Efficient Delivery to the Lungs of Flunisolide Aerosol from a New Portable Hand-Held Multidose Nebulizer

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Abstract ☐ In order to provide asthmatic patients with an inhaler that does not use chlorofluorocarbon propellants, a novel multidose hand-held nebulizer (RESPIMAT, Boehringer Ingelheim Ltd.) has been developed. This device delivers 200 × 15 μL metered doses of drug solution, but does not use propellants of any kind. In this study of 10 healthy volunteers, the deposition pattern in the lungs and oropharynx of an ethanolic solution of flunisolide delivered *via* a prototype III multidose nebulizer has been determined by γ scintigraphy. A comparison was made with the same dose (250 μg) of flunisolide delivered by a pressurized metered dose inhaler (MDI) and MDI plus Inhacort spacer. Mean (SD) whole lung deposition from the multidose nebulizer (39.7 (9.9) % of the metered dose) was significantly higher than that from either MDI (15.3 (5.1) %, $P < 0.01$) or MDI plus spacer (28.0 (7.0) %, $P = 0.01$). A mean 10.4% of the dose was recovered from an exhaled air filter for the multidose nebulizer, but less than 2% of the dose for MDI or MDI plus spacer. Oropharyngeal deposition was significantly reduced for the multidose nebulizer (39.9 (9.4) %) compared to MDI (66.9 (7.1) %), but was reduced further for the MDI plus spacer (27.3 (11.3) %). The multidose nebulizer delivers an unusually high percentage of an aerosol dose to the lungs, and it "targets" flunisolide to the lungs more effectively than the MDI. The multidose nebulizer could constitute a viable alternative to MDIs in asthma maintenance therapy.

Introduction

Efficient aerosol inhalers are required for delivering asthma medications to the lungs. The pressurized metered dose inhaler (MDI) has been the cornerstone of asthma maintenance therapy for several decades, but delivers only a small percentage of the drug dose directly into the lungs, with the majority of the dose being deposited in the oropharynx.[1−3] The MDI thus confers poor selectivity of drug deposition, which may increase the incidence of both local and systemic side effects for high dose inhaled corticosteroids.[4] The use of a spacer attachment to the MDI may reduce the incidence of these side effects.[5,6] The MDI uses chlorofluorocarbon (CFC) propellants, the production and import of which have been banned in many countries because of their contribution to ozone depletion.[7] In order to overcome these limitations of the pressurized MDI, a novel concept in inhalation therapy that operates without the need for propellants, a hand-held multidose nebulizer (RESPIMAT, Boehringer Ingelheim Ltd.), has been developed. (The RESPIMAT device was formerly known as the BINEB.) In this scintigraphic study, we have compared in a group of healthy volunteers the deposition patterns of the corticosteroid flunisolide (Inhacort, Boehringer Ingelheim Ltd.) delivered by a prototype III multidose nebulizer as an ethanol-based solution, by pressurized MDI, and by MDI plus spacer device. We chose to compare the multidose nebulizer against an MDI containing a suspension of micronized drug since the latter is the formulation currently marketed.

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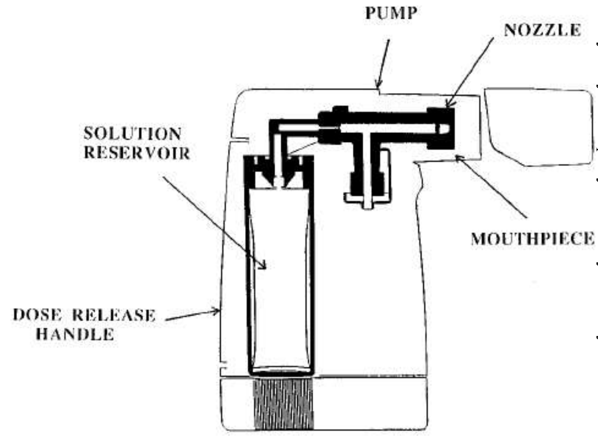

Figure 1—Prototype III multidose hand-held nebulizer.

Multidose Nebulizer

The multidose nebulizer (Figure 1) comprises a fluid reservoir of volume 3.5 mL, from which individual metered doses of 15 μL are delivered.[8] When the base of the device is rotated through 180°, a spring is compressed, and the energy required for the nebulization process is stored. Simultaneously, fluid is pumped into a dosing chamber, and when the dose release handle is operated, decompression of the spring forces the fluid through a fine nozzle in the mouthpiece. The nozzle contains channels of approximate diameter 8 μm in a silicone wafer, together with a filter system to prevent clogging.

The spray produced has a mass median diameter of <6 μm and an initial droplet velocity of approximately 10 m s^{-1}, which are markedly less than the size and velocity of droplets emerging from a pressurized aerosol canister.[8] This system differs from a conventional unit-dose nebulizer since it contains over 200 metered doses, delivers a dose in about 1.2 s, and offers levels of compactness, portability, and convenience comparable to those of a pressurized MDI. In this study the multidose nebulizer was used to deliver doses of 250 μg of flunisolide in a 96% solution of ethanol, without the addition of preservatives or any other excipients. The relative standard deviation of the delivered dose for a 96% ethanol solution is less than 5%.[8]

Experimental Section

Subjects—Ten healthy nonsmoking volunteers (6 male, 4 female; age range 19−28 years) took part in a randomized three-way crossover study to assess the deposition patterns of flunisolide. Their forced

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expiratory volumes in 1 s (FEV_1) ranged from 92 to 114% predicted.[9] Each subject underwent a medical examination before entering the study to ensure that they were healthy and gave written informed consent to taking part. The Quorn Research Review Committee, Leicestershire, U.K., approved the study protocol, and permission to administer radioactive aerosols was granted by the Department of Health, London. The study was performed in accordance with the Declaration of Helsinki.

Radiolabeling—The aerosol formulations were radiolabeled by the addition of the radionuclide ^{99m}Tc, such that each metered dose delivered not only 250 μg of flunisolide but also 10 MBq of ^{99m}Tc. Pressurized MDIs were radiolabeled using a previously described technique,[3,10,11] by which ^{99m}Tc was placed in an empty canister and evaporated to dryness, following which the contents of a filled canister were added at below −60 °C and a valve was crimped in place. In order to radiolabel the contents of the multidose nebulizer, ^{99m}Tc as sodium pertechnetate was extracted into butanone, which was then evaporated to dryness before addition of 3.5 mL of flunisolide solution. The flunisolide and radiolabel were mixed for 10 min by an ultrasonic shaker before being transferred to the reservoir of a multidose nebulizer. Both MDI and multidose nebulizer were primed before use until a constant plume of spray was emitted per metered dose, and the multidose nebulizer was weighed during the priming procedure to ensure that a constant dose weight was released.

The radiolabeling methods were validated by examination of particle size distributions in a high-precision multistage liquid impinger (HPMLI, Copley Instruments, U.K.) operated at a flow rate of 60L/min.[12] The size distribution of drug to which no radiolabel had been added ("unlabeled" drug) was compared with that of "labeled" drug from inhalers containing ^{99m}Tc, and with that of the radiolabel itself. The HPMLI consisted of a 90° inlet (throat) and four impaction stages. The impinger stages were washed with ethanol, and the washings were assayed for drug content (either by HPLC at Boehringer Ingelheim, Germany, or by UV spectrophotometry at Pharmaceutical Profiles Ltd.) and for radioactive content by scanning with a γ camera (General Electric Maxi camera). The "respirable fraction" was determined as the amount of drug or radiolabel penetrating to stages 3 and 4 of the HPMLI expressed as a percentage of total recovery. Stage 3 collected droplets between 3.1 and 6.8 μm, while stage 4 collected droplets of $\leq$3.1 μm diameter.

Clinical Procedures—Each volunteer received a single dose (250 μg) of flunisolide on each of three randomized study days involving (a) a prototype III multidose nebulizer equipped with a C16a nozzle, (b) a pressurized metered dose inhaler (MDI), and (c) an MDI coupled to an Inhacort spacer device (volume 250 mL). The same inhalation maneuvre was used for each device, and this maneuvre was practiced, prior to administration of the radiolabeled aerosol, using a placebo MDI or a placebo multidose nebulizer until it could be performed reproducibly. Subjects were taught to inhale slowly and deeply and, after a 10 s breath-holding pause, to exhale through a filter in order to trap any aerosol particles in the expired air. The device was fired by the investigator approximately 1 s after the subject began to inhale. Subjects wore a nose clip when inhaling from the multidose nebulizer, to ensure that very small ethanol droplets were not lost *via* the nose. The inhalation maneuvre was recorded by a respiratory inductance plethysmograph (Respitrace, PK Morgan Ltd., U.K.) from which the average inhaled flow rate, inhaled volume, duration of inhalation, and breath-holding pause could be calculated.

Immediately following inhalation of the radioaerosol, posterior and anterior images of the chest (each 100 s) were taken by General Electric Maxi camera coupled to a Bartec Micas V data processing system. These images were followed by a lateral image of the oropharynx (30 s), and by further images of the abdomen if any of the radioactivity had spread beyond the field of view in the chest images. The MDI actuator, the nebulizer mouthpiece (detached from the nebulizer), the spacer device, and the exhaled air filter were imaged. In order to ensure that all the radioactivity released from the nozzle was counted, the nozzle was wiped after use with a swab, and the counts of the wipings were added to those of the multidose nebulizer mouthpiece. Counts were corrected for background radioactivity and, where appropriate, decay and attenuation of γ-rays by tissue.[13] The geometric mean of anterior and posterior lung and abdomen counts was calculated.[14] In this way, the metered dose was fractionated between amounts initially deposited in the lungs, deposited in the oropharynx, retained on the actuator/mouthpiece and spacer, and recovered from the exhaled air filter.

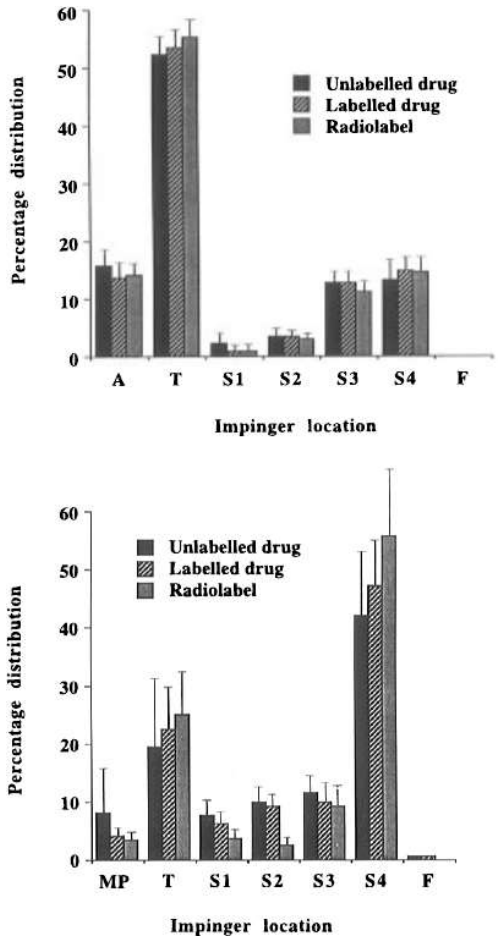

Figure 2—Radiolabeling validation data. Distribution of "unlabeled" drug, "labeled" drug, and radiolabel among different particle size bands for (a) (top) pressurized MDI and (b) (bottom) multidose nebulizer. Locations in impinger as follows: A = actuator; MP = nebulizer mouthpiece; T = throat; S1–4 = stages 1–4; F = final filter. All data are expressed as mean (SD) of five replicates from different inhalers.

On one study day a posterior lung ventilation scan was performed using the radioactive inert gas ^{81m}Kr. The lung outlines from the ^{81m}Kr ventilation scan were used to define the edges of the lung fields on the aerosol views, and the lungs were subdivided into central, intermediate, and peripheral zones, representing approximately large, medium, and small airways, respectively. The peripheral lung zone/central lung zone ratio (penetration index) was calculated.

FEV_1, forced vital capacity (FVC), and peak expiratory flow rate (PEFR) were recorded on each study day before inhalation, and then 15, 30, and 60 min postdose by Vitalograph Compact Spirometer (Vitalograph, Buckingham, U.K.).

Statistical Tests—The Wilcoxon matched-pairs signed ranks test was used to assess the significance of the differences between the deposition patterns for the three devices. A P value of $\leq$0.05 was considered statistically significant.

Results

In Vitro Radiolabeling Data—The distributions of unlabeled drug, labeled drug, and radiolabel from MDIs delivering flunisolide are shown in Figure 2a. Mean respirable fractions for these three quantities were 25.8%, 27.8%, and 25.8%, respectively. Data are also shown in Figure 2b for the multidose nebulizer. The agreement between distributions

Table 1—Mean (SD) Percentages of the Metered Dose Located at Various Sites, and Distribution Pattern within the Lungs for Studies with Multidose Nebulizer, MDI, and MDI Plus Spacer

Deposition Site	Nebulizer	MDI	MDI + Spacer
Lungs (%)	39.7 (9.9)	15.3 (5.1)	28.0 (7.0)
Oropharynx (%)	39.9 (9.4)	66.9 (7.1)	27.3 (11.3)
Mouthpiece/actuator (%)[a]	10.0 (7.8)	16.4 (3.8)	16.0 (2.2)
Spacer (%)			27.9 (9.3)
Exhaled air (%)	10.4 (4.9)	1.4 (1.3)	0.8 (0.4)
Central lung zone (%)	10.7 (2.5)	4.5 (1.8)	8.6 (2.1)
Intermediate lung zone (%)	14.9 (3.6)	5.4 (1.9)	10.3 (2.5)
Peripheral lung zone (%)	14.1 (4.3)	5.4 (1.4)	9.1 (3.0)
Peripheral zone/central zone ratio	1.31 (0.22)	1.28 (0.23)	1.08 (0.27)

[a] Includes wipings of nebulizer nozzle.

of unlabeled drug, labeled drug, and radiolabel for the multidose nebulizer was less precise than for the MDI, and the respirable fractions for these three quantities were 54.5%, 57.8%, and 65.1%, respectively. Since both drug and radiolabel were in solution, it was anticipated that they were distributed uniformly through different size bands according to droplet volume. However, for logistic reasons it was not possible to use the same nozzle throughout these *in vitro* experiments, and the differences between drug and radiolabel size distributions were ascribed mainly to internozzle variations. The radiolabeling validation data were considered adequate to perform a scintigraphic study.

Scintigraphic Data—The fractionation of the dose between lungs, oropharynx, apparatus, and exhaled air is shown in Table 1, and typical scans for each device are shown in Figure 3. Mean (SD) whole lung deposition was 39.7 (9.9) % of the metered dose for the multidose nebulizer, compared to 15.3 (5.1) % for the MDI ($P < 0.01$) and 28.0 (7.0) % for the MDI plus spacer ($P = 0.01$). Lung deposition for the MDI plus spacer was also significantly ($P < 0.01$) higher than that for the MDI alone. Depositions in each of the central, intermediate, and peripheral lung zones followed the same rank order as that for whole lung deposition (Table 1), although the peripheral lung zone/central lung zone deposition ratio averaged less for the MDI plus spacer than for either MDI or multidose nebulizer, and this difference was significant ($P = 0.02$) in comparison with the multidose nebulizer.

Oropharyngeal deposition (Table 1) was highest for the MDI (mean 66.9%) and was lowest for the MDI plus spacer (mean 27.3%, $P < 0.01$). The multidose nebulizer gave an oropharyngeal deposition (mean 39.9%) significantly higher than MDI plus spacer ($P = 0.02$), but significantly ($P < 0.01$) lower than the MDI.

A mean 10.4% of the dose was recovered from the exhaled air filter for the multidose nebulizer, compared with means of only 1.4% and 0.8% of the dose for MDI and for MDI plus spacer, respectively. A mean of 27.9% of the dose was deposited on the walls of the spacer. The remainder of the dose not accounted for elsewhere was retained on the mouthpiece or actuator.

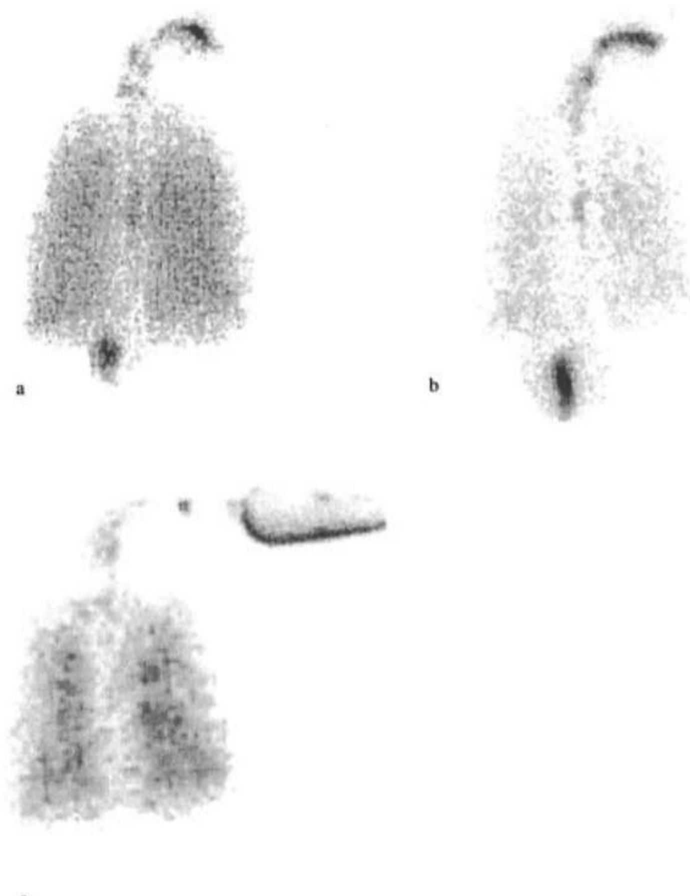

Figure 3—Typical scans in one individual from (a) multidose nebulizer, (b) pressurized MDI, and (c) MDI with spacer. The distribution of aerosol on the walls of the spacer is shown in scan c.

Table 2—Mean (SD) Details of Inhalation Maneuvres and Changes in FEV_1 for Studies with Multidose Nebulizer, MDI, and MDI Plus Spacer

Parameter	Nebulizer	MDI	MDI + Spacer
Inhaled flow rate (L/min)	18.8 (12.2)	26.7 (14.6)	32.3 (15.0)
Inhaled volume (L)	1.24 (0.53)	1.96 (0.70)	2.00 (0.71)
Duration of inhalation (s)	5.0 (2.0)	4.9 (1.5)	4.1 (1.6)
Breath-holding pause (s)	9.2 (0.7)	9.4 (0.9)	9.8 (0.9)
FEV_1 predosing (L)	4.60 (0.75)	4.54 (0.84)	4.45 (0.81)
FEV_1 15 min postdosing (L)	4.66 (0.83)	4.81 (1.03)	4.55 (0.75)
FEV_1 30 min postdosing (L)	4.67 (0.88)	4.84 (1.03)	4.54 (0.80)
FEV_1 60 min postdosing (L)	4.69 (0.84)	5.08 (1.20)	4.62 (0.83)

Inhalation Details and Lung Function Parameters—Parameters of inhalation (Table 2) were similar for MDI (mean flow rate 26.7 L/min) and for MDI plus spacer (mean 32.3 L/min), but when using the multidose nebulizer, subjects took slower (mean 18.8 L/min) breaths and inhaled a smaller volume of air. There was no evidence of bronchoconstriction in any subject following inhalation of flunisolide solution. Values of FEV_1 (Table 2) and of FVC and PEFR before and after inhalation were similar.

Discussion

This study has shown that the multidose nebulizer device is able to deliver an unusually high percentage of the metered aerosol dose to the lungs of healthy volunteers. This results in part from the formulation of drug in an ethanolic solution, which evaporates rapidly, leaving many fine droplets in the spray, such that over 10% of the metered dose was contained in droplets small enough to enter the lungs but to be exhaled subsequently. Whole lung deposition values as high as the mean value of 39.7% in this study have also been reported previously for MDI formulations containing a propellant soluble radiolabel,[15,16] which would also comprise rapidly evaporating droplets. When an aqueous solution of fenoterol was delivered by the multidose nebulizer, lung deposition of >30% of the dose was recorded.[17] However, aqueous and ethanolic solutions have different spray characteristics, and it is necessary to assess the lung deposition of the two formulations separately. A mean whole lung deposition value exceeding 30% of the dose has also been reported recently for terbutaline sulfate pressurized aerosol delivered via a large-volume spacer device,[18] although lung deposition measured in other studies with pressurized MDIs has generally averaged <20% of the dose, as described in a recent review.[19]

The data in the present study were obtained in healthy volunteers, and lung deposition from the multidose nebulizer has not yet been determined in patients. The results of previous studies suggest that whole lung deposition values from the multidose nebulizer would be similar in asthmatic patients, while a reduction in the penetration of aerosol to the peripheral lung zone would be expected.[20] The airways of patients with obstructive airways disease are narrowed by a combination of bronchospasm, edema, and mucus hypersecretion, making impaction of particles in large central airways more likely. An alternative possibility is that whole lung deposition from the multidose nebulizer would be higher in patients than in healthy volunteers. We recorded 10% of the dose in the exhaled air, a figure which is unusually high for portable asthma inhalers, and it is possible that the exhaled fraction would be reduced in patients with asthma, leading to even higher lung deposition.

Drug delivery from MDIs varies according to the nature of the drug formulation,[21] but the value obtained in this study (mean 15.3%) was comparable with that observed in other studies for MDIs delivering similar amounts of drug per metered dose, and contained in similar propellant mixtures.[22] The increased whole lung deposition from the multidose nebulizer compared with the MDI was also reflected in an increased respirable fraction in the *in vitro* radiolabeling validation experiments. If the multidose nebulizer were to double the amount of drug deposited in the lungs of asthmatic patients compared to an MDI, then it might prove possible to control asthma with the multidose nebulizer using a smaller daily dose of flunisolide. This would in turn reduce the amount of drug delivered to the oropharynx, which might lower the incidence of local oropharyngeal side effects associated with topical corticosteroid treatment.[5] In addition, the multidose nebulizer reduced the percentage of the dose deposited in the oropharynx, which would further decrease the potential for oropharyngeal side effects.

Since the multidose nebulizer enhanced lung deposition and reduced oropharyngeal deposition compared to the MDI, it improved the "targeting" of drug to the site of action and would be likely to result in an improved therapeutic ratio, i.e., ratio of desired effects to side effects for a given administered dose. Spacer devices always decrease oropharyngeal deposition compared to an MDI,[23] and they may increase drug delivery to the lungs, dependent upon the design of the spacer, the characteristics of the formulation, the inhalation technique adopted by the subject, and the extent to which the effects of electrostatic charge on the spacer walls are controlled.[24–27] In this study, lung deposition from the spacer was almost double the value obtained from the MDI. If the lung deposition is expressed as a fraction of the total amount of drug deposited in the body, then this parameter averaged 0.19 for the MDI, 0.51 for the spacer, and 0.50 for the multidose nebulizer. Thus both the multidose nebulizer and spacer produce comparable selectivity of lung deposition, although the multidose nebulizer is significantly more compact and convenient to use in routine clinical practice. It is possible that the absolute amount of oropharyngeal deposition could be reduced by adding a spacer or other attachment to the multidose nebulizer, but this remains to be investigated.

Volunteers took slower, shallower, inhalations from the multidose nebulizer in the present study than from the MDI or from the MDI plus spacer; this may have been a result of wearing a noseclip for the multidose nebulizer leg of the study, or it may have been coincidence. We believe that any difference in lung deposition resulting from inhaling from the multidose nebulizer at ca. 20 L/min and from the other two devices at a ca. 30 L/min would be small, since much larger differences in flow rate (say 30 vs 100 L/min) are normally required before differences in deposition can be shown.[19] There was no evidence of bronchoconstriction in any volunteer taking part in this study. This effect has been observed in some asthmatic patients inhaling ethanol solutions[28] although for larger volumes of inhaled ethanol compared with those used in the present study. Pressurized MDIs containing ethanol have been in widespread use for many years in North America.

The multidose nebulizer device tested in this study is not the only compact multidose nebulizer system to be described recently. Other nebulizers in which the aerosol is generated by compressed air[29,30] or by ultrasonic principles[31–33] have been developed, and one of these has been assessed by γ scintigraphy. A mean 8% of the dose was deposited in the lungs from one of these devices when used alone, increasing to 13% of the dose when the spray was inhaled via a spacer device.[29,30] Portable multidose nebulizers may thus play an important future role in inhalation therapy and could constitute a viable alternative to pressurized metered dose inhalers and powder inhalers.

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