



Review Article

METERED DOSE INHALER: A REVIEW

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Abstract: Pressurized metered dose inhalers (pMDI) are portable, convenient, multi-dose devices used to administer aerosolized drugs that use a propellant, and delivered a fixed dose of medication with each actuation. They have a metallic chamber containing a suspension or solution. A key piece in this system is the dosage valve, which releases at each pulse a controlled, reproducible dose of medication. The drug is released at a high speed (at more than 30m/s through the mouth-piece) and in the form of particles with an MMAD of between 2 and 3µm. Chlorofluorocarbon propellants are being replaced by hydrofluoroalkane propellants that do not have ozone depleting properties. Two new propellants have been approved for CFC substitutes: hydrofluoroalkane HFA-134a and HFA-227ea. The change from CFCs to HFAs in metered-dose inhalers was not a straight forward exchange. Indeed, substantial new technology had to be developed to make the HFAs suitable for use in metered-dose inhalers. More significant advances, related to the direct operation of metered-dose inhalers. Based on this objective, breath-actuated pressurized inhalers, breath-coordinated metered-dose inhalers, and velocity-modifying inhalers were developed. Recent advancements in pMDI technology associated with the transition to HFA propellants have resulted in highly efficient pMDI systems that are broadly applicable to treating a wide variety of diseases.

Keywords: Propellant, MMAD, Spacer, pMDI

INTRODUCTION

Pressurized metered dose inhalers (pMDI) are portable, convenient, multi-dose devices used to administer aerosolized drugs that use a propellant, and delivered a fixed dose of medication with each actuation.¹ In the past, the propellant used was chlorofluorocarbons (CFC), but due to their harmful effects on the ozone layer, they have been banned by the United Nations.² In accordance with the Montreal Protocol of 1987,³ chlorofluorocarbon propellants are being replaced by hydrofluoroalkane propellants that do not have ozone depleting properties.⁴

Two new propellants have been approved for CFC substitutes: hydrofluoroalkane HFA-134a and HFA-227ea. have a series of advantages, such as their small size (making them easy to handle), the exactness of the dosage, the possibility to fit them to spacer chambers, the fact that they do not require high flows to be inhaled and their low cost in general. Their main drawbacks are the difficulty inherent in synchronizing activation–inhalation and the low dose that reaches the lungs, which has been estimated at approximately 10%–20% of the dose emitted. The high release speed and the large size of the particles generated mean that more than half of these impacts in the oropharyngeal region. Another drawback of pMDI is the possible variation in the dose released at each pulse if the device is not correctly shaken.⁵ The change from CFCs to HFAs in metered-dose inhalers was not a straight forward exchange. Indeed, substantial new technology had to be developed to make the HFAs suitable for use in metered-dose inhalers. Valves have been improved to function in

HFA propellants, meet more stringent regulatory requirements on dosing uniformity and extractables/leachable. Canister technologies (e.g., novel coatings) have been developed to reduce drug degradation and deposition. The transition to HFA formulations resulted in pMDIs with increased lung deposition and technologies to control residual particle size (i.e., the size of the particle remaining after all volatile components evaporate). Transition to HFA propellants led to the development of pMDI actuators with improved delivery efficiency. Dose counters have been incorporated for improved patient compliance.⁶ The patents are related to novel valves, dose-counters, formulations, add-on devices, reduction of propellant leakage and inkjet technology. Recently patented dose-counters provide mechanisms that are less susceptible to inaccuracy, and are battery-less electronic dose-counters with the help of miniature electromechanical generators. Regarding the formulation aspect, recent patents provide methods for combinational pMDIs and more stable products. Advantages of recently patented valves are being spring-free and less subject to loss of prime. Recent developments in micromachining have allowed patents that incorporate inkjet technology to develop inhalers that are similar to pMDIs, but produce uniform aerosol droplets. Coating canisters with suitable polymers has reduced need for excipients. Recently patented add-on devices reduce aerosol deposition in the spacer by creating turbulence on the walls of the chamber. Blockage of nozzles in actuators is prevented by providing tapered nozzle channels. In conclusion, these patents show better understanding of pMDIs and provide methods to achieve products with much improved reliability, aerosol performance and stability.⁷

PARTS OF METERED DOSE INHALER

Pressurized metered dose inhalers consist of several components, the active substance formulated with propellant and excipients, a container, a metering valve crimped onto the container, an actuator that connects the metering valve to

an atomization nozzle, and a mouth piece. Additionally, holding chambers or spacers may also form part of the delivery system by connection to the actuator mouthpiece. Figure 1 shows the basic components of pMDI, consisting of a canister sealed with a metering valve which is inserted into actuator.⁸

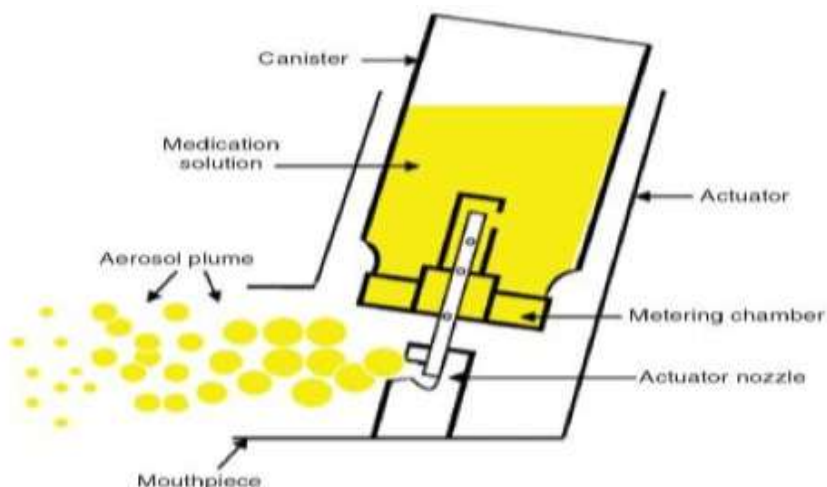


Figure 1: Components of a pressurized metered-dose inhaler⁹

FORMULATION

In general there are two types of pMDI formulations: suspension formulations and solution formulation, in suspension formulation micro-particulate drug (typically micronized material) is dispersed in a propellants; and solution formulations, in which the drug freely dissolves in either the propellant or a combination of propellant and an acceptable co-solvent, typically ethanol^{10, 11}. Both types of formulation have inherent advantages and disadvantages. Traditionally, suspension formulations have been the more common dosage form, but with the advent of the hydrofluoroalkane propellants (HFC-134a; HFC-227ea), which have poor solvency characteristics, the use of co-solvents has become more common and solution formulations being used more.^{12, 13} A number of excipients have been included in pMDI formulations; however, nature of the excipients has changed with the introduction of the HFA propellant aerosols. Oleic acid and sorbitan trioleate (SPAN 85) and lecithins were used in CFC suspension pMDIs as suspending agents and valve lubricants.¹⁴ Recently developed, HFA-soluble excipients expand the range of drug molecules, which can be formulated into highly respirable solution pMDIs. Some of these excipients, such as oligolactic acid, interact with the drug to form drug/excipient complexes that are highly soluble in HFA propellants. This approach leads to significant improvement in the solubility of the drug. This allows poorly soluble

drugs to be formulated with little or no cosolvent, thus increasing the drug delivery efficiency.^{15, 16, 17, 18}

PROPELLANT

Pressurized metered dose inhaler contains propellants, which are currently being changed from chlorofluorocarbons (CFCs) to hydrofluoroalkanes (HFAs) because the former damage the ozone layer in the stratosphere¹⁹. Their potential for damage to the ozone layer is nonexistent, and while they are greenhouse gases, their global warming potential is a fraction (one-tenth) of that of CFCs.²⁰ Two new propellants have been approved for CFC substitutes: hydrofluoroalkane (HFA)-134a and HFA-227.²¹ However, HFAs cannot simply be substituted for CFCs in inhalers of identical design. Their use has required changes in many aspects of the drug formulation, inhaler design and manufacture.²² Although the HFAs have similar physicochemical properties to the CFCs they have replaced, they also differ in some physical properties. In particular, HFAs have high polarity, which results in poor solvation of previously used surfactants or excipients such as oleic acid, lecithin, or sorbitan trioleate.²³

Higher lung deposition and lower oropharyngeal deposition may be achieved with some recent formulations, where the drug is formulated as a solution in HFA propellant, rather than as a suspension of micronised particles.²⁴

Table no 1: Properties of Potential Propellants²⁷
Selected Properties of Potential Propellants

Property	Trifluoromonofluoroethane	Heptafluoropropane
Molecular formula	CF ₃ CH ₂ F	CF ₃ CHFCF ₃
Numerical designation	134a	P-227
Molecular weight	102	107
Vapor pressure (psig), 70°F	70.0	44.1
Vapor pressure (psig), 130°F	198.7	135.1
Liquid density (g/mL), 20°C	1.21	1.41

VALVE

The metering valve crimped onto the container is the most critical component of the pMDI, and has a volume ranging from 25 μL to 100 μL . While there are many designs of metering valve, they all operate on the same basic principle.²⁶ The principle of aerosol delivery from pMDIs is based on the following sequence of events. A small volume of a homogeneous dispersion of the drug, in solution or suspension, in a high vapor pressure propellant or a propellant blend from a reservoir, is isolated. The small-volume container (the metering chamber) is opened through

an actuator nozzle. The metering chamber filling and opening to the atmosphere are achieved by means of a metering valve. Once opened to the atmosphere, the high vapour pressure contents of the metering valve immediately begin to equilibrate with atmospheric pressure. This has the effect of propelling the contents rapidly through the nozzle, which causes shear and droplet formation. Throughout this process the propellant is evaporating propelling, shearing, and ultimately reducing the size of the droplets produced.^{27, 28} Figure 2 Showing mechanism of particle formation after actuation.

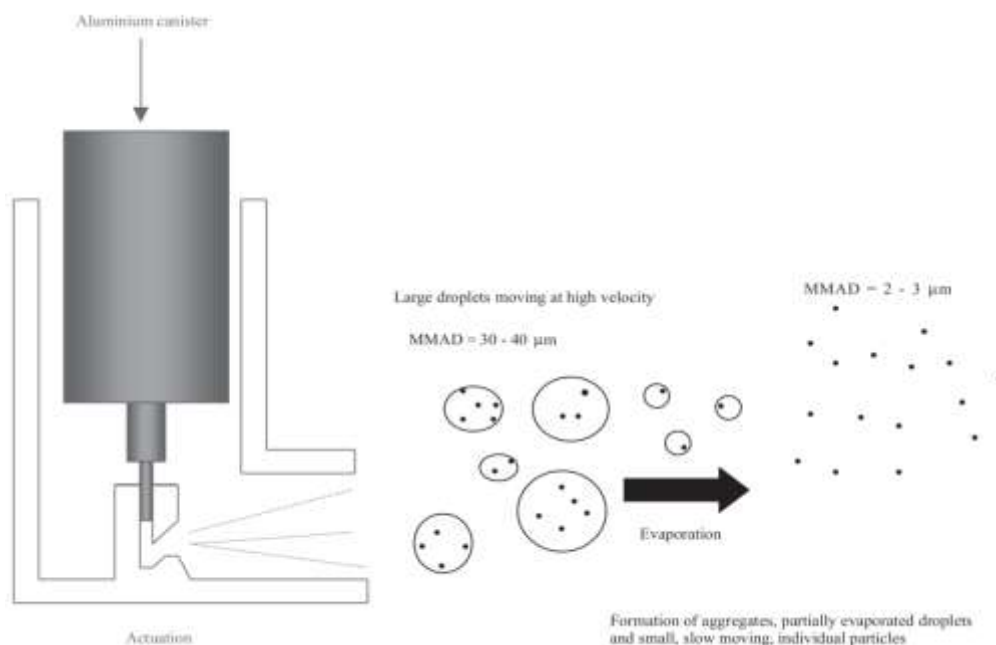


Figure 2. Diagram of a typical metered dose inhaler showing mechanism of particle formation

Loss of prime (LOP) and dose content variability are major patient compliance issues associated with all capillary retention valves fitted to pMDIs. Conventional pMDI valves fill a metering chamber immediately after the last dose is fired and this chamber may partially empty if the inhaler is inverted or left for any length of time. For the inhaler to then deliver an optimum dose, the patient should ideally fire one shot into the air to ensure the valve chamber is completely refilled from the main can reservoir. This requirement results in high levels of wastage and, of course assumes that the patient has been shown how to use the inhaler properly or has read the (often ignored) patient information leaflet that came with the medication. Often, this is not the case, so the only reliable method to guarantee a full dose is taken is to recommend a regime based on two puffs from the inhaler.²⁹

Bespak, a leading designer, developer and manufacturer of speciality medical devices, has developed a unique pMDI valve to eliminate LOP and improve dose content uniformity (DCU). The BK361 'Easi-fill' valve is designed with fast-fill/fast-drain characteristics that allow the metering chamber to fully refill after actuation or storage. This eliminates LOP, reduces dosing variability and therefore helps to improve patient compliance.³⁰

Canister

A typical pMDI system includes a metal canister containing medication in the form of a pressurized aerosol. A cap containing the drug metering valve is crimped onto the mouth of the canister, and the entire system is enclosed in a plastic actuator through which the patient inhales the drug. Pressurized metered dose inhaler cans, however, have important roles that go beyond storage of the formulation, with the potential to significantly affect product stability and shelf life, patient safety, and dosing consistency. Canister size depends mostly on dosing requirements and, therefore, the volume of drug formulation. Canisters come in a range of standard sizes, generally ranging from about 10 ml to about 30 ml. Most of the world's canisters are manufactured from aluminum as it is compatible with the majority of formulations. Aluminum does present several challenges; however, manufacturers have developed ways to deal with those issues. For example, aluminium may react with certain formulations, so manufacturers may add a barrier coating on the inside of the can to prevent degradation.

For solution formulations, internal coating with a polymer or anodization of the canister can change the surface characteristics of the canister and ultimately act as protective barrier. Low surface energy coatings can be used with suspension formulations to reduce drug deposition.³¹

Actuator

The actuator or mouthpiece of an pMDI is generally constructed from range of polyethylene or polypropylene material by injection molding techniques. The common design of actuators is the classic "L" shape. The actuator, which is critical for aerosol formation, is partly responsible for determining the aerosol size and is based on the diameter of the nozzle; although aerosol particle size has been described to increase in a step-wise fashion directly with the nozzle size, a nozzle that is too narrow can emit a wide, spray-cone angled mist that results in a large amount of drug being deposited on the mouthpiece of the actuator.³²

Spacer or add on devices

Spacer devices have been developed as another alternative to overcome the problems associated with patients

coordinating the beginning of their inspiratory effort with actuation of the MDI.³³ A spacer device is a tube extension to an MDI or a holding chamber with a port at one end to which the MDI is attached a mask or mouthpiece being fitted at the other end. The most important factors influencing output from an MDI plus add-on device are: spacer material and volume; dead space between inlet and outlet; inlet and outlet valve controls, drug formulation, propellants evaporation rate, and humidity. The inhalation method is also an important variable in the delivery of inhaled drugs. Inhalation from the spacer must be slow and multiple actuations should be avoided.³⁴ A novel breath-actuated antistatic spacer with integrated vortex chamber (Synchro-Breathe_) device has been developed, which is compact, portable and user friendly as compared to conventional spacers which are bulky.³⁵

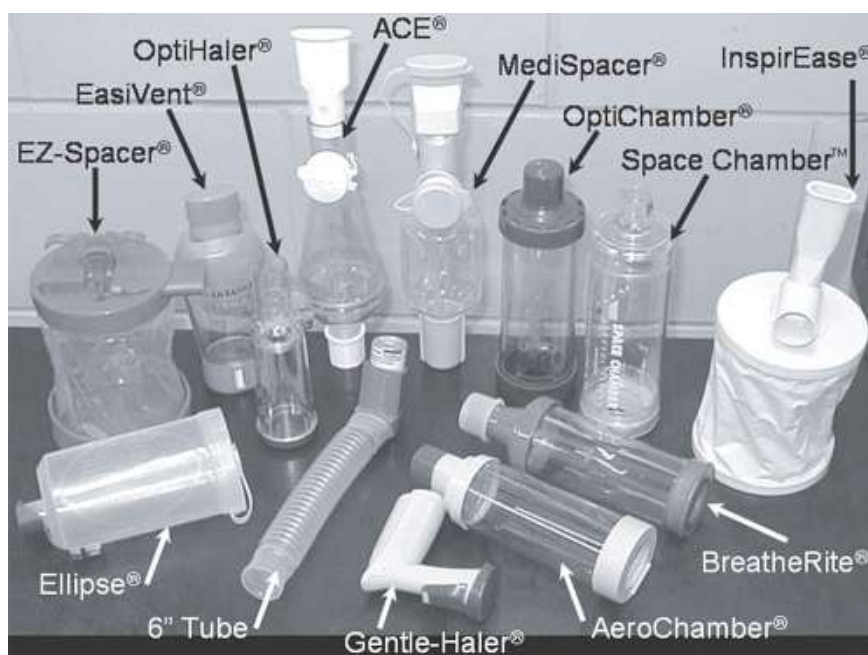


Figure 3: Different categories of marketed spacer device³⁶

MANUFACTURING METHOD OF METERED DOSE INHALER

The manufacture of metered dose inhaler with metering valves requires special consideration because of the particular nature of this form of product. It should be done under conditions which minimise microbial and particulate contamination. Presently there are two common manufacturing and filling methods of metered dose inhaler namely pressure and cold filling method. Pressure filling techniques for pMDIs are most commonly employed. These can be accomplished in either a one or two step process. *In the single step process*, the formulation is placed in a pressurized mixing vessel. The empty canister is purged with propellant to remove the air. The valve is then crimped onto the canister and the formulation is metered through the valve. *In the two step process*, the formulation (excluding the propellant) are mixed together to form a concentrate. Previously, liquefied CFC 11 was used in this step of the process. However, there is no suitable HFA propellant that is liquid at room temperature. Therefore, cosolvents such as ethanol and glycerol are employed during this step to form the product concentrate. The concentrate is metered in to the

empty canister. The valve is then crimped onto the canister and the propellant is filled through the valve. Cold filling is carrying out at a temperature substantially lower than the boiling point of the propellant to allow manipulation at room temperature in open vessel. Cold filling requires cooling the propellants to below (-50°F) and filling at that temperature prior to crimping the valve onto the canister.^{37, 38}

EVALUATION OF METERED DOSE INHALER

MDIs require a greater amount testing for evaluation of efficacy valve, oral adapter and formulation are collectively responsible for delivering the therapeutically active ingredient to the appropriate site and reproducible manner. It is assume that the patient will administer the product properly, so that both the dose and depth of penetration of the medication can be ensure. Like other dosage forms, analytical characterization is important to ensure a stable and effective product. Evaluation parameter of metered dose inhaler derescribe as follows
Dose Content Uniformity.

This test determines the amount of drug substance delivered per actuation from the mouthpiece of different container from the same batch. This test involves assaying the first dose and last label claim dose from ten inhalers, where a dose constitutes the mean of two consecutive actuations, namely actuations 1 and 2 and actuations 119 and 120.³⁹

Uniformity of the delivered dose

Uniformity of delivered dose can be measured by dosage unit sampling apparatus (DUSA). The minimum set-up for delivered dose testing comprises a sample collection tube, fitted at one end with a suitable mouthpiece adapter to accept the inhaler under test and connected at the other end to a vacuum pump capable of continuously drawing 28.3 L/min through the assembled system (including the filter and inhaler). A flow meter should be used to adjust the flow at the inlet to the correct rate prior to testing, using the flow meter adapter. The Delivered Dose is measured by firing the test device into a sampling apparatus containing a filter. The dose is captured, the active drug is dissolved in solvent and an aliquot then analysed, normally using High Pressure Liquid Chromatography (HPLC).⁴⁰

Number of doses delivered.

Number of dose delivered from one canister can be determine by actuating the contents of the pressurized container to waste at intervals of not less than 5 seconds, and recorded the number of doses discharged.⁴⁰

Particle Size Distribution.

The aerodynamic particle size distribution is commonly measured using cascade impactore. The Andersen Cascade Impactor is a multi-stage impactor system through which the aerosol cloud discharged from the inhaler under test is drawn. Drug particles are deposited on the various stages depending on their aerodynamic particle size. By analysing the amounts of drug deposited on the various stages of the cascade impactor, it is possible to generate aerodynamic particle size distribution information for the product under examination.⁴⁰ The effective cut-off diameters for each stage of the impactor system when operated at a flow rate of 28.3 l/min are given in table no :2

Table: Effective cut-off diameter (ECD) for the stages of the Andersen Cascade Impactor⁴¹

Stage	0	1	2	3	4	5	6	7
ECD(μm)	9.0	5.8	4.7	3.3	2.1	1.1	0.7	0.4

Spray Pattern and Plume Geometry

Spray pattern and plume geometry are determined using an optical instrument which takes high speed images of the emitted dose. The images are used to calculate the angle of the aerosol plume and diameter at a specified distance as it exits the actuator. These measurements are used to determine actuator design based on the formulation characteristics

as the density and viscosity can affect the spray pattern.⁴³

Leak Rate

Leaking of propellant is measured by weight change of MDIs as a function of time stored at controlled conditions. Weight loss is determined by measuring the initial weights of canisters that are placed on condition and then reweighed at subsequent time points. Leak rate testing should be performed in addition to both the on-line leak test which culls out the occasional gross leakers and the testing that follows the lag or equilibration time instituted before the release of pMDIs. The leak rate test is important in stability studies because it may provide information on pressure loss and may predict, at subsequent test stations, failures in testing for dose content uniformity through container life.⁴²

Valved delivery or Shot Weight

This test is directly related to the metering ability of the valve, and it evaluates valve-to-valve reproducibility of the drug product. Valve delivery, also known as shot weight, is a measure of the weight of the formulation delivered. It is measured by the difference of weight per actuation or per dose.⁴²

In-vitro drug deposition

Pulmonary deposition pattern of pMDI formulations can be determine by using two different impactor apparatus i.e. Twin impinger apparatus and Multistage Anderson Cascade Impactor.

Twin impinger: It consists of two collecting chambers that are filled with required amount of of mobile phase (7 ml in stage I and 30 ml in stage II). MDI can be attached to the device by a rubber collar and 10 sprays should fire into the apparatus. Side arm tube is connected to vacuum pump with flow rate of 60 l/min which mimicked the respiratory flow in normal patients. Gap of 5 seconds is maintained between two successive sprays and MDI is thoroughly shaken before each spray is fire. The reservoirs should be rinse with mobile phase and amount of drug deposited on adaptor, valve and collar (Device, Stage I and stage II) is determined by HPLC. The deposition of drug at the device represented the non-respirable fraction.

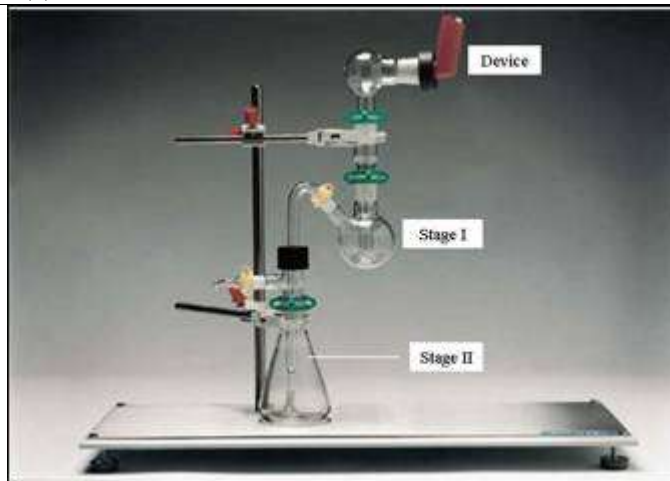


Figure 4 : Twin stage liquid impinger ⁴⁴

Anderson cascade impactor: Anderson cascade impactor having eight perforated plates and they arrange in ascending order of their diameter with '0th' plate on the top and '7th' plate on the bottom. Cascade impactor plates are placed below each of these and the base plate should connect to vacuum with flow rate of 28.3 l/min. An induction port is connected to the top of the impactor. The metered dose

inhaler is attached to the device by means of rubber collar. Exactly 10 sprays should be fired in a manner similar to that for twin impinger. Each plate is rinsed with suitable solvent and amount of drug deposited on each plate is determined by HPLC. Deposition of drug from stage 2 to filter known as "Respirable fraction".

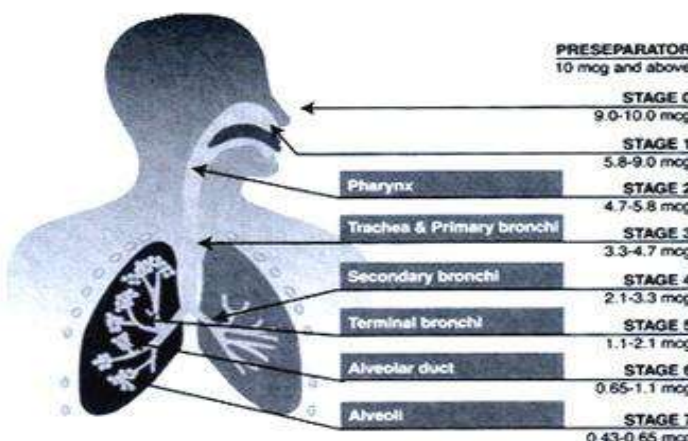


Figure 5: Relationship between stage of Anderson cascade impactor with different parts of cascade impactor. ⁴⁵

Recent Advances in pressurized metered-dose inhalers

Metered-dose inhalers have been a success in terms of efficacy and patient acceptance. However, some aspects of these devices need improvement. An apparently simple, but important, aspect concerns the patient's perception of when the canisters are empty. To overcome this problem, dose counters were developed, which may be direct (based

on an active firing mechanism, actuated by temperature or pressure changes) or indirect (based on a digital pressure or movement on the reservoir). In some cases there is a window in the inhaler that changes colour from green to red. Green indicates the inhaler is full and red indicates the inhaler is empty. Half green and half red in the window indicate it's time to change the inhaler.



Figure 6: Metered dose inhaler with dose indicator.

Another advancement related to dose counter is Puff Minder DOSER. It is an electronic digital counter that can attach to metered dose inhaler (pMDI) and keeps track of how often the inhaler is used. It tracks both the total number of inhalations, and the number of inhalations taken each day. The PuffMinder DOSER is a pressure activated device. Every time press down on the inhaler to take a puff (inhalation) the device records the actuation. The

PuffMinder DOSER will continue to count down the number of inhalations in the canister until it reaches 0. When the count is at 0 (zero) which means that finished the total number of metered doses in the canister. Need to replace the canister with a new, full canister, and reset the PuffMinder DOSER to the number of inhalations in the new canister.



Figure 7: Puff Minder DOSER

However, more significant advances, related to the direct operation of metered-dose inhalers, were required not only to increase the effectiveness of the devices but also to improve patients' comfort. Based on this objective, breath-actuated pressurized inhalers, breath-coordinated metered-dose inhalers, and velocity-modifying inhalers were developed.

Breath actuated pMDI, the Autohaler. To prime the Autohaler, the patient simply lifts a lever on the top of the actuator body, which applies pressure on the canister via a spring mechanism. The canister is blocked from moving under this pressure by the triggering mechanism resting on a vane located behind the mouthpiece. When the patient inhales through the mouthpiece, the vane rotates, activating the triggering mechanism and releasing the drug. Importantly, however, because the Autohaler device uses a pressurised propellant system, dose delivery is actuated with an inspiratory flow of 30 L/min or more.^{46, 47} Velocity-modifying metered-dose inhalers reduce aerosol velocity when it is released from the device, reducing drug deposition in the oropharynx.

Pressurized metered dose inhalers have long been the preferred delivery system for treatment of lung diseases, such as asthma and COPD. The large amount of research and development associated with the transition from CFC to HFA propellants has resulted in major improvements in pMDI technology. Many HFA pMDIs exhibit significantly improved drug delivery compared to CFC pMDIs or DPIs. Modern HFA pMDIs now have the capability to efficiently deliver high doses of drug to the lung. The drug delivery efficiency of HFA pMDIs can be further improved using new HFA soluble excipients and other technologies related to device redesign. This review has attempted to describe the current state-of-the-art surrounding the formulation and reformulation of pressurized inhalers containing hydrofluoroalkane propellants and recent changes in pMDI technology related device redesign that will make drug delivery more efficient and consistent. Recent advancements in pMDI technology associated with the transition to HFA propellants have resulted in highly efficient pMDI systems that are broadly applicable to treating a wide variety of diseases.

SUMMARY

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