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(54) **Title:** INHALER FOR A SINGLE DOSE OF DRY POWDER

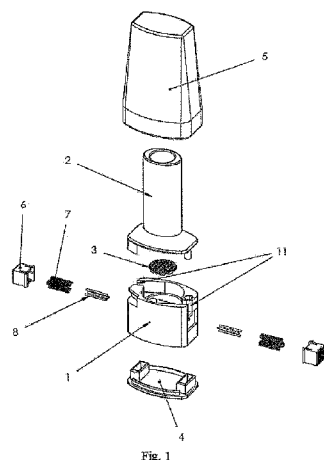


Fig. 1

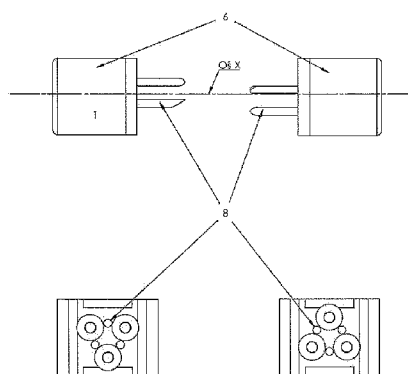


Fig. 6

(57) **Abstract:** An inhaler for a single dose of dry powder, comprising a capsule chamber (1) connected with two puncturing mechanisms consisting of the needles (8) connected with springs (7) and a puncturing push-button (6), comprising also a mouthpiece (2) and a dispersing element (3) between the capsule chamber (1) and the mouthpiece (2), characterised in that every puncturing mechanism is equipped with three needles with a diameter of 0.7 ± 0.1 mm located in a triangular arrangement, while the puncturing mechanisms are rotated mutually by 180° .

Inhaler for a single dose of dry powder

The invention relates to an inhaler for a single dose of dry powder, adapted for capsules containing medication.

Various structural solutions of inhalers adapted for capsules containing medication in the form of dry powder are known, e.g. those disclosed in patent descriptions Nos. US3991761, EP0005585 and EP1603615. In inhalers of such a type, the medication-containing capsule is placed in a chamber, through which the inhaled air flows. Usually, the inhaler is provided with two puncturing mechanisms with needles, which puncture the capsule located in the chamber: most often with four needles (e.g. US3991761), less often with one needle (EP0005585, EP1603615). As a result of rotation of the capsule in the chamber, caused by the inhaled air, the medication exits the capsule thanks to centrifugal force through holes formed by the needles. Rotation of the capsule and of the inhaled air forms an aerosol, or a dispersion of the solid phase (medication) in air, delivered to the patient's respiratory system. The therapeutic effect of such an inhalation depends on the quality of the formed aerosol. The important things are a complete liberation of the medication dose from the capsule and that the liberation occurs at the proper moment.

The inhaler of dry powder presented in patent description No. US3991761 consists of a mouthpiece, a capsule chamber, to which a capsule is inserted before inhalation, and a puncturing mechanism, containing four needles at each end of the capsule chamber, creating 8 holes in the capsules in total (4 on each side). The needles are driven by push-buttons located in the external section of the capsule chamber. The 8 puncturing needles have diameters of 0.6 ± 0.1 mm in this device. On the other hand, in the device presented in patent description No. EP1603615, four needles with a diameter of 0.6 ± 0.1 mm, located at each end of the capsule chamber, were replaced with a single needle at each end of the capsule chamber (2 needles in total), though with a larger diameter: 1.2 ± 0.1 mm. The points of these larger needles are bevelled, which facilitates puncturing of the capsules (the needle points in the four-needle device are conical). In this device, the puncturing systems are arranged so that the equivalent diameter of the hole or holes cut by each puncturing system, after its removal from the hole or holes, amounts to 10% to 31% of the equivalent diameter of the cross-section of the external surface part of the container to be punctured, situated between two punctured terminal parts.

Moreover, known devices are usually equipped with a grate dispersing the powder and lids.

The number and size of the holes created in the capsule has an important influence on formation of the aerosol. With too high a number of holes or too large a diameter of the puncturing needles, damage (cracking) of the capsule often occurs, resulting in too rapid liberation of the medication in the initial phase of aerosol formation. Cracking of the capsule may also lead to passing of fragments of the capsule into the patient's respiratory system, causing discomfort. Too low a number of holes or too small a diameter may lead to a situation in which the entire dose of the medication is not liberated from the capsule. In both these cases, the repeatability of the administered dose decreases, as does the effectiveness of the therapy.

Moreover, the deposition of the active substance is determined by the substance particle size, which should be lower than 5 micrometres, and the composition of the lactose mixture used as a vehicle. Coarsely ground lactoses give the mixture to be encapsulated the proper fluidity and ensure more accurate and faster dosing to the capsules during the encapsulation process. However, they have amorphous spots on their surface, where molecules of the active substance may be adsorbed, hindering liberation of these molecules from the lactose surface. Significant strength is necessary to separate the molecules of the active substance from the surface of coarse-grained lactose having particle sizes approx. 70-200 micrometres.

In order to avoid adsorption of medication particles on amorphous spots of coarsely ground lactose, the addition of finely ground lactose with a particle size below 5 micrometres is used. This lactose is added before the addition of the active substance and mixed. The finely ground lactose fills the amorphous spots of the coarsely ground lactose. After the addition of the active substance and mixing with the so-prepared premix of the finely and coarsely ground lactoses, proper deposition parameters of the active substance are obtained. However, in order to obtain pharmacopoeic results of deposition of the active substance, a lactose mixture with a relatively high fraction of finely ground lactose should be used. Meanwhile, the more finely ground lactoses is contained in the product, the lower the fluidity of the blend; therefore, the dosing accuracy during the encapsulation process is decreased.

Thus, there is a need for improvement of the devices in order to provide homogeneous and precise administration of a defined dose of medication to the patient.

The essence of the invention consists in an inhaler for a single dose of dry powder, containing a capsule chamber connected with a puncturing mechanism at two ends of the capsule chamber, and having a dispersing element between the capsule chamber and the mouthpiece. The inhaler according to the invention is characterised in that every puncturing mechanism is equipped with three needles with a diameter of 0.7 ± 0.1 mm located in an equilateral triangular arrangement, while the puncturing mechanisms, as well as the triangular arrangement of the needles, are rotated by 180° to one another. Every needle is connected with a spring, and the puncturing mechanism is connected with the puncturing push-button. Preferably, the needle points are bevelled.

The inhaler according to the invention, with an asymmetrical arrangement of needles of the proper diameter, is intended to facilitate the formation of a proper aerosol. The active substance escapes from the capsule by the centrifugal force of the capsule's rotation caused by the patient's inhalation. Molecules of the therapeutic substance and the lactose particles accompanying them mix and collide with each other, facilitating the resorption of the medication from the particles of coarsely ground lactose. The highest number of collisions occurs in the areas of punctures in the capsule, because the centrifugal force drives the particles in this direction. Asymmetric arrangement of the needles increases the dispersion of punctures on the surface of the capsule, which, together with the proper diameter of the holes, favours suitable mixing of the therapeutic substance and the lactose and, more importantly, also leads to a higher number of collisions of particles. Thanks to these collisions, the adsorbed active substance may be more efficiently separated from particles of coarsely ground lactose and form a proper aerosol. Mutual rotation of the puncturing mechanisms additionally increases this effect. Resorption of the therapeutic substance from coarsely ground lactose significantly affects the repeatability of the dose of medication administered to the patient during inhalation.

A very important and surprising effect of the invention consists in relatively smaller inhalation strength necessary for obtaining the proper deposition of the active substance. This effect is significant in the therapy of children, elderly people or patients with chronic obstructive pulmonary disease or asthma.

The inhaler according to the invention is adapted for use with gelatine or cellulose capsules. In both cases, it ensures obtaining higher deposition limits of the active substance from the inhalation powder, being a mixture of lactose of various particle sizes. In the case of application of the inhaler according to the invention, the lactose mixture may contain a

higher fraction of coarsely ground lactose while maintaining high depositions of the active substance (aerodynamic particle size). On the other hand, the applied lactose mixture with a higher percentage of the coarse fraction ensures a higher uniformity of the content of the active substance in individual capsules. The microdose encapsulation process occurs faster and more accurately.

Another important advantage is that thanks to the design of the inhaler and guarantee of higher deposition, a larger amount of coarsely ground lactoses may be used, as well as the total lactose mass (the vehicle) may be higher. This is an unexpected function of the invention, both increasing the safety of the product's use and facilitating the production process which warrants dose uniformity.

The subject of the invention is illustrated as an embodiment in the drawing, where:

Fig. 1 shows an assembly drawing of the inhaler,

Fig. 2 shows a view of the inhaler with a lid protecting the mouthpiece,

Fig. 3 shows a longitudinal section of the inhaler along the AA axis,

Fig. 4 shows a longitudinal section of the inhaler along the BB axis,

Fig. 5 shows the arrangement of holes in the chamber of the inhaler,

Fig. 6 shows the manner of mutual rotation of the puncturing mechanisms,

Fig. 7 shows a graph of the square root of the pressure drop vs. the airflow intensity through the inhaler.

A description of the inhaler's operation is presented in the examples below.

Example 1.

The inhaler shown in the figure has a capsule chamber 1, connected with two puncturing mechanisms located at two sides of the chamber 1. Each puncturing mechanism consists of three needles 8 with bevelled points, placed in an equilateral triangular arrangement, as shown in Fig. 5, and three springs 7 and a puncturing push-button 6. The capsule chamber 1 is connected separably with a mouthpiece 2, and there is a dispersing grid 3 between the chamber 1 and the mouthpiece 2. The capsule chamber 1 is closed separably with a lid 4 from the bottom, and the mouthpiece is protected with a separable lid 5.

The medication-containing capsule is placed in the chamber 1 of the inhaler, in the hollow for capsules. The capsule is punctured using puncturing mechanisms equipped with needles 8. The needles are introduced to the inhaler's chamber through holes, and their return to the off-position is ensured by the springs 7. After the capsule is punctured, the medication escapes from it as a result of rotation of the capsule in the chamber 1. The

rotation is caused by inhaled air, entering the chamber via inlet channels 11. The air rotation forms an aerosol from the medication and the air, which enters the patient's respiratory system via the mouthpiece 2.

Example 2.

The inhaler described in Example 1 was filled with the active substance – formoterol fumarate with particle micronisation of 90% below 5 micrometres, and the following lactose available from Meggle Pharma, having the trade name Inhalac, with the following particle size ranges measured by laser diffraction:

Inhalac 70 – d10: 100-150 μm ; d50: 180-250 μm ; d90: 270-340 μm ;

Inhalac 120 – d10: 70-105 μm ; d50: 110-155 μm ; d90: 160-215 μm ;

Inhalac 230 – d10: 30-60 μm ; d50: 70-110 μm ; d90: 110-150 μm ;

Inhalac 400 – d10: 0.8-1.6 μm ; d50: 4.0-11.0 μm ; d90: 15.0-35.0 μm .

A series of measurements was carried out with a constant amount of finely ground lactose Inhalac 400 at a level of 7% and a constant amount of formoterol fumarate active substance at a level of 12 micrograms per dose (1 capsule), and with a variable amount of the other lactose. All blends intended for encapsulation were prepared according to the same procedure known to individuals skilled in the art.

The studies were carried out using an NGI cascade impactor from Copley Scientific (this is a type E apparatus according to the European Pharmacopoeia).

The deposition value is reported as the mass of fine particles (with a diameter below 5 μm) [μg] at the airflow through the inhaler of 90 dm^3/min . The percentage content of fine particles in relation to the declared dose is also reported. The same tests were carried out for known eight-needle and two-needle inhalers for comparison. The results are presented in Table 1.

The obtained results indicate that use of the inhaler according to the invention ensures obtaining an aerosol with the best aerodynamic properties, irrespective of the proportions of finely and coarsely ground lactose in the composition of the inhalation powder. It has also been shown that an increase in the content of coarsely ground lactose and an increase in total mass of the powder has the slightest adverse effect on the quality of the obtained aerosol in the case of use of the inhaler according to the invention.

Table 1.

Substance	Quantity per capsule				
	12 mcg	12 mcg	12 mcg	12 mcg	12 mcg
Formoterol fumarate	12 mcg	12 mcg	12 mcg	12 mcg	12 mcg
Inhalac 400	7%	7%	7%	7%	7%
Inhalac 70	20%	30%	40%	30%	40%
Inhalac 120	20%	30%	40%	30%	40%
Inhalac 230	53%	33%	13%	33%	13%
Capsule mass	15.012 mg	15.012 mg	15.012 mg	25.012 mg	25.012 mg
Blend fluidity, visual assessment	The blend bridges in the charging hopper	The blend partially covers the holes left by feeders	The blend fills the holes left by feeders	The blend partially covers the holes left by feeders	The blend fills the holes left by feeders
Deposition value while using a two-needle inhaler	4.19 μ g 34.9%	3.99 μ g 33.3%	3.27 μ g 27.6%	3.26 μ g 27.2%	2.98 μ g 24.8%
Deposition value while using an eight-needle inhaler	4.04 μ g 33.7%	3.81 μ g 31.8%	3.10 μ g 25.8%	3.17 μ g 26.4%	2.53 μ g 21.1%
Deposition value while using an inhaler with 6 needles in an asymmetric arrangement	4.33 μ g 36.1%	4.10 μ g 34.2%	3.35 μ g 27.9%	3.77 μ g 31.4%	3.19 μ g 26.6%

Example 3.

Tests of particle size distribution for particles emitted from inhalers and proper resistances of the inhalers.

The tests were carried out using an NGI cascade impactor from CopleyScientific.

In order to determine the proper resistances of the inhalers, the pressure drop accompanying the airflow of various intensities through the inhaler was measured. A dependence of the pressure drop (ΔP [hPa]) on the volumetric flow of air through the inhaler (Q [dm³/min]) and the linear dependence between $\sqrt{\Delta P}$ and Q were determined. The coefficient of proper resistances of the inhaler (R_D [hPa^{0.5}·min·dm⁻³]) was determined as the slope of the obtained straight line.

Measurements for 5 inhalers according to the invention (Inhaler) were carried out by measuring the pressure drop at 5 different airflow intensities in the range of 27-102 dm³/min. The determined proper resistance value of 0.0509 hPa^{0.5}·min·dm⁻³ classifies the tested inhaler as a low-resistance inhaler and is close to the values obtained for other inhalers of the cyclohalers described in literature. Such proper resistance of the inhaler provides patients with the ease of obtaining high airflow during inhalation, consequently warranting a high quality of the obtained aerosol.

The results are presented in Fig. 9.

At the same time, comparative measurements of proper resistances of the inhalers available on the market with reference drugs: a low-resistance inhaler with a single needle at each end of the capsule chamber containing formoterol fumarate (A) as the active substance and a medium-resistance disc-type inhaler containing fluticasone propionate as the active substance (B).

A two-needle inhaler was selected for the comparison, as it is more up-to-date and has better parameters than the eight-needle inhaler used previously.

The obtained proper resistance values of the inhalers are gathered in Table 2.

Table 2.

Inhaler type	Inhaler	A	B
Proper resistance of the inhaler	0.051	0.058	0.074

Example 4.

Tests of emitted dose, as well as mass and dose of fine particles.

According to the requirements of the European Pharmacopoeia, dry powder inhalers (DPI) should be tested at an airflow providing a 4 kPa pressure drop in the inhaler. Such airflow may be determined based on the following formula:

$$Q = \frac{\sqrt{40}}{R_D}$$

For low-resistance inhalers (with proper resistance below 0.063 hPa^{0.5}·min·dm⁻³), the so-calculated value of airflow intensity is higher than 100 dm³/min, and it is assumed that these inhalers should be tested with an airflow equal to 100 dm³/min. For a medium-resistance inhaler, such as inhaler B, the determined value of the airflow intensity amounts to approx. 90 dm³/min.

In order to define the quality of the aerosol obtained from the tested inhalers, the following quantities of the aerosol were determined:

- ED – emitted dose, or the amount (mass) of the medication dosed during liberation of a single dose (from one capsule),
- FPM – fine particles mass, or amount of the medication in the form of particles with an aerodynamic diameter lower than 5 μm ,
- FPF – fine particles fraction, or percentage of particles with a diameter below 5 μm in relation to the emitted dose.

Measurements were carried out at three values of airflow intensity: 60, 90 and 100 dm^3/min . For each airflow, 3 measurements were carried out, each for a different specimen of the tested inhaler. The medication retained on the individual impactor stages was transferred quantitatively to graduated flasks using a proper solvent. Concentrations in the obtained samples were determined by Ultra High Performance Liquid Chromatography (UHPLC) with UV-Vis detection, using Waters CSH C18 50 x 2.1 mm, 1.7 μm columns. Cut-off diameters d_{50} [μm] for the individual stages of the NGI cascade impactor at the applied airflows are presented in Table 3.

Table 3.

	60 dm^3/min	90 dm^3/min	100 dm^3/min
Pre-separator	> 8.06	> 6.48	> 6.12
1	8.06	6.48	6.12
2	4.46	3.61	3.42
3	2.82	2.30	2.18
4	1.66	1.37	1.31
5	0.94	0.76	0.72
6	0.55	0.43	0.40
7	0.34	0.26	0.24
POWER	< 0.34	< 0.26	< 0.24

The test was carried out for developed formulations with fluticasone propionate and formoterol fumarate for the inhaler according to the invention and products A (formoterol fumarate) and B (fluticasone propionate).

Before the measurement, the impactor stages were covered with a thin layer of silicon oil in order to avoid secondary entrainment of particles already deposited. For both products containing fluticasone propionate and formoterol fumarate, 10 doses were emitted into the impactor in each measurement. The dosing time of every unit was adequately selected to

the airflow so that 4 dm³ of air flowed through the inhaler during the dosing and amounted to: 4, 2.7 and 2.4 sec for airflows of 60, 90 and 100 dm³/min, respectively.

Owing to the fact that the NGI impactor does not have a stage with a cut-off diameter equal to exactly 5 µm, the following formula was used for the calculation of FPM:

$$FPM = m_n + \frac{(5 - d_n)(m_{n-1} - m_n)}{(d_{n-1} - d_n)}$$

where:

FPM particle mass below 5 µm,

m_n cumulated dose corresponding to the impactor stage with a cut-off diameter of d_n

d_n the closest cut-off diameter with a value below 5 µm,

m_{n-1} cumulated dose corresponding to the impactor stage with a cut-off diameter of d_{n-1}

d_{n-1} the closest cut-off diameter with a value above 5 µm.

The obtained results are presented in the tables below.

Table 4. List of emitted dose values [µg] for formoterol fumarate using the tested inhalers at an airflow of 60 dm³/min.

	Inhaler	A
Measurement 1	9.66	9.84
Measurement 2	9.71	9.78
Measurement 3	9.62	9.9
Average	9.66	9.84
S	0.0451	0.0600
RSD	0.47%	0.61%

Table 5. List of fine particle mass (FPM) values for formoterol fumarate using the tested inhalers at an airflow of 60 dm³/min.

	Inhaler	A
Measurement 1	4.10	3.95
Measurement 2	4.07	3.87
Measurement 3	4.01	4.01
Average	4.06	3.94
S	0.0458	0.0702
RSD	1.13%	1.78%

Table 6. List of emitted dose values [μg] for formoterol fumarate using the tested inhalers at an airflow of $90 \text{ dm}^3/\text{min}$.

	Inhaler	A
Measurement 1	9.54	9.20
Measurement 2	9.41	9.28
Measurement 3	9.51	9.44
Average	9.49	9.31
S	0.0681	0.1222
RSD	0.72%	1.31%

Table 7. List of fine particles mass (FPM) values for formoterol fumarate using the tested inhalers at the airflow of $90 \text{ dm}^3/\text{min}$.

	Inhaler	A
Measurement 1	4.14	4.00
Measurement 2	4.07	4.12
Measurement 3	4.13	4.02
Average	4.11	4.05
S	0.0379	0.0643
RSD	0.92%	1.59%

Table 8. List of emitted dose values [μg] for formoterol fumarate using the tested inhalers at an airflow of $100 \text{ dm}^3/\text{min}$.

	Inhaler	A
Measurement 1	9.42	9.35
Measurement 2	9.44	9.19
Measurement 3	9.35	9.23
Average	9.40	9.26
S	0.0473	0.0833
RSD	0.50%	0.90%

Table 9. List of fine particle mass (FPM) values for formoterol fumarate using the tested inhalers at an airflow of $100 \text{ dm}^3/\text{min}$.

	Inhaler	A
Measurement 1	4.14	4.10
Measurement 2	4.19	3.96
Measurement 3	4.12	4.06
Average	4.15	4.04
S	0.0361	0.0721
RSD	0.87%	1.78%

Table 10. List of fine particles fraction (FPF) values for formoterol fumarate using the tested inhalers at airflows of 60, 90 and 100 dm³/min.

	60 dm ³ /min	90 dm ³ /min	100 dm ³ /min
Inhaler	42%	43.3%	44.1%
A	40.1%	43.5%	43.6%

Table 11. List of emitted dose values for fluticasone propionate using the tested inhalers at an airflow of 60 dm³/min.

	Inhaler	B
Measurement 1	38.97	39.15
Measurement 2	39.91	37.44
Measurement 3	40.21	39.52
Average	39.70	38.70
S	0.6469	1.1096
RSD	1.63%	2.87%

Table 12. List of FPM values for fluticasone propionate using the tested inhalers at an airflow of 60dm³/min.

	Inhaler	B
Measurement 1	14.22	13.14
Measurement 2	14.60	12.58
Measurement 3	14.69	12.99
Average	14.5	12.9
S	0.2495	0.2899
RSD	1.72%	2.25%

Table 13. List of emitted dose values for fluticasone propionate using the tested inhalers at an airflow of 90 dm³/min.

	Inhaler	B
Measurement 1	37.82	40.16
Measurement 2	36.93	39.09
Measurement 3	38.02	37.85
Average	37.6	39.0
S	0.5803	1.1560
RSD	1.54%	2.96%

Table 14. List of FPM values for fluticasone propionate using the tested inhalers at an airflow of 90 dm³/min.

	Inhaler	B
Measurement 1	15.06	13.81
Measurement 2	14.87	13.22
Measurement 3	15.30	12.79
Average	15.1	13.3
S	0.2155	0.5121
RSD	1.43%	3.86%

Table 15. List of emitted dose values for fluticasone propionate using the tested inhalers at an airflow of 100 dm³/min.

	Inhaler	B
Measurement 1	36.54	40.06
Measurement 2	36.94	38.61
Measurement 3	37.70	39.28
Average	37.1	39.3
S	0.5892	0.7306
RSD	1.59%	1.86%

Table 16. List of FPM values for fluticasone propionate using the tested inhalers at an airflow of 100 dm³/min.

	Inhaler	B
Measurement 1	15.11	13.55
Measurement 2	15.53	13.02
Measurement 3	15.60	13.08
Average	15.4	13.2
S	0.2650	0.2902
RSD	1.72%	2.20%

Table 17. List of FPF values for fluticasone propionate using the tested inhalers at airflows of 60, 90 and 100 dm³/min.

	60 dm ³ /min	90 dm ³ /min	100 dm ³ /min
Inhaler	36.5%	40.2%	41.5%
B	33.3%	34.1%	33.6%

Claims

1. An inhaler for a single dose of dry powder, comprising a capsule chamber (1) connected with two puncturing mechanisms consisting of the needles (8) connected with springs (7) and a puncturing push-button (6), comprising also a mouthpiece (2) and a dispersing element (3) between the capsule chamber (1) and the mouthpiece (2), characterised in that every puncturing mechanism is equipped with three needles with a diameter of 0.7 ± 0.1 mm located in a triangular arrangement, while the puncturing mechanisms are rotated mutually by 180° .
2. An inhaler according to claim 1, characterised in that the needles (8) are located in an equilateral triangle arrangement.
3. An inhaler according to claim 1, characterised in that the needle points are bevelled.

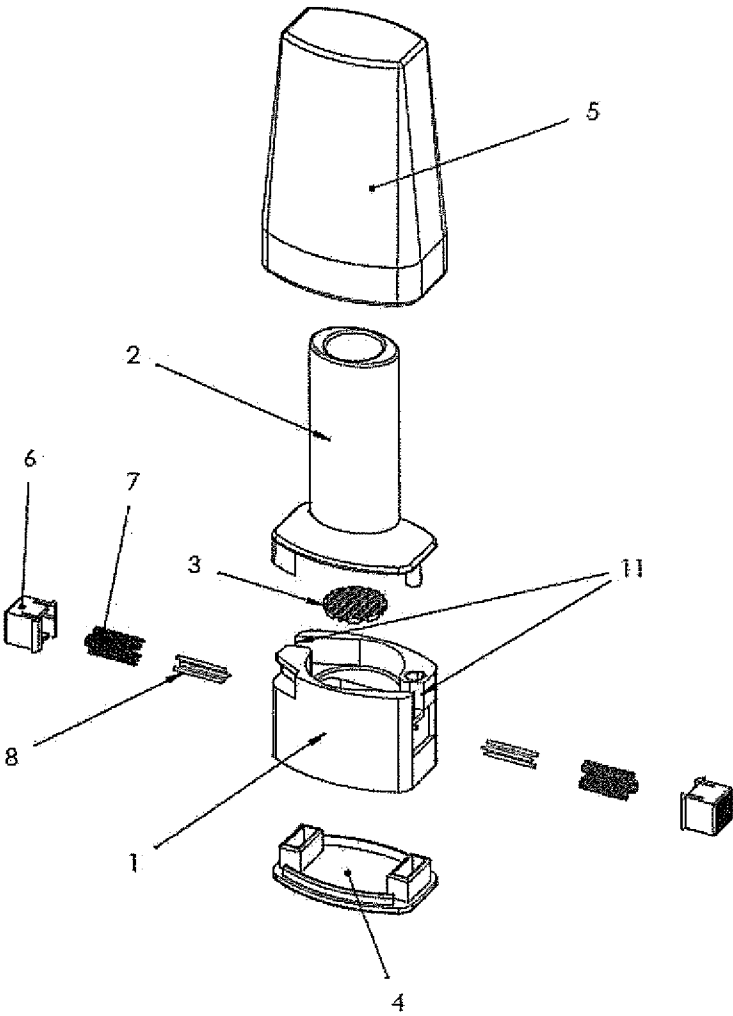


Fig. 1

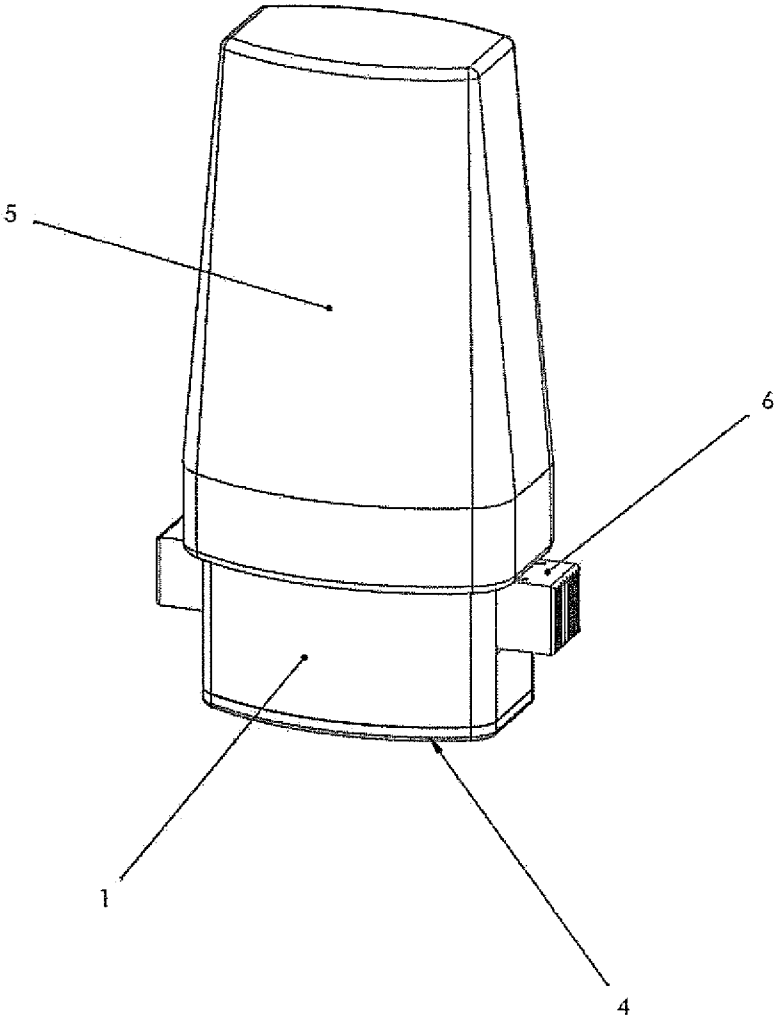


Fig.2

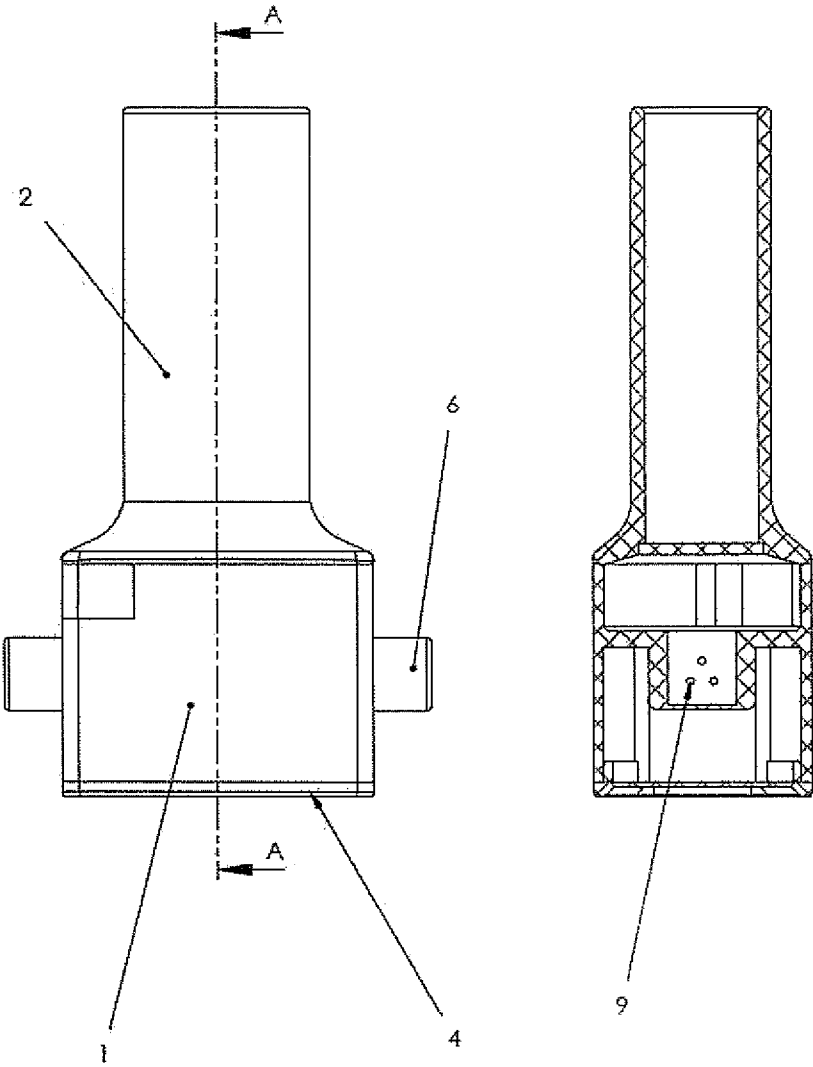


Fig. 3

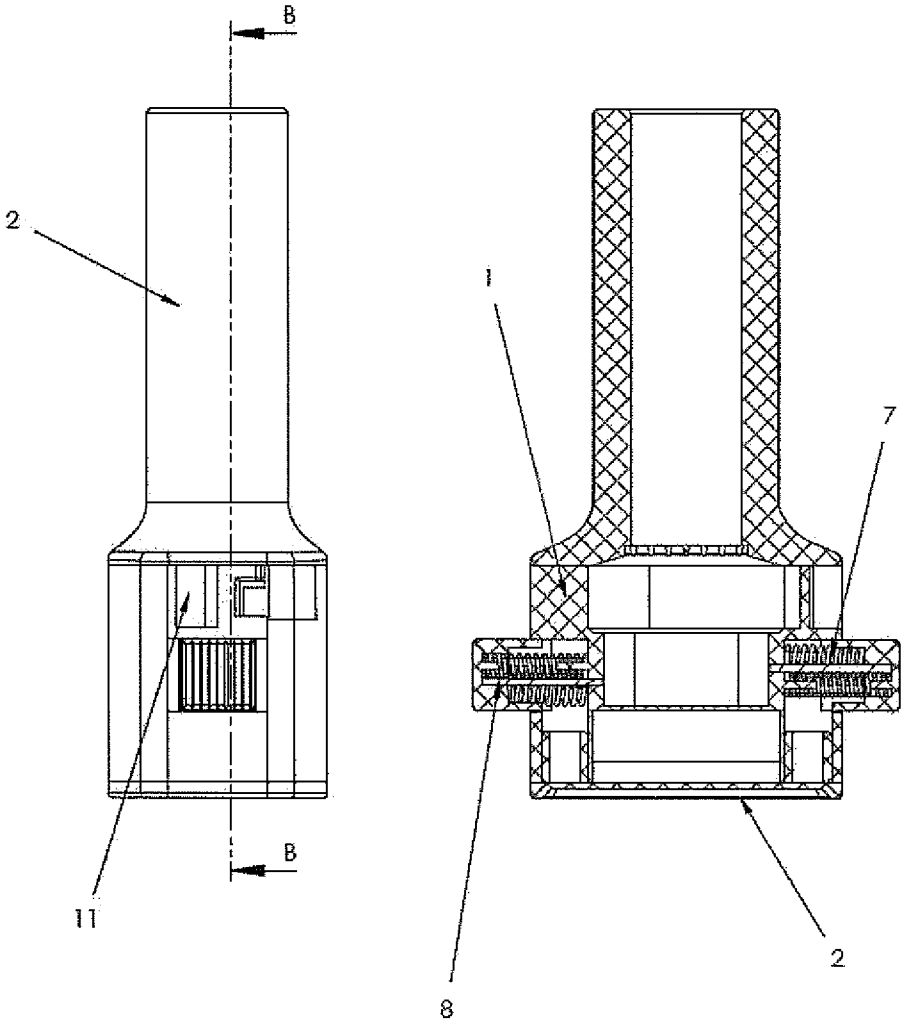


Fig. 4

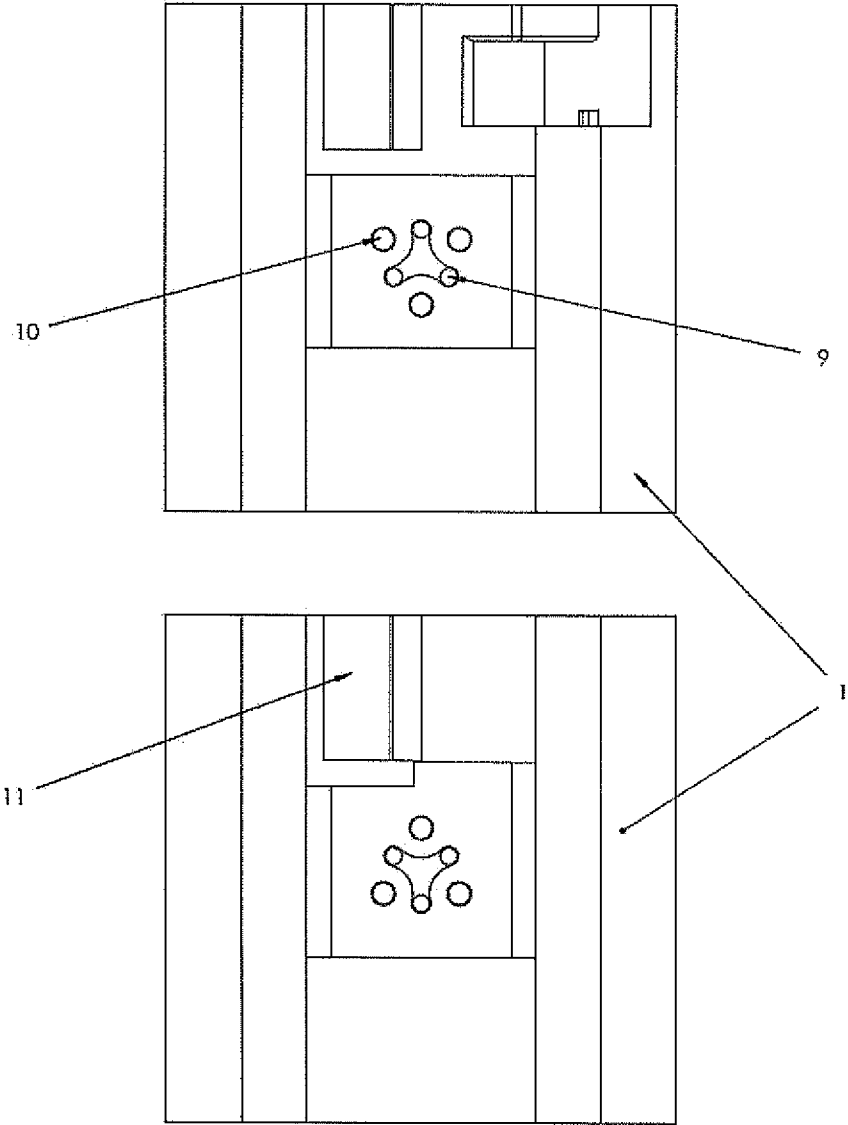


Fig. 5

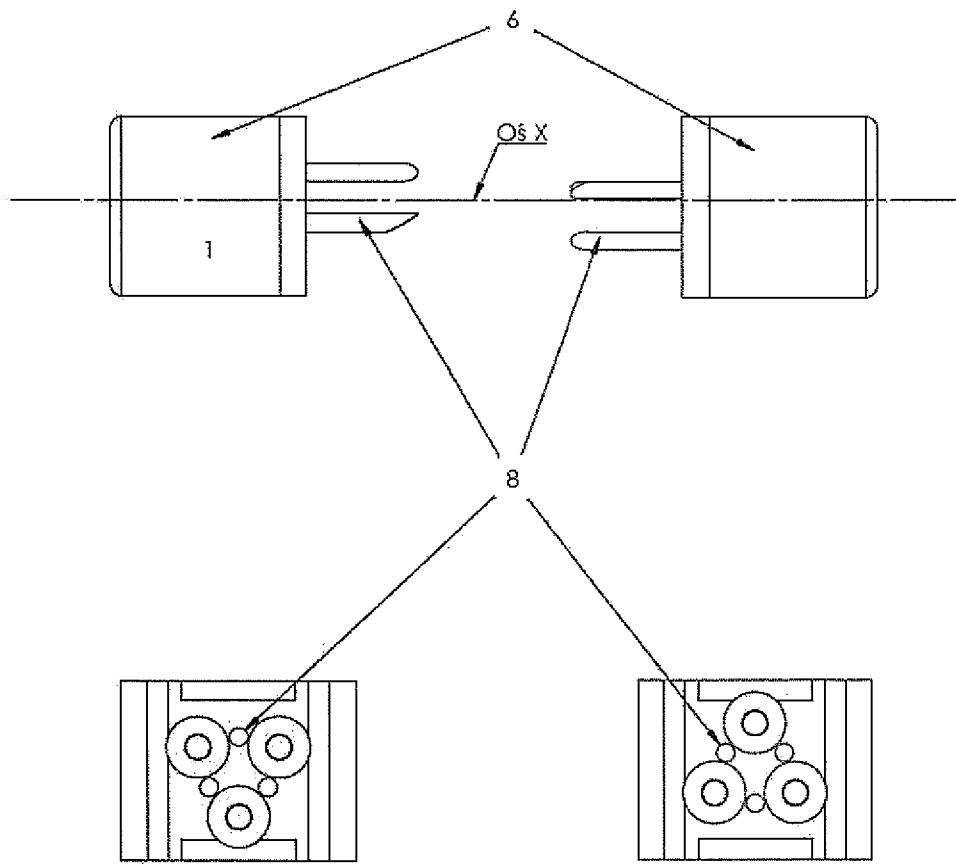


Fig. 6

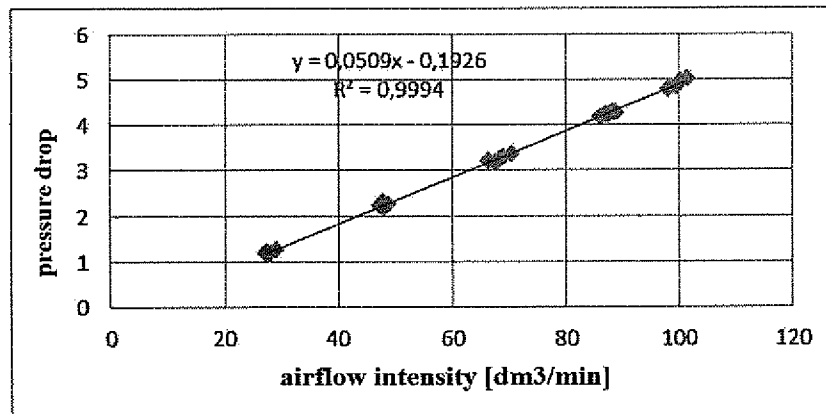


Fig. 7

INTERNATIONAL SEARCH REPORT

International application No
PCT/PL2016/000040

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61M15/00

ADD. A61M11/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61M

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 1 603 615 A1 (GALEPHAR M F [BE]) 14 December 2005 (2005-12-14) cited in the application	1,3
Y	paragraph [0001] - paragraph [0029] paragraph [0031] - paragraph [0047] figures 1-9	1-3
Y	----- US 3 991 761 A (COCOZZA SALVATORE) 16 November 1976 (1976-11-16) cited in the application column 1, line 5 - column 2, line 29 column 2, line 67 - column 5, line 37 figures 1-11 ----- -/--	1-3



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search

17 June 2016

Date of mailing of the international search report

28/06/2016

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Authorized officer

Aguado, Miguel

INTERNATIONAL SEARCH REPORT

International application No

PCT/PL2016/000040

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
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A	EP 0 666 085 A1 (PLURICHEMIE ANSTALT [LI]) 9 August 1995 (1995-08-09) column 1, line 1 - column 7, line 20 column 7, line 40 - column 10, line 18 figures 1-8 -----	1-3

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