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## Formulation and Quality Control of Metered-Dose Inhaler: A Review



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### ABSTRACT

The MDI is now accepted as the principal dosage form of inhalation drug therapy for bronchial asthma and chronic obstructive pulmonary diseases. The MDI consists of an active drug substance dissolved or suspended in a liquefied propellant system held in a pressurized container and that is sealed with a metering valve. MDI can be taken in the form of either suspension or solution. Sometimes the additional excipient like surfactant and co-solvent has been used to improve the quality of dispersion. Quality control testing of MDI Batches applied to the individual inhaler components previous to manufacture as in-process control during the manufacturing and to the finished product.



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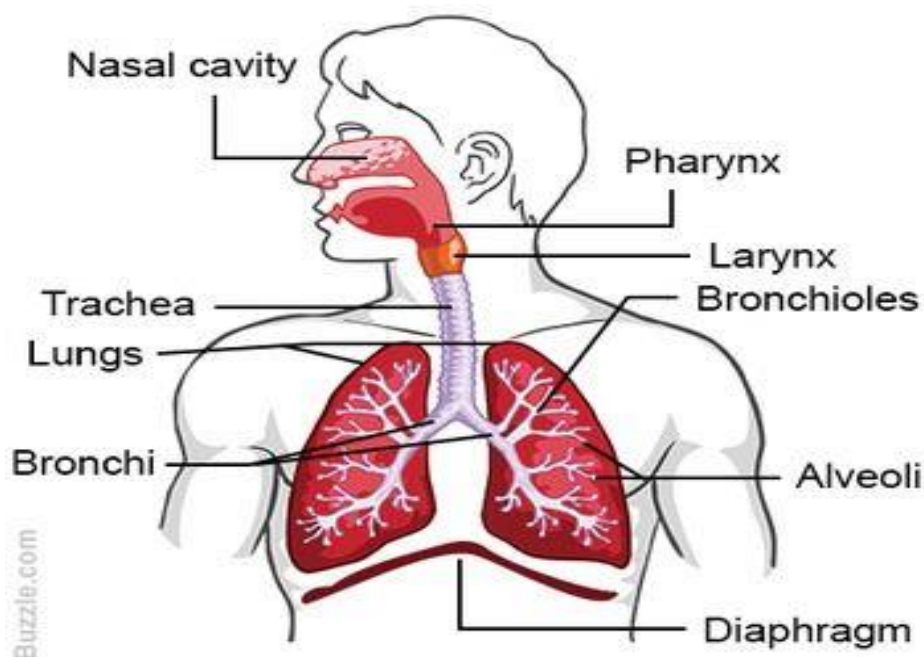
## **INTRODUCTION:**

### **THE HUMAN RESPIRATORY SYSTEM–**

The respiratory system is one of the important systems in the human body. The respiratory system is divided into three different regions. The primary region is the head airway region, the second is the lung airway, and the third is the alveolar. The respiratory tract can be divided into two main portions: upper and lower. The upper part consists of the nose, sinuses, pharynx, and upper larynx. However, the lower part consists of the lower larynx, trachea, bronchi, and lung. (1)The treatment of different respiratory conditions requires the use of medications that are delivered through an inhaler. (2)

### **ASTHMA AND CHRONIC OBSTRUCTIVE PULMONARY DISEASES-**

Asthma is an anachronic inflammatory disorder of the airways. (3) It is identified by variable and regular symptoms, airflow obstruction, hyperreactivity, and inflammation. (3)Asthma treatment aims to control frequent symptoms of asthma and improved forced expiratory volume or pulmonary function. Drugs for asthma can be administered orally, parenterally, or by inhalation. With the inhaled preparation drug is delivered directly to the bronchial tract. (5)For the patient with persistent asthma inhaled corticosteroids have been the first-line treatment unbothered of disease severity(6). COPD is expressed as persistent respiratory symptoms and airflow limitation due to a combination of small airways disease and parenchymal destruction. (7)The most prime factor for the development of COPD is tobacco smoking. Tobacco smoke destroys lung tissue and obstructs the small airways with inflammation and mucus.(8)The extreme economic product of inhaled formulation is developed for the treatment of a local condition or diseases active in the respiratory tract.(9)The development of the first commercial pMDI was carried out by Riker Laboratories in 1995 and marketing in 1956 as the first portable multidose delivery system for bronchodilators. Although the pMDI has become the most widely prescribed inhalation device to treat obstructive airway disease such as asthma and COPD.(10)pMDI provide some important advantages such as multidosing, consistent dosing, rapid delivery, resistance to bacterial contamination and humidity, ease of use and cost-effectiveness.(11) pMDIs are a complex system and realize to be technically challenging to develop. (12)



**Figure No. 1: Respiratory system**

The treatment of choice for asthma and COPD is an anti-inflammatory agent and bronchodilator. But on systemic administration, these agents produce major side effects. To reduce this problem and to have a quicker onset of action, better efficacy inhaled medications are most widely used.

#### **FORMULATION –**

There are two types of MDI Formulation. Suspension Formulation and Solution Formulation. In suspension formulation, micronized drugs are dispersed in a propellant or combination of propellants. And in solution formulation drug is dissolved in the propellant or a combination of propellant and co-solvent. A suspension formulation is the most common dosage form when used together with hydrofluroalkane propellant.

#### **SOLUTION FORMULATION –**

The drug is dissolved in HFA Propellant and appropriate co-solvent. Ethanol is added to produce the solution. This is two-phase system gas and liquid. (13) Compared with suspension formulation solution MDI provides the benefit of the homogeneous formulation.

#### **Advantage-**

1 Homogeneous and uniform drug delivery.

2 No particle growth and aggregation.

**Disadvantages-**

1 Adequate solubility is required in the vehicle.

2 Possible reduction in chemical stability.

**SUSPENSION FORMULATION –**

In suspension formulation, Micronized drug is suspended in the propellant, or a combination of the propellant drug must be insoluble in the propellant. (13)

**Advantages-**

1 formulation has good chemical stability.

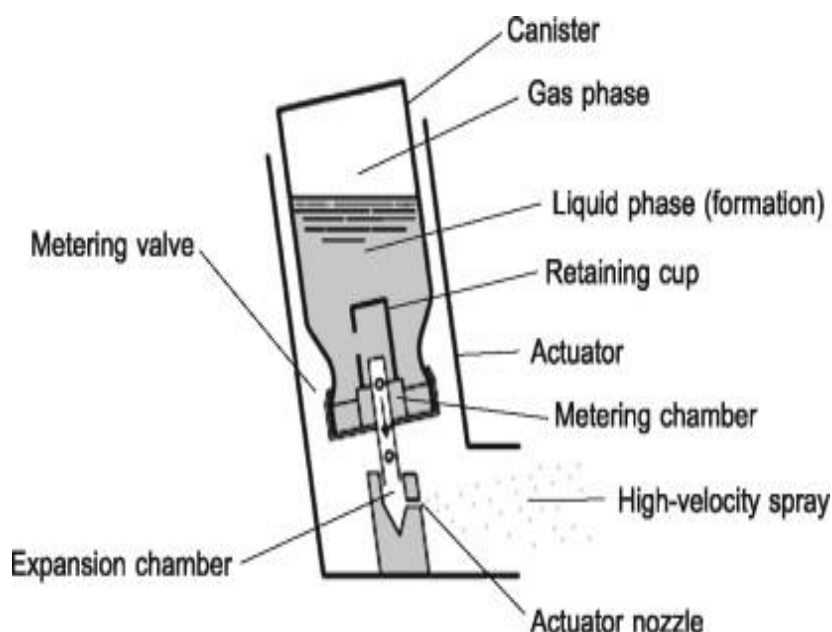
2 No additional excipient needs to add which may be toxic.

**Disadvantage –**

1 The density difference between the propellant and drug affects dose uniformity.

2 Flocculation happens due to dissimilarity in hydrophilicity and hydrophobicity.

**BASIC MDI FORMULATION COMPONENT-**



**Figure No. 2: Basic MDI Formulation Component**

The fundamental components of pMDI are drug formulation, metering valve, propellant, actuator, and container. All play important role in the formulation of the aerosol plume and determining the amount of drug delivered to the lung. (13)

### **CANISTER-**

The pMDI container should resist the high pressure generated by the propellant. It should be made of inert material. The aluminum container is most widely used because it is lighter, less fragile, and lightproof. (13)

### **Ideal properties-**

- 1 Material used for the canister must be adaptable with the formulation.
- 2 It should have lightweight.
- 3 It should be break-resistant.
- 4 It must protect concentrate from sunlight.

### **METERING VALVE –**

The metering valve of a pMDI is an acritical component in the potency of the delivery system. The role of the metering valve is to deliver an accurate dose. (13)

### **ACTUATOR–**

The actuator of pMDI is generally made from polyethylene or polypropylene material. The design of aerosol plays an important role in the production of appropriate aerosol including particle size, droplet size, and plume emitted from pMDI.(13)An actuator is operated to activate the valve and direct the aerosol toward the patient's mouth. The shape of the actuators can affect the spray pattern and droplet or particle size of the aerosol and should be designed for optimum performance. (14)A proportion of active ingredients is generally placed on the inner surface of the actuator so the amount available is less than the amount released by the actuation of the valve. The actuator is a single piece produced by injection molding and that consists of mouthpiece, body, and nozzle.

-The mouthpiece is the interface part to the patient mouth.

-The body provides the support for the canister.

-The nozzle has an important role in the automatization process.

Its regular capacity is around 15-30 ml.

## **FORMULATION –**

MDI Formulations are of two types -suspension formulation and solution formulation.

### **Suspension formulation-**

Suspension formulation consists of a mixture of micronized drugs, surfactant, co-solvent, and propellant. In suspension formulation particle size of the drug is critical because it increases pulmonary deposition and also affects suspension stability. (15)

### **Solution formulation-**

MDI can be formulated with the drug completely dissolved in the formulation. Compared with suspension formulation solution MDIs provide the benefit of the homogeneous formulation. (16)

## **FORMULATION COMPONENT –**

- Active pharmaceutical ingredient
- Propellant
- Stabilizing agent
- Co-solvent
- **Active pharmaceutical ingredient–**



Active pharmaceutical ingredient first checks for pre-formulation study. Particle size should be below 10 um for suspension formulation.

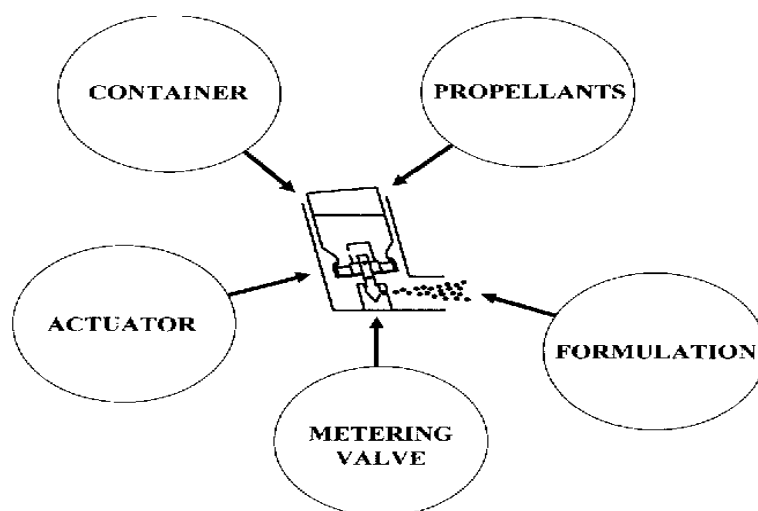


Figure No. 3: Key components of pressured metered dose inhaler

### PROCESSING-

The specific media milling process was developed and designed to operate at high pressure allowing preparation of dispersions using the propellant itself as the milling medium. This HPMM process yields stable, fine particle dispersion of medicament in liquid HFC propellant. The milling is performed with the entire MDI formulation so that surfactant and co-solvent are available to the drug actives during the milling process. (17)

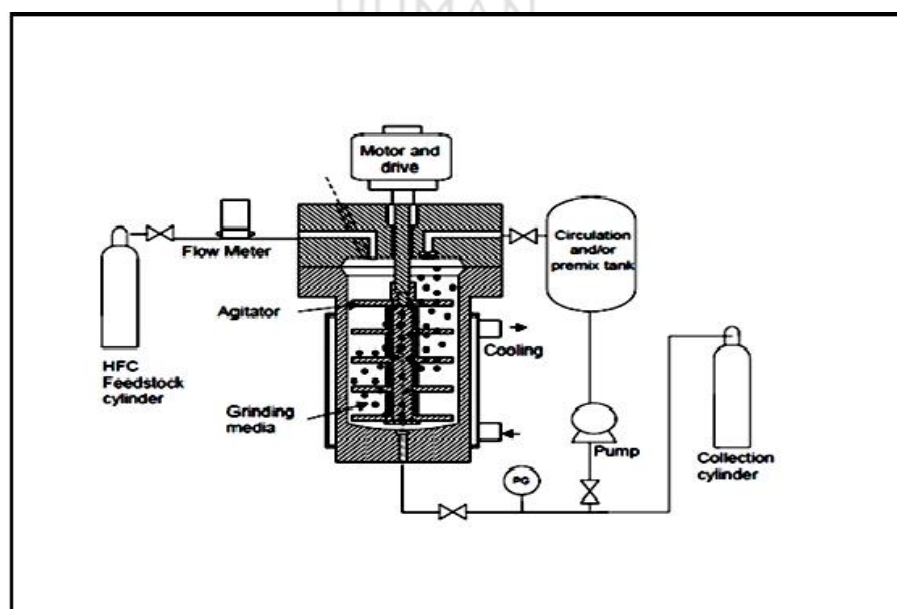


Figure No. 4: High Pressure Media Mill

➤ **Propellant –**

One of the most essential components of an MDI is its propellant. The propellant is used to provide the energy to generate a fine aerosol of drug particles and expel the concentrate from the container and deliver it to the lung. (17) Propellants are volatile substances that form liquids when cooled or compressed but are gaseous at ambient temperature and pressure. So they evaporate rapidly when ejected from the pressurized storage container. (18) A compressed liquefied gas gives consistent pressure through the use of content. The traditional pMDI propellant has been chlorofluorocarbon. Nowadays CFC has been replaced by hydro fluoro alkane due to the environmental effect of CFCs on the ozone layer which filters ultraviolet radiation and increases the risk of skin disease and global warming. Hydrofluoroalkane does not contain chlorine and thus has no ozone-depleting potential. Also, an extensive safety program was conducted by the International Pharmaceutical Aerosol Consortium for toxicity testing which found that HFA is safer than CFC.

**Ideal Properties of Propellant –**

- 1 Noncombustible.
- 2 It must be non-toxic and pure.
- 3 It should be inert and non-reactive in the formulation.
- 4 It must have an acceptable taste and odor.
- 5 Boiling point should be between -100 to 30°C.
- 6 Density should be in between 1.2 to 1.5 g/cm<sup>3</sup>.
- 7 Vapour pressure must be between 40 -80 psig.
- 8 It must be compatible with primary packaging material.
- 9 It should be inexpensive.

➤ **Stabilizing Agent –**

Surfactant is mainly used to stabilize the suspension formulation. It also helps in solubilizing drugs and prevents crystal growth during the storage period. It also enhances valve lubrication. (17)



➤ **Co-Solvent-**

Surfactants are extremely dissolved in CFC but not dissolved in HFA. Therefore, co-solvent is used to dissolve the surfactant in the HFA propellant. Ethanol is one of the most commonly used co-solvent in pMDI formulation. It lowers the vapor pressure of the HFA propellant and produces smaller particles. (17)

**QUALITY CONTROL TEST FOR METERED-DOSE INHALER –**

**Individual component testing-**

- Propellant
- Metering Container
- Valve
- Surfactant
- Actuator

**In-process control testing –**

- Drug suspension concentration
- Drug suspension
- Filled canister
- Control of leakage rate
- Metering valve function
- Analytical testing applied to finished product.
- Identity
- Microbial limit test
- Spray pattern
- Water content



### **Drug product specification test for inhalation product –**

- Leak test
- Number of doses delivered
- Content of active ingredient delivered per actuation
- Uniformity of delivered dose
- Drug content
- Spray pattern
- Vapour pressure
- Retention on Actuator
- Sterility
- Moisture content
- Preservative Content



#### **Leak test**

The leak rate is most important in the stability study. The test is performed by randomly selecting 12 canisters of known weight which are kept in a water bath and maintained at 50°C. Then the canisters are checked after equilibrium for the presence of any leak in the form of air bubbles rising from the orifice or the valve crimp. The weight of these canisters was recorded as W1. Then the canisters are placed in overturned position for NLT 3 days and their weight is recorded as W2. The leakage rate is determined by a formula.

#### **Number of doses delivered**

The content of MDI is discharged by actuating the valve at an interval of NLT 5 seconds and the number of doses discharged from the MDI is observed.

#### **Content of active ingredient delivered per actuation**

The inhaler is discharged in the inverted position under the surface of diluents then pressurized. The content of the active ingredient delivered per actuation of the valve is

determined by discharging the pressurized container through the stainless steel base plate that is kept in a 100 ml beaker. In this beaker 60 ml diluent is added, the inhaler is shaken for 30 seconds before dose collection. Ten deliveries at the beginning, middle, and end of the calculated number of doses are discharged below the surface of diluent maintaining the pressurized container in the vertical plane and released the aerosol through the hole in the center of the base plate. (13)

### **Uniformity of delivered dose**

The delivered dose is the dose delivered from the inhaler to the patient. The main purpose of this test is to ensure dose uniformity within discharges from multiple containers of the batch. The Unit spray sampling apparatus USP is used. This test is designed to demonstrate the uniformity of medication per actuation expected with the label claim discharged from the mouthpiece of a sample. (13)

### **Drug content**

It gives the guarantee of uniformity of dose content in the drug product. The concentration of drug substance in the whole container is determined by using HPLC analytical method. The label of the container is removed by ethyl acetate and the container is placed in the refrigerator at  $-70^{\circ}\text{C}$  for 5-10 minutes. After 10 minutes make a hole in the canister, then the canisters are cut and rinsed. Then the different dilutions are made and analyzed by the HPLC method.

### **Spray pattern**

The spray pattern test is useful for determining the performance of a specific formulation-valve combination and ensure therapeutic performance. The spray transfer through MDI has impinged onto a glass plate containing an activated silica gel dye mixture. The MDI is kept at a distance of 3cm from the plate. Then the spot is observed under UV light.

### **Vapor Pressure –**

The Vapor pressure is determined by using a pressure gauge. The pressure difference indicates the presence of air in the headspace. A canister punctuating device is also widely used for exactly measuring the vapor pressure. The unit of vapor pressure is expressed in psig. (19)

### **Retention on actuator**

At the time of spraying from MDI, some amount of drug may get retained on the actuator. This indicates the waste drug which is not available for inhalation. Deliveries are fired through pMDI with an actuator attached to it in the sample collection tube adjusting air flow rate 28.3 L/min. Then the drug is extracted by adding diluent to the beaker and the actuator is separated, rinsed with diluent, and sonicate for 5 minutes. The solution collected is examined for the content of the drug. (17)

### **Sterility**

Sterility testing should be conducted according to an accepted pharmacopeia test.

### **Moisture content**

Chromatography and Karl Fischer method are most commonly used for the determination of moisture content. Karl Fischer is a most accurate technique for determining the moisture specifically for water content by using the Karl Fischer reagent. Karl Fischer reagent contains a basic solution of sulfur dioxide iodine and solvent as alcohol is most widely used.

### **Preservative content –**

Preservative assay testing must be conducted.

### **Patient Education**

Patient training is most important for the proper use of aerosol devices because an error in the use of devices and in administering therapy was much more common when training was not given to a patient. Patient's poor knowledge regarding their disease and poor competency among dispensers are among the factor leading to improper use.

### **CONCLUSION**

For the treatment of COPD and asthma, inhalation is the best treatment. From different categories of inhalation, the metered-dose inhaler is developed firstly with CFC but because of ozone layer depletion, MDI comes with newly propellant HFA.

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