

A REVIEW: GENERAL CONCEPT ABOUT THE METERED DOSE INHALER

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ABSTRACT:

Inhalation is the best treatment of COPD (chronic obstructive pulmonary disease) and Asthma, The primary goal of inhalation therapy for local treatment is to reduce pulmonary symptoms, through the alleviation and/or prevention of airway inflammation and constriction. In this article inhalation was categorized by dosage form with the action in treatment on body organ. The phase of technological development accelerated in the 1950s, resulting in the refinement of delivery devices with two fundamentally different designs: pMDIs and DPIs. The evolution of pMDI was starting with the first CFC-pMDIs represented a real step forward in inhaler design, challenges remained in terms of device handling and drug delivery. Some patients found the sensation of the high-velocity cold plume produced by the CFC propellant unpleasant, and this contributed to poor inhaler technique. Inhalers using HFA rather than CFC propellants were developed, and the first HFA-pMDI was launched in 1994. In this review article gives details idea about pressurized metered dose inhaler (pMDI) components with formulation procedure and types of it. The article contains the operation mechanism of the meter dose inhaler and the evolutionary test in the mentioned in the guideline by FDA (Food Drug Administration) with their summary of the testing system. It also contains the guidelines generally followed by the industries for the development of a metered dose inhaler.

KEYWORDS:

chronic obstructive pulmonary disease, metered dose inhaler, dry powder inhaler.

ABBREVIATION:

MDI- Metered Dose Inhaler, DPI- Dry Powder Inhaler, DUSA- Dosage Unit Sampling Apparatus.

HISTORICAL PERSPECTIVE AND BACKGROUND [1, 2, 3]

Inhalation is the best treatment for COPD (chronic obstructive pulmonary disease) and Asthma. Inhalation treatment was started in the 1950s by introducing the first pressurized aerosol inhaler. For more than a century, patients were advised to smoke cigarettes containing the anticholinergic botanical, *Datura stramonium* to treat acute asthma. The use of steam inhalation is well described in ancient medical literature and is still used as a home remedy for respiratory tract conditions. The first pressurized aerosol inhaler was introduced in the 1950s. One of the first clinical trials was published by Freedman in 1956, using a pressurized inhaler called Medihaler (Riker Laboratories). Two types of Medihaler were introduced containing either 0.5% aerosol solution of epinephrine (Medihaler Epi.) or 0.25% solution of isoproterenol hydrochloride (Medihaler Iso.), respectively, in an inert propellant. Since their introduction, MDIs have become a cornerstone in the management of asthma.

INTRODUCTION [3, 4, 5, 6, 7, 8, 9, 10, 11,]

The concept of inhalation therapy is not new. Inhalation therapy has gained importance in recent decades. Today, inhalation represents the administration route of choice for the delivery of drugs to treat respiratory disorders and local nasal disorders such as asthma and chronic obstructive pulmonary disease (COPD) and allergic rhinitis. The inhalation route is also being investigated in some instances for the systemic delivery of drugs. The primary goal of inhalation therapy for local treatment is to reduce pulmonary symptoms, for example, through the alleviation and/or prevention of airway inflammation and constriction. Typical examples of inhaled drugs are corticosteroids, beta-sympathomimetic, muscarinic antagonists, and antibiotics. The inhalation of these drugs offers substantial benefits over their systemically administered formulations. Crucially, high pulmonary drug concentrations can be achieved by directly delivering the drug to the target organ, the lung. As a result, considerably lower inhaled doses can be therapeutically equivalent or even superior to higher doses of systemically administered therapy.

Inhalation is fine distributed in various dosage forms for delivering the good efficacy of API (Active Pharmaceutical Ingredient) using a suitable medium. In the pharmacopeial forum the inhalation dosage forms very well distributed various categories as like showed in figure.1.

Introduction of pMDIs and DPIs [13, 14, 15, 17, 18]

The phase of technological development accelerated in the 1950s, resulting in the refinement of delivery devices with two fundamentally different designs: pMDIs and DPIs. In pMDIs, drugs (either in solution or in suspension) are actively expelled from a pressurized storage container by a propellant. By contrast, DPIs have a passive mechanism that relies on the inspiratory force generated by the patient, first to extract the powdered drug from a reservoir or blister, and then to disaggregate the powder into respirable particles. The introduction of the first aerosol-driven pMDI by Riker Laboratories (now 3M Health Care, St. Paul, MN, USA) in 1956 was a significant milestone. The inhaler, which contained the nonselective β -agonists isoprenaline or adrenaline, was marketed as Medihaler-Iso and Medihaler-Epi, and was increasingly used by patients with asthma. The DPI first appeared in 1948, when Abbott (Maidenhead, UK) launched the Aerohaler for the inhalation of penicillin, using a lactose-based formulation. The turn of the twenty-first century has also seen the development of alternatives to pMDIs and DPIs, including the Soft Mist inhaler (Respimat) and breath-actuated pMDIs.

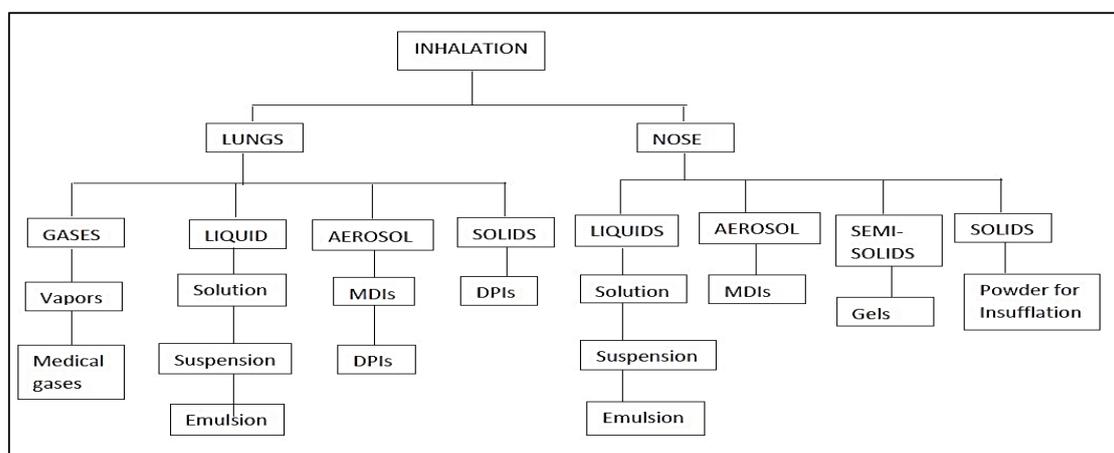


Fig. 1: categories of inhalation dosage form.

Evolution of the Modern pMDI pMDIs using CFC propellants^[17]

Propellants are volatile substances that form liquids when cooled or compressed but are gaseous at ambient temperature and pressure, so they evaporate rapidly once ejected from a pressurized storage container. In pMDIs that used CFC propellants (CFC-pMDIs), the propellant was typically a combination of highly volatile dichlorodifluoromethane (CFC-12) with less volatile trichlorofluoromethane (CFC-11) and/or dichlorotetrafluoroethane (CFC-114). Other compounds were also added to the drug-propellant mix to improve the performance of pMDIs. Surfactants such as oleic acid are used in inhalers containing drug suspensions to reduce the aggregation of drug particles, thereby stabilizing the suspension, and to lubricate the valve. In solution inhalers, co-solvents such as ethanol may be added to increase drug solubility. Although the first CFC-pMDIs represented a real step forward in inhaler design, challenges remained in terms of device handling and drug delivery. CFC-pMDIs produced a rapid spray with a short duration. Owing to technical factors such as actuator nozzle size, the spray contained relatively large droplets and drug particles. For many patients, coordinating device actuation with inhalation proved difficult with pMDIs, impeding drug deposition in the lungs and therefore reducing effectiveness. The fairly large droplets produced by CFC-pMDIs increased oropharyngeal deposition this was compounded by the high spray velocity that further increased impaction on the back of the throat. Furthermore, some patients found the sensation of the high-velocity cold plume produced by the CFC propellant unpleasant, and this contributed to poor inhaler technique.

Introduction of the modern pMDI^[16,17]

Owing to environmental concerns about CFCs, other propellants were sought for use in pMDIs. Two hydrofluoroalkanes (HFAs) were identified as suitable alternatives, namely HFA-134a (tetrafluoroethane) and HFA-227 (heptafluoropropane). Inhalers using HFA rather than CFC propellants were developed, and the first HFA-pMDI (Airomir[®], 3M Health Care) was launched in 1994. However, the development of HFA-pMDIs was far from straightforward, presenting several technical challenges. Apart from the propellant, some of the other compounds and components used in CFC inhalers, such as surfactants and seals, were not suitable for use with HFAs, so alternatives had to be found. Other issues, such as valve design to improve emptying and reduce the need for priming, adhesion of the formulation to the canister walls, and the possibility of delivering higher drug doses per shot also needed to be considered. Additional clinical trials were required to investigate the efficacy and safety of these new formulations. The switch to HFA propellants, however, provided the opportunity to address some of the drawbacks associated with CFC-pMDIs. While some HFA-pMDIs retained similar plume characteristics to CFC-based devices, many HFA pMDIs were designed to deliver smaller particles, at a lower spray velocity and warmer temperature.

Advantages of pMDI:^[19]

1. It delivers a specified amount of dose.
2. It is small in size, portable and convenient for use.
3. It is usually less expensive as compared to dry powder inhalers and nebulizers.
4. Quick to use.
5. The contents are protected from contamination by pathogens.
6. It is having multi-dose capability more than 100 doses available.

Disadvantages of pMDI:^[19]

1. It is difficult to deliver high doses through pMDI.
2. Accurate coordination between actuation of a dose and inhalation is required.
3. Drug delivery is dependent on patient technique.

COMPONENTS OF PMDI:^[19 20 21 22]

The key components of pMDI are drug formulation, propellant, metering valve, actuator, and container. All play an important role in the formation of the aerosol plume and in determining the amount of drug to the lung.

Product Concentrate consists of a single active ingredient or combination of active ingredients and may contain other ingredients depending upon the type of MDI formulation. Other ingredients include co-solvents, surfactants, stabilizers, lubricants, bulking agents, etc. The active ingredient is the material for which the product is designed. Active ingredient used for MDI aerosol must be therapeutically effective at a relatively low dose and non-irritating to the respiratory airways. It should be stable and compatible.

The majority of MDI formulations contain conventional co-solvents in addition to liquefied gas propellants. The co-solvents are used to obtain a solution of the active ingredients in the liquid phase of the aerosol. They help to modify the discharge properties of the aerosol. They also help to reduce the vapor pressure of propellant. Ethyl alcohol is mostly used but polyethylene glycol 200-400, diethyl ether, methoxy polyethylene glycol are the new solvents used. Dimethyl ether (DME) is found to be an excellent solvent for many surfactants but its flammability and insufficient toxicological data limits its use in MDI. The amount of co-solvent can range from 5-30% w/w.

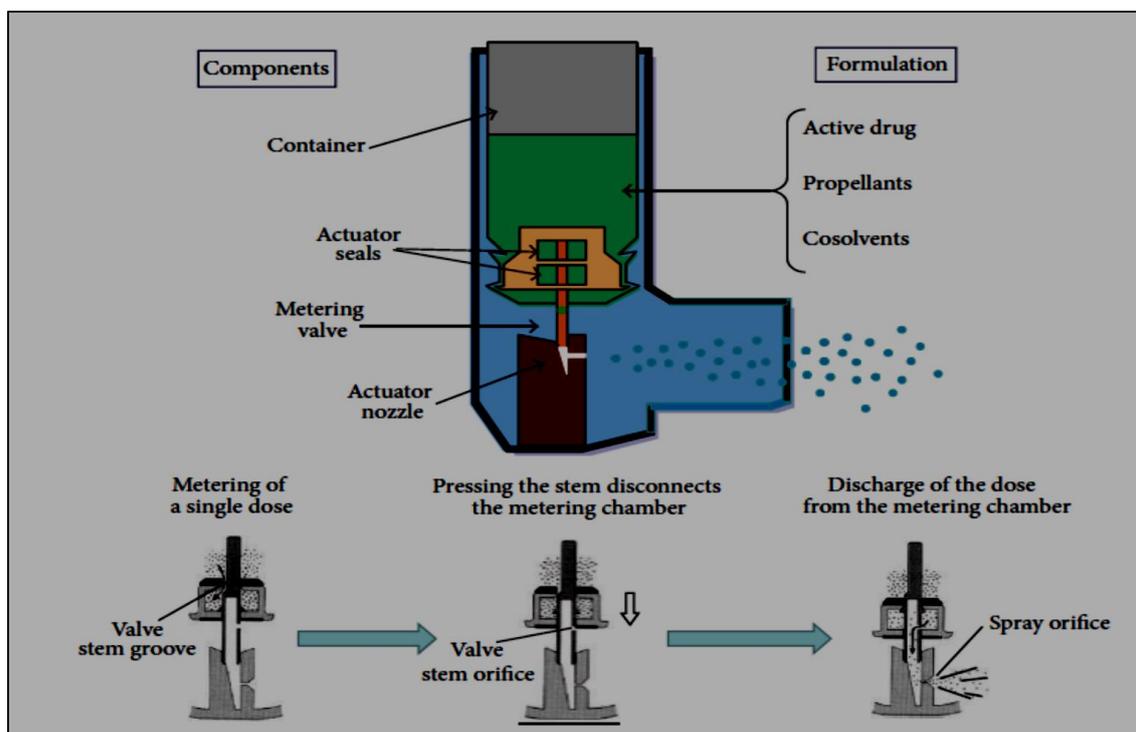


Fig.2.components of a pressurized metered-dose inhaler, lower panels illustrate the process of aerosol generation.

MDI, solution and suspension formulations typically contain a surfactant or a dispersing agent. The surfactants have some solubility in the propellant blend. Commonly used surfactants include sorbitan trioleate (span 85), oleic acid and lecithin at levels between 0.1% and 2% w/w.

These agents maintain the dispersed nature of the drug in the propellant blend and provide lubrication for the operation of the metering valve. They also help to alter the lipoidal solubility thereby enhancing the pulmonary absorption rates of the active ingredient and act as a permeation enhancer by reducing the interfacial tension between drug surface and lung membrane.

Propellant:

One of the most crucial components of an MDI is its propellant. The propellant is described as liquefied gas with a vapour pressure greater than atmospheric pressure (14.7 Psia) at a temperature of 105°F. The Propellant is responsible for developing proper pressure within the container. It expels the product when the valve is opened. Propellants perform the essential function of expelling the material from the container by supplying the necessary pressure within the aerosol system. Mixtures of Propellants are often used to obtain necessary delivery and spray characteristics of aerosol. Propellants in MDIs typically make up more than 99% of the delivered dose, so it is the properties of the propellant that dominate more than any other individual factor. Suitable propellants must pass a stringent set of criteria, they must:

- Odourless, colourless, non-irritant, non-reactive and stable.
- Have a boiling point in the range -100 to +30°C
- Have a density of approximately 1.2 to 1.5 g cm⁻³ (approximately that of the drug to be suspended or dissolved)
- Have a vapour pressure of 40 to 80 psig have no toxicity to the patient
- Be non-flammable
- Be able to dissolve common additives. Active ingredients should be either fully soluble or fully insoluble.

There are general classes of the liquefied gas propellants depending upon their chemical nature.

1. Fluorinated Hydrocarbons: ^[23]

They are also known as Chlorofluorocarbons (CFCs). They are the propellants of the choice for oral inhalation and nasal aerosols. The most important propellants include trichloromonofluoromethane (P-11), dichlorodifluoromethane (P-12) and dichlorotetrafluoroethane (P-114). Although CFCs are stable and non-toxic in the lower atmosphere, in the stratosphere, slow decomposition of CFCs by solar radiation results in the free chlorine content. Destruction of the ozone layer allows increased transmission of ultraviolet radiation to the earth's surface. For this reason they are being replaced by Non-CFCs.

2. Hydrofluoroalkanes: ^[24, 25]

These are also known as Non-chlorofluorocarbons (Non-CFCs) eg. HFA-134a, HFA-152a and HFA-227. These propellants do not contain chlorine and therefore have zero ozone depleting potential.

3. Hydrocarbons:

Hydrocarbons like propane, butane, and isobutane, are used in topical pharmaceutical aerosols. They are preferred for use as propellants because of their environmental acceptance and low cost. However, they are flammable and explosive.

4. Semifluorinated alkanes (SFA): ^[26]

These are with fluorocarbon and hydrocarbon segments. These are colourless non-aqueous liquids with low surface tension, high gas dissolving capacities, strong intramolecular bonds, and weak intermolecular interactions. E.g. Perflorobutyl pentane (F4H5), Perfluoro hexyl Hexane (F6H6), Perfluoro hexyloctane (F6H8).

Packaging Components:

Proper choice of packaging components is necessary as they affect the product performance. As given in MDI has three packaging components.

1) **Containers (Canisters):** ^[27]

Containers made up of as glass, stainless steel and aluminum have been used for pharmaceutical aerosols because of aesthetics and excellent compatibility with drugs. Aerosol containers must withstand pressures as high as 180 Psig at 130°F. Mostly Aluminum type canisters used in pMDI formulation filling.

2) **Metering Valves:** ^[28]

The valve regulates the flow of active ingredients and Propellant from the container and determines the spray characteristics of aerosol. It must be manufactured from materials that are inert to the contents of aerosol. The function of the metering valve is to meter accurately and repetitively, small volumes of liquid containing the drug and to seal the pack against undue leakage of propellant vapour. The valve is a complex assembly of at least seven component parts, which are made of various materials.

An integral part of these valves is the metering chamber, which is directly responsible for the delivery of the desired amount of therapeutic agent. The size of the metering chamber can be varied so that from 25µl to 75µl of product can be delivered per actuation. The chamber is sealed by the metering gasket and the stem gasket. In the actuated position, the stem gasket will allow the content of the metering chamber to be dispensed while the metering gasket will seal off any additional product from entering the chamber. Therefore, the chamber is always filled and ready to deliver the desired amount of therapeutic agent.

3) **Actuator (Adaptor) and special devices:** ^[29,30]

Actuator allows for easy opening and closing of the valve and is an integral part of MDI. The actuator (adaptor) is designed for oral inhalation. It incorporates the discharge orifice called spray nozzle and a socket to engage and form a seal with the metering valve stem. The expansion chamber is very important in influencing the physical characteristics of spray where active ingredients must be delivered in a proper particle size range. The actuator should restrain sideways motion of the container during actuation to minimize side stresses on the valve stem that may cause faulty metering or leakage between the valve stem and actuator. The actuator should provide adequate air ducting for inhalation to the mouthpiece at an acceptable low flow resistance.

4) **Spacers:**

Metered-dose inhalers are sometimes used with add-on devices referred to as holding chambers or spacers, which are tubes attached to the inhaler that act as a reservoir or holding chamber and reduce the speed at which the aerosol enters the mouth. They serve to hold the medication that is sprayed by the inhaler. This makes it easier to use the inhaler and helps ensure that more of the medication gets into the lungs instead of just into the mouth or the air. With proper use, a spacer can make an inhaler somewhat more effective in delivering medicine. Spacers can be especially helpful to adults and children who find a regular metered-dose inhaler hard to use. People who use corticosteroid inhalers should use a spacer to prevent getting the medicine in their mouth, where oral yeast infections and dysphonia can occur. The respiratory spacer devices eliminates the need for coordination of actuation and inspiration and reduces the primary droplet size by providing extra time for complete evaporation of propellant and reduces the velocity of the aerosol particles passing through the device.

MECHANISM OF OPERATION OF PMDI:

The MDI is a complex dosage form in that the container/closure system is integral to the delivery of the drug to the patient. The MDI consists of a solution or suspension of the drug dispersed in the propellant, a valve and container, and an actuator. All parts of the system are required to work in concert so that a reproducible respirable dose is delivered to the patient. It was the invention of the metered-dose valve that allowed the development of the first MDIs. Although several metered-dose valve designs are available, the basic mechanism of action remains the same. At rest, the metering chamber of the valve is in communication with the bulk formulation.

On actuation, just before the side stem hole entering the metering chamber, the volume contained in the metering chamber is sealed off from the rest of the formulation. Thus the metered volume is determined by the volume of the valve metering chamber. The difference between the pressure of the propellant and the ambient pressure, approximately 50 pounds per square inch, allows the liquid propellant to boil explosively, causing the formulation to be expelled through the valve stem. Finally, as the stem is allowed to return to the rest position, the formulation refills the metering chamber. The filling of the metering chamber after actuation is largely due to the pressure differential between the bulk formulation and the empty metering chamber. It is important to realize that the next dose to be delivered to the patient, whenever that may be, is filled into the metering chamber immediately after the current dose has been taken. This has implications for how patients use an MDI.

FORMULATION DEVELOPMENT OF METERED DOSE INHALER: ^[19, 33, 34]

pMDIs drug formulations can be solution or suspensions in single propellant mixture and may include excipients such as ethanol or surfactants to solubilize the drug or stabilized a drug suspension.

There are two type of the formulation types

1) **Solution formulation :**

Drug is completely dissolved in HFA propellant and appropriate co-solvent (e.g. Ethanol) is added to produce the solution. This is a two-phase system of gas and liquid.

Advantages:

1. Homogeneous and uniform drug delivery.
2. Enhance the efficiency of aerosolization and increase lung deposition.
3. No issue of particle growth and aggregation.
4. Very less drug particle deposition on component.

Disadvantages:

1. Sufficient solubility is required in vehicles.

2. Possible reduction in chemical stability.
3. Few options of co-solvent for inhalation formulation.
4. Co-solvent decreases vapor pressure which is required for automation.

2) Suspension formulation :

Micronized drug is suspended in propellant or combination of propellant. Drugs should be insoluble in a propellant. This is a three-phase system consisting of gas, liquid and solid.

Advantages:

1. Formulation resulting good chemical stability.
2. No additional excipients need to add which may be toxic.

Disadvantages:

1. The density difference between propellant and drug affect dose uniformity.
2. Difference in hydrophilicity and hydrophobicity cause flocculation.

There are the two type filling process of pMDI formulation

A. Cold filling Method:

In the cold filling method the product concentrate is chilled to a temperature of -30 to -40°F. The chilled product concentrate is added to the chilled aerosol container. The chilled propellant is added through an inlet valve present underside of the valve of the aerosol container. In this method cold temperatures are used to convert the drug formulation to a liquid phase. Initially, active pharmaceutical ingredient (API) and solvent are mixed to form either a homogenous suspension or a solution. Simultaneously, the propellant is placed into a pre-chilled vessel. The low temperature ensures that the propellant is in liquid form in the batching vessel. The concentrate is then transferred into the manufacturing vessel and the entire formulation is mixed. In the next step of the cold filling process formulation is dispensed into appropriate sized canisters by pumping the formulation to a filling head and feeding a predetermined portion of the chilled liquid formulation into an open canister. The valve is placed on top of each canister and then crimped into place.

B. Pressure filling method:

In this method the product concentrate is filled to the aerosol container through the metering pressure filling burette at room temperature. In contrast to cold filling, the pressure fill process uses pressure instead of low temperature to condense the propellant.

Pressure filling manufacturing can follow two methods:

In one method, known as a two-stage pressure filling method, the drug concentrate is placed in an open canister. A valve is then placed on top of the canister and crimped into position to form the seal. The propellant is then driven under pressure through the valve and into the canister. Using this method, the mixing of the concentrate and propellant happens in the canister. The other method of pressure fill manufacturing is referred to as single-stage pressure filling. In this process the API and propellant are mixed and held under pressure in the vessel. An empty canister is then fed onto the filling table and a valve is placed on top and crimped into place. The complete formulation is then filled under pressure into the canister.

EVALUATION OF THE FORMULATION OF pMDIs: ^[35]

For the evaluation of the pMDI the refer the guideline of “**Quality control Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Products - Quality Considerations Guidance for Industry**”. In this guideline their having guidance for the development of product MDI & DPI with information about to submit the application to the FDA for approval of the product in detail.

Taking reference to that guideline here are some important parameters to be studied for the evaluation of pMDI. These are the **Quality Target Product Profile (QTPP) and Critical Quality Attributes (CQAs)**

A) Quality Target Product Profile (QTPP)

To development of an MDI product we should establish the desired quality target product profile (QTPP). The QTPP is a summary of the quality characteristics of a drug product. This ideally will be achieved to ensure the desired quality, taking into account the safety and efficacy of the MDI product. QTPP elements of the pMDI are the proposed dosage form and delivery system, strength (e.g. targeted delivered dose for MDIs), purity, stability, and aerodynamic performance.

B) Critical Quality Attributes (CQAs) :

Early in the development process of an MDI, We should develop a list of potential CQAs for the product. A CQA is a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality (ICH Q8 (R2)). Knowledge of the QTPP for the product, in combination with information from prior knowledge, risk assessments, and/or experimentation, can be used to develop the list of product CQAs. The list of product CQAs can be modified as product development progresses and new knowledge is gained. CQAs for the drug substance(s), excipients, and container closure system (including the device constituent part) should also be developed. For MDIs, potential product CQAs typically include assay, impurities and degradants, delivered dose, aerodynamic particle size distribution (APSD), spray pattern, leachables, alcohol/excipient content, foreign particulate matter, moisture content, net content (drug substance and excipients), microbial load and device constituent part characteristics such as component dimensions and valve delivery (shot weight). The force and distance necessary to advance the dose counter¹⁰ and the product actuation force (force to deliver the drug from the device constituent part) are CQAs. If the MDI product is actuated by the patient’s inhalation, the airflow necessary to actuate the device for drug release can be considered a CQA.

Characterization study of the MDI:

These studies are used to demonstrate the robustness and performance of the product and support labeling. Studies for MDIs are listed in table 1, below. The applicability of each of the characterization studies outlined below for a given product. The studies should be conducted on the to-be-marketed configurations and versions of MDI products. A minimum of three batches using the formulation and device constituent part of the to-be-marketed configuration and version should be studied to support the reliability of the manufacturing processes and the reproducibility of product performance.

Table No.1: characterization study for mdi

Study	MDI
In-Used Period	✓
Temperature Cycling	✓
Priming and Repriming	✓
Effect of Patient use	✓
Effect of storage and Shaking (Suspension formulation)	✓
Drug Deposition on Mouthpiece and/or Accessories	✓
Cleaning Instruction	✓
Profiling of Actuation Near Device Exhaustion	✓
Effect of flow rate and Inhalation Delay on MDIs with Spacers	✓
Robustness	✓

SUMMARY OF INHALER TESTING SYSTEM (MDI & DPI):^[36]

Inhalation testing is done according to the guideline respective country authority. Some common testing parameters or we called as test for evaluation for the MDIs and DPIs products and testing system which used in it as showed in the table.

Table No.2: summary of testing system using in evaluation of pmdis & dpis products.

Description of Drug Delivery Device	Metered Dose Inhaler	Dry Powder Inhaler
Delivered Uniformity (DDU) Dose	<ul style="list-style-type: none"> • DUSA for MDIs • Mouthpiece Adapter • Vacuum pump • Flow Meter • Waste Shot Collector • Breath Actuation Controller 	<ul style="list-style-type: none"> • DUSA for MDIs • Mouthpiece Adapter • Vacuum pump • Critical Flow Controller • Flow Meter • Waste Shot Collector • Breath Actuation Controller
Aerodynamic Particle Size (APSD)	Cascade Impactor: <ul style="list-style-type: none"> • ACI (Anderson Cascade Impactor) • NGI (Next Generation Impactor) • MSLI (Multi-stage Liquid Impinger) • GTI (Glass Twin Impinger) • Mouthpiece Adapter • Vacuum pump • Flow Meter 	Cascade Impactor: <ul style="list-style-type: none"> • ACI (Anderson Cascade Impactor) + Preseparator • NGI (Next Generation Impactor) + Preseparator • MSLI (Multi-stage Liquid Impinger) • GTI (Glass Twin Impinger) • Mouthpiece Adapter • Vacuum pump • Critical Flow Controller • Flow Meter
APSD Data Analysis	Copley Inhaler Testing Data Analysis Software (CITDAS)	

GUIDELINE AND REGULATION FOR MDI & DPI:^[37]

Table 3, contains the all guideline and regulation which followed by the industry for reference purpose of the development of pMDI & DPI products.

Table No.3: guideline and regulation for mdi & dpi

Regulatory	Metered-Dose Inhaler	Dry Powder Inhaler
EMA Guidelines	Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products (2006)	
	Guideline on the Requirements for Clinical Documentation for Orally Inhaled Products (OIP) including the Requirements for Demonstration of Therapeutic Equivalence between Two Inhaled Products for use in the Treatment of Asthma and Chronic Obstructive Pulmonary Disease (COPD) in Adults and for use in the Treatment of Asthma in Children and Adolescents (2009)	

FDA Draft Guidance for Industry	Metered-Dose Inhaler (MDI) & Dry Powder Inhaler (DPI) Products (2018) - Quality Considerations
Drug Efficacy	
European Pharmacopoeia 2017 (9th Edition)	Preparations for Inhalations (Dosage Forms 0671) Aerodynamic Assessment of Fine Particles (Chapter 2.9.18)
US Pharmacopoeia 2018 (USP 41)	Inhalation & Nasal Drug Products - General Information & Product Quality Tests <5> Aerosols, Nasal Sprays, Metered-Dose Inhalers and Dry Powder Inhalers <601> Uniformity of Dosage Units <905> Pharmaceutical Dosage Forms (Aerosols - Inhalations) <1151>
	Spacers & VHCs <1602>
Chinese Pharmacopoeia 2015	Inhalation Products - Metered-Dose, Dry Powder Inhalers and Nebulisers - Delivered Dose Uniformity <0111> Aerodynamic Particle Size Distribution (APSD) <0951>
Device Efficacy	
International Standards Organisation	Aerosol Drug Delivery Devices - Requirements and test methods (ISO 20072: 2013)
Expert Groups	
European Pharmaceutical Aerosol Group (EPAG)	EPAG European based industry expert group involved in orally inhaled and nasal drug products
International Pharmaceutical Consortium on Regulation & Science (IPAC-RS)	IPAC-RS US based industry expert group involved in orally inhaled and nasal drug products
Product Quality Research Institute (PQRI)	PQRI A collaborative research organisation involving FDA's CDER, industry and academia

CONCLUSION:

For the treatment of COPD, the inhalation is the best technique. The starting of inhalation in 1950 with smoke cigarettes containing the anticholinergic botanical, Datura stramonium to treat acute asthma. From various categories of inhalation, the Metered Dose Inhaler is developed with firstly CFC because of ozone layer depletion MDI comes with newly propellant HFA. In this the having various component that will give efficient efficacy with a measured way using the metering valve which can deliver the exact amount of drug to a patient with the explanatory mechanism of operation of the MDI. Formulation aspects were clearly understood in this article with the filling procedure of the MDI. For evaluation of the mdi there are some guideline which was reported in this by using summary of inhaler testing or evaluation system.

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