

# Formulation and product development of pressurised metered dose inhaler: An overview

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## ABSTRACT

Pressurized metered dose inhalers (MDIs) are widely used dosage form for treatment of respiratory diseases, such as asthma and chronic obstructive pulmonary disease. The metered dose inhaler (MDI) contains the active pharmaceutical ingredient dispersed or solubilised in a high vapour pressure propellant and metered accurately in tens to hundreds of micrograms and administered directly to the lungs. The most dominant characteristics of MDI include their portability, convenience of use and quick effect. MDI comprises of drug formulation, propellant, metering valve, actuator, and container. This review contains overview of excipient selection, primary packaging material, propellant selection and formulation development of pMDI. Two of the most commonly used methods for the manufacturing of MDIs are cold filling method and pressure filling method. This review demonstrates different analytical techniques for characterization of pMDI's like uniformity of delivered dose, water content, spray pattern and plume geometry were discussed. This review also presents in-vitro characterization, pharmacokinetic and pharamcodynamic study of MDI.

**Keywords:** Pressurised Metered Dose Inhaler, formulation, propellant, In vitro, In vivo Evaluation

## INTRODUCTION

Pulmonary delivery is used from ancient times in the delivery of drug for both local and systemic drug delivery. The inhaled therapies started since 4000 years ago in India, from that time leaves of the Atropa Belladonna plant smoke, aromatic plants are used to treat cough and other respiratory disorders. Pulmonary drug delivery is mainly used in the treatment of asthma, cystic fibrosis and COPD. It minimizes systemic side effects, required small dose and provides fast response.<sup>[1]</sup>

The inhalation therapies involved the use of leaves from plants, vapours from aromatic plants and balsams. Around the turn of the 19th century, the invention of liquid nebulizers as a newer treatment developed into valid pharmaceutical therapies. In 1920 adrenaline was introduced as a nebulizer solution, in 1925 nebulizer porcine insulin was used in investigational studies in diabetes, in 1945 pulmonary delivery of the newly revealed penicillin was investigated. Steroids had been introduced in 1950 in the form of nebulizers for the treatment of asthma. In 1956 the pressured metered dose inhaler

(pMDI) was introduced and become the major stay for the asthma treatment. It may found that certain drugs taken by pulmonary route are readily absorbed by the alveolar region direct in to blood circulation because of the some unique physiological characteristics of the respiratory route of drug administration.

### Advantages

1. Pulmonary drug delivery requires small fraction of oral dose. (i.e. drug content of one 4 mg tablet of salbutamol equals to 40 doses of meter doses.)
2. It delivers drug locally at low concentration that reaches systemic circulation thus reducing systemic side-effects.
3. Onset of action is very quick with pulmonary drug delivery.
4. It avoid first pass metabolism. (e.g. Budesonide almost completely absorbed from the gastrointestinal tract but its bioavailability is low i.e. about 10% due to extensive first-pass metabolism in the liver).

5. Large surface area around 100 m<sup>2</sup> and thin 0.1 to 0.2  $\mu\text{m}$  thickness of pulmonary epithelium increase the permeation of the drug.

6. Bioavailability of larger drug molecules can be improved by means of absorption enhancer.<sup>[2]</sup>

### Disadvantages

1. Oropharyngeal deposition causes local side effect.
2. Patient faces difficulty in using the pulmonary drug devices correctly.
3. The total amount of drug per puff delivered to the lung is too less than 1000 mcg.

### DEVICES FOR PULMONARY DRUG DELIVERY

There are three main methods of delivering respiratory drugs for most of the asthma patients metered dose inhaler (MDI), dry powder inhaler (DPI) and nebulizers. In case of dry powder inhalers (DPI) active pharmaceutical ingredient (API) powder with or without carrier (e.g. lactose) fine micronized particles are inhaled. The aggregates are converted into an aerosol by inspiratory airflow and this minimizes the problem of coordination between the delivery of the drug and the initiation of inspiration. But it is unsuitable for patients who are unable to generate high inspiratory flow rates. Active drug particles have a typical length-scale of 5  $\mu\text{m}$ , while the carrier particles (usually a form of lactose) have a much wider size distribution. The most common carrier blend,  $\alpha$ -lactose monohydrate, has particles ranging between order of magnitude larger and smaller than the active drug particles. This powder is stored within the device in different ways depending on the design.<sup>[3]</sup>

Nebulizer is a devices used to administer aerosolized medication in the form of a mist inhaled into the

lungs. Nebulizer uses oxygen, compressed air or ultrasonic powder to break up medical solutions and suspensions into small aerosol droplet called mists that can be directly inhaled from the mouthpiece of the device. Nebulizers have also many disadvantages such as operation noise especially with jet nebulizers, bulky design, long administration period, unportable, variable performance because of gas flow for jet nebulizers, reservoir volume and drug physicochemical properties such as viscosity for ultrasonic nebulizers.<sup>[4]</sup>

In the metered dose inhaler (MDI) the API dispersed or solubilised in a high vapour pressure propellant and metered accurately in tens to hundreds of micrograms and administered directly to the lungs. pMDIs are most widely used device for drug delivery to the lungs. With this method, a medication is mixed in a canister with a propellant, and the preformed mixture is expelled in precise measured amounts upon actuation of the device.

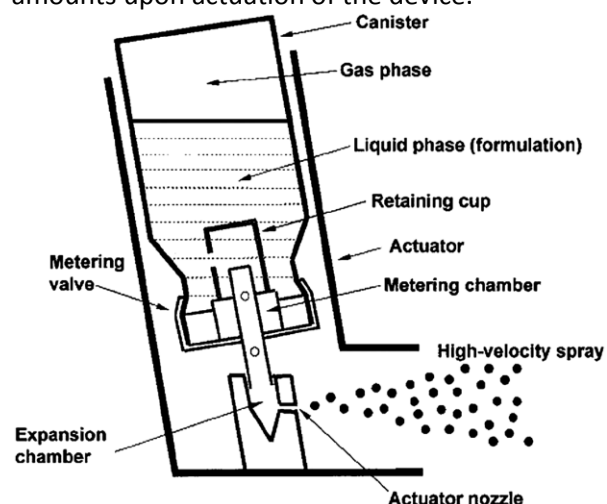


Figure 1. Pressurized metered dose inhaler<sup>[5]</sup>

### History:

Table 1. History of Metered dose Inhaler

1956	First MDI "Medihaler" by Riker Laboratories now owned by 3M Healthcare Ltd.
1974	This year saw the publication of the 'ozone depletion theory', put forward by two American scientists, Rowland and Molina.
1987	"Montreal protocol" This agreement set target dates for significant reductions in the use of CFCs. The protocol was revised in 1990, in order to phase out the use of CFCs by the year 2000. CFC propellants are now only used in certain 'exempt' products.
1995	First HFA MDI. "Airomir"

### Advantages

1. It delivers specified amount of dose.
2. It is small in size, portable and convenient for use.
3. It is usually less expensive as compare 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

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

### COMPONENTS

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

**1. Canister:** The pMDI container should be able to withstand the high pressure generated by the propellant and it should be made of inert materials. Aluminium container is nowadays preferred because it is lighter, more compact, less fragile and light proof. Coatings on the internal surfaces of canister may be useful to prevent drug adsorption, corrosion and drug degradation. Common coatings include epoxy resins, anodized aluminium, epoxy-phenol and perfluoroalkoxyalkane.<sup>[6]</sup>

### Ideal properties

1. Material used for canister should be compatible with formulation.
2. It should have ability to withstand pressure up to 1500 kPa.
3. It should have light weight.
4. It should be break resistant.
5. It should protect concentrate from sunlight.

**2. Metering Valve:** The metering valve of a pMDI is critical component in the effectiveness of the delivery system. The function of the metering valve is to deliver dose accurately and reproducibly. The volume measured by it ranges from 20-100  $\mu\text{L}$  and form a propellant-tight seal for high pressure in the

canister. The elastomeric seals and the gaskets are important components of the metering valve. The valves must be constructed from a variety of inert materials to ensure the compatibility of the formulation with the valve components. They form the barrier to the external environment and prevent the leakage of the product. The solvency properties of the propellant and storage temperature can affect the degree of swelling of valve elastomer. The valve regulates the flow of the content from the container and determines the spray characteristics of the aerosol.<sup>[7]</sup>

**3. Actuator:** The actuator which is fitted to the aerosol valve stem is a device which on depression or any other required movement opens the valve and directs the spray to the desired area. The actuator of a pMDI is generally made from polyethylene or polypropylene materials. The design of actuator is important for the production of appropriate aerosols including the particle size, droplet size and the characteristics of the aerosol plume emitted from a pMDI. The design of an actuator which incorporates an orifice of varying size, shape and expansion chamber are crucial factors in influencing the physical characteristics of the spray particularly in the case of inhalation aerosols, where the active ingredient must be delivered in the proper particle size range. A proportion of the active ingredient is usually deposited on the inner surface of the actuator, the amount available is therefore less than the amount released by actuation of the valve.<sup>[8]</sup>

**4. Formulation:** There are two types of MDI formulations: i) Suspension formulations, in which micronized drug are dispersed in a propellant or combination of propellants; and ii) Solution formulations, in which the drug is dissolved in either the propellant or a combination of propellant and co-solvent.<sup>[9]</sup>

Suspension formulations are the more common dosage form, when used along with the hydrofluoroalkane propellants such as HFA-134a. However, propellants like HFA-227ea have poor solvency characteristics there for the use of co-solvents has become more common. Some of the products of suspension and solution are given in table 2.

**Table 2.** Solution and suspension formulations of pMDI

Sr. No.	Brand Name	Active Ingredient	Dose	Type of Formulation
1	Serovent	Salmeterol	25µg/dose	Suspension
2	Ventoline	Albuterol sulfate	100 µg/dose	Suspension
3	Qvar	Beclomethasone Dipropionate	50 µg/dose 100 µg/dose	Solution Solution
4	Fluvent HFA	Fluticasone Propionate	50 µg/dose 125 µg/dose 250 µg/dose	Suspension
5	Atrovent	Ipratropium Bromide	20 µg/dose	Solution

**A) 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.<sup>[10]</sup>

**Advantages**

1. Homogeneous and uniform drug delivery.
2. Enhance 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 vehicle.
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.

**B) Suspension Formulation**

Micronized drug is suspended in propellant or combination of propellant. Drug should be insoluble in 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.

**Formulation Component****1. Active Pharmaceutical Ingredient**

Active pharmaceutical ingredient first checked for preformulation studies and particle size (D<sub>97</sub>) should be below 10 µm in case of suspension formulation.

**2. Propellant**

The propellant is used to provide the energy to generate a fine aerosol of drug particles and to expel the concentrate from the container and deliver to lung. The liquefied compressed gases are mainly used because discharge of aerosol undergoes evaporation of propellant to give aerosol of very small particles. A compressed liquefied gas gives consistent pressure throughout the use of content.

The traditional pMDI propellant has been chlorofluorocarbon (CFC). However, nowadays CFC has been replaced by hydrofluoroalkane (HFA) due to concern about the environmental effects of CFCs on the ozone layer which filters ultraviolet (UV) radiation posing an increased risk of skin disease and global warming. HFAs do not contain chlorine and thus have no ozone-depleting potential. The Montreal Protocol was adopted in 1987 because of complete phase-out of the CFCs. From 2005 the Food and Drug Administration (FDA) ruled out that the sale of CFC pMDI should be prohibited in the United States after 2008. HFAs have greenhouse gas potential less than that of CFCs.<sup>[11]</sup>

**Ideal Properties of Propellant**

1. Boiling point should be between -100 ° to 30 °C.

2. Density should be in between 1.2 to 1.5 g/cm<sup>2</sup>
3. Vapor pressure 40 to 80 psig.
4. Nonflammable.
5. It should be nontoxic and pure.
6. It should be inert and not reactive in formulation.
7. It should have acceptable taste and odor.
8. It should be compatible with primary packaging material.
9. It should have acceptable solvency properties.
10. Low cost.

The chemical industry has developed HFA 227ea (Heptafluoropropane) and HFA 134a (Tetrafluoroethane) as CFC substitutes. Presently, they have been used by the pharmaceutical industry as propellants for medical aerosols, particularly for asthma sprays. HFA 134a and HFA 227 propellants met the criteria required for MDI propellants with

regard to non-combustibility, toxicological safety, availability and technical suitability in terms of physicochemical characteristics. Physicochemical properties of HFA 134a and HFA 227ea are given in the table 3.

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**Table 3.** Physicochemical properties of Propellant

Sr. No.	Propellant	HFA 227	HFA 134a
1	Chemical Name	Heptafluoropropane	Trifluoromonofluoroethane
2	Mol. Formula	CF <sub>3</sub> CHFCF <sub>3</sub>	CF <sub>3</sub> CH <sub>2</sub> F
3	Vapour Pressure (psia)	390	572
4	Boiling Point (°C)	-16	-26
5	Viscosity (mPas)	1.42	1.23
6	Water solubility (ppm)	2220	610
7	Density (g/cm <sup>2</sup> )	1.42	1.23

### 3. Stabilizing Agent

Surfactants are used to stabilize the suspension formulation. It also helps in solubilising drug and prevents crystal growth during the storage period. It improves valve lubrication. Surfactants such as oleic acid, sorbitan trioleate and soya derived lecithin are highly soluble in CFC but are not soluble in HFAs, therefore co-solvent are used to dissolve these surfactants in the HFA propellants.

### 4. Co-solvent

Surfactants are highly soluble in CFC but are not soluble in HFA therefore co-solvent is used to dissolve the surfactants in the HFA propellants. Ethanol is one of the most commonly used co-solvents in pMDI formulation. It lowers the vapour pressure of HFA propellants which produce smaller particle and more respirable drug fractions. It can even increase the solubility of certain APIs which

lead to an increased problem of crystal growth. Also increase in ethanol causes decrease in volatility and vapour pressure of the formulation inside the container.

## MANUFACTURING OF PRESSURIZED METERED DOSE INHALER

### a) Cold filling Method

In cold filling method the product concentrate are chilled to temperature of -30 to -40°F. The chilled product concentrate are added to the chilled aerosol container. The chilled propellant is added through an inlet valve present under side 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 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 actually happens in the canister.

The other method of pressure fill manufacturing is referred 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.

### Advantages

1. The emulsion, suspensions are unstable at very low temperature. So the pressure filling method is more preferred method than that of cold filling method.
2. The absence of moisture reduces the chance of contamination.

3. The rate of production is high.
4. The chance of loss of propellant is less.

## CHARACTERIZATION OF PMDI

### 1. Water Content

Water or moisture cause changes in particle size distribution, morphic form and crystal growth or aggregation. Therefore water should be strictly limited to prevent changes. Testing for the presence of water in the container is determined by using Karl fisher titration method using KF Coulometer apparatus.

### 2. Microscopy

Microscopic examination of the formulation provides information on the presence of large particles, changes in morphology of the drug substance particles, extent of agglomerates, crystal growth and foreign particulate matter. Additionally this gives information about morphic change in case of crystalline drug substance which can affect the bioavailability, performance and stability.

Metered dose inhaler is sprayed on glass slide by holding slide 5 cm from the end of the actuator, perpendicular to the direction of spray. One drop of oil is added on slide. After placing cover slip on it the slide is examined under a microscope by oil immersion method.

### 3. Leak test

The leak rate test is important in stability studies because it may provide information on pressure loss at subsequent test stations and failures in testing for dose content uniformity through container life.

The test is performed by randomly selecting the 12 cans of the known weight which are kept in a water bath maintained at 50°C. After equilibration, canisters are checked for the presence of any leaks in the form of air bubbles arising from the orifice or the valve crimp. These cans are weighed and their weight (W1) is recorded. The cans are placed in inverted position for not less than 3 days and weighed (W2). The leakage rates are then calculated by using formula.<sup>[11]</sup>

$$\text{Leakage Rate (mg/year)} = \frac{366 * 24 * (W1 - W2)}{T \text{ (Time)}}$$



#### 4. Average Weight per Metered Dose (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. It determines the capacity of the metering valve in terms of the weight of the delivered substance. The shot weight is mainly affected by the density of the propellant. The first prime sprays are fired in air as prime dose. After the test fire, the canisters are wiped with a tissue paper and their weights are recorded. Five successive deliveries are sprayed from the inhaler after placing the canisters back into their actuators. The canisters are subsequently removed from the actuator and the valve stem and the orifice are wiped clean. The containers are weighed again and their weights are recorded. Average shot weight is calculated.

#### 5. Number of deliveries per container

These are checked by counting the total number of actuations, till the contents of the canister are exhausted completely. The content of the pressurized container is discharged to the waste by actuating the valve at intervals not less than 5 seconds and the number of deliveries are measured.

#### 6. Drug Content (Assay)

The concentration of drug substance in the entire container is determined by using HPLC analytical method. It gives assurance of consistency of drug content in the drug product.

The label of container is removed by using ethyl acetate. The can is kept in refrigerator at -70 °C for 5 minutes in upward position. After 5 minutes can is pierced by piercing apparatus, then can is cut and rinsed. Then dilutions are made and analyzed by HPLC Method.

#### 7. Content of active ingredient delivered per actuation

The content of the active ingredient delivered by actuation of the valve is determined by discharging the pressurized container through the stainless steel base plate that is placed in 100 ml beaker. The 60 ml volume of diluent is added into the vessel. The inhaler is discharged in the inverted position under the surface of the diluent. The pressurized inhaler is shaken for 30 s prior to dose collection. Ten deliveries at the beginning, middle and end of the

calculated number of doses are discharged below the surface of diluent actuating the valve at interval of NLT 5 seconds, maintaining the pressurized container in the vertical plane and discharging the aerosol through the hole in the centre of base plate.

#### 8. Uniformity of delivered dose

The delivered dose is the dose delivered from the inhaler to the patient. This test is designed to demonstrate the uniformity of medication per actuation, consistent with the label claim discharged from the mouthpiece of a sample. The primary purpose of this test is to ensure dose uniformity within discharges from multiple containers of a batch. The USP unit spray sampling apparatus is used.

Apparatus consist of filter support base with an open mesh filter-support of stainless steel screen, sample collection tube is screwed to the filter-support base and a mouth piece adapter is joined to sample collection plate to ensure airtight seal between sample collection tube and the mouth piece. The vacuum connector is connected to a system comprising a vacuum source and flow regulator. The source is adjusted to draw air through the complete assembly, including the filter and inhaler to be tested at 28.3 (± 5%) liters per minute.

The inverted inhaler is attached to apparatus; valve is depressed for 5 seconds and discharges the delivery to waste. The inverted inhaler is fitted to the apparatus, discharged once immediately then the valve is released. Then diluent is added in sample collection tubes and analyzed for drug content.

This test involves determining the dose content uniformity at the beginning of unit life, at the actuations corresponding to 50 percent of the fill weight and at the label claim number of actuations per container for an appropriate number of containers.<sup>[12]</sup>

#### 9. Retention on actuator

At the time of spraying from MDI, some amount of drug may get retained on the actuator. This represents the waste drug which is not available for inhalation and hence to be restricted to minimum. Deliveries are fired through pMDI with actuator

attached to it in the sample collection tube adjusting air flow rate  $28.3 \pm 5\%$  L/min. Drug is extracted adding diluent in beaker and actuator is separated, rinsed with diluent and sonicated for 5 minute. The collected solution is analyzed for the content of drug.

### 10. Spray pattern and Plume geometry

There are two methods for determination of spray pattern, impaction (thin-layer chromatography plate impaction) and non-impaction (laser light sheet technology). The spray pattern test is carried out at range of 3 to 6 cm from the actuator mouthpiece. Spray pattern is measured in terms of ovality ratio and area within the perimeter of the true shape. Ovality ratio is defined as the ratio of  $D_{max}$  to  $D_{min}$ .  $D_{max}$  and  $D_{min}$  are the longest and shortest diameters, respectively, that pass through the centre of mass or the centre of gravity, as appropriate.

The plume geometry is measured in terms of plume angle and width.

### 11. In-vitro Drug Deposition of Emitted Dose

#### A. Twin stage impinger

Twin stage glass impinger apparatus is considered as apparatus A in European Pharmacopoeia. Twin stage impinger apparatus consists of two stage reservoirs; where stage I represents the extent of drug deposited in the oropharyngeal region and stage II represents the extent of drug deposition in the lungs. Schematic diagram of twin stage impinger given in Figure 2.

Stage I: Upper Impinger Chamber: MDI is attached to the equipment by means of a rubber collar of the upper impinger chamber. The throat consists of modified glass tubing with precise diameter (A). This tubing is attached to a round bottom glass reservoir of 50 ml capacity and contained 7 ml of the analyzing liquid (B).

Stage II: Lower Impinger Chamber: Flask I is connected to the lower impinger by means of a coupling glass tube (C1). The tube has a plastic screw cap and a side arm outlet which can be connected to the vacuum pump. The lower jet assembly is made up of polypropylene filter holder. This is connected to a lower end of a plastic coupling tube. The filter assembly consists of a circular disc comprising of 4

jets arranged on a projected circle of diameter 5.3mm. The stage II terminates with a conical flask of 250 ml capacity (C2). This contains 30ml of the analyzing liquid. The amount of active ingredient deposited in this stage represents the "net respirable fraction". The fraction is supposed to mimic the amount of drug bioavailable to the lungs for exerting the required therapeutic effect.

Procedure: The two collecting chambers are filled with the required amount of distilled water (7ml in stage I and 30ml in stage II). The pMDI is attached to the device by means of the rubber collar. 10 sprays are fired into the apparatus. The side arm tube is connected to the vacuum pump. The flow rate is adjusted to 60 L/min with the help of flow-Meter. This mimics the respiratory or inspiratory flow rate of normal individual. A gap of 5 seconds is maintained between two successive sprays. The reservoir is rinsed with the distilled water.

The amount of drug deposited on the adaptor, collar and valve is termed as device and stage I represents the fraction of the drug that is not available for inhalation or the 'non-respirable fraction'. The amount of drug deposited in stage II, is the amount of drug available to the lungs and represents the 'net respirable fraction'.

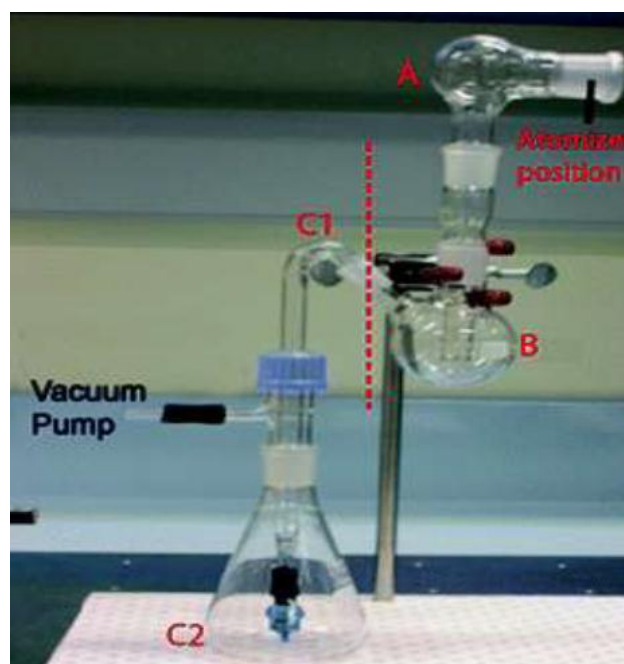


Figure 2. Twin stage glass Impinger apparatus <sup>[13]</sup>



### b) Cascade Apparatus

The Andersen Cascade Impactor is arguably the most commonly used impactor within the pharmaceutical industry for the testing of inhaled products. It consists of 8 stages (Figure 3) which was originally developed as a bacteriological air sampler and then adopted by the pharmaceutical industry for inhaler testing. Many drug applications are based on data collected from the ACI due to its longevity within the industry. The aerodynamic diameter of a medicinal aerosol has a direct effect on the ability of the aerosolised drug to deposit in the lungs and is thus an important parameter when developing pressurised metered dose inhalers (pMDIs). In vitro measurements are used to assess pMDI performance. For in vitro pMDI testing, it is generally accepted that aerodynamic particle size is the single most important parameter for pulmonary drug delivery and can be used as an estimate of aerosol deposition efficacy. The aerodynamic size distribution may be characterised by the mass median aerodynamic diameter (MMAD) and the

geometric standard deviation (GSD). The MMAD is the most important parameter defining particle size, i.e. drug deposition. Theoretically, a monodisperse aerosol will exhibit a GSD of 1.0, in practice however, a GSD of  $\leq 1.22$  is considered as monodisperse. Cascade impactors operate on the principle of inertial impaction. Each stage of the impactor comprises a single or series of nozzles or jets through which the sample laden air stream is drawn directing any airborne 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 size. 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 assembled in a stack, in order of decreasing particle size. As the jets get smaller, the air velocity increases and finer particles are collected. Any remaining particles are collected on an after-filter.<sup>[14]</sup>

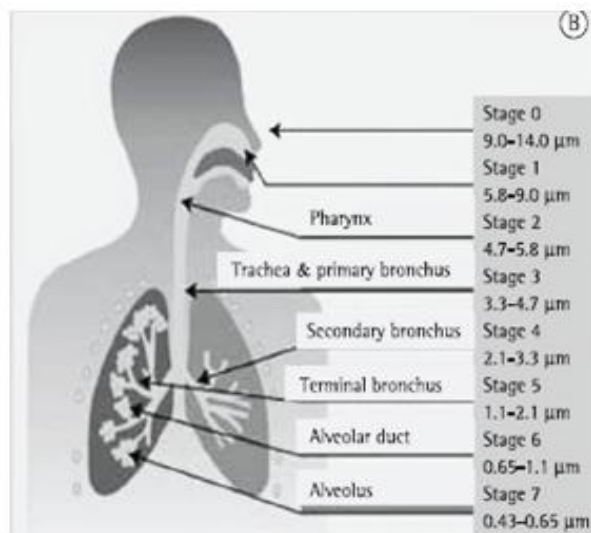
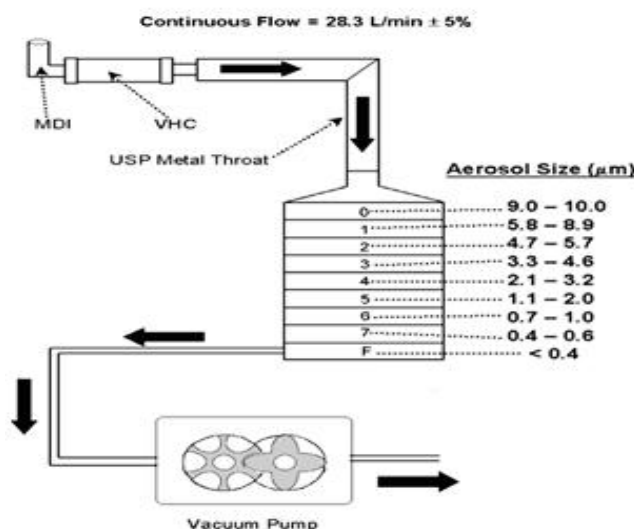


Figure 3. Cascade impactor<sup>[15]</sup>

### b) Next Generation Pharmaceutical Impactor (NGI)

The Next Generation Pharmaceutical Impactor (NGI) was launched in 2000, and monographs were subsequently incorporated into USP (as Apparatus 5 & 6) and Ph. Eur. (as Apparatus E) in 2005. The NGI is a high performance, precision, particle classifying cascade impactor having seven stages plus a micro-orifice collector (Figure 4).<sup>[16]</sup>

#### Main features of the Next Generation Impactor (NGI) include:

- State-of-the-art aerodynamic principles
- User friendly design for ease of use
- Designed to a pharmaceutical industry specification
- Collection cups for easier automation
- Archivaly calibrated flow rate range: 30 - 100 L/min

- Additional calibration at 15 L/min for nebuliser applications
- Particle size range: 0.24 - 11.7 microns (dependent on flow rate)
- Accepts USP style induction port (without use of O-rings)
- Good drug recovery (mass balance)
- Electrically conductive; unaffected by static
- Two-stage preseparator available
- Seven stages: at least five with cut-offs between 0.5 and 6.6 microns at all flow rates
- Low internal particle losses; minimal washing between tests
- Meets USP system suitability requirements
- Excellent stage efficiency, accuracy and reproducibility
- Corrosion resistant construction
- Design and archival calibration formally documented and published

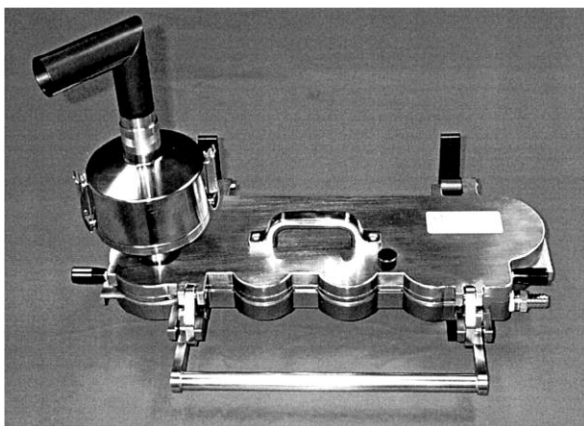


Figure 4. Next generation impactor<sup>[17]</sup>

## 12. In-vivo

In vivo measurement of drug deposition in the lungs and efficacy can be determined by various methods which consist of radionuclide lungs imaging method (gamma scintigraphy) pharmacokinetic technique and spirometry.<sup>[18]</sup>

### a) Radionuclide imaging

In this method drug deposition in lungs is measured using formulation labelled with radionuclides (to create the radio-labelled product). Two dimensional (gamma scintigraphy) and three dimensional [single photon emission computed tomography (SPECT) or

position emission tomography (PET)] can be used for determination of drug deposition in lungs.

### b) Pharmacokinetic (PK)

PK studies performed under conditions that do not allow oral absorption of the swallowed fraction of drug, by using charcoal block method. So that the lung is the only compartment from which drug is absorbed into the systemic circulation and there for systemic plasma concentration time profiles gives absorption processes and deposition in the lungs. It may gives information on pulmonary retention time, particle size distribution and central-to-peripheral deposition pattern.

The charcoal block method which prevents gastrointestinal (GI) absorption of the swallowed fraction of drug is used for PK studies. Furthermore mouth rinsing is also recommended, that would minimize the fraction of the dose that may absorb through mouth epithelia.

This is carried out by using single-dose, two-way crossover design, upon healthy males and non-pregnant females. Drug concentration is measured in plasma and pharmacokinetic parameters such as AUC, T<sub>max</sub> and C<sub>max</sub> are determined.

### c) Pharmacodynamics (PD)

Clinical model are employed in study of efficacy of pMDI FEV<sub>1</sub> (forced expiratory volume in one second) is used as the primary endpoint. Two study models are used for the PD assessment of short-acting beta agonist efficacy by careful assessment of bronchodilation caused by the beta agonist and b-agonist-induced inhibition of bronchoprovocation with methacholine or histamine.

Design for conducting PD studies includes single-dose, double-blind, double-dummy, randomized, crossover study with not less than 24 hour washout period between treatments. Subjects for study should males and non-pregnant female asthma patients. Effectiveness should be determined in terms of areas under the effect curve calculated from the zero time to four hours (AUECO-4h) and from zero time to six hours (AUECO-6h) and maximum FEV<sub>1</sub> (FEV<sub>1max</sub>).

**Table 4.** Clinical study model

Sr. No.	Drug Category	Clinical Study Model	Advantages	Disadvantages
1	Beta-2 Agonists	Bronchodilation	Technically simple	Easy to fail if subjects are not properly selected
		Bronchoprotection	Greater probability of success	Technically more difficult to Conduct
2	Inhaled Corticosteroids	Improvement in lung Function	Clinically relevant	Carry over between treatment arms prevents crossover design
		Asthma stability model	clinically relevant, sufficiently steep dose-response	Technically more difficult to conduct large screen failure rate to identify suitable subjects
		Exhaled nitric oxide	Easy to measure	Careful Subject selection required. Clinical relevance less clear than asthma stability model
		Amp, methacholine or Mannitol challenge	Easier to conduct than asthma Stability	Clinical relevance uncertain. Careful subject Selection required.
		Sputum eosinophilia	Easier to conduct than asthma Stability.	Practical concerns include inability of some patients to generate sputum careful subject selection Required.

## CONCLUSIONS

MDIs are a compact and convenient delivery system that has the advantage of convenience to the patients. The multi-dose nature of MDIs makes them more affordable than most competing inhalation delivery systems. The various characterisation techniques such as uniformity in delivered dose gives consistency in delivered dose through container life and in-vitro characterization test such as twin stage impinger, Andersen cascade impactor (ACI) and next generation impactor helps to determine respiratory lungs deposition of the drug fraction. This technique gives the information about aerodynamic particle size distribution which simulates in-vivo lung deposition. Pharmacokinetic characterization provides information about systemic exposure of drug and spirometry technique used for pharmacodynamic determination of drug efficacy. Furthermore, MDI device technologies are in development and it is constantly improving day by day. MDI technology will increase the ability of MDI systems to meet patient's requirement. It is ensured that MDI will remain a mainstay in the treatment of pulmonary diseases in spite of expansion into new therapeutic areas, combination products, increased access to medication in developing markets and increasing cost pressures in developed markets.

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