C and differential Rh = 50 %

A high barrier container may be made quite small and may contain from micrograms to many milligrams of dose, depending on the active substance and its potency. The inhaler device according to the present invention may also be made very small, not larger than a credit card except for the thickness, making it possible for a user to carry the inhaler almost anywhere.

Some prior art inhaler devices 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, although the act of inhaling from the opened container may be delayed uncontrollably, e.g. because the user is distracted by something. 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. Also, there should be no room for behavioural errors on behalf of the user.

To protect the FPD up to the very point of aerosolizing of the dose a method of opening the dose container a fraction of a second before the dose starts to be aerosolized is described in WO 02/24266 A1 (US 6,651,341), the relevant disclosure of which is incorporated herein by reference. In this context it is also important to prevent a voluntary or involuntary exhalation from a user of a DPI, who is about to inhale a dose, from reaching the selected dose, because of the high moisture content in the exhalation air. In US 6,439,227 B1, the relevant disclosure of which is incorporated herein by reference, a device is disclosed, which closes the DPI, should the user exhale, so that exhalation air does not reach the dose container and the selected dose in the DPI. The device also controls the release of an opener and a suction nozzle such that the opener cannot open the container and inspiration air cannot begin to aerosolize the dose until a certain selected pressure drop is first present due to a suction effort by the user.

An inhaler providing a prolonged delivery of a dose during the course of a single inhalation from a high barrier seal container produced from aluminum foils constitutes a particular embodiment of an inhaler for the delivery of a 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.

Summarizing the most important aspects of a particular embodiment of the present invention, a single dose inhaler device should be executed such that

- the operation of the inhaler is powered and controlled by the user, who provides hand force to push a dose container into the inhaler and open the container to make the dose accessible for a concurrent suction effort by the user, which releases and aerosolizes the enclosed dose into an inhalation airstream;

- a seal of the container is arranged such that an opener, when in motion relative the container, penetrates the seal at one or more points of the container. The opener slits the seal open and exits the seal preferably at different point(s) of the container, such that the point(s) of penetration is(are) preferably different from the point(s) of exit of the foil;
- the opener folds the slitted seal away from the powder dose, such that a suction nozzle following the opener in its track can access the powder dose;
- the slitted, folded seal can be folded back into approximately the original, closed position by a suitable arrangement in the inhaler device, whereby retained powder cannot easily escape from the dose container;
- the bottom dose bed area of the container carrying the dose is arranged such that the distance between the dose bed and the suction nozzle can be kept reasonably constant to ensure consistent airflow conditions during dose delivery.

Inhaler drawbacks common in prior art

In prior art, opening of a container for a metered dose to make the dose accessible for inhalation inside a DPI, is accomplished in many different ways. If dose capsules are used then e.g. the capsule is split in two and the content poured out in an intermediate area in the DPI from where the powder is later aerosolized. Another common method is to punch one or more holes in the capsule, blow air into the capsule and optionally vibrate the capsule such that the powder in the dose can be aerosolized and sucked out of the capsule. In the case of a blister container, the cover foil can be peeled off such that the dose is made available directly from the open blister or else poured out in an intermediate area for inhalation.

A prior art container or capsule is thus opened in a first step and aerosolizing is begun in a second step. The time between step 1 and step 2 is different from one DPI to the next, depending on the deployed technical solution, but in many cases the period is not defined and can be anything up

to minutes and hours depending on the actions of the user. This is not acceptable from a medical point of view if the dosage can be detrimentally affected by being exposed to the environment inside or outside of the DPI.

Yet another drawback of prior art containers is that the stream of air sucked in to aerosolize the dose attacks all of the powder in the dose at the same time, so that the shearing power of the air stream is distributed over a large area where the dose is stored and the aggregates and particles in the dose are arbitrarily subjected to very different, uncontrolled shearing forces depending on how the powder and particle clusters in the dose are distributed relative the air stream. Most of the powder in the dose is delivered instantaneously with no control of the timing. Where holes are made in the container, e.g. a capsule or a blister, by a sharp, pointed tool or needle, edges of the broken container material will bend inwards towards the dose and the edges may then disturb the flow of air into the container, such that some parts of the dose are not properly aerosolized and de-aggregated.

In some cases all of the powder in the dose is not subjected to the same power of shearing stress because the airflow is unevenly distributed across or through the dose. This tends to further hamper the delivered fine particle dose and raise the proportion of retained powder in the container.

Another problem is incident to aerosolizing a dose in a prior art container and that is that the speed of the aerosolizing air stream starts at zero when the aerosolization process begins. The consequence is that most of the dose is quickly sucked up in aggregated form and the aggregates cannot then be completely de-aggregated during the transport through the air channel of the DPI before entering the airways of the user.

Because of these drawbacks a high degree of de-aggregation is difficult to achieve consistently, and the delivered fine particle dose is relatively small as a percentage of the metered dose.

The present invention, on the other hand, solves these problems. In a particular embodiment of the present invention, when applied to a suitably designed DPI, a certain suction power must first be applied to a mouthpiece of the DPI, before e.g. a valve opens to let air into the appropriate air channel in the DPI and further into a suction nozzle connected to the mouthpiece. This ensures that a fairly high air speed begins to build up around the inlet aperture of the suction nozzle. A seal opening operation is released simultaneously with opening of the air valve, but there is an interval before the opener contacts and penetrates the seal at one end of the container. In a relative motion, opener vis-à-vis container, the seal is gradually slit open and simultaneously folded away. The suction nozzle follows the opener in its track, but before the suction nozzle reaches the nearest dose particles inside the container, the air speed into the inlet aperture of the suction nozzle has already accelerated to a high speed, sufficient to de-aggregate the powder aggregates that are accessed a moment later. Following the opener closely in its track the powder in the dose is gradually aerosolized and de-aggregated at the same time. Keeping the distance constant between the inlet aperture of the suction nozzle and the dose bed, i.e. the container bottom, ensures that the shearing power of the air stream going into the nozzle is evenly distributed and therefore used to its full potential in aerosolizing and de-aggregating all of the powder in the dose, regardless of where the powder is located on the dose bed of the container, presuming that the dose has been deposited in the area covered by the nozzle motion. Retention is minimized. The time period between exposing the dose to the atmosphere and delivering the dose to the airways of a user is clearly extremely short, normally only fractions of a second, ensuring that the dose is unaffected by the surrounding atmosphere, when inhaled.

The folded edges of the cut seal may be folded back in the original position by the DPI, which closes, at least partially, the container so that any powder retained in the container does not fall out into the mechanisms of the DPI or into an air channel, where the powder may affect the operation of the DPI or present a risk to the user.

The above written description of the invention provides a manner and process of making and using it such that any person skilled in this art is enabled to make and use the same, this enablement being provided in particular for the subject matter of the appended claims, which make up a part of the original description and including a medicament container enclosing a dry powder medicament dose for use in a dry powder inhaler, characterized in that a first component of the dry powder medicament consists of a fine particle dose of at least one pharmacologically active ingredient; the container constitutes a dry, high barrier seal, whereby the high barrier seal of the container prevents ingress of foreign matter, especially moisture, thereby preserving the original fine particle fraction of the dry powder dose; and the dry powder medicament dose in the container is adapted for either volumetric or electric field dose forming methods.

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 spirit and scope of the invention as defined in the appended claims.

CLAIMS

1. A dry powder inhaler device loaded with an replaceable medicament container enclosing a metered, dry powder medication dose, **characterized in** that

the inhaler device comprises a hand-operated slide loaded with the replaceable medicament container, a container opener and a suction nozzle in fluid connection with a mouthpiece;

a user pushes the slide from a first, loading position to a second, end position in the inhaler device by applying hand force on the slide at the same time as carrying through an inhalation;

the container is opened by the opener and the enclosed medication dose is sucked up and delivered by the suction nozzle and mouthpiece to the inhaling user while the slide is being pushed from the first to the second position in the inhaler device;

2. The inhaler device according to claim 1, **characterized in** that

the hand-operated slide requires a low to moderate force to move from the first position to the second position in the inhaler device;

the slide is locked in the first position until a suction dependent catch releases it.

3. The inhaler device according to claim 2, **characterized in** that

the catch is released by a suction effort exceeding a selected value applied to the mouthpiece.

4. The inhaler device according to claim 2, **characterized in** that

an initial, high force applied to the slide releases the catch such that the container may be pushed from the first to the second position using only low to moderate force.

5. The inhaler device according to claim 2, **characterized in** that

a damper exerts an opposing force to the force provided by the user on the slide, such that a speed of the slide when in motion is prevented from becoming too high.

6. The inhaler device according to claim 1, **characterized in** that

an Air-razor method and device are applied in the inhaler device to release the medication dose gradually.

7. The inhaler device according to claim 1, **characterized in** that

the slit seal is folded away from the dose in the container such that the suction nozzle gets full access to the powder in the dose, while the slide is being pushed from the first to the second position in the inhaler device.

8. The inhaler device according to claim 7, **characterized in** that

the slit seal is folded back into its original position in the container, when the slide is moved from the second position into the first position.