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(71) Applicant: **CHIESI FARMACEUTICI S.P.A.** [IT/IT]; Via Palermo, 26/A, I-43100 Parma (IT).

(72) Inventors: **DAVIES, Rebecca, Jayne**; Flat 3, 18 Walcot Parade, Bath BA1 5HF (GB). **GANDERTON, David**; "Crooked Chimneys", Cheriton Bishop, Exeter EX6 6JL (GB). **LEWIS, David, Andrew**; 37 Marsons Way, Corsham, Nr Bath SN13 9XW (GB). **MEAKIN, Brian, John**; Sussex Lodge, 5 Oakley, Claverton Down, Bath BA2 6DS (GB).

(74) Agent: **ADAM, Holger**; Kraus & Weisert, Thomas-Wimmer-Ring 15, 80539 Munich (DE).

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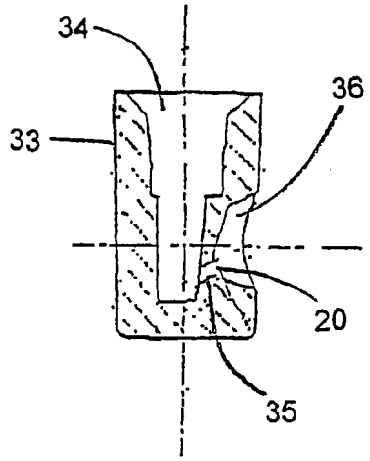

(57) Abstract: The present invention relates to pressurized metered dose inhaler (pMDI) actuators (2) with laser drilled orifices and to medicinal aerosol solution formulation products comprising these actuators (2). In particular, the present invention relates to the optimisation of the output characteristics of drug solution formulations in hydrofluoroalkanes (HFAs) by use of pMDIs with actuators (2) with laser drilled orifices of specific dimensions. Moreover, the actuators (2) of the present invention allow the use of solution formulations with a high ethanol content and a high ratio of ethanol to active ingredients and thus, the use of poorly soluble active ingredients in solution formulations and allow the use of solution formulations which are substantially free of low volatility components.

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Metered Dose Inhaler

The present invention relates to pressurized metered dose inhaler (pMDI) actuators with laser drilled orifices and to medicinal aerosol solution formulation products comprising these actuators. In particular, the present invention relates to the optimisation of the output characteristics of drug solution formulations in hydrofluoroalkanes (HFAs) by use of pMDIs with actuators with laser drilled orifices of specific dimensions. Moreover, the actuators of the present invention allow the use of solution formulations with a high ethanol content and a high ratio of ethanol to active ingredients and thus, the use of poorly soluble active ingredients in solution formulations and allow the use of solution formulations with high ethanol content which are substantially free of low volatility components.

The pharmaceutical solution formulations in hydrofluoroalkanes used in the present invention may be filled into canisters suitable for delivering pharmaceutical aerosol formulations. Canisters generally comprise a container capable of withstanding the vapour pressure of the HFA propellant, such as plastic or plastic-coated glass bottle or preferably a metal can, for example a stainless steel can or aluminium can which is preferably anodised, organic coated, such as lacquer-coated and/or plastic coated (WO00/30608 of the applicant), which container is closed with a metering valve. The metering valves comprising a metering chamber are designed to

deliver a metered amount of the formulation per actuation and incorporate a gasket to prevent leakage of propellant through the valve. The gasket may comprise any suitable elastomeric material such as for example low density polyethylene, chlorobutyl, black and white butadiene-acrylonitrile rubbers, butyl rubber and neoprene. Thermoplastic elastomer valves as described in WO92/11190 and valves containing EPDM rubber are especially suitable. Suitable valves are commercially available from manufacturers well known in the aerosol industry, for example, from Valois, France (e.g. DF10, DF30, DF31, DF60), Bespak plc UK (e.g. BK300, BK356, BK357) and 3M-Neotechnic Ltd. UK (e.g. Spraymiser™).

Valve seals, especially the gasket seal, and also the seals around the metering chamber, will preferably be manufactured from a material which is inert to and resists extraction into the contents of the formulation, especially when the contents include ethanol.

Valve materials, especially the material of manufacture of the metering chamber, will preferably be manufactured of a material which is inert to and resists distortion by contents of the formulation, especially when the contents include ethanol. Particularly suitable materials for use in manufacture of the metering chamber include polyesters eg polybutyleneterephthalate (PBT) and acetals, especially PBT.

A valve stem extends from the metering valve and acts as a conduit to pass the metered dose into a nozzle block situated in the actuator body, in which the valve stem is seated.

Materials of manufacture of the metering chamber and/or the valve stem may desirably be fluorinated, partially fluorinated or impregnated with fluorine containing substances in order to resist drug deposition.

Each filled canister is conveniently fitted into a suitable channelling device prior to use to form a metered dose inhaler for administration of the medicament into the lungs or nasal cavity of a patient. Suitable channelling devices comprise, for example a valve actuator and cylindrical or cone-like passage through which medicament may be delivered from the filled canister via the metering valve to the nose or mouth of a patient e.g. a mouthpiece actuator.

In a typical arrangement (Figure 1) the valve stem 7 is seated in a nozzle block which comprises an actuator insert 5, which comprises an actuator orifice 6 leading to an expansion chamber. Conventional pressurized metered dose inhaler actuators have variable actuator orifice diameters from 0.25 to 0.42mm and a length from 0.30 to 1.7mm. In other types of actuators the lengths can vary. International Patent Application WO01/19342 discloses actuator orifice diameters in the range of 0.15 to 0.45mm, particularly 0.2 to 0.45mm. According to this prior art reference it is advantageous to use a small diameter e.g. 0.25mm or less, particularly 0.22mm since

this tends to result in a higher FPM (fine particle mass) and lower throat deposition. Moreover it is stated that 0.15mm is also particularly suitable. However, this prior art reference does not disclose how to obtain actuator orifices of less than 0.2mm. The examples only relate to pMDIs having actuator orifices of 0.22mm, 0.33mm and 0.50mm. Thus, although referring in general to small actuator orifice diameters of less than 0.2mm, the prior art does not provide a solution how to obtain such small orifices with a high precision, i.e. with tightly controlled tolerances.

WO 01/58508 discloses an actuator for a metered dose inhaler containing a liquefied propellant and a medicament. The actuator comprises a nozzle block having a fluid flow path extending therethrough, the fluid flow path defined by an internal chamber having an inlet and an outlet; the outlet being defined in a portion of said nozzle block and comprising an exit channel extending therethrough. The exit channel has a narrow portion wherein the diameter of the channel is 0.3mm or less, the narrow portion being 0.5mm or less in length; and the narrow portion optionally including a constriction having a diameter of less than 0.3mm. According to WO 01/58508, the increased degree of material deposition typically encountered with the use of nozzle orifices having a diameter of 0.3mm or less may be reduced to a level at or below that experienced with larger diameter nozzles while still producing the high fine particle fractions achievable through using small diameter orifice nozzles (0.3mm or less). This is accomplished by limiting the length of the portion of the nozzle channel which is 0.3mm or less in diameter to 0.5mm or less in length.

WO 99/55600 discloses a medicinal aerosol product having a blockage resistant metered-dose valve with a metal valve stem, particularly for use with CFC-free solution formulations using hydrogen containing propellants, such as 134a and/or 227, and ethanol. Moreover, a metered dose inhaler comprising an actuator and an aerosol product is disclosed. The actuator comprises a nozzle block and a mouth piece, the nozzle block defining an aperture for accommodating the end of the valve stem and an orifice in communication with the aperture directed towards the mouth piece, the orifice having a diameter of less than 0.4mm, preferably about 0.3mm.

Metered dose inhalers are designed to deliver a fixed unit dosage of medicament per actuation shot or "puff", for example in the range of 25 to 250µg medicament per puff, depending on the metering chamber volume used.

In the accompanying drawings, figure 1 shows a conventional pressurized metered dose inhaler comprising a canister 1, an actuator 2, a metering valve 3 with a valve stem 7, an oral tube 4, and a nozzle block comprising an actuator insert 5 and an actuator orifice 6.

Figures 2, 3 and 4 show a conventional actuator nozzle block. Figure 3 is a section on line 2-2 of figure 2, and figure 4 is an enlarged reversed view of the circled part of figure 3.

Referring to the figures, a conventional pressurized metered dose inhaler consists of a body portion 10 of an actuator into which a pressurized canister 1 containing a medicinal aerosol solution formulation may be inserted, and located by means of ribs 11.

A nozzle block 14 of the body portion 10 has a bore 15 which receives the valve stem 7 of the canister 1. The end of the stem beares on a step 16 within the base so that compressing the body portion 10 and canister 1 together opens the valve 3 and causes the discharge under pressure of a single measured quantity of the drug in its carrier medium.

The dose passes down a passage 17 in the nozzle block 14, through a conduit 18 (with an actuator orifice length), e.g. a parallel-bore conduit to a discharge nozzle 20 (with an actuator orifice diameter), and thence through a mouthpiece 22 of the body portion 10 of the actuator.

The shape and direction of the discharge plume and the dispersion of the droplets or particles therein are critical to effective administration of a controlled dose to the patient.

Conventionally the discharge nozzle 20 is positioned in a cylindrical recess 23 in the nozzle block 14 having a parallel sided portion 24 and a frusto-conical base 26. In order for the patient to insert the mouthpiece at the correct orientation for discharge of the spray whilst at the same time hold-

ing the body portion 10 of the actuator and the canister 1 at a convenient angle, the axis of the mouthpiece 22 is inclined at an obtuse angle of about 105 degrees to that of the body portion 10 of the actuator and nozzle block 14. Because of this geometry, the conical recess is not perpendicular to the surface of the nozzle block 14, resulting in the parallel sided portion 24 being shorter on one side than the other.

The dimension of the discharge nozzle 20 (actuator orifice diameter) and the recess 23 are such that the discharge plume dose not impinge directly upon the sides of the recess 23.

A problem with known inhaler spray nozzles is that of adequately matching the dimensions of the conduit 18 (actuator orifice length) and nozzle 20 (actuator orifice diameter) to the particular drug formulation and carrier-propellant. Different drugs have different flow and dispersion characteristics (particularly as between suspensions wherein drug particles are dispersed in the formulation and solutions wherein the drug is completely dissolved in the formulation) and it is often difficult to achieve the optimum balance between the plume shape, total dose volume and plume duration.

It has been disclosed (Lewis D.A. et al., Respiratory Drug Delivery VI, 363-364, 1998) that using commercially available actuators for delivering solution formulations of aerosol pressurized with HFA, the reduction in the orifice diameter from 0.42 to 0.25mm induces an increase in the fine particle dose (FPD) of the aerosol produced.

FPD, which provides a direct measurement of the aerosol particles considered suitable for deposition and retention in the respiratory tract, is calculated as the mass of the particles deposited from stage 3 to filter (particles with an aerodynamic diameter less than 4.7μm) of the Andersen Cascade Impactor.

The aerodynamic particle size distribution of an aerosol formulation is characterised using a Multistage Cascade Impactor according to the procedure described in European Pharmacopoeia 2nd edition, 1995, part V.5.9.1, pages 15-17. Generally an Andersen Cascade Impactor (ACI) is utilised. Deposition of the drug on each ACI plate is determined by high performance liquid chromatography (HPLC). Mean metered dose is calculated from the cumulative deposition in the actuator and ACI stages; mean delivered dose is calculated from the cumulative deposition in the ACI. Mean respirable dose (fine particle dose, i.e. FPD) which provides a direct measurement of the aerosol particles considered suitable for deposition and retention in the respiratory tract, is obtained from the deposition on Stage 3 (S3) to filter (AF) corresponding to particles ≤ 4.7μm. Smaller particles, with an aerodynamic diameter ≤ 1.1μm correspond to the fraction obtained from the deposition on Stage 6 to filter.

The FPD can also be expressed as a percentage of the ex-valve dose or recovered dose (i.e. Fine Particle Fraction: $FPF_{\leq 4.7\mu m}$ or $FPF_{\leq 1.1\mu m}$). Shot weights are measured by weighing each canister before and after the actuation.

HFA solution formulations usually contain a co-solvent, generally an alcohol and specifically ethanol, to dissolve the active ingredient in the propellant. Depending on the concentration and solubility characteristics of the active ingredient, the concentration of solubilisation agent (e.g. ethanol) can increase. Large amounts of ethanol increase, proportionally to their concentration, the velocity of the aerosol droplets leaving the actuator orifice. The high velocity droplets extensively deposit into the oropharyngeal tract to the detriment of the dose which penetrates in the lower airways (i.e. respirable fraction or fine particle fraction (FPF)).

The technical problem underlying the present invention is to provide pressurized metered dose inhaler actuators with an optimisation of the output characteristics of drug solution formulations in hydrofluoroalkanes (HFAs). In particular, it is a technical problem underlying the present invention to provide actuators with an extremely efficient atomisation also with HFA solution formulations containing high levels of ethanol and high ratios of ethanol to active ingredient, i.e. showing a fine particle fraction (i.e. particles with a diameter smaller than 4.7μm) of at least 50%, preferably at least 60% and more preferably at least 70% and an optimum balance of the plume shape, total dose volume and the plume duration. Moreover, blockage and clogging problems due to material deposition should be avoided.

These technical problems have been solved by an actuator as claimed in claim 1 and a medicinal aerosol solution formulation product according to claim 7.

According to the present invention an actuator is provided with an actuator orifice having a diameter below 0.20mm over the entire actuator orifice length, preferably in the range from 0.10 to 0.20mm, more preferably 0.11 to 0.18mm and in particular from 0.12 to 0.18mm over the entire actuator orifice length, wherein a diameter of 0.12mm, 0.14mm, 0.16mm and 0.18mm is particularly preferred. The orifice diameter can be different at the inlet and at the outlet of the actuator orifice, however, has to be in the given ranges over the entire actuator orifice length. Preferred orifice diameter combinations inlet/outlet (mm) are 12/18, 18/12, 14/18, 18/14, 16/18, 18/16, 12/16, 16/12, 14/16 and 16/14. The small actuator orifice diameters are obtained by using a laser to drill the actuator orifices. The advantages of using a laser to drill the actuator orifices include, very high precision down to a few microns, smooth interior bore, tightly controlled taper and dimensional tolerances, entry angle holes down to 10 degrees and minimal heat damage. Thus, the present invention provides an alternative to existing moulding technics and provides pMDI actuators with very small actuator orifice diameters with tightly controlled tolerances which is necessary to be able to provide tightly controlled reproduceability of the unit dosage of medicament per actuation.

In addition to the actuator orifice diameter, the actuator orifice length is an essential feature according to the pre-

sent invention. Preferably, the actuator orifice has a length in the range from 0.60mm to 1.00mm, in particular from 0.60mm to 0.80mm.

For example a copper vapour laser (CVL) (Oxford Lasers ltd.) can be used to produce actuators with tightly controlled tolerances on orifice diameter and length.

The dimensions of the actuator orifices are checked using a Mitntoyo TM WF20X microscope and Dolan-Jenner Fiberlite.

According to the present invention, specific combinations of actuator orifice diameter and length provide actuators with improved actuator blockage/device clogging characteristics, in particular in combination with drug solution formulations in hydrofluoroalkanes having a high ethanol and/or water content and a high ratio of ethanol to active ingredient and having a low content or being devoid of low volatility components such as glycerol. Water can be present as a co-solvent in an amount of up to 5% by weight. Furthermore, the presence of water can improve the chemical stability of certain active ingredients.

Actuator orifice length of the nozzle blocks of the present invention refers to the distance between the external face (outlet) and the internal surface (inlet) which due to the design of the nozzle blocks are parallel.

According to the present invention, a medicinal aerosol solution formulation containing an active ingredient, preferably a corticosteroid selected from beclometasone dipropionate, budesonide, dexbudesonide, ciclesonide, fluticasone propionate and mometasone propionate, and a β_2-agonist selected from formoterol, salmeterol xinafoate and TA 2005, a hydrofluorocarbon propellant such as HFA 134a, HFA 227 and mixtures thereof, ethanol as a cosolvent in an amount of at least 7% by weight, preferably at least 15% by weight and up to 20 or 25% by weight or more, based on the solution formulation, and in a ratio of ethanol:active ingredient of at least 20:1, preferably 30:1 and more preferably of at least 35:1 by weight, and optionally a low volatility component, such as glycerol, propyleneglycol, polyethyleneglycol and isopropylmyristate in an amount of from 0 to 0.5% by weight, based on the solution formulation is used in a pressurised metered dose inhaler, comprising a canister equipped with a metering valve and the actuator of the present invention as defined above.

Other preferred solution formulations contain a medicament which could take advantage from a pulmonary delivery to produce a systemic therapeutic effect.

The use of the above-described medicinal aerosol solution formulations of the present invention in a pressurized meter dose inhaler comprising an actuator of the present invention as described above results in a medicinal aerosol solution formulation product providing an aerosolised medicament showing a fine particle fraction of at least 50% and an optimum

balance of the plume shape, total dose volume and the plume duration. Moreover, blockage and clogging problems due to materials depositions are avoided by a solution formulation being substantially free of low volatility components, i.e. containing 0 to about 0.5%, preferably 0 to about 0.3% and in particular 0 to 0.1% by weight of a low volatility component such as glycerol. The use of these kinds of solution formulations results in particles with a MMAD (Mass Median Aerodynamic Diameter) $\leq$ 2. Thus, the present invention provides a medicinal aerosol solution for a medicinal aerosol solution formulation product comprising actuators with an extremely efficient atomisation in combination with solution formulations consisting substantially of an active ingredient, ethanol and a hydrofluorocarbon as propellant. If a further additive is present in the solution formulation, it is only present in such an amount that it does not have any detrimental influence on the MMAD of the atomised particles.

In one embodiment of the invention the nozzle structure is manufactured as a separate actuator insert piece which is fitted into the nozzle block 14. Alternatively or in addition, the nozzle block may be a separate component fitted into the body portion 10.

Preferably, the actuator insert pieces are constructed of aluminium or stainless steel, as using a CVL to micro drill plastic results in to much heat damage. However, according to one embodiment of the invention it is possible to laser drill into plastics without heat damage, by frequency doubling the visible output of the CVL. This generates three ultra-violet

wave lengths, e.g. 255nm, 271nm and 289nm. With these ultra-violet wave lengths plastics can be drilled to high precision without heat damage.

Any kind of actuator inserts known in the art, or of nozzle structures known in the art (e.g. as described in GB-A-2276101 and WO99/12596) can be provided with laser drilled orifices. Preferably, the actuator inserts or nozzle structures are made of aluminium or stainless steel.

In one embodiment of the present invention an aluminium nozzle block known in the art as the "Chiesi Jet piece" is provided with a laser drilled orifice. Figures 5 and 6 show the dimensions of the "Chiesi Jet piece" used in the examples of the present invention. Figure 5 is a front view of the T shaped nozzle block. Figure 6 is a section view of the nozzle block along lines A-A of figure 5. The "Chiesi Jet piece" is a separate component fitted into the body portion 10. For a detailed description reference is made to international patent application WO99/12596.

The nozzle block (30) is shaped as a T, consisting of an upper bar composed by two fins (31, 32) to be housed and retained in two seats provided in the two shells forming the device and of a vertical stem (33) shorter than the horizontal upper bar.

The vertical stem (33) comprises a socket (34) provided with a seat to house a hollow stem of a pressurized can.

In the thickness of the stem (33) is bored a conduit (35) that connects the socket (34) with the mouth piece (22) of the device through the orifice (20) positioned in a recess (36).

Examples

Example 1

The "Chiesi Jet piece" was used as a model for the aluminium nozzle block in the examples of the present invention. Once drilled the aluminium nozzle block was housed in a modified Bespak 630 series actuator. Test pieces were also constructed and used to check the orifice entrance (inlet) and exit (outlet) diameters. Adjusting the laser power and focus controls the converging and diverging of the orifice. The dimensions of all actuator orifices were checked using a Mitntoyo TM WF20X microscope and Dolan-Jenner Fiberlite.

Table 1 shows the dimensions of a range of actuator orifice diameters from 0.10mm to 0.18mm, with 0.60 mm orifice length (n=2). The various shaped orifices that can be produced are slot, cross, clover leaf and peanut having an orifice area comparable to a diameter of 0.10 to 0.18mm. The dimensions of the peanut are shown in table 2. Multiple holed actuator orifices were also produced. The dimensions of the multiple holed orifices are included in table 2.

Table 1: Diameters of the milled actuator inserts with 0.60mm orifice length.

Orifice diameter (mm)	0.18
OrificeLength (mm)	0.60

Orifice diameter (mm)	0.14	0.12	0.10
OrificeLength (mm)	0.60	0.60	0.60

Table 2: Diameters of milled actuator inserts with either shaped or multiple holed orifices (* holes are 0.5mm apart).

Area Cf. (mm)	0.10	0.12	0.12
Orifice Shape	Peanut	2 hole*	4 hole*

A high precision can be achieved with laser drilling into aluminium. In table 2 the peanut with an area comparable to a 0.10mm conventional actuator was produced with two laser drillings.

Example 2

The experiments of example 2 consisted of discharging beclometasone dipropionate (BDP)/ethanol/HFA 134a formulations, with and without glycerol, through the actuator insert housed in the modified Bespak actuator (630 series) into an Andersen Cascade Impactor operated at 28.3 $Lmin^{-1}$. Two product strengths, 50µg/dose (with 7% w/w ethanol, no glycerol) and 250µg/dose (with 15% w/w ethanol and 1.3% w/w glycerol) were used. The drug deposited on the actuator, the throat and the stages of the impactor were measured. The delivered dose, the mass median aerodynamic diameter (MMAD), the geometric standard deviation (GSD), the fine particle dose ≤4.7µm ($FPD_{\leq 4.7}$)

and the fine particle dose ≤1.1μm ($FPD_{\leq 1.1}$) were calculated. The FPDs were also expressed as a % fraction of the ex-valve dose ($FPF_{\leq 4.7}$, $FPF_{\leq 1.1}$). Shot weight was measured by weighing the pMDI before and after discharge.

The data for the clouds generated by a range of laser drilled orifice diameters all with 0.60mm length for the 250μg BDP formula (comparison, with glycerol) and 50μg BDP formula (according to the invention without glycerol) are given in Table 3a and 3b respectively. Table 4a and 4b gives comparative data generated for the 250μg and 50μg BDP formula with the laser drilled orifices with 0.30mm orifice length.

Table 3a: Comparative data generated with BDP 250μg formula (with 15% w/w ethanol, 1.3% w/w glycerol) and a range of laser drilled orifice diameters all with 0.60mm length.

Inlet Diameter (mm)	0.30	0.22	0.18	0.14	0.12
Length (mm)	0.6	0.6	0.6	0.6	0.6
Recovered (μg)	252.22	250.11	246.84	250.96	251.38
Delivered (μg)	235.60	232.15	233.65	13363	234.65
Actuator (μg)	16.63	17.94	13.17	13.88	16.74
Throat (μg)	135.47	92.06	53.38	23.65	31.24
Stage 0 - 2 (μg)	20.46	25.52	21.20	20.97	32.04
Stage 0 - 2 (%)	8.11	10.2	8.59	8.36	12.75
FPD < 4.7μm (μg)	79.67	114.59	159.1	192.47	171.37
FPF<4.7 (%)	31.59	45.82	64.45	76.69	68.17
Dose < 1.1μm (μg)	11.93	12.62	18.44	23.27	19.79
FPF<1.1μm (%)	4.73	5.04	7.47	9.27	7.87
MMAD (μm)	2.7	2.7	2.5	2.4	2.6
GSD	2.1	1.9	1.8	1.8	1.9
Average Shot Weight	57.8 ± 0.7	58.5 ± 0.8	57.1 ± 0.7	58.1 ± 0.5	55.4 ± 2.0

Table 3b: Data generated with BDP 50µg formula (with 7% w/w ethanol, no glycerol) and a range of laser drilled orifice diameters all with 0.60mm length.

Inlet Diameter (mm)	0.3	0.22	0.18*	0.14*	0.12*
Length (mm)	0.6	0.6	0.6	0.6	0.6
Recovered (µg)	50.24	51.97	49.97	50.35	49.77
Delivered (µg)	47.05	49.00	46.65	47.00	47.10
Actuator (µg)	3.23	2.95	3.33	3.39	2.66
Throat (µg)	15.49	9.07	4.45	3.50	3.01
Stage 0 - 2 (µg)	1.33	1.62	1.11	1.22	1.47
Stage 0 - 2 (%)	2.65	3.12	2.22	2.42	2.95
FPD < 4.7µm (µg)	30.2	38.34	41.08	42.25	42.63
FPF<4.7 (%)	60.11	73.77	82.21	83.91	85.65
Dose < 1.1µm (µg)	14.91	19.21	24.14	27.44	24.72
FPF<1.1µm (%)	29.68	36.96	48.31	54.5	49.67
MMAD (µm)	1.1	1.1	1.0	0.9	1.0
GSD	2.0	1.9	1.9	1.9	1.9
Average Shot Weight	59.8 ± 0.7	59.6 ± 0.7	61.7 ± 0.5	60.2 ± 0.5	59.4 ± 0.9

*: according to the invention

Table 4a: Comparative data generated with BDP 250µg formula (with 15% w/w ethanol and 1.3% w/w glycerol) and a range of laser drilled orifice diameters all with 0.30mm length.

Inlet Diameter (mm)	0.30	0.22	0.14
Length (mm)	0.3	0.3	0.3
Recovered (µg)	265.66	261.45	254.91
Delivered (µg)	243.05	242.80	242.65
Actuator (µg)	22.63	18.64	12.27
Throat (µg)	136.75	100.16	27.58
Stage 0 - 2 (µg)	23.65	31.34	22.18
Stage 0 - 2 (%)	8.90	11.99	8.70
FPD < 4.7µm (µg)	82.64	111.32	192.89
FPF<4.7 (%)	31.11	42.58	75.67
Dose < 1.1µm (µg)	12.39	12.97	22.23
FPF<1.1µm (%)	8.66	4.96	8.72
MMAD (µm)	2.8	3.0	2.5
GSD	2.2	2.1	1.8
Average Shot Weight	58.0 ± 1.0	58.8 ± 0.5	57.7 ± 0.3

Table 4b: Comparative data generated with BDP 50µg formula (with 7% w/w ethanol, no glycerol) and a range of laser drilled orifice diameters all with 0.30mm length.

Inlet Diameter (mm)	0.30	0.22	0.14
Length (mm)	0.3	0.3	0.3
Recovered (µg)	53.92	54.59	48.76
Delivered (µg)	48.70	50.45	45.25
Actuator (µg)	5.20	4.11	3.49
Throat (µg)	17.86	14.22	7.81
Stage 0 - 2 (µg)	2.52	3.21	4.43
Stage 0 - 2 (%)	4.67	5.88	9.09
FPD < 4.7µm (µg)	28.34	33.06	33.03
FPF<4.7 (%)	52.56	60.56	67.74
Dose < 1.1µm (µg)	14.90	15.17	21.35
FPF<1.1µm (%)	27.63	27.79	43.79
MMAD (µm)	1.2	1.4	1.2
GSD	2.4	2.3	2.9
Average Shot Weight	58.3 ± 0.8	60.1 ± 0.8	59.1 ± 5.05

The data generated with the 0.60mm and 0.30mm orifice length actuators for the BDP 250µg and 50µg formula show a very clear increase in $FPF_{\leq 4.7}$ as orifice diameter decreases . An optimum orifice diameter/length of 0.14mm/0.60mm is seen with the BDP 250µg formulation giving 76.69% $FPF_{\leq 4.7}$ and a MMAD of 2.4. However, an improved $FPF_{\leq 4.7}$ of 83.91% and 85.65% and an improved MMAD of 0.9 and 1.0, respectively, is seen with the BDP 50µg formulation of the present invention containing no glycerol at an optimum orifice diameter/length of 0.14/0.60 and 0.12/0.60. The increase in $FPF_{\leq 4.7}$ is accompanied by a decrease in throat deposition and MMAD as orifice diameter decreases. There is very little change in actuator deposition.

Comparisons between the 0.60mm and 0.30mm orifice length show no differences for the BDP 250µg formula in the presence of glycerol. However with the BDP 50µg formula in the absence of glycerol greater $FPF_{\leq 4.7}$ and smaller MMAD are achieved with the longer orifice length. For the 0.14mm diameter orifice a $FPF_{\leq 4.7}$ of 83.91% is achieved with the 0.60mm length while a $FPF_{\leq 4.7}$ of 67.74% is achieved with the 0.30mm orifice length.

In summary, the actuators of the present invention having an orifice diameter in the range of 0.12 to 0.18mm and a orifice length of 0.6mm to 0.8mm result in combination with a solution formulation being substantially free of low volatility components in an optimisation of the plume characteristics (such as plume duration and fine particle fraction).

Example 3

The data generated for the peanut orifice shape with the BDP 250µg and 50µg formula of Example 2 are shown in table 5a and 5b respectively. The data for the multiple orifice actuator inserts is shown in table 6.

Table 5a: Comparison data generated with BDP 250µg formula.

Shape	Peanut
Area comparable to (mm)	0.1
Recovered (µg)	80.14
Delivered (µg)	11.95
Actuator (µg)	68.22
Throat (µg)	3.65
Stage 0 - 2 (µg)	1.58
Stage 0 - 2 (%)	1.97
FPD < 4.7µm (µg)	6.7
FPF<4.7 (%)	8.36
Dose < 1.1µm (µg)	2.00
FPF<1.1µm (%)	2.50
MMAD (µm)	(2.1)
GSD	(2.5)

Table 5b: Data generated with BDP 50µg formula (orifice created with two drillings).

Shape	Peanut
Area comparable to (mm):	0.1
Recovered (µg)	45.12
Delivered (µg)	41.2
Actuator (µg)	3.92
Throat (µg)	4.92
Stage 0 - 2 (µg)	3.8
Stage 0 - 2 (%)	8.42
FPD < 4.7µm (µg)	32.48
FPF<4.7 (%)	71.99
Dose < 1.1µm (µg)	18.79
FPF<1.1µm (%)	41.64
MMAD (µm)	1.2
GSD	2.7

Table 6: Data generated with BDP 250µg and 50µg formula and the multiple orifice actuator inserts.

BDP/Dose	250µg		50µg	
Shape	2-holes	4-holes	2-holes	4-holes
Area comparable to (mm)	0.12	0.12	0.12	0.12
Recovered (µg)	225.35	204.17	48.96	45.98
Delivered (µg)	207.97	180.95	46.05	43.65
Actuator (µg)	17.37	23.24	2.91	2.31
Throat (µg)	31.77	29.25	4.12	7.53
Stage 0 - 2 (µg)	30.42	24.58	1.97	4.34
Stage 0 - 2 (%)	13.50	12.04	4.02	9.44
FPD < 4.7µm (µg)	145.79	127.10	39.97	31.81
FPF<4.7 (%)	64.69	62.25	81.64	69.18
Dose < 1.1µm (µg)	16.11	17.26	20.64	16.07
FPF<1.1µm (%)	7.15	8.45	42.16	34.95
MMAD (µm)	2.7	2.5	1.2	1.4
GSD	1.9	1.9	2.0	2.7
Average Shot Weight	52.6 ± 3.0	47.1 ± 4.1	59.4 ± 0.6	56.0 ± 1.6

Better results were obtained for the BDP 50µg formula without glycerol in comparison with the BDP 250µg formula with glycerol. No additional improvement in $FPF_{\leq 4.7}$ is achieved with the two and four hole actuator inserts when compared to the single orifice (0.14mm diameter).

Example 4

The effect of ethanol content, using the 0.22mm Bespak actuator as comparator is given in table 7a and 7b for the BDP 250µg and 50µg formulations respectively.

The effect of ethanol concentration was assessed using configuration 0.14mm actuator orifice diameter / 0.60mm orifice length (0.14/0.60) with a 50µg BDP formula containing 7%, 15%

and 25% ethanol. A 250µg BDP formulation containing 15% and 25% ethanol with and without glycerol was also evaluated. The plume characteristics were assessed visually and the duration of dose generation measured acustically.

Table 7a: Effect of percentage of ethanol on atomisation of a BDP 250µg formula with and without glycerol for 0.14, 0.6 orifice actuator inserts (* indicates no glycerol in formulation). 0.22mm Bespak actuator included for comparison.

	Bespak (0.22,0.7)	Laser drilled orifice (0.14,0.6)		
Ethanol (%)	15	15	25	25*
Recovered (µg)	249.30	250.96	261.18	255.75
Delivered (µg)	231.90	237.10	238.75	238.85
Actuator (µg)	18.10	13.88	22.42	16.89
Throat (µg)	96.20	23.65	60.11	56.58
Stage 0 - 2 (µg)	26.60	20.97	45.68	13.35
Stage 0 - 2 (%)	10.60	8.36	17.49	5.22
FPD < 4.7µm (µg)	108.40	192.47	133.00	168.94
FPF<4.7 (%)	43.50	76.69	50.92	66.06
Dose < 1.1µm (µg)	12.00	23.27	11.52	36.90
FPF<1.1µm (%)	4.80	9.27	4.41	14.43
MMAD (µm)	2.9	2.4	3.3	1.8
GSD	2.0	1.8	1.9	1.9
Average Shot Weight	58.5 ± 1.5	58.1 ± 0.5	53.7 ± 0.5	54.1 ± 0.6

Table 7b: Effect of percentage of ethanol on atomisation of a BDP 50µg formula without glycerol for 0.14, 0.6 orifice actuator inserts, 0.22mm Bespak actuator included for comparison.

	Bespak 0.22,0.7	Laser drilled orifice (0.14,0.6)	
Ethanol (%)	7	7	15
Recovered (µg)	49.0	50.35	48.3
Delivered (µg)	44.9	47.0	46.2
Actuator (µg)	4.2	3.4	2.2
Throat (µg)	6.7	3.5	4.9
Stage 0 - 2 (µg)	0.9	1.2	1.2
Stage 0 - 2 (%)	1.9	2.4	2.5
FPD < 4.7µm (µg)	37.2	42.3	40.0
FPF<4.7 (%)	76.0	83.9	82.8
Dose < 1.1µm (µg)	22.4	27.4	18.6
FPF<1.1µm (%)	45.8	54.5	38.4
MMAD (µm)	0.9	0.9	1.2
GSD	1.9	1.9	1.8
Average Shot Weight	58.7 ± 0.3	60.2 ± 0.5	57.5 ± 0.3

The 0.14, 0.6 orifice actuator insert was used to evaluate the effect of increasing the percentage of ethanol in the BDP 250µg formula and 50µg formula. Even with 25% ethanol in the BDP 250µg formula the 50.9% $FPF_{\leq 4.7}$ obtained is greater than the $FPF_{\leq 4.7}$ obtained with the 15% ethanol formula and a 0.22mm conventional Bespak actuator. However, as a consequence of increasing the ethanol content the MMAD obtained is also increased. This can be corrected by removing or altering the percentage of glycerol (or in general the low volatility component) in the formula. This gives the formulator great scope for manipulating the formulation and achieving high drug loading and efficient atomisation if required. This is further demonstrated by the BDP 50µg results (without glycerol) where no loss in $FPF_{\leq 4.7}$ is seen when the ethanol content is increased from 7 to 15%.

Example 5

Through life testing by carrying out Andersen Cascade Impactor determinations for shots 6-15 and shots 191-200 was also carried out to evaluate actuator blockage.

The results of the through life tests with no actuator cleaning are shown in table 8.

Table 8: Through life testing with no actuator cleaning on drilled actuator inserts with a BDP 250µg formulation.

	15% Ethanol, 1.3% Glycerol				25% Ethanol	
Orifice	0.14, 0.6		0.18, 0.6		0.14, 0.6	
Shots	6-15	191-200	6-15	191-200	6-15	191-200
Recovered (µg)	244.83	226.63	237.06	243.51	254.87	234.02
Delivered (µg)	233.00	215.20	226.70	237.70	238.10	222.90
Actuator (µg)	11.83	11.44	10.35	5.81	16.74	11.12
Throat (µg)	25.09	32.92	41.36	65.52	56.11	55.06
Stage 0 - 2 (µg)	25.61	60.88	25.24	27.34	13.96	21.99
Stage 0 - 2 (%)	10.46	26.86	10.65	11.23	5.48	9.40
FPD < 4.7µm (µg)	182.30	121.39	160.10	144.84	168.06	145.85
FPF<4.7 (%)	74.46	53.56	67.54	59.48	65.94	62.32
Dose < 1.1µm (µg)	16.92	9.44	14.60	16.51	36.02	29.07
FPF<1.1µm (%)	6.91	4.17	6.16	6.78	14.13	12.42
MMAD (µm)	2.6	3.5	2.7	2.6	1.8	2.1
GSD	1.8	1.9	1.8	1.8	1.9	2.4
Average Shot Weight	55.4 ± 0.5	55.5 ± 1.6	55.9 ± 0.3	55.2 ± 0.9	54.2 ± 0.9	52.2 ± 0.7

Through life testing was conducted with the 250µg BDP formula. It is clear from the results that the efficiency of atomisation is decreased at the end of the can life with the 0.14, 0.6 orifice insert. A major increase in the MMAD is also observed. The results obtained with the formula contain-

ing 25% ethanol and no glycerol shows a small increase in the MMAD and GSD. However no change in $FPF_{\leq 4.7}$ is seen between beginning and end of can life. The results obtained with the 0.18, 0.6 insert show only a small decrease in efficiency through life.

Example 6

Finally, the relation of spray (plume) duration and fine particle dose for laser drilled actuator inserts generated with BDP 250µg formulation with 15% w/w ethanol and 1.3% w/w glycerol is given in figure 7. The term "(0.14, 0.6)" describes an actuator with an actuator orifice diameter of 0.14mm and an orifice length of 0.6mm.

In summary, it can be concluded that orifice diameter decrease and length increase combine to produce fine sprays. Figure 7 clearly shows that spray duration increases as orifice diameter decreases. A spray duration of over one second can be produced with an orifice of 0.14mm diameter and 0.6mm length, with no loss in the $FPF_{\leq 4.7}$ obtained.

Thus, the present invention confirms that changes in diameter and length of actuator orifices influence the speed (duration) and fine particle characteristics of clouds.

Example 7

In example 7, the actuator blockage/device clogging has been tested for beclometasone dipropionate (BDP, 250µg) solution formulations with and without a low volatility component (LVC).

Table 9 shows the results of an actuator test

Table 9: Effect of the low volatility component on actuator blockage (actuator orifice length = 0.6mm)

Drug	% EtOH	% LVC	Orifice Diameter		Actuator material	Pass/ Fail
			Inlet (mm)	Outlet (mm)		
BDP 250	15	1.3% Glycerol	0.14	0.14	Aluminium	Fail
BDP 250	15	0% Glycerol	0.14	0.14	Aluminium	Pass

Actuator orifice length of the nozzle blocks of the present invention refers to the distance between the external face (outlet) and the internal surface (inlet) which due to the design of the nozzle blocks are preferably parallel.

According to the results shown in table 9, the presence of 1.3% glycerol resulted in actuator blockage for an actuator made of aluminium and having an inlet and outlet orifice diameter of 0.14mm. On the other hand, a corresponding solution formulation containing no glycerol passed the actuator blockage test.

Example 8

In Example 8, the influence of the presence of a low volatility component in a solution formulation containing dexbudesonide in 17% by weight ethanol has been tested for an actuator with an orifice diameter of 0.14mm and an orifice length of 0.6mm. The $FPF_{\leq 4.7\mu m}$ and MMAD have been determined (Table 10).

Table 10

Drug Dose (µg)	Ethanol (EtOH) %	Glycerol %	Orifice diameter mm	$FPF_{\leq 4.7\mu m}$ %	MMAD µm
Dexbudesonide 160	17	0.3	0.14	82.8	1.8
Dexbudesonide 160	17	1.3	0.14	70.1	2.9

According to the results shown in table 10, an increase of the amount of low volatility component (glycerol) results in a lower $FPF_{\leq 4.7\mu m}$ and a higher MMAD. Accordingly, a low content of 0 to 0.5%, preferably 0 to 0.3% low volatility component in the solution formulation not only has a beneficial effect with respect to blockage problems of the actuator, however, in addition, the $FPF_{\leq 4.7\mu m}$ and the MMAD is improved considerably.

Additional results have been obtained with 80µg dexbudesonide HFA solution formulation comprising 15 % by weight ethanol and 2% by weight water delivered through a 0.14mm diameter

and 0.7mm length laser drilled orifice that gives a FPF of over 75%. The same formulation provided with a conventional 0.22mm Bespak actuator gives a FPF of 45%.

The data has revealed major new insights in the use of pMDI. Extremely efficient atomisation can be achieved with formulations containing high levels of ethanol and with a high ratio of ethanol to active ingredient and being substantially free of low volatility components such as glycerol. No loss of atomisation efficiency is seen with formulations containing up to 15% ethanol. $FPF_{\leq 4.7}$ of over 50% can be achieved with formulations containing 25% ethanol. This allows the use of poorly soluble active ingredients in HFA solution formulations having a high ethanol content in order to transfer the poorly soluble active ingredient in solution. Accordingly, the present invention allows the use of new solution formulations also with poorly soluble active ingredients, which was not possible before the present invention was made.

Moreover, the data demonstrates that formulations previously unsuitable for pulmonary delivery (7% or more ethanol with a ratio of ethanol to active ingredients of at least 20:1, 0 to about 0.5% glycerol) when used with the small diameter drilled inserts can produce highly efficient sprays with a much smaller MMAD, reduced throat and actuator deposition, while actuator blockage and clogging problems can be avoided.

Other preferred formulations which can be used according to the present invention are the following:

Formulation 1:

Salmeterol xinafoate	3mg/can (~0.025% w/v)
Ethanol	30% (w/w)
Water	3% (w/w)
HFA 134a	67% (w/w)

Formulation 2:

Fluticasone propionate	15mg/can (~0.12% w/v)
Ethanol	30% (w/w)
Water	3% (w/w)
HFA 134a	67% (w/w)

Formulation 3:

Mometasone propionate	6mg/can (~0.05% w/v)
Ethanol	30% (w/w)
Water	3% (w/w)
HFA 134a	67% (w/w)

The formulation is actuated by a metering valve capable of delivering a volume of between 50 µl and 100 µl.

The choice of the metering valve and type will be made according the knowledge of the person skilled in the art.

Claims

1. A pressurized metered dose inhaler actuator (2) comprising a nozzle block (14; 30, 33) which comprises an actuator orifice (20) leading to an expansion chamber characterized in that the actuator orifice diameter is in a range of from 0.10mm to 0.20mm over the entire actuator orifice length and the actuator orifice length is in a range from 0.60mm to 1.0mm.

2. The actuator according to claim 1, wherein the actuator orifice diameter is in a range of from 0.11mm to 0.18mm, preferably 0.12mm to 0.18mm, and in particular it is 0.12mm, 0.14mm, 0.16mm or 0.18mm.

3. The actuator according to anyone of claims 1 or 2, wherein the actuator orifice length is in a range of from 0.60 to 0.80mm.

4. The actuator according to anyone of claims 1 to 3, wherein the actuator orifice is in the shape of a slot, cross, clover leaf or peanut.

5. The actuator according to anyone of claims 1 to 4, wherein the nozzle block comprises two or a plurality of orifices.

6. The actuator according to anyone of claims 1 to 5, wherein the nozzle block and/or the actuator insert piece is made of aluminium or stainless steel.

7. A medicinal aerosol solution formulation product comprising

a pressurized metered dose inhaler,

comprising a canister (1) equipped with a metering valve (3) and containing a medicinal aerosol solution formulation containing an active ingredient, a hydrofluorocarbon propellant, 7% (w/w) or more ethanol as a co-solvent, based on the solution formulation, wherein the ratio of ethanol:active ingredient is at least 20:1, and optionally a low volatility component in an amount of from 0 to 0.5% by weight, and an actuator (2) as defined in anyone of claims 1 to 6.

8. The product according to claim 7, wherein the medicinal aerosol solution formulation contains at least 15%, preferably at least 20% (w/w) ethanol as a co-solvent.

9. The product according to claim 7 or 8, wherein the active ingredient is a corticosteroid selected from beclometasone dipropionate, budesonide, dexbudesonide, ciclesonide, fluticasone propionate and mometasone propionate, or a β_2-agonist selected from formoterol, salmeterol xinafoate and TA 2005.

10. The product according to anyone of claims 7 to 9, wherein the low volatility component is selected from the group consisting of glycerol, propylene glycol, polyethylene glycol and isopropylmyristate.

11. The product according to anyone of claims 7 to 10, wherein the propellant is selected from HFA227, HFA134a and their mixtures.

12. A method for manufacturing a pressurized metered dose inhaler actuator comprising a nozzle block which comprises an actuator orifice leading to an expansion chamber,

characterized in that the method comprises a step of laser drilling said actuator orifice.

13. The method according to claim 12 characterized in that the method is designed so as to manufacture a pressurized metered dose inhaler actuator according to anyone of claims 1 to 6.

Fig. 1

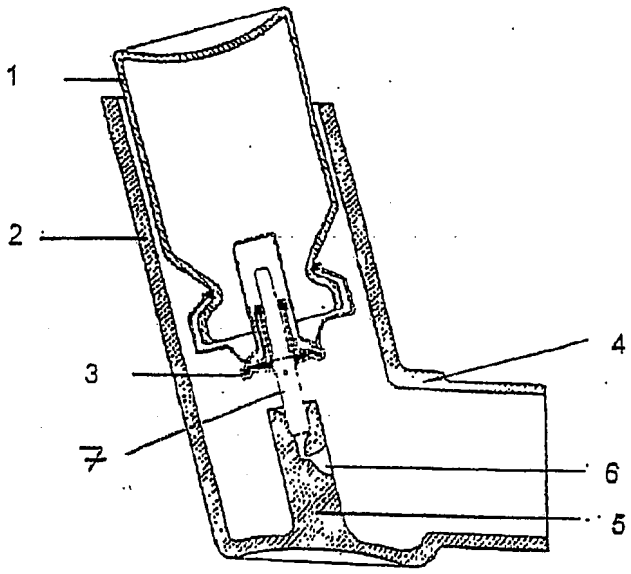

Fig. 2

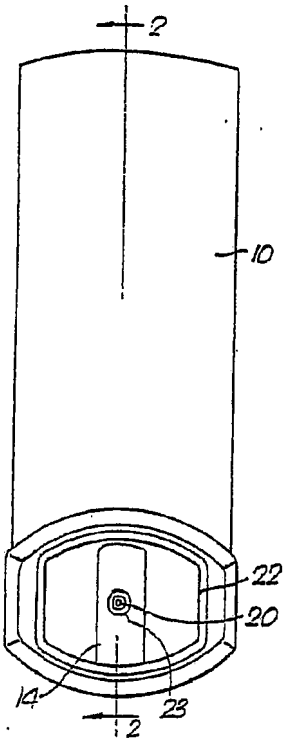

Fig. 3

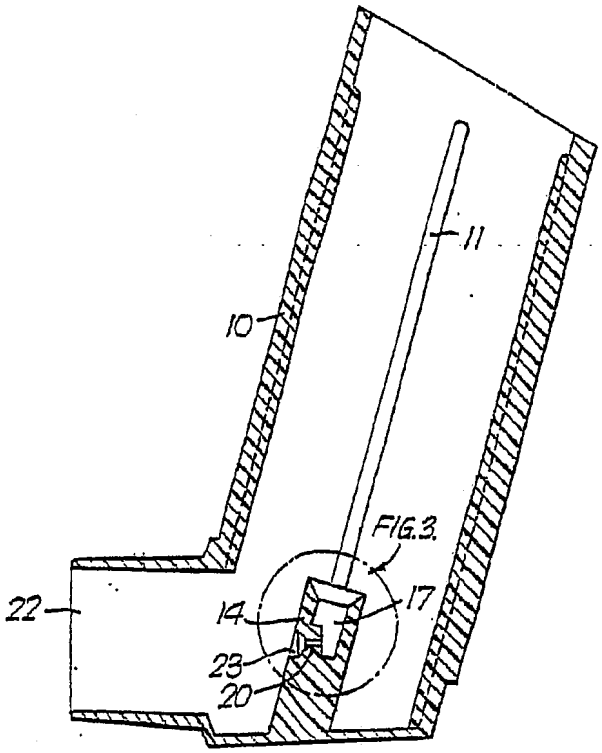

Fig. 4

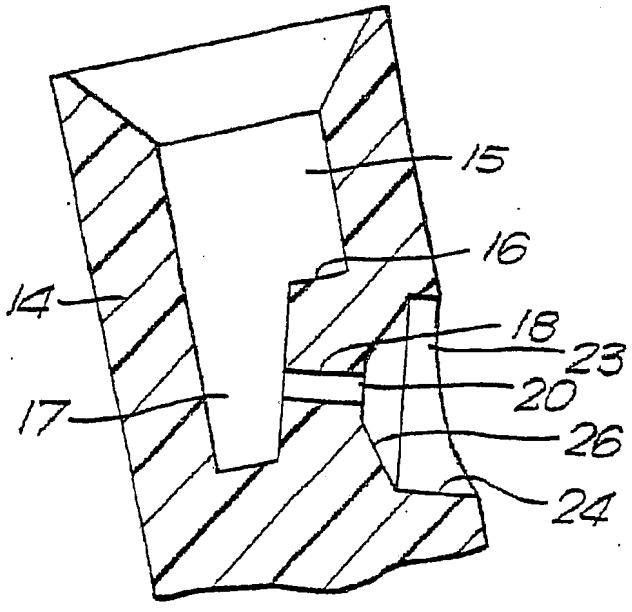

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Fig. 5

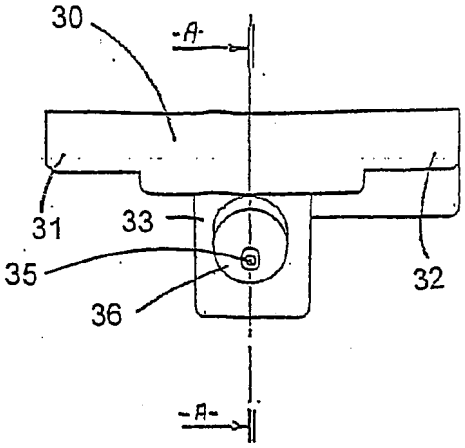
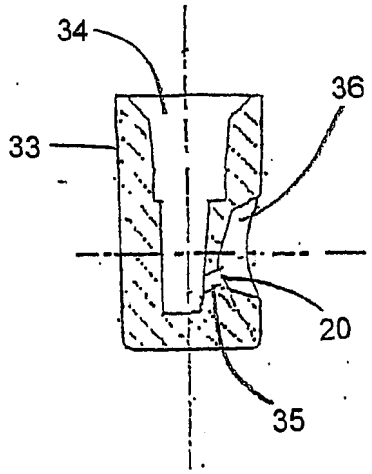


Fig. 6



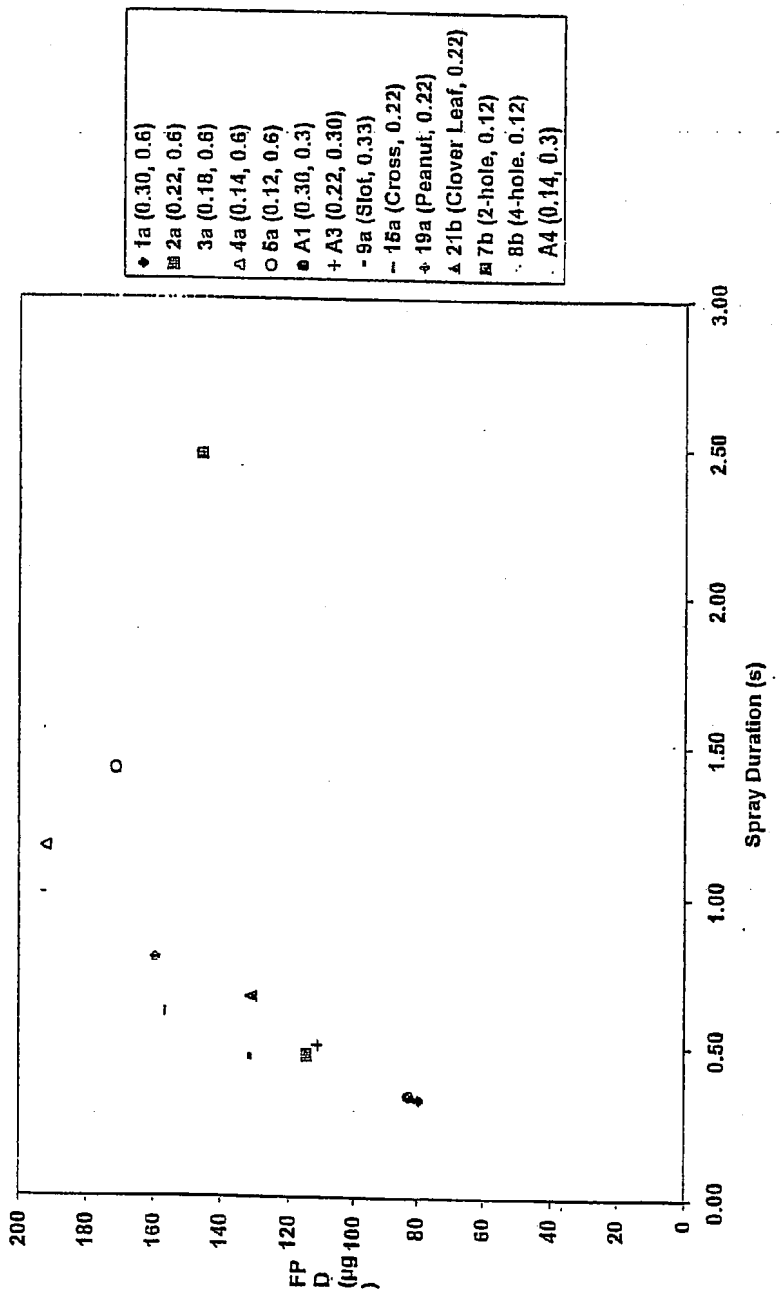

1a (0.30, 0.6)
2a (0.22, 0.6)
3a (0.18, 0.6)
4a (0.14, 0.6)
6a (0.12, 0.6)
A1 (0.30, 0.3)
A3 (0.22, 0.30)
9a (Slot, 0.33)
16a (Cross, 0.22)
19a (Peanut, 0.22)
21b (Clover Leaf, 0.22)
7b (2-hole, 0.12)
8b (4-hole, 0.12)
A4 (0.14, 0.3)
FPD (µg)
Spray Duration (s)
0
20
40
60
80
100
120
140
160
180
200
0.00
0.50
1.00
1.50
2.00
2.50
3.00

Fig. 7

參考檔號：DCSL/KKSW/6619722/0

(54) 標題：計量劑量吸入器

(圖)

(57) 摘要：本發明有關具有激光鑽孔的壓力計量劑量吸入器(pMDI)致動裝置(2)，及含有此等致動裝置(2)的藥物煙霧劑溶液配方產品。特別是，本發明有關透過使用的 pMDI (具有特定大小的激光鑽孔的致動裝置(2))優化在氫氟鏈烷中的藥物溶液配方的成效特性。此外，本發明的致動裝置(2)容許含高乙醇含量及高比例乙醇的溶液配方用於活性配料，即容許在溶液配方使用難溶的活性配料，並容許使用實質不含低揮發性成分的溶液配方。