

## **BASIC UNDERSTANDING OF PRESSURIZED METERED DOSE INHALERS AND ITS AERODYNAMIC PARTICLE SIZE TESTING: A REVIEW**

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**Abstract—** There are so many classical pharmaceutical dosage forms available in market such as Tablets, Capsules, Syrups, Parenterals etc for treatment of different respiratory diseases. but they are with so many limitations such as long time taken for giving desired effect, kids can't take tablets and capsules, while parenterals are painful for adults also as needle insert inside the body gives much pain. So, now a days a new and advance dosage form namely aerosol dosage forms (or Pulmonary dosage forms) such as Pressurized metered dose inhalers, Dry powder Inhalers and Nebuliser solutions or suspensions gets attraction and became more popular due to its so many advantages over the classical pharmaceutical dosage forms.

**pMDI (Pressurized metered dose inhaler)** is one of the aerosol dosage form. pMDI dosage form is mainly used for the treatment of respiratory diseases such as chronic obstructive pulmonary disease (COPD) and Asthma. Key components of Pressurized metered dose inhaler device are Aluminium Canister, Metering valve and Actuator. It contains propellants such as HFA 134a or HFA 227ea and formulation inside the canister. These devices are mainly multi dose devices and are known for consistent pre-metered delivery of drug in the form of short burst of aerosol cloud directly to the lungs of the patient. Aerodynamic particle size distribution is very important parameter in testing of pMDI products. Advanced analytical instruments such as Anderson cascade impactor with vacuum pump and Flow meter is used for analysis of aerodynamic particle size distribution.

**Keywords—** Metered dose inhalers, COPD, Asthma, Anderson cascade impactor, Aerosol devices, Aerodynamic particle size distribution.

### **INTRODUCTION:**

The pressurized metered dose inhaler (pMDI) was introduced to deliver asthma medicines with a easy and reliable multi-dose presentation to the lungs of patient. The main components of the pressurized metered dose inhaler device are propellants, drug formulation, propellants, metering valve, and actuator. all components of the pressurized metered dose inhaler device play roles in the formation of the spray, and in determining drug delivery to the lungs of patient. Hence the design of a pMDI product by adjusting the formulation, metering-valve size, and actuator nozzle diameter in order to obtain the required spray characteristics and fine-particle dose.

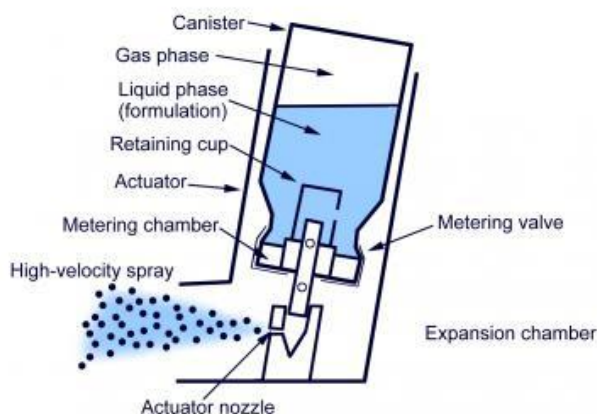


Fig-1 :- Pressurized metered dose inhaler

### **CANISTERS:**

Aluminum canister is preferred for design of pressurized metered dose inhaler, compared to glass, it is lighter, more compact, less fragile, and light-proof<sup>1</sup>. Coatings on the internal container surfaces may be useful to prevent adhesion of drug particles and chemical degradation of drug. Different types of aluminium canisters are used for design of pMDI.

1. Plain aluminium canister.
2. Anodised canister.

3. FCP plasma canister (Fluorocarbon polymerisation plasma anodised canister).

Different types of anodised canisters are used to restrict the sticking of drug particles to the internal walls of canister.



Fig-2 :- Aluminium canisters (B and C) (A= Metering valve)

#### METERING VALVE:

Metering valve contains a metering chamber by which exact amount of medication is dispensed. Metering valve plays a vital role in dispensing of potent medication of drug products. It is used for dispensing of 50, 75, 100, 125, 150 mg  $\pm$  10% of drug per actuation.

The metering valve crimped on the canister is the most critical component of the pressurized metered dose inhaler, there are so many different designs of metering valve available but all are operate on the same basic principle. Before firing, a channel between the body of the canister and the metering chamber is open, but as the pressurized metered dose inhaler is fired, this channel closes, and another channel connecting the metering chamber to the atmosphere opens. The pressurized formulation is expelled rapidly into the valve stem, which, together with the actuator seating, forms an expansion chamber in which the propellant begins to boil. The canister is used in the inverted position, with the valve below the container so that the valve will refill under gravity. Some valves are surrounded by a retaining cup that contains the next few doses of drug<sup>1</sup>.

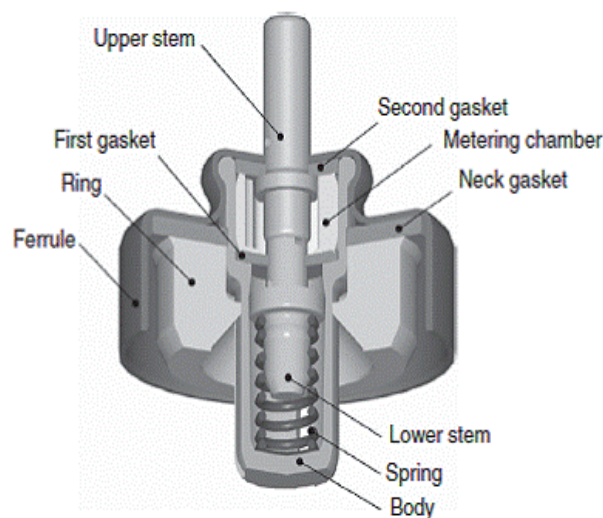


Fig-3 :- Metering valve

#### ACTUATOR:

The pressurized metered dose inhaler canister is fitted into a plastic actuator for use by the patient. The design of the actuator is very important, particularly because the aerosol particle size is determined partly by the orifice diameter, which ranges between 0.14 mm and 0.6 mm. Aerosol particle size varies directly with nozzle diameter of the actuator and particle size affects lung deposition<sup>1</sup>.

Actuator is an integral part of metered dose inhaler. The actuator has been the patient interface of the metered dose inhaler. The actuator has contributed to the much for the success of pMDI products as a clinically effective and cost effective device. In market many pMDI products are available with different types of actuators such as simple actuators, Actuators with dose indicator, Actuators with dose counter etc.



Fig-4 :- Actuators for Pressurized metered dose inhaler

#### PROPELLANTS:

Propellants in pMDIs are liquefied compressed gases that are in the gaseous form at atmospheric pressure, but in the liquid form when compressed. They are nontoxic, nonflammable, compatible with formulated drugs either as suspensions or solutions. Propellants should have appropriate boiling point and density to ensure consistent dosing, the vapor pressure must be constant throughout the life of inhaler product<sup>2</sup>.

Initially chloro fluoro carbons were used as propellants for pMDI products. But due to toxic nature and ozone depleting characteristics they are banned. Then mostly HFA 134a (1,1,1,2- tetra fluoro ethane) and/or HFA 227ea (1,1,1,2,3,3,3-Hepta fluoro propane) or mixture of both in different ratios are used for pMDI products design. Drug particles are soluble or suspended inside the globules of propellants. Once the actuation is done drug particles are coming out of the canister with propellants and reaches to the lungs of patient.

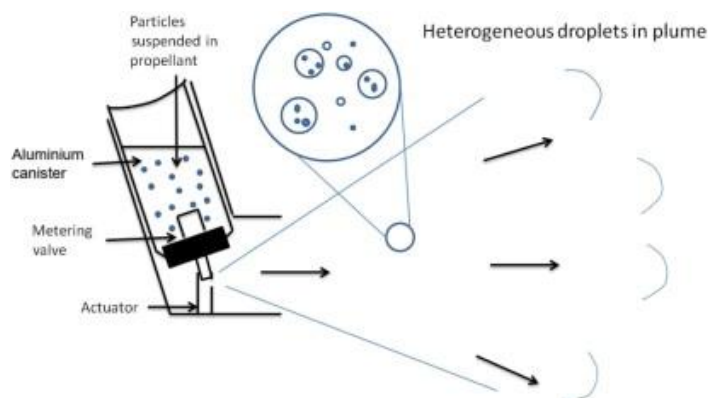


Fig-5 :- Drug particles suspended in droplets of propellants in spray

#### FORMULATED DRUGS :

Pressurized metered dose inhalers contains drugs in the form of either suspensions or solutions. Suspensions are formed by micronization. Suspensions have been widely used for pressurized metered dose inhalers, because propellants are nonpolar liquids in which many drugs have low solubility, and good chemical stability is achieved. Surfactants are also used in pMDIs to reduce particle aggregation and lubricate the valve mechanism (e.g. sorbitan trioleate, oleic acid, or soya lecithin, in concentrations ranging from 0.1% to 2%). However, these surfactants are mostly insoluble in HFA-134a and HFA-227, so the ethanol as a low-volatility co-solvent is also used while designing of pMDI product<sup>3</sup>.

Anti asthmatic drugs, Anti Inflammatory Drugs, Glucocortico steroids, Anticholinergics and quaternary ammonium compounds such as Azelastine hydrochloride, Salbutamol, Ipratropium bromide, Fluticasone, beclomethasone, Salmeterol xinafoate, Formoterol fumarate, Budesonide etc are used in different aerosol formulations for treatment of COPD and asthma.

#### MECHANISM OF SPRAY :

The particle size of drugs used for the design of pressurized metered dose inhaler must be below ten microns in size, because drug particles below 5 microns can penetrate the lungs of the patient and give desired local effect and give on the spot relief from asthma attack or dilate the inflammation of respiratory tract. While particles bigger than 5 micron will get deposited on the throat of the patient and goes in to the systemic circulation<sup>5</sup>.

Shaking before spray is must for suspension based pressurized metered dose inhaler before firing of spray. On shaking of canister the drug suspended inside the canister is homogeneously dispersed in propellant and than on firing of canister spray is coming out of the pressurized metered dose inhaler. The spray dispensed from canister is exactly measured with the help of metering valve and the than it gets aerosolized with the help of orifice of the actuator. Propellant gets evaporated in the trachea or up to primary bronchi of the respiratory tract. These compressed propellants inside pMDI canister gives throttle to the drug particles and this drug particles reaches to the lungs of patient in the form of small burst of aerosol cloud<sup>6</sup>.

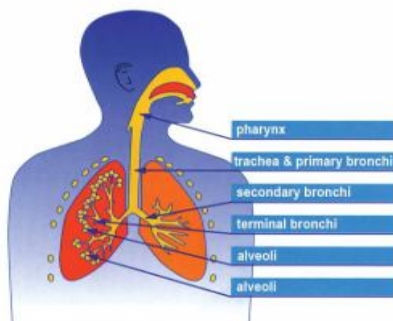


*Fig-6:- Human respiratory tract*

#### **ADVANTAGES OF PRESURRIZED METERED DOSE INHALER:**

Presurized metered dose inhalers are used as a life saving drugs during asthma attacks. It gives quick relief through local effect after reaching to the lungs of patient. presurized metered dose inhalers can deliver single or combination of drugs at a same time. It can deliver to all patient ages with minimum patient cooperation required. In pressurized metered dose inhalers concentration and dose can be modified. Presurized metered dose inhalers are pain less and easy to administer by patient in comparison with tablets, capsules or injections. Presurized metered dose inhalers are also very cost effective medication devices so they are in reach of poor patients also<sup>4</sup>.

#### **AERODYNAMIC PARTICLE SIZE TESTING OF PRESURRIZED METERED DOSE INHALERS:**

Aerodynamic particle size is the size of particles in flight (moving in air stream) after releasing from nozzle of actuator. Measurement of aerodynamic particle size is one of the very important analytical testing parameter for presurized metered dose inhaler. As we can easily predict the drug deposition to the whole respiratory tract of patient by analysing aerodynamic particle size by cascade impaction technique.

Cascade impaction is very useful technique to measure the aerodynamic particle size of aerosol products. Anderson cascade impactor is mainly used. The cascade impactors has three unique features which currently no other technique can replicate:

- 1. Cascade impactors measure aerodynamic particle size:** Cascade impactors measure aerodynamic particle size which is a function of density and viscosity as well as the physical dimensions and shape of the particles concerned. This is important since it helps to explain how particles behave in a moving air stream.
- 2. Cascade impactors measure active pharmaceutical ingredient:** Cascade impactors provide a direct means of recovering and quantifying the active pharmaceutical ingredient (API) contained in the aerosol cloud as opposed to the overall formulation. This is important since the aerosol clouds generated by pharmaceutical inhalers typically comprise a combination of API and other excipients or components.
- 3. Cascade impactors measure the entire dose:** Cascade impactors capture the entire dose allowing complete characterization of the formulation concerned<sup>4</sup>.



*Fig-7:- Vacuum pump, Flow meter and Anderson cascade impactor*

#### IMPACTOR SYSTEM

Anderson cascade impactor comprises the following components:

- Mouthpiece Adapter
- Induction Port
- Different impaction stages with plates
- Vacuum Pump and flow meter.

The cascade impactor consists of eight stages normally arranged in the form of a vertical stack. These separate the particles entrained in the aerosol stream, passing through them into a series of size bands or fractions, broadly corresponding to their likely deposition sites in the respiratory tract. The entrance to the cascade impactor is fitted with a right angled port called induction port. Induction port is designed to mimic the throat. The inhaler is connected to the induction port by a mouthpiece adapter which provides an airtight seal between the induction port and the pressurized metered dose inhaler device under test. Once discharged from the inhaler, the aerosol cloud is drawn through the impactor by means of a vacuum pump connected to the outlet of the impactor by a suitable length of tubing<sup>4</sup>.

| Anderson cascade impactor (Standard at 28.3 ltr/min configuration) |                  |                |                     |
|--------------------------------------------------------------------|------------------|----------------|---------------------|
| Stage No.                                                          | Cut off diameter | No. of nozzles | Nozzle diameter(mm) |
| 0                                                                  | 9.0              | 96             | $2.55 \pm 0.025$    |
| 1                                                                  | 5.8              | 96             | $1.89 \pm 0.025$    |
| 2                                                                  | 4.8              | 400            | $0.914 \pm 0.0127$  |
| 3                                                                  | 3.3              | 400            | $0.711 \pm 0.0127$  |
| 4                                                                  | 2.1              | 400            | $0.533 \pm 0.0127$  |
| 5                                                                  | 1.1              | 400            | $0.343 \pm 0.0127$  |
| 6                                                                  | 0.7              | 400            | $0.254 \pm 0.0127$  |
| 7                                                                  | 0.4              | 201            | $0.254 \pm 0.0127$  |

*Fig-8:- Cut off diameter and Nozzle details for Anderson cascade impactor*

Principle of operation in Cascade impactors is inertial impaction. Each stage of the impactor comprises a single or series of nozzles or holes through which the sample laden air is drawn, directing particles towards the surface of the collection plate for that particular stage. Whether a particular particle impacts on that stage is dependent on its aerodynamic diameter. Particles having sufficient inertia will impact on that particular stage collection plate, whilst smaller particles with insufficient inertia will remain entrained in the air stream and pass to the next stage where the process is repeated. The stages are normally assembled in a vertical stack in order of decreasing particle size. As the jets get smaller, the air velocity increases and finer particles are collected. The particle mass relating to each stage collection plate is recovered using a suitable solvent and then analysed by using HPLC to determine the amount of drug. By analysing the amount of drug deposited on the various stages in this manner, it is possible to calculate the particles of drug below 5 microns which is called Fine Particle Dose (FPD). and percentage of that particles below 5 microns which is called Fine Particle Fraction (FPF). Based on FPD and FPF we can also calculate Mass Median Aerodynamic Distribution (MMAD) and Geometric Standard Deviation (GSD).

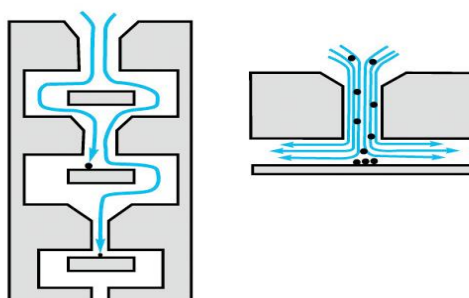


*Fig-9:- understanding of inertial impaction in Anderson cascade impactor.*

#### CONCLUSION

Pressurized metered dose devices are advanced aerosol formulation devices. These devices are easy to use and cost effective and life saving devices used for treatment of Asthma and chronic obstructive pulmonary diseases. Cascade impaction is advanced and very useful technique for the analysis of aerodynamic particle size of pressurized metered dose inhalers as well as other aerosol formulations. The Anderson cascade impactor almost mimic the human respiratory tract and gives an overall idea of drug distribution inside the lungs.

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