INHALER USED FOR DELIVERY OF MEDICAMENT IN DRY POWDER FORM

ABSTRACT

The present invention relates to an inhaler which is appropriate for delivering the medicament in dry powder form used in the treatment of respiratory diseases, particularly in asthma, chronic obstructive pulmonary disease (COPD) and allergic rhinitis by the oral route and has a mechanism preventing the problems resulting from inadvertent actuation of the device.

Fig. 5c

I claim:

1. An inhaler (1) suitable for delivery of the medicament in dry powder form from a blister package (15) composed of a plurality of blister pockets (15a) each of which comprises medicament in dry powder form and which are spaced at equal intervals; said inhaler comprising:

- a mouthpiece (14) enabling the patient to inhale the medicament in dry powder form from the opened blister pocket (15a) ,

- a rotatable mouthpiece cover (2) covering the mouthpiece (14),

- a gear mechanism enabling the blister package (15) to be indexed and the medicament in dry powder form to become ready for inhalation,

- a housing (10) situated between the upper housing member (4a) and the lower housing member (4b) in which the blister package and the gear mechanism are enclosed,

- a manifold (20) through which the air entering from the air inlet (22) passes, and

- a channel (25a and 25b) interconnecting the manifold outlet (20c) and the mouthpiece outlet (14a)

characterized in that the ratio of the cross-section of the manifold outlet (20c) to the cross-section of the mouthpiece outlet (14a) is in the range of 1:10 to 1:50.

2. The inhaler (1) according to claim 1, wherein the ratio of the cross-section of the manifold outlet (20c) to the cross-section of the mouthpiece outlet (14a) is preferably in the range of 1:20 to 1:30.

3. The inhaler (1) according to claim 1, wherein the pressure decrease caused by the airflow resistance in said device is at least 4 kPa.

4. The inhaler (1) according to claim 1, wherein the channel interconnecting the manifold outlet (20c) and the mouthpiece outlet (14a) in said device is preferably tapered.

20. The inhaler (1) according to claim 19, wherein each of the layers constituting the lid (15b) and the base (15b) sheets of the blister package are chosen from a group comprising polymeric layers preferably made of various polymeric substances, aluminum foil and fluoropoylmer film.

21. The inhaler (1) according to claim 20, wherein at least one of the layers constituting the lid (15b) and the base (15b) sheets of the blister package comprise at least one of the desiccant agents preferably including silica gel, zeolite, alumina, bauxite, anhydrous calcium sulfate, activated carbon and clay which has the property of water absorption.

22. The inhaler (1) according to claim 19, wherein the thickness of the aluminum foil comprised in the lid or the base sheet of the blister package is preferably in the range of 5 to 80 μm, more preferably in the range of 15 to 65 μm.

23. The inhaler according to claim 20, wherein the thickness of the polymeric layer comprised in the lid (15b) or the base sheet (15c) of the blister package is preferably in the range of 5 to 100 μm, more preferably in the range of 15 to 60 μm.

24. The inhaler (1) appropriate for delivery of the medicament in dry powder form according to any one of the preceding claims, wherein said medicament in dry powder form comprises at least one active agent selected from a group comprising cromolyns, anti-infectives, antihistamines, steroids, anti-inflammatories, bronchodilators, leukotirene inhibitors, PDE IV inhibitors, antitussives, diuretics, anticholinergics, hormones, xanthines and pharmaceutically acceptable combinations thereof.

25. The inhaler (1) appropriate for delivery of the medicament in dry powder form according to any one of the preceding claims, wherein said medicament in dry powder form is used in monotherapy or combined therapy.

26. The inhaler (1) appropriate for delivery of the medicament in dry powder form according to any one of the preceding claims, wherein said medicament comprises at least one excipient along with the active agent or agents it comprises.

- the winding wheel gear (6) which moves the winding wheel (13) via the mechanism wheel (5) upon the rotation of the indexing wheel (8);

- the pinion gear (11) and the base gear (7) that provide to transmit the movement of the indexing wheel (8) to the counter wheel (9);

- the counter wheel (9) which displays the number of the unused blister pockets (15a) remained in the device (1).

13. The inhaler (1) according to claim 1, wherein there is at least one air inlet (22) providing the air flow on the upper housing member (4b).

14. The inhaler (1) according to claim 13, wherein the air inlet (22) that the external air enters the device has been designed not to be close to the parts where the patient holds the device (1) in order not to hinder the airflow.

15. The inhaler according to any of the proceeding claims, further comprising a blister package (15) composed of a plurality of blister pockets (15a) each of which comprises medicament in dry powder form and which are spaced at equal intervals.

16. The inhaler (1) according to claim 1, wherein the blister package (15) it comprises is preferably a blister strip.

17. The inhaler (1) according to either one of the claim 1, wherein the blister package (15) it comprises is preferably peelable.

18. The inhaler according to claim 17, wherein said blister package is composed of a lid (15b) and a base (15c) sheet.

19. The inhaler (1) according to claim 18, wherein the lid (15b) and the base (15c) sheets composing the blister package (15) preferably comprises a plurality of layers.

27. The inhaler (1) appropriate for delivery of the medicament in dry powder form according to claim 26, wherein the excipients comprised by said dry powder medicament can be selected from a group comprising monosaccharides (glucose, arabinose, etc.), disaccharides (lactose, saccharose, maltose, etc.), oligo- and polysaccharides (dextran, etc.), polyalcohols (sorbite, mannite, xylite), salts (sodium chloride, calcium carbonate, etc.) or combinations thereof.

28. The inhaler (1) appropriate for delivery of the medicament in dry powder form according to claim 26 or 27, wherein the excipient comprised in the dry powder medicament is preferably lactose.

Dated this 04th day of June 2012

Prathiba.

PRATHIBA M. SINGH
(AGENT FOR THE APPLICANT)

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Applicant Name: **BILGIC, Mahmut**

Total Sheets: 16
Sheet No. : 01

FIG. 1

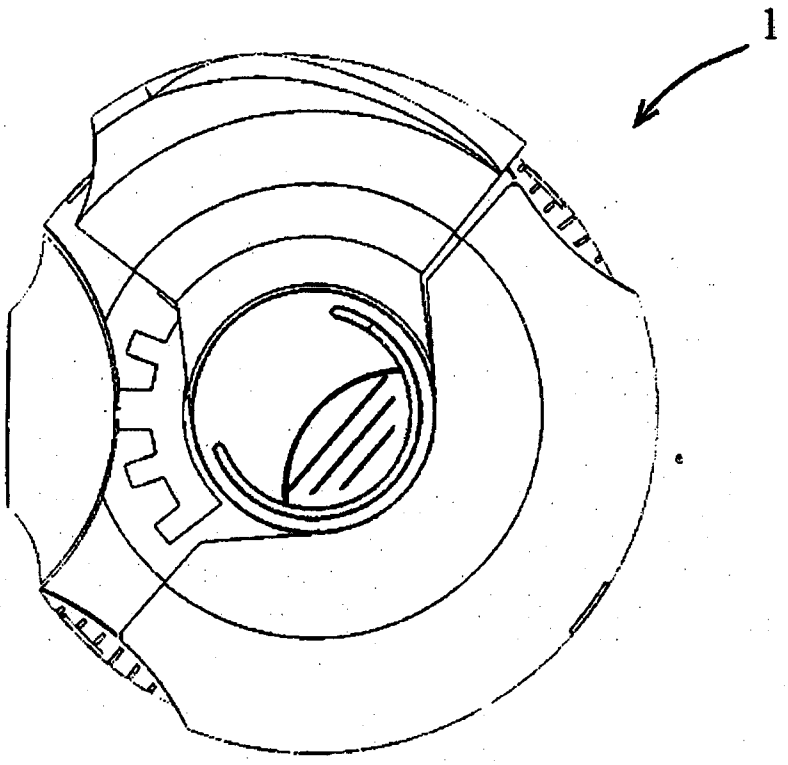

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FIG. 2

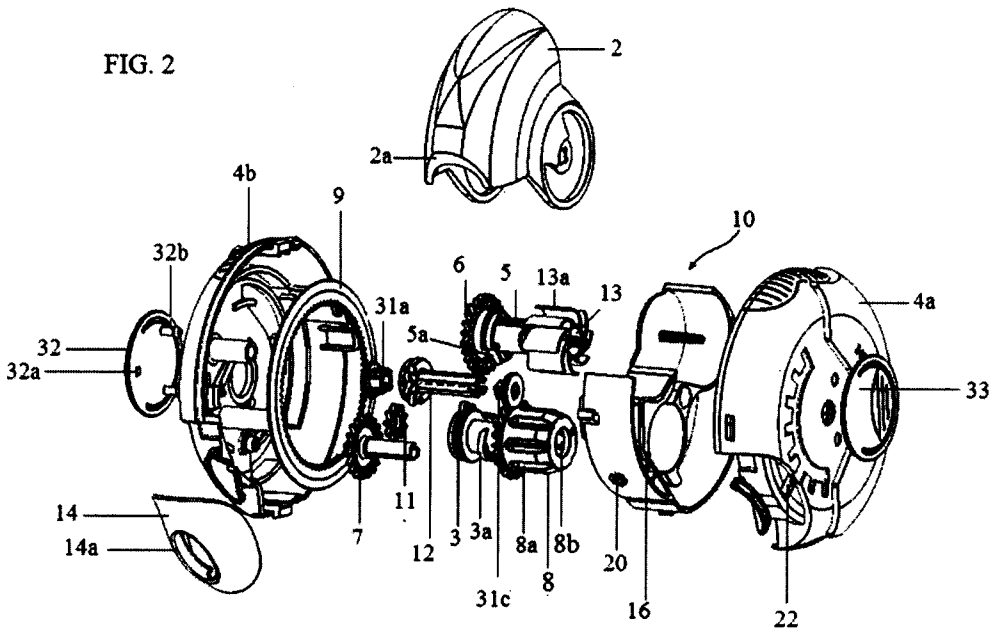

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FIG. 3

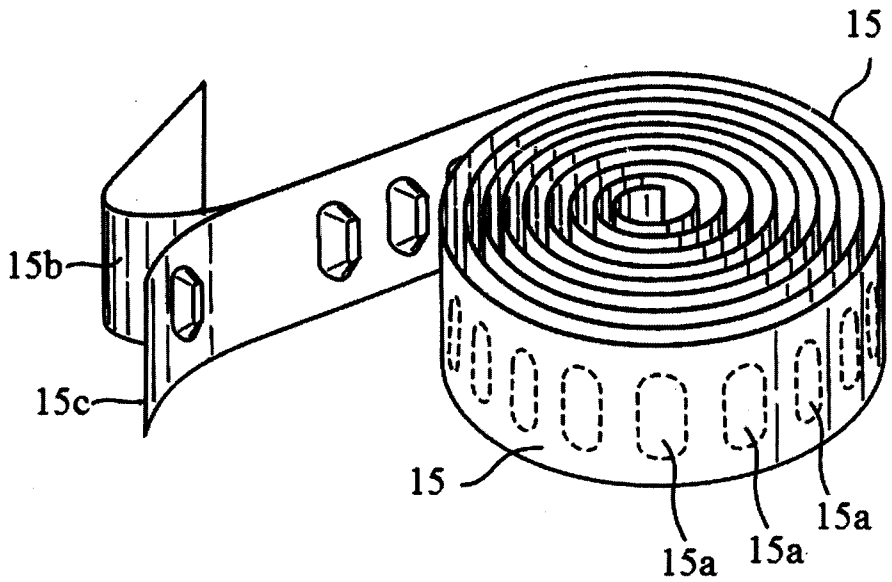

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FIG. 4a

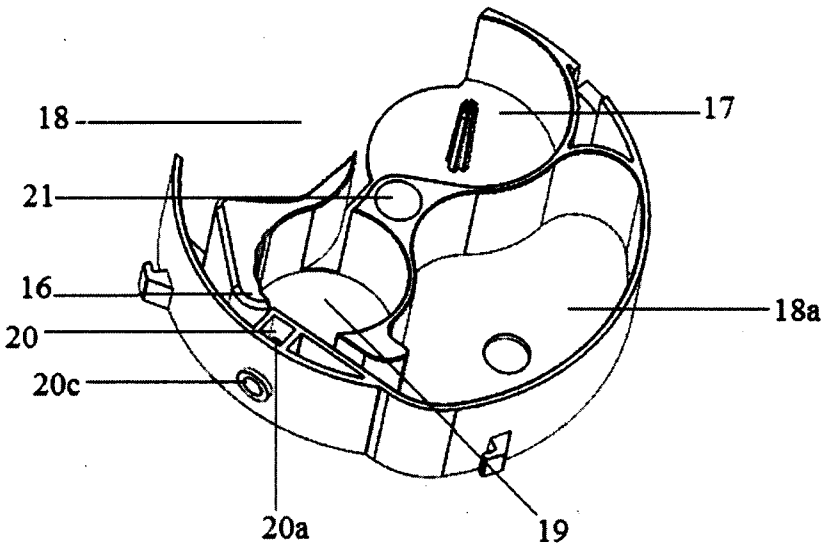

FIG. 4b

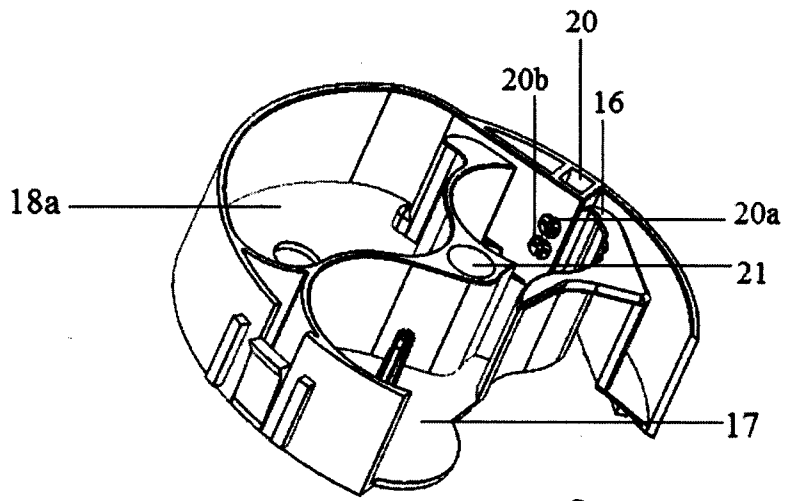

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FIG. 5a

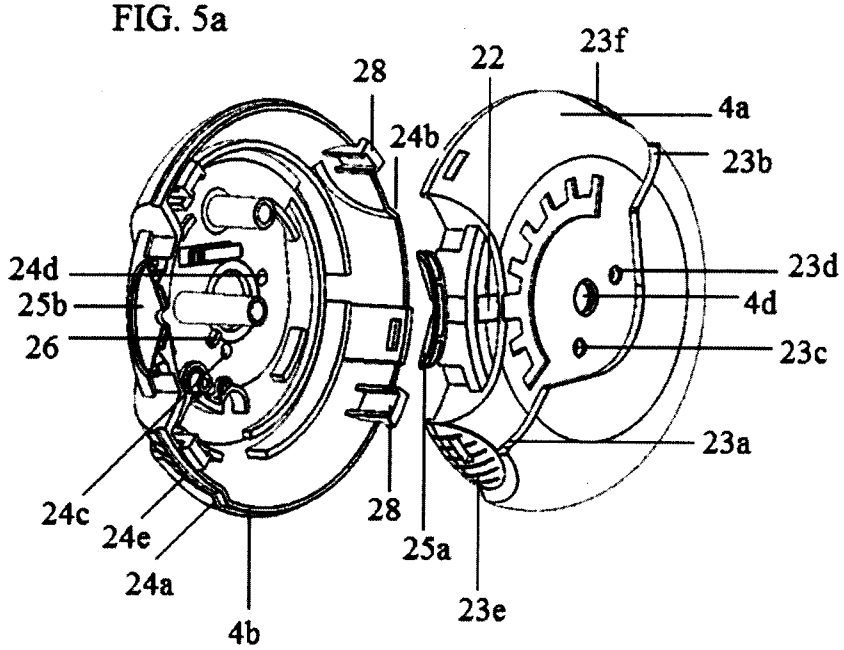

FIG. 5b

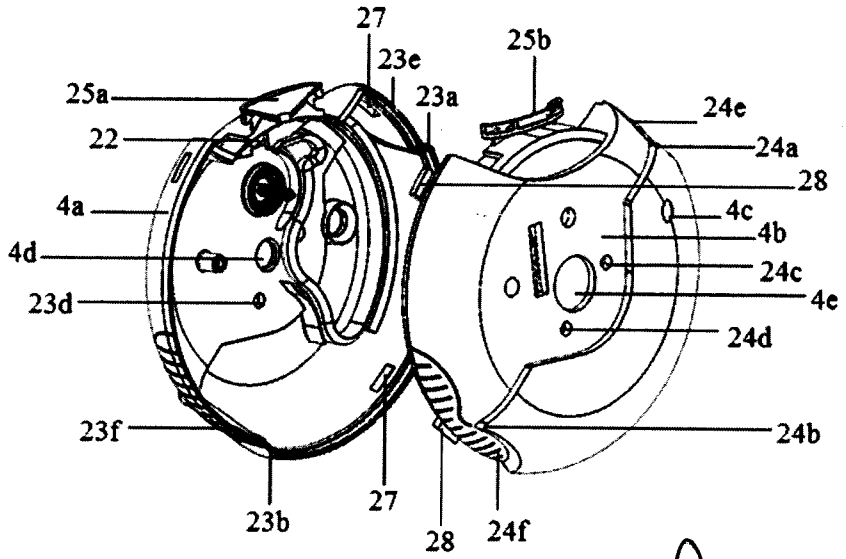

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Fig. 5c

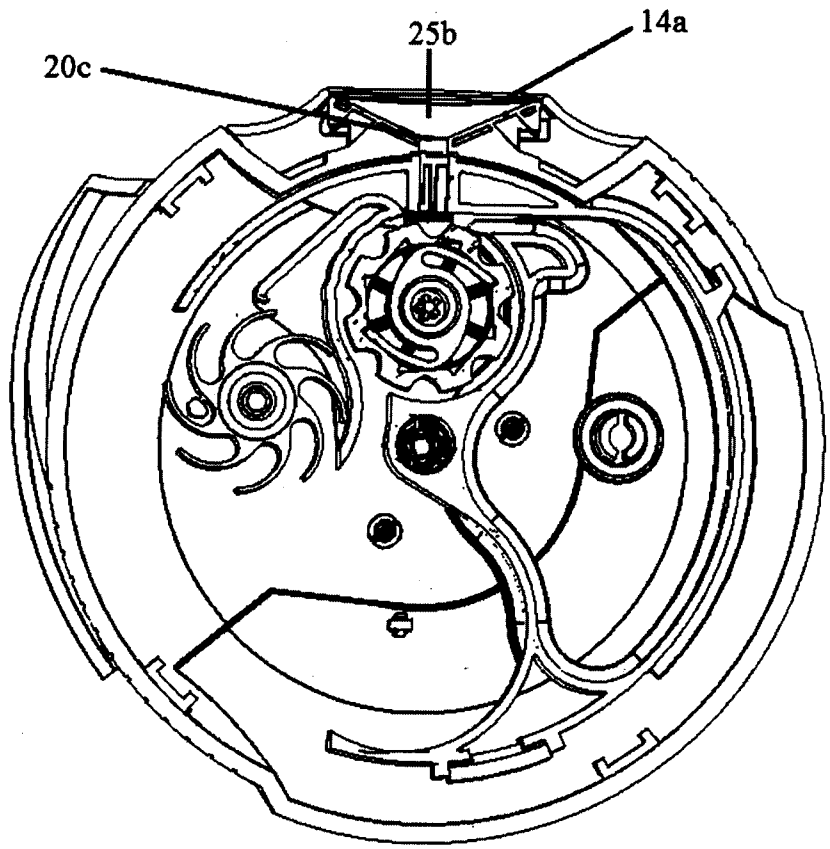

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FIG. 6a

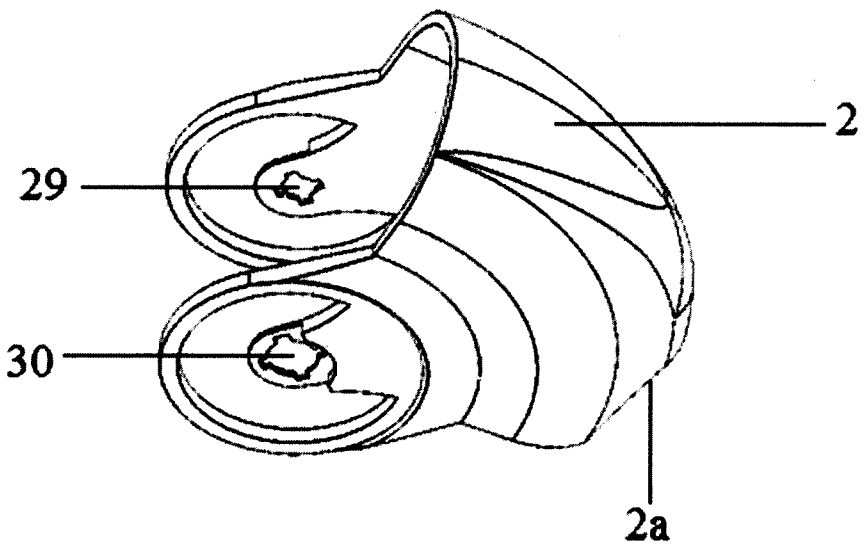

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FIG. 6b

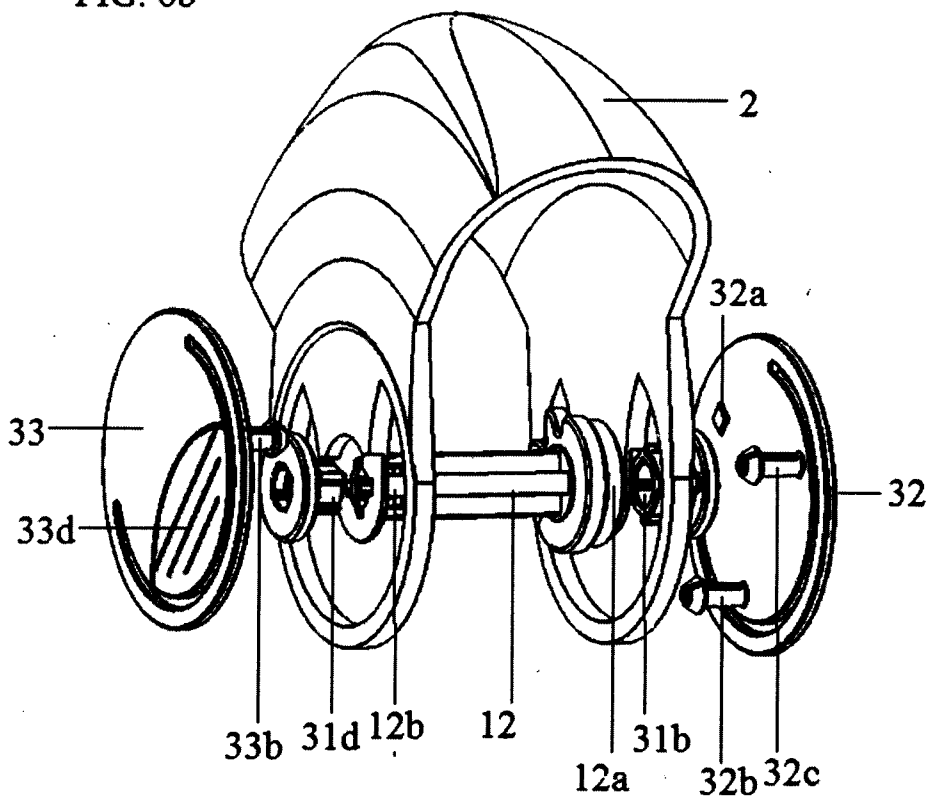

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FIG. 6c

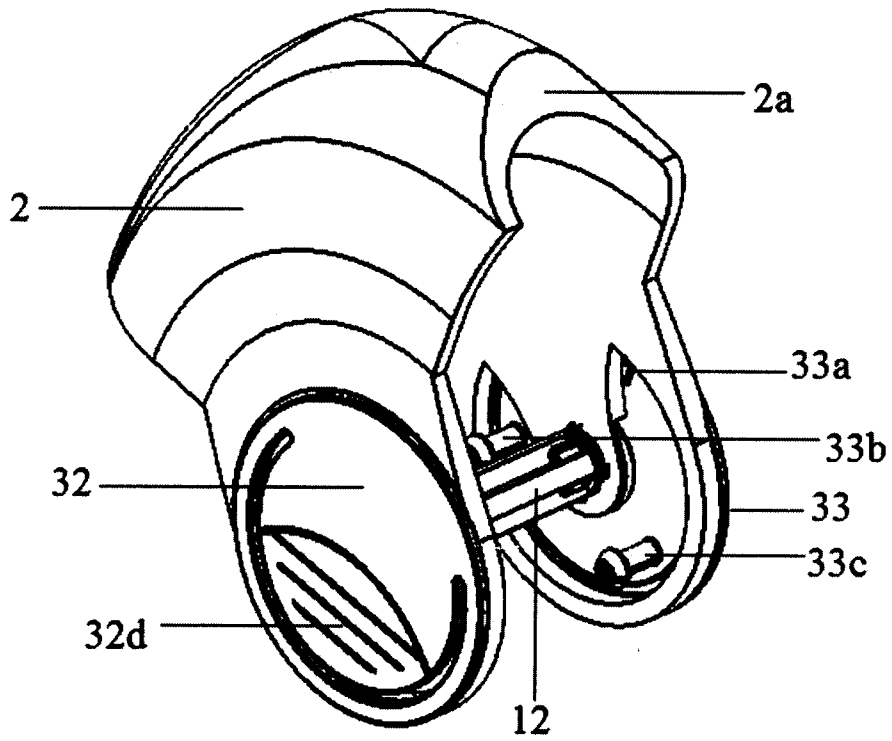

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FIG. 6d

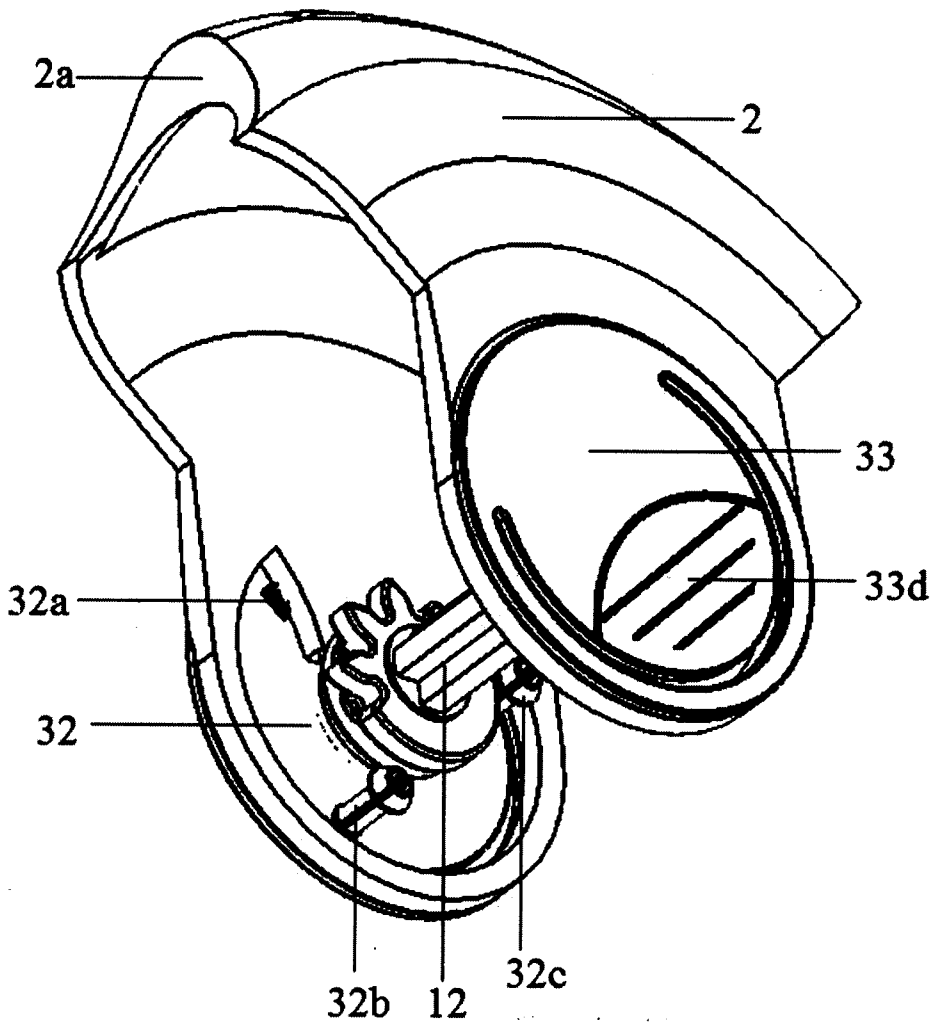

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FIG. 6e

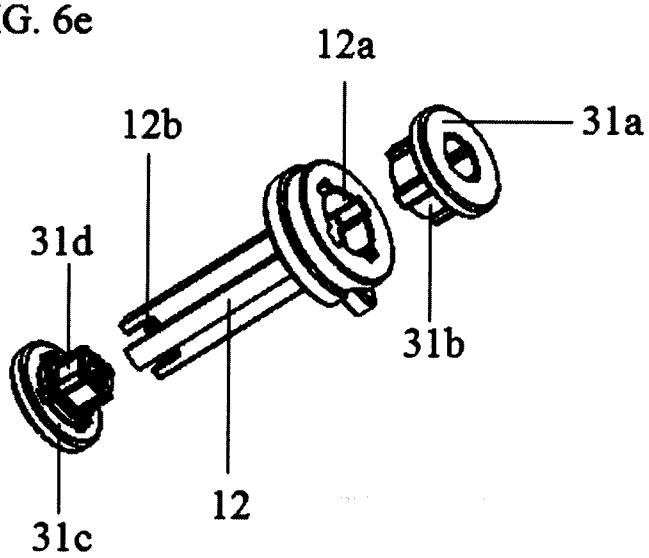
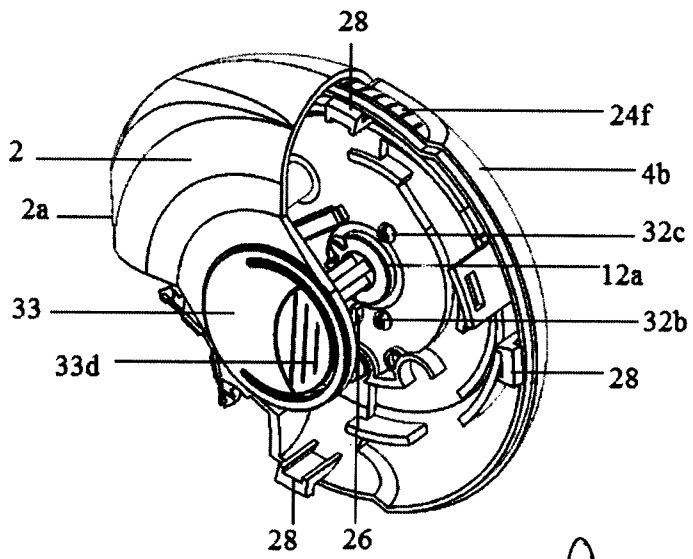


FIG. 6f



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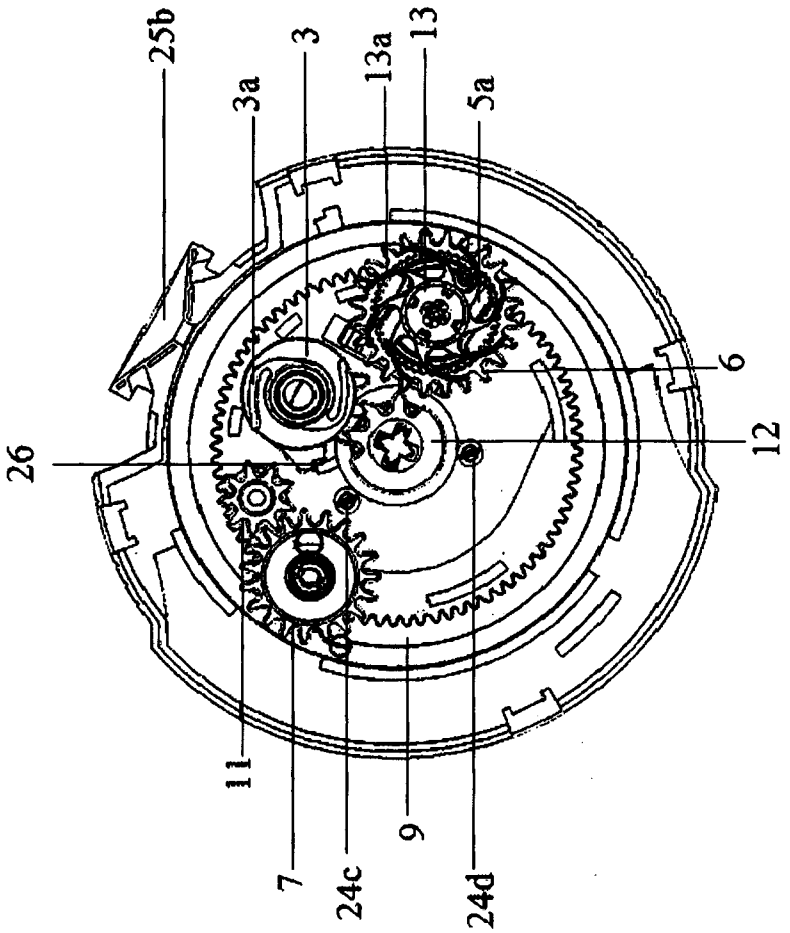
Sheet No. : 12

FIG. 7a



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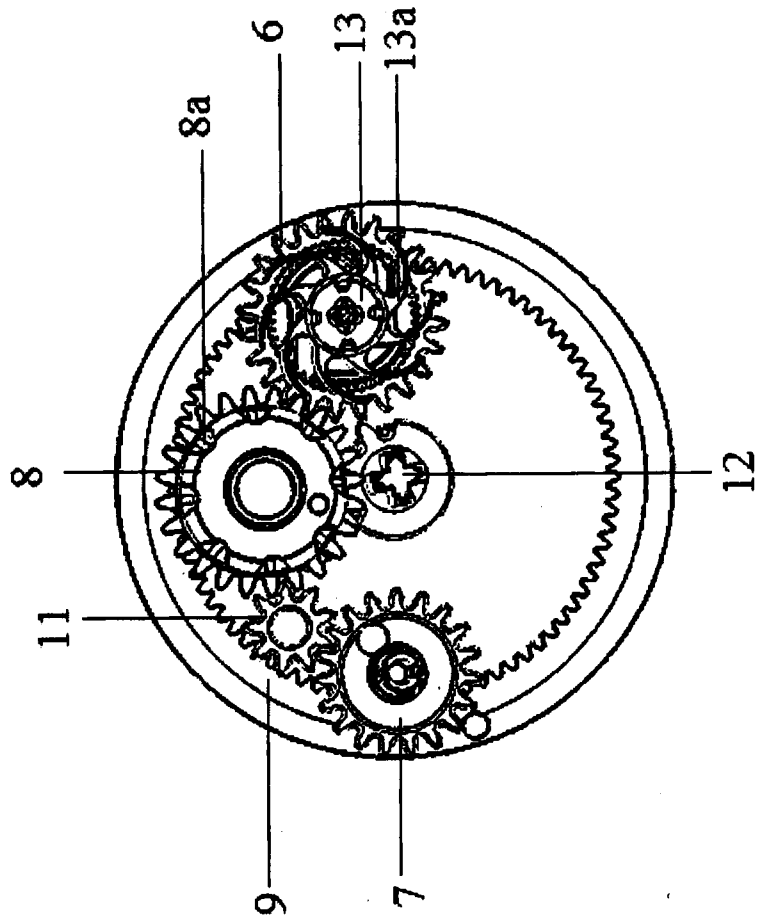

FIG. 7b

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FIG. 7c

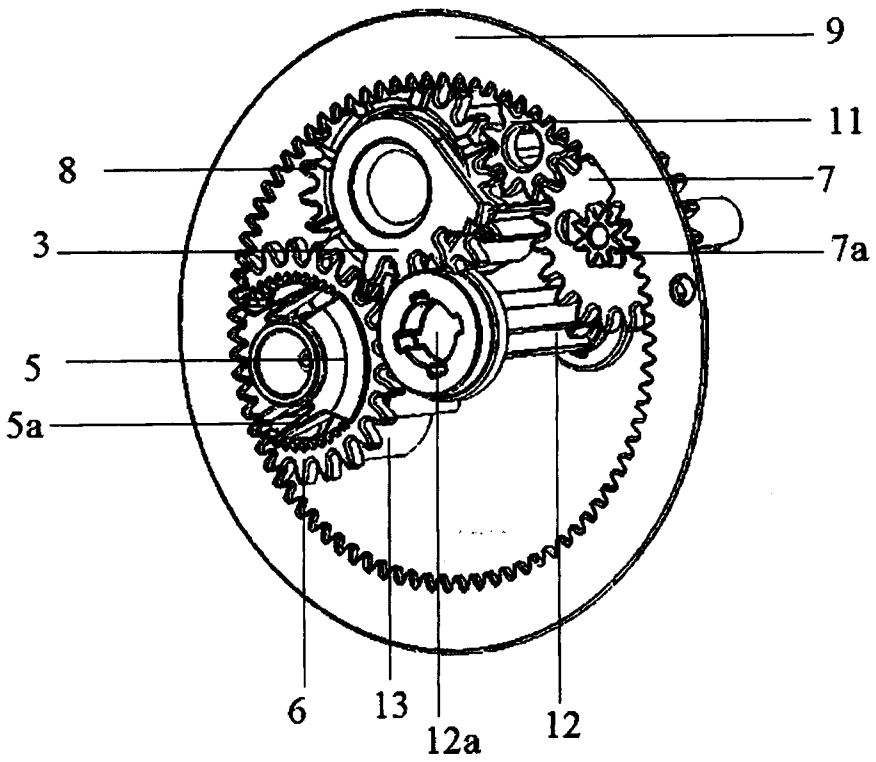

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FIG. 8

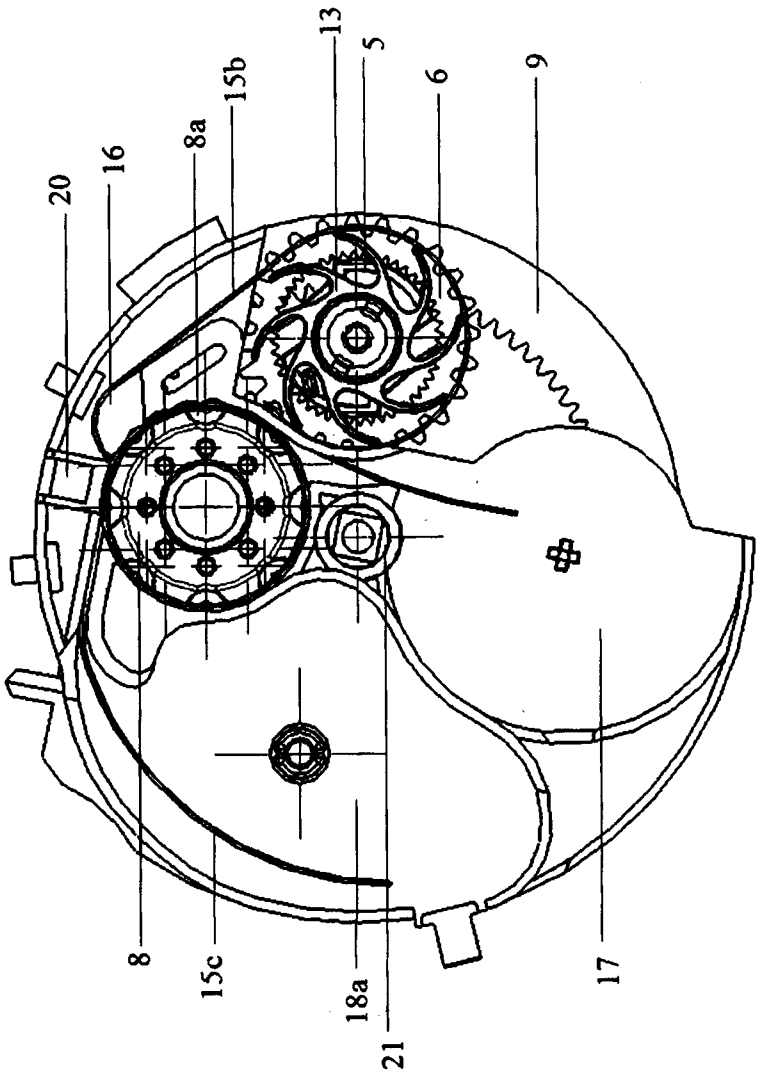

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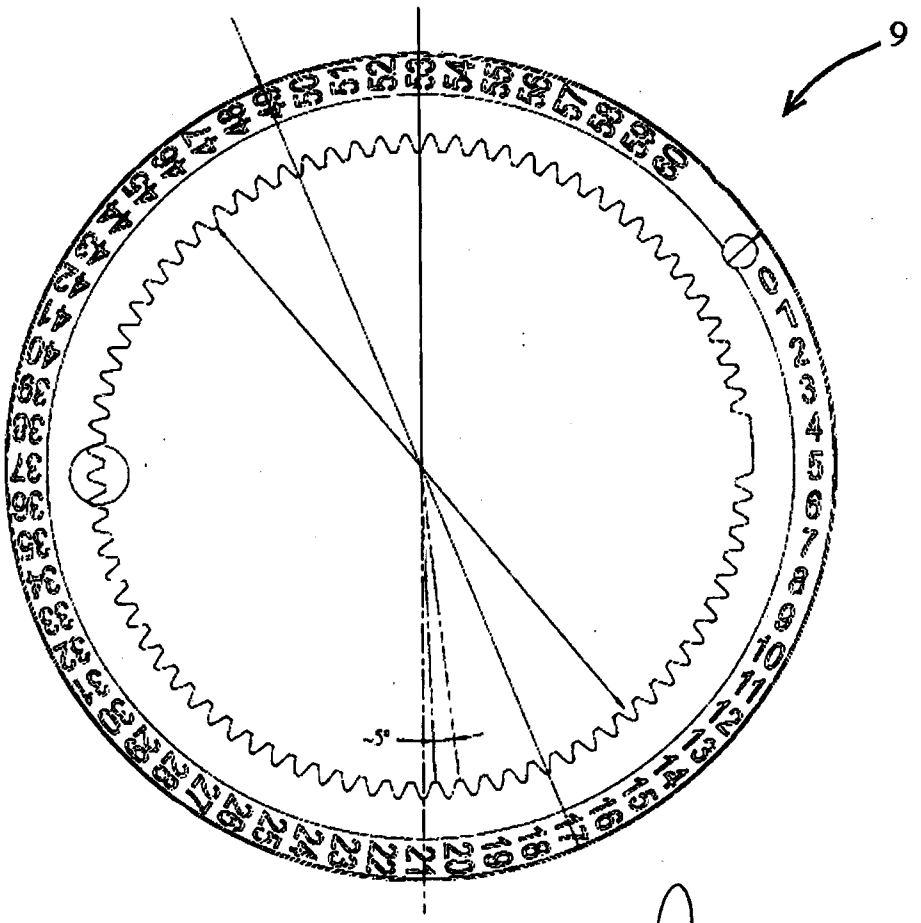
FIG. 9



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INHALER USED FOR DELIVERY OF MEDICAMENT IN DRY POWDER FORM

Field of Invention

The present invention relates to an inhaler which is appropriate for delivering the medicament in dry powder form used in the treatment of respiratory diseases, particularly in asthma and chronic obstructive pulmonary disease (COPD). In addition, the present invention relates to the inhaler used to realize an effective inhalation which comprises a blister package appropriate for carrying dry powder medicament.

Description of the Prior Art

It is quite common to use inhalers for delivering medicaments utilized in the treatment and prophylaxis of respiratory diseases. Inhalation treatment is the most commonly preferred treatment method in these diseases as the inhalers provide ease of use; the medicaments have rapider onset of time resulting from local administration and they have fewer side effects. Various inhalers have been designed in order to provide effective and sufficient delivery of the medicaments used in the treatment of respiratory diseases, particularly in asthma and chronic obstructive pulmonary disease. These inhalers vary according to their operating mechanisms and the physical form of the medicament to be delivered.

In the inhalers used to deliver the medicaments in dry powder form, the medicament is carried in reservoirs, capsules or blisters packages. It is highly significant to deliver each dose to the patient with exact accuracy and preciseness since the required medicament dose in the inhalation is very low.

At least 98% of the medicament in dry powder form contained in the blister pocket or the capsule should be delivered to the patient in the inhalers used for delivery of medicament in dry powder form. In this dry powder medicament to be inhaled, the medicament particles called "fine particles" size of which are in the range of 1 μm to 6 μm can be absorbed in the lungs. The active agent particles comprised in the medicament in dry powder form are fine particles, too. The ratio of the measured dry powder medicament in the blister or the capsule is at least 25%, preferably more than 30% by weight. To this respect, it is desired that more than 25% of the medicament in dry powder form to be delivered to the patient is composed of fine particles for an effective inhalation to be realized.

The airflow resistance in the inhaler used for delivery of medicaments in dry powder form is one of the most significant factors affecting fine particle amount, thus the active agent amount of the dry powder medicament delivered to the patient's lungs because the pressure decrease and flow velocity realized by the patient depend on the airflow resistance of the inhaler and the patient's inhalation capability. Low airflow resistance of the inhaler causes high airflow velocity while high airflow resistance of the inhaler leads to low airflow velocity.

As the patient should respire deeply in the cases that the airflow resistance of the inhaler is so high, the inhaler cannot be used effectively by most patients, particularly by children or in all cases. The fact that the airflow resistance of the inhaler is very low causes the medicament in dry powder form to be delivered to the patient without the need to respire deeply. However, a large portion of the medicament in dry powder form is accumulated in the mouth of the patient and cannot reach to the lungs in the case that the patient realizes the inhalation without respiring deeply. In addition, some of the medicament in dry powder form accumulates in the mouthpiece of the device upon the respiration of the patient in course of inhalation and cannot be delivered to the patient. Hence, an ineffective inhalation is realized as the amount of the active agent delivered to the patient's lungs is not sufficient.

The inhalation device marketed under the trade mark Diskus® by GlaxoSmithKlein is one of the most well-known inhalers on the market. In these inhalers, the medicament in dry powder form is carried in single doses in each blister pocket of the blister package. An effective inhalation cannot be realized in this device since a large portion of the dry powder medicament delivered to the patient remains in the patient's mouth and a sufficient amount of the active agent is not delivered to the patient's lungs during the inhalation of the medicament in dry powder form upon the actuation of the inhaler resulting from the fact that the airflow resistance of this device is quite low.

When the inhalers developed or on the market are taken into consideration, there seems a need for an inhaler which fully fulfills all the requirements mentioned above and guarantees the sufficient amount of active agent to be inhaled for an effective inhalation.

The inventor has surprisingly found that the airflow resistance induced as a result of the fact that the ratio of the cross-section of the manifold outlet to the cross-section of the mouthpiece outlet is at a particular value range enables the delivery of the required amount of the active

agent comprised in the medicament in dry powder form to be inhaled to the patient's lungs and to realize an effective inhalation. According to this, the present invention relates to the inhaler which is appropriate for delivery of the medicament in dry powder form and enables the delivery of the required amount of the active agent comprised in the medicament in dry powder form to the patient's lungs.

Summary of the Invention

An inhaler suitable for delivery of the medicament in dry powder form according to the present invention comprising;

- a blister package composed of a plurality of blister pockets each of which comprises medicament in dry powder form and which are spaced at equal intervals;

- a mouthpiece enabling the patient to inhale the medicament in dry powder form from the opened blister ;

- a rotatable mouthpiece cover covering the mouthpiece;

- a gear mechanism enabling the blister package to be indexed and the medicament in dry powder form to become ready for inhalation;

- a housing situated between the upper housing member and the lower housing member in which the blister package and the gear mechanism are enclosed;

- a manifold through which the air entering the device from the air inlet passes and

- a channel interconnecting the manifold outlet and the mouthpiece outlet

is characterized in that the ratio of the cross-section of the manifold outlet to the cross-section of the mouthpiece outlet is in the range of 1:10 to 1:50.

Delivery of sufficient quantity of the active agent comprised in the dry powder medicament contained in the blister package which is opened by the actuation of the device pertaining to the present invention to the patient's lungs substantially depends on the inhaler's resistance. The resistance of the inhaler, on the other hand, affects the flow velocity and the pressure decrease of the external air entering the device. Approximate value of the pressure decrease

is calculated with the equation of $\Delta P = K.\rho.\upsilon^2/2$. Pressure decrease can be calculated for each component of the device through which the external air entering the inhaler passes. In this equation, K value is a geometric factor and it is 0,5 in the case that the cross-section instantaneously contracts while it is 1 in the case that the cross-section instantaneously expands; ρ represents air density and it is approximately 1,3 kg/ m^3; υ (m/s) value is the average velocity of air. The resistance value for each components is obtained dividing the square root of ΔP (in kPa) value obtained from the abovementioned equation by the flow velocity (minutes/liter) of the external air entering the inhaler. Flow velocity of provided airflow is obtained by dividing the total pressure decrease induced in the inhaler by the resistance value.

The inventor has found that the resistance in the mouthpiece and the manifold outlet of the inhaler affects the pressure decrease, therefore the flow velocity of the air to a substantial extent and there should be a pressure decrease higher than 4 kPa in the inhaler for an effective inhalation to be realized. The resistance and the airflow velocity in the manifold outlet and mouthpiece outlet are directly proportional to the average velocity of air. The average velocity of air, on the other hand, is determined according to the cross-section of the manifold outlet and the mouthpiece outlet. A pressure decrease higher than 4kPa which is required for an effective inhalation to be realized is provided in the case that the ratio of the cross-section of the manifold outlet to cross-section of the mouthpiece outlet is in the range of 1:10 to 1:50, preferably in the range of 1:15 to 1:40, more preferably in the range of 1:20 to 1:30. Thus, the breath that the patient takes to deliver the medicament in dry powder form to his lungs can enable the delivery of the required amount of the active agent with fine particle sizes comprised in the dry powder medicament to the patient's lungs. In addition, the change in the airflow velocity induced when the ratio the cross-section of the manifold outlet to the cross-section of the mouthpiece outlet is in the range of 1:10 to 1:50 prevents the large amounts of residual dry powder medicament to accumulate in the mouthpiece and the patient's mouth.

The inhaler pertaining to the present invention wherein the ratio of the cross-section of the manifold outlet to the cross-section of the mouthpiece outlet is in the range of 1:10 to 1:50 is preferably a manual device which is appropriate to be used for delivery of medicament in dry powder form and comprise blister package.

The inhaler pertaining to the present invention has a mechanism preferably triggered by the rotation of the mouthpiece cover. According to this, the housing of the device pertaining to the present invention has been designed such that each component of the blister package and the gear mechanism which have a significant role in enabling the device to work properly is situated accurately and works harmoniously. To this end, the housing is divided into several compartments. The used portion and the unused portion of the blister package are accommodated in separated compartments in order to prevent the medicament in dry powder form remained in the opened blister pocket to spill on the other components of the housing. Furthermore, the housing also comprises the beak which enables the blister package to be peeled and the manifold through which the dry powder medicament in the open blister passes before reaching the mouthpiece during the inhalation. In addition, the housing can be in any appropriate shape while it is preferably elliptic or circular.

The upper and the lower housing members interlock with each other and enclose the housing in order to keep the housing and the gear mechanism fixed together. The mouthpiece cover hiding the mouthpiece is rotated by being slid on the upper and lower housing members. The grids on the surface of the lower and the upper housing members provide an effective actuation by preventing the slipping of the finger while rotating the mouthpiece cover. The upper and the lower housing members can be in any appropriate shape which provides ease of use.

The mouthpiece cover hiding the mouthpiece of the device pertaining to the present invention has been designed such that it also provides to actuate the device. Before each inhalation

mouthpiece cover is completely covered and the device is in standby mode. When the mouthpiece cover is in the second position, the mouthpiece cover resides on the protrusion in the other end of the rotational path and one dose of the dry powder medicament becomes ready for inhalation upon the actuation of the device.

The mouthpiece cover of the device is joined with the gear mechanism via the connection points. One end of the drive gear passes through the center of the lower housing member and tightly joins with the mouthpiece cover in one connection point while the other end passes through the center of the upper housing member and joins with the mouthpiece cover in the other connection point. For each end of the drive gear to make a stable connection between the connection points of the mouthpiece cover, one side cover is used for each end of the drive gear. Thus, the ends of the drive gear are carved such that they can tightly engage with the ends of the side covers from inside. The shape of the inside faces of these carved parts on both ends of the drive gear match with the shape of the ends of the side covers that fit into its.

On each connection point of the mouthpiece cover, there is a stabilizing resilient cover. The stabilizing resilient covers on both sides of the inhaler prevent the mouthpiece cover to move on both sides. Before the inhalation, the resilient parts of each stabilizing resilient cover that match with the shape of the fingers are pressed on for raising the pawls and releasing the mouthpiece cover in order to move the mouthpiece cover which actuates the device.

According to the present invention, each gear of the gear mechanism in the device is directly or indirectly engages with each other. Before the inhalation, the device is actuated by pressing on the stabilizing resilient covers on both faces of the device and rotating the mouthpiece cover along the rotational path, and the drive gear which is joined with the both connection points of the mouthpiece cover via the side covers precisely transmits the movement of the mouthpiece cover to the indexing ratchet wheel owing to the side covers upon the actuation of the device. The indexing ratchet wheel which interlocks with the indexing wheel from inside thanks to its arms enables the indexing wheel to rotate. Upon the indexing wheel's movement, the blister package is indexed and it is peeled by means of the beak present in the housing. As the indexing wheel engages with the winding wheel gear and the pinion gear, these gears move upon the indexing wheel's move, too. Since the mechanism gear engages both with the winding wheel gear and the winding wheel, the rotation of the

winding wheel gear causes the winding wheel to move and lid sheet of the blister package coils on the winding wheel tightly. Pinion gear engages with the base gear while the small gear under the base gear engages with the counter gear. Thus, the rotation of the indexing wheel triggered by the actuation of the device is transmitted to the counter gear via the small gear which is immediately under the base gear.

The counter gear in the device pertaining to the present invention displays the number of the unused blister pockets remained in the device. In response to the actuation of the device by the mouthpiece cover, the mouthpiece is uncovered, the blister package is indexed and one dose of the dry powder medicament is prepared for inhalation while the counter gear rotates as well. Thus, the movement of the mouthpiece cover leads to the mouthpiece cover to be uncovered; one dose of the dry powder medicament to be ready for inhalation after the blister pocket is opened as well as providing the counter gear to rotate and display the new value of the unused blister pockets remained.

On the counter gear, there exist numerals equal to the number of the blister pockets present in the device and they are spaced by equal angles. In a device comprising 60 doses, the angle between the numerals is approximately 5°. The counter gear rotates as a result of the reflection of the rotation of the indexing wheel via the pinion gear and the base gear. In response to the each actuation of the device, rotation of the indexing wheel by the same angle each time due to the accurate transmission of the movement of the mouthpiece to the gear mechanism via the drive gear results in the rotation of the counter wheel approximately by the same angle as well and each numeral on the counter wheel is clearly seen through the display aperture on the upper housing member. Therefore, the patient makes sure about the number of the unused blister pockets remained in the device.

The inhaler according to according to the present invention, further comprises a blister package composed of a plurality of blister pockets each of which comprises medicament in dry powder form and which are spaced at equal intervals. The blister package carries the medicament in dry powder form in one-dose portions and it is preferably a blister strip and it is preferably peelable. The blister pockets comprised in the blister package are spaced in equal intervals and each of them carries one dose of the medicament in dry powder form.

While the blister package is indexed on the indexing wheel, the beak on the housing peels the blister. Therefore, one dose dry powder medicament becomes ready for inhalation after the blister package is peeled to be opened in each actuation of the device.

The base sheet of the blister package on which the blister cavities are spaced is accumulated in the separated compartment of the housing. The lid sheet that provides impermeability of the blister package, on the other hand, is coiled on the winding wheel which is one of the components of the gear mechanism positioned in the other side of the housing.

The blister opened by the beak is situated immediately under the manifold. Upon the inhalation of the patient, the airflow that preferably enters the device through at least one air inlet on the upper housing member entrains the dry powder medicament in the opened blister pocket via the manifold to the mouthpiece and enables the delivery of said medicament to the patient. The air inlet on the upper housing member that allows the entry of air can be in any suitable shape and size that also enable external air to enter the device easily and at convenient speed.

The mouthpiece is designed to fit the mouth for the patient to comfortably inhale the medicament in dry powder form. According to the shape of the device, the mouthpiece can be in any suitable shape or size as well as being fixed or movable. Furthermore, it could be attached or unattached to the upper and/or the lower cover.

The air inlet that the external airflow passes through is preferably designed not to be close where the patient holds the device in order not to prevent the air flow. Furthermore, in order to deliver the required amount of the dry powder medicament in the opened blister to the patient, the air inlet has been designed such that it allows the entry of the airflow through the air inlet by a convenient angle.

One end of the manifold between the opened blister and the mouthpiece communicates with the opened blister while the other end communicates with the mouthpiece. During the respiration of the patient, the external air passes through the air inlet and enters the manifold. The air which enters the inhaler through the air inlet upon the inhalation of the patient passes through one of the apertures with four sub-apertures on the end of the manifold, enters the opened blister, entrains the one dose of medicament in dry powder form; passes it through the

other aperture with four sub-apertures on the end of the manifold and reaches the manifold. The air entraining the medicament in dry powder form to the other end of the manifold which is close to the mouthpiece, namely to the outlet of the manifold, passes through preferably the tapered channel interconnecting the mouthpiece and the manifold, then reaches the mouthpiece. The angle of the peak point of the tapered channel is in the range of 30° to 150°, preferably 45° to 135°, most preferably 50° to 125°. In addition, the distance between the manifold outlet and the mouthpiece outlet, namely the length of the tapered channel, is at least 2 mm, preferably in the range of 2 mm to 5 mm. This length can be counted as one of the factors influencing the airflow resistance in the inhaler.

In order to realize an effective inhalation using the inhaler pertaining to the present invention, the ratio of the cross-section of the manifold outlet to the cross-section of the mouthpiece outlet is in the range of 1:10 to 1:50, preferably in the range of 1:15 to 1:40, more preferably in the range of 1:20 to 1:30 so as to provide the pressure decrease higher than 4 kPa in the inhaler. Thus, the required amount of the active agent for the treatment in the dry powder medicament contained in the blister pocket that is opened upon the actuation of the inhaler is delivered to the lungs.

The term "an effective inhalation" used throughout the text refers to the desired result which is induced as a result of the delivery of the active agent in quantities required for inhalation treatment to the patient's lungs.

Each component of the device pertaining to the present invention can be made of any appropriate substance while it is preferably made of plastics. These plastic substances are selected from a group comprising styrene-acrylonitrile, polyoxymethylene (it is generally named as POM and it is also known as polyacetal or polyformaldehyde), acrylic-polymethylmetacrylate, cellulose acetate, polyetheretherketone, polyvinyl choloride, polyethylene, polypropylene, acrylonitrile butadiene styrene, polycarbonate, polyamide, polystyrene, polyurathane or fluoropolymer types while it is more preferably polyoxymethylene. The components made of plastics can be produced by methods such as injection molding. Furthermore, each component of the device can be in any appropriate color.

The lid and the base sheets constituting the blister package preferably consist of a plurality of layers. Each of these layers are preferably chosen from a group comprising polymeric layers that are made of various polymeric substances; aluminum foil and fluoropolymer film.

According to the present invention, the lid and base sheets composing the blister package are sealed very tightly by at least one of the methods comprising cold formed bonding, hot metal bonding, hot metal welding, radio frequency welding, laser welding or ultrasonic welding in order to provide impermeability, more preferably by cold formed bonding method. Since these cold formed bonding methods can be carried out at lower temperatures than hot sealing methods, they are the most appropriate methods to use in the case that the medicament carried in the blister is heat sensitive.

Fluoropolymer film is a polymeric film which is used in blister packs and provides excellent moisture barrier. This chemically inert polymeric film does not cause any change in the taste of the formulation when it is in contact with the dry powder formulation. In addition, it easily constitutes a layered structure with the other polymeric layers which are composed of various polymers. It is appropriate to be transacted with heat.

For preserving the stability of the dry powder formulation stored in the blister package, preferably at least one of the polymeric layers comprises at least one desiccant agent including silica gel, zeolite, alumina, bauxite, anhydrous calcium sulfate, activated carbon and clay which has the property of water absorption in order to decrease gas and moisture permeability of the layer.

According to the invention, the thickness of the aluminum foil in the lid and the base sheets of the blister package are preferably chosen to be in the range of 5 to 80 μm, more preferably in the range of 15 to 65 μm.

According to the invention, the polymeric layers in the lid and the base sheets of the blister pack are made of the same or different polymers. The thickness of these polymeric layers varies according to the type of the polymeric substance used and its properties while they are preferably in the range of 5 to100 μm, more preferably in the range of 15 to 60 μm.

The polymers composing the polymeric layer are preferably selected from thermoplastics such as polyethylene, polypropylene, polystyrene, polyolefin, polyamide, polyvinyl chloride, polyurethane or synthetic polymers.

The blister pockets in the blister package can be in any appropriate shape. The plurality of blister pockets spaced at equal intervals on the base sheet of the blister package can be in the same or different shape, structure or volume.

The reference numbers of the drawings added to exemplify the present invention and the detailed description of the invention according to these drawings are given below but the scope of the invention should not be limited to these drawings.

Brief Description of the Drawings

Figure 1 is a perspective view of an inhaler according to the inhaler described in the present invention;

Figure 2 is an exploded view of the inhaler pertaining to the invention;

Figure 3 is a perspective view of the blister pack for use with the inhaler pertaining to the invention;

Figures 4a and 4b are perspective views of the housing of the inhaler according to the invention;

Figures 5a and 5b are perspective views of upper and lower housing members of the inhaler according to the invention;

Figure 5c is a vertical cross-sectional view of the inhaler pertaining to the present invention;

Figure 6a is a perspective view of the mouthpiece cover of the inhaler pertaining to the invention;

Figure 6b is an exploded view of the communication between the mouthpiece cover, the drive gear and the stabilizing resilient covers in the inhaler pertaining to the invention;

Figure 6c is a cross-sectional view of the communication between the mouthpiece cover, the drive gear and the stabilizing resilient covers in the inhaler pertaining to the invention;

Figure 6d is a cross-sectional view of the communication between the mouthpiece cover, the drive gear and the stabilizing resilient covers in the inhaler pertaining to the invention;

Figure 6e is an exploded view of the communication between the drive gear and the side covers in the inhaler pertaining to the invention;

Figure 6f is a cross-sectional view of the connection of the stabilizing resilient cover with the lower housing member in the inhaler pertaining to the invention;

Figures 7a-7c are cross-sectional views of the engagement of the gears composing the gear mechanism with each other in the inhaler pertaining to the present invention;

Figure 8 is a cross-sectional view of the blister package delaminating in course of operation of the inhaler pertaining to the present invention;

Figure 9 is a perspective view of the counter gear used in the inhaler pertaining to the present invention.

Detailed Description of the Drawings

The inhaler (1) pertaining to the present invention comprises a gear mechanism situated in the housing (10) between the upper housing member (4a) and the lower housing member (4b) in order to enable the inhalation of the dry powder medicament carried in a blister package (15) as displayed in figures 1 and 2. Each component of the inhaler (1) is positioned at appropriate spots of the device to guarantee their working properly and accurately.

The inhaler (1) pertaining to the present invention shown in Figure 1 is ready for inhalation. In this case, the mouthpiece cover (2) is in the second position and the mouthpiece (14) is entirely exposed. The mouthpiece cover (2) has to be rotated by holding on the carved part (2a) on one end of the mouthpiece cover (2) in order to switch to the second position from the first position wherein the mouthpiece is completely covered. In this way, the mouthpiece (14) is completely exposed when the mouthpiece cover (2) is switched to the second position from the first position and the gear mechanism is triggered by the drive gear (12). The drive gear

(12) precisely transmits the movement of the mouthpiece cover (2) to the indexing ratchet wheel (3).

The indexing wheel (8) which engages with the indexing ratchet wheel (3) enables the blister package (15) shown in figure 3 to be indexed. The blister pockets (15a) composing the blister package are received in the recesses (8a) on the indexing wheel and the blister package (15) is indexed when the indexing wheel (8) rotates. In the inhaler pertaining to the present invention, shapes of the recesses (8a) on the indexing wheel (8) have been designed to match the shapes of the blister pockets (15) composing the blister package (15) for the blister package to be indexed properly.

The blister package (15) shown in figure 3 is composed of the lid sheet (15b) which provides impermeability and the base sheet (15c) on which the blister pockets (15a) are spaced at equal intervals. Each blister pocket contains medicament in dry powder form comprising one or more active agents.

The rotational movement that the mouthpiece cover (2) of the device executes while switching from the first position to the second is transmitted to the indexing ratchet wheel (3) via the drive gear (12) that the mouthpiece cover (2) engages with. As displayed in figure 2, arms (3a) of the indexing ratchet wheel interlocks with protrusions inside the indexing wheel (8) and rotates the indexing wheel (8) unidirectionally. Therefore, the blister package (15) is indexed forward while the indexing wheel (8a) rotates as the blister pockets (15a) composing the blister package (15) are received in the recesses (8a) of the indexing wheel. The beak (16) in the housing (10) provides the blister package (15) to be peeled while the blister package (15) is indexed and provides one blister pocket (15a) to be opened in response to each actuation of the device (1).

The winding wheel gear (6), which is another component of the gear mechanism, engages with the indexing wheel (8) as displayed in figure 2. The mechanism gear (5) that interlocks the winding wheel (13) from inside has arms (5a) to interlock with the interior teeth of the winding wheel gear (6). When the indexing wheel (12) rotates the winding wheel gear (6), the winding wheel rotates unidirectionally owing to the arms of the mechanism gear (5a) which interlock with the interior teeth of the winding wheel gear (6) and the lid sheet (15b) which is peeled away while the blister package is indexed is tightly coiled on the wings (13a)

of the winding wheel. The base sheet (15c) of the blister package (15) where the blister pockets are spaced is accumulated in a separate part (18a) of the device.

Different perspective views of the housing (10) wherein the gear mechanism and the other components of the inhaler (1) pertaining to the present invention are arranged are displayed in figures 4a and 4b. Furthermore, as can be seen in figures 4a and 4b, the housing (10) also comprises the other components having significant roles in the actuation of the device such as the beak (16), the manifold (20), the apertures with four sub-apertures (20a, 20b). Each component comprised in the housing is situated in appropriate parts of the housing (10) in order to enable the inhaler (1) to work properly. The drive gear (12) passes through the center (21) of the housing and joins the mouthpiece cover (2) at two points. The blister package (15) is in the lower part (17) of the housing as coiled up. In response to each actuation of the device (1), the blister package (15) is peeled by the beak (16) in the housing while being indexed by the indexing wheel (8) situated in the upper part (19) of the housing. The lid sheet (15b) of the blister package (15) which provides impermeability is indexed over the beak (16) and coiled on the winding wheel (13) which is situated in the side part (18) of the housing. The base sheet (15c) of the blister package (15) on which the blister pockets (15a) are spaced, on the other hand, is accumulated in the separated compartment (18a) of the housing (10). Upon the inhalation of the patient, the air passes through the air inlet with four sub-apertures (20a) under the manifold (20) into the opened blister pocket; entrains the dry powder medicament contained in the opened blister pocket (15a) in response to each actuation of the device; provides it to pass through the other aperture with four-sub-apertures (20b) and reach the mouthpiece via the manifold (20).

The housing (10) and the other components of the inhaler (1) pertaining to the present invention are stably kept together as the upper housing member (4a) and the lower housing member (4b) displayed in figures 5a and 5b are joined together. The engagement tabs (28) on the inside surface of the lower housing member (4b) engage with the engagement recesses (27) on the inside surface of the upper housing member (4a) and the upper and lower housing members are fixed tightly. Therefore, the protrusions (23a, 23b) on the upper housing member (4a) and the protrusions (24a, 24b) on the lower housing member (4b) are joined end to end and they define the restricted path for the rotational movement of the mouthpiece cover (2). The mouthpiece cover (2) can be moved along this path. When the mouthpiece cover (2)

is in the first position, the mouthpiece is completely covered, the device is in standby mode and the mouthpiece cover (2) leans on the first protrusion (23a) on the upper housing member and the first protrusion (24a) on the lower housing member. The mouthpiece (2) is manually slid along the rotational path with the help of the carved part to switch to the second position. The mouthpiece is completely exposed when the cover is in this position, one dose of the dry powder medicament is ready for inhalation and the mouthpiece cover (2) leans on the second protrusion (23b) on the upper housing member and the second protrusion (24b) on the lower housing member.

As displayed in figures 5a and 5b, one half (25a) of the tapered channel that interconnects the manifold (20) that exist in the housing (10) with the mouthpiece (14) is comprised in the upper housing member (4a) while the other half of it (25b) is comprised in the lower housing member (4b). The channel is constituted as a whole when the upper (4a) and the lower (4b) housing members are joined together. Upon the inhalation of the patient, the air that enters the device through the air inlet (22) arranged in the upper housing member (4a) passes through the aperture with four sub-apertures (20a), reaches the opened blister (15a) and entrains the dry powder medicament there to the manifold (20) by passing it through the other aperture with four sub-apertures (20b). The air entraining the dry powder medicament to the manifold (20) entrains the medicament in dry powder form, as is seen in figure 5c, from the manifold outlet (20c) to the mouthpiece outlet (14a) via the tapered channel (25a and 25b) and enables the delivery of the medicament in dry powder form to the patient.

The grids on the upper housing member (23e, 23f) and the grids on the lower housing member (24e, 24f) prevent the slips of fingers when rotating the mouthpiece cover.

The mouthpiece cover (2) of the inhaler pertaining to the present invention is displayed in figure 6a. The carved part (2a) in one end of the device enables to easily move the mouthpiece cover manually. The mouthpiece cover (2) is joined with the gear mechanism via the connection points. The drive gear (12) is joined with the connection points (29, 30) of the mouthpiece cover via the side covers (31a, 31c) as it can clearly be seen in figures 6b, 6c and 6d illustrating the communication between the mouthpiece cover (2), the drive gear (12), side covers (31a, 31c) and the stabilizing resilient covers (32,33). Each of these side covers (31a; 31c) passes through the center (4d) of the upper housing member or the center (4e) of the

lower housing member and joins with the end (12a; 12b) of the drive gear. It can clearly be seen in figure 6d that the both ends (12a; 12b) of the drive gear is carved such that the end of the side cover (31b; 31d) can pass through. Each end of the side covers (31d; 31b) passes through one of the connection points (29; 30) of the mouthpiece cover and it is received in the recess in one end (12b; 12a) of the drive gear, thus it provides to tightly and stably interconnect the mouthpiece cover (2) with the drive gear (12). It is provided that the mouthpiece cover (2) synchronizes with the drive gear (12) as the connection point (29; 30) of the mouthpiece cover which has a matching shape with the ends (31d; 31b) of the side covers that passes through it on both sides of the device and the end (12b; 12d) of the drive gear that it communicates with are on the same component.

As is seen from figures 6a-6e, the shapes of the ends (31b; 31d) of the side covers that are received in the carved parts on the ends of the drive gear and the shapes of the connection points (29, 30) of the mouthpiece cover are not identical since the two ends (12a, 12b) of the drive gear are not identical.

There is one stabilizing resilient cover (33; 32) on each connection point (29; 30) of the mouthpiece and on each side cover, as displayed in figures 2, 6a-6d and 6f. When the mouthpiece cover (2) is in the first position, the pawls (32a, 33a) under the stabilizing resilient covers, which are on the connection points (29, 30) of the mouthpiece, interlock with the mouthpiece cover (2) on both sides as clearly seen in figures 6c and 6d. The pawl (33a) under the stabilizing resilient cover that is on the first connection point (29) interlocks with the mouthpiece cover on one side (figure 6c). Identically, the pawl (32a) under the stabilizing resilient cover that is on the second connection point (30) of the mouthpiece cover interlocks with the mouthpiece cover (2) on the other side (figure 6d).

The extensions (32b, 32c; 33b, 33c) under the stabilizing resilient covers pass through the apertures (23c, 23d; 24c, 24d) on the upper and the lower housing members illustrated in figures 5a and 5b and provide the stabilizing resilient covers to remain stable. Namely, the extensions (33b; 33c) under the stabilizing resilient cover that is on the first connection point (29) of the mouthpiece cover pass through the apertures (23c; 23d) on the upper housing member and provide the stabilizing resilient cover (33) to be stably joined with the device. Identically, the extensions (32b, 32c) under the stabilizing resilient cover on the second

connection point (30) of the mouthpiece cover pass through the apertures (24c, 24d) on the lower housing member and provide the stabilizing resilient cover (32) to be stably joined with the device as clearly illustrated in figure 6f.

Before the inhalation, the resilient parts (32d, 33d) of each stabilizing resilient cover illustrated in figures 6c and 6d are pressed on for raising the pawls (32a, 33a) and releasing the mouthpiece cover (2) in order to actuate the gear mechanism of the device to prepare one dose of dry powder medicament before inhalation. Therefore, the gear mechanism of the device is actuated and one blister pocket (15a) is opened for one dose of the dry powder medicament to be ready for inhalation when the resilient parts (32d, 33d) of the stabilizing resilient covers are pressed on and the mouthpiece cover (2) is switched from the first position to the second position simultaneously.

In figure 7a, it is displayed that the stopper (26) interlocks with the tooth of the indexing ratchet wheel (3) and hinders its rotation. The rotational movement of the mouthpiece cover (2) by the same angle in response to each actuation of the device (1) is accurately transmitted to the indexing ratchet wheel (3) by the drive gear (12) which engages with the mouthpiece cover (2) on its both ends and the drive gear (12) is enabled to rotate by the same angle in each actuation of the device (1). The stopper component (26) in the lower housing member (4b) prevents the backwards movement of the blister package (15) indexed by the indexing wheel (8) which synchronizes with the indexing ratchet wheel by keeping the position of the indexing ratchet wheel (3) fixed and provides the blister package (15) to be precisely positioned.

As can be seen in figure 7b, the indexing wheel (8) which synchronizes with the indexing ratchet wheel (3) is engaged with the winding wheel gear (6) and the pinion gear (11) and the rotation of the indexing wheel (8) causes the pinion gear (11) and the winding wheel gear (6) to rotate. Thus, both the peeled lid sheet (15b) of the blister package (15) which is indexed by the rotation of the indexing wheel (8) is tightly coiled on the winding wheel (13) engaging with the winding wheel gear (6) and also the counter wheel (9) is provided to be moved by the pinion gear (11) and the base gear (7) as a result of the rotation of the indexing wheel (8).

As is seen in figure 8, the lid sheet (15b) of the blister package (15) which is peeled away by the beak (16) and the base sheet (15c) are enclosed in separate compartments. The lid sheet

(15b) that provides impermeability is indexed over the beak (16) and tightly coiled on the wings (13a) of the winding wheel. The base sheet (15c) of the blister package (15) where the blister pockets (15a) each of which carries one dose of the dry powder medicament are spaced is accumulated in the separated compartment (18a) of the housing (10). In response to each actuation of the device (1), one dose of the dry powder medicament which is prepared for inhalation after one blister pocket (15a) is opened and the air entering the device through the air inlet (22) upon the inhalation of the patient provides to deliver one dose of the dry powder medicament to the patient by entraining it from the blister pocket (15a) to the mouthpiece (14).

The rotation of the indexing wheel (8) is transmitted to the base gear (7) engaging with the pinion gear (11) by the pinion gear (11). The small gear which is under the base gear (7) as attached engages with the counter gear (9) (figure 7c). Thus, the movement of the indexing wheel (8) is transmitted to the counter wheel (9) shown in figure 9 by the pinion gear (11) and the base gear. There are numerals incrementing from 1 to 60 in the counter gear (9) displayed in figure 9. The angles between these numerals are all equal and approximately 5°. In response to each actuation of the device, the counter gear rotates approximately 5° and the number of the unused blister pockets remained in the device are clearly seen through the display aperture (4c) on the lower housing member (4b).

In use of the device described in figures 1-9, the mouthpiece (14) is exposed when the mouthpiece cover (2) is slid from the first position to the second on the upper housing member (4a) and the lower housing member (4b); the gear mechanism is triggered by the drive gear (12) and one dose of dry powder medicament is prepared for inhalation; the counter gear (9) is indexed and the numeral seen through the display aperture (4c) on the lower housing member (4b) is incremented.

The medicament in dry powder form which is stored in blister cavities is manufactured according to the prior art. According to the present invention, the particle sizes of the active agents comprised in the dry powder medicament are smaller than 20 μm, preferably smaller than 10 μm.

The inhaler pertaining to the present invention has been designed so as to deliver the dry powder medicament used in monotherapy or combined therapy. The term "monotherapy"

refers to inhalation treatments in which dry powder medicaments comprising a single active agent are used whereas the term "combined therapy" refers to inhalation treatments in which dry powder medicaments comprising more than one active agents are use used.

The dry powder medicament delivered via the device pertaining to the present invention comprises at least one excipient in addition to the active agent or agents. These excipients are generally chosen from a group comprising monosaccharides (glucose, arabinose, etc.), disaccharides (lactose, saccharose, maltose, etc.), oligo- and polysaccharides (dextran, etc.), polyalcohols (sorbite, mannite, xylite), salts (sodium chloride, calcium carbonate, etc.) or combinations thereof. According to the present invention, the medicament in dry powder form comprises lactose as the excipient. The medicament in dry powder form comprises fine or coarse excipients particles preferably having various particle size ranges in order to deliver the required amount to the lungs.

The active agent or the active agents comprised in the dry powder medicament which is stored in blister packages used in the device pertaining to the present invention can be selected from a group comprising cromolyns, anti-infectives, antihistamines, steroids, anti-inflammatories, bronchodilators, leukotirene inhibitors, PDE IV inhibitors, antitussives, diuretics, anticholinergics, hormones, xanthines and pharmaceutically acceptable combinations thereof.

The active agent comprised in the medicament in dry powder form delivered via the inhaler pertaining to the present invention is preferably selected from a group comprising tiotropium, oxitropium, flutropium, ipratropium, glicopironium, flunisolid, beclomethasone, budesonide, fluticasone, mometasone, ciclesonide, rofleponide, dexamethasone, montelukast, methylcyclopropane acetic acid, sodium cromoglicat, nedocromil sodium, Npropylene, teophylline, roflumilast, ariflo (cilomilast), salmeterol, salbutamol, formoterol, terbutaline, carmoterol, indacaterol, cetirizine, levocetirizine, efletirizine, fexofenadine and their racemates, free base, enantiomers or diastereomers and their pharmaceutically acceptable salts, solvates and/or hydrates or a combination of said active agents.

The device pertaining to the present invention is used in the administration of the medicament in dry powder form which is utilized in the treatment of many respiratory diseases, particularly in asthma, chronic obstructive pulmonary disorder (COPD) and allergic rhinitis.

Accordingly, the respiratory diseases include, but not restricted to, allergic or non-allergic asthma at any phases, acute lung injury (ALI), acute respiratory distress syndrome (ARDS), exacerbation of airways hyperactivity, bronchiectasis, chronic obstructive pulmonary including emphysema and chronic bronchitis, airways or lung diseases (COPD, COAD or COLD), pneumoconiosis, aluminosis, anthracosis, asbestosis, chalicosis, ptilosis, siderosis, silicosis, tabacosis and byssinosis. The device pertaining to the invention can be used in prophylactic or symptomatic treatment. In addition, the medicament in dry powder form which is preferably used in the symptomatic treatment of allergic asthma and COPD is administered to the patient via the device pertaining to the present invention.