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FORMULATION AND DEVELOPMENT OF SALBUTAMOL PRESSURIZED METERED DOSE INHALER

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ABSTRACT

Pulmonary delivery has gained increased interests over the past few decades. For respiratory conditions, targeted drug delivery directly to the site of action can achieve a high local concentration for efficacy with reduced systemic exposure and adverse effects. For systemic conditions, the unique physiology of the lung evolutionarily designed for rapid gaseous exchange presents an entry route for systemic drug delivery. Although the development of inhaled formulations has come a long way over the last few decades, many aspects of it remain to be elucidated. The purpose of the present research work was to develop a robust and physiochemically stable Pressurized Metered Dose Inhaler formulation for pulmonary delivery of a bronchodilator, the-Salbutamol. Salbutamol in the plasma following oral administration is predictable from its very high clearance, which would be expected to result in a high first pass metabolism. Therefore, targeting Salbutamol as pMDI form, as spray formulation for the management of Asthma & Chronic Obstructive Pulmonary Disease. Salbutamol was formulated by pressure filling technique as Metered Dose Inhaler formulation. Salbutamol Pressurized Metered Dose Inhaler. 100 mcg was evaluated for different parameters like identification of Pressurized Metered Dose Inhaler type, physical, chemical and packaging characterizations. Hence the studied suspension for pulmonary delivery was found to be physically stable at 30°C/65%RH, 40°C/75%RH for 3 months in final container.

KEYWORDS: Salbutamol, Bronchodilator, Pressurized Metered Dose Inhaler, Chronic Obstructive Pulmonary Disease.

1. INTRODUCTION

"Pharmaceutical aerosols are pressurized dosage forms that upon actuation emit a fine dispersion of liquid and/or solid materials containing one or more active ingredients in a gaseous medium."[1] The origin of inhaled therapies can be traced back 4000 years ago to India, where people smoked the leaves of the *Atropa belladonna* plant to suppress cough. In the 19th and early 20th centuries, asthmatics smoked asthma cigarettes that contained stramonium powder mixed with tobacco to treat the symptoms.

1.1 Principle of Aerosol

The principle of aerosol delivery from pMDIs is based on the following sequence of events. A small volume of a homogeneous dispersion of the drug, in solution or suspension, in a high vapor pressure propellant or a propellant blend from a reservoir, is isolated. The small-volume container (the metering chamber) is opened through an actuator nozzle. The metering chamber filling and opening to the atmosphere achieved by means of a metering valve. Once opened to the atmosphere, the high vapor pressure contents of the metering valve immediately begin to equilibrate with atmospheric pressure. This has the effect of propelling the contents rapidly through the nozzle, which causes shear and droplet formation. Throughout this process the propellant is evaporating propelling, shearing, and ultimately reducing the size of the droplets produced.[2]

1.2 Types of Aerosol

1) Solution system / two phase system

Consist of two phases: Liquid phase – propellant + product concentrate

Vapor phase Active ingredients soluble in the propellent no other solvent required.

2) Water based system /three phase system

Consist of large amount of water, usually to replace all or a portion of nonaqueous solvent. Three phase system consists of a layer of water immiscible liquid propellant, a layer of highly aqueous product concentrate, a vapor phase the formulation must consist of a dispersion of active ingredients and other solvents in an emulsion system in which the propellant is in the external phase, and Ethanol is used as co solvent in these systems. Surfactants (0.5-2%) are added for homogenous dispersion.

3) Suspension or dispersion system

It is prepared by dispersion active ingredients in the propellant or a mixture of propellants by using suspending agent developed primarily for oral inhalation aerosols. Eg. Ephedrine bitartrate aerosol the physical stability of suspension can be incersed by: control of moisture content – must be below 300 ppm use of derivative of AI having minimum solubility in propellant. Reduction of initial partical size to less than 5 micron adjustment of density difference use of surfactant HLB<10; 0.01- 1%).

4) Foam system Consist of AIs, aqueous or non-aqueous vehicle, surfactants and propellant, dispensed stable or quick-breaking foam. Stable foam liquefied propellant is emulsified and is found in internal phase both hydrocarbons and compressed gas propellants may be used. Quick breaking foam liquefied propellant is in the external phase.[3]

1.3 Pulmonary Drug Delivery

Now a day's pulmonary drug delivery remains the preferred route for administration of various drugs. Pulmonary drug delivery is an important research area which Impacts the treatment of illnesses including asthma, chronic obstructive pulmonary disease and various other diseases. Inhalation gives the most direct access to drug target. In the treatment of obstructive respiratory diseases, pulmonary delivery can minimize systemic side effects, provide rapid response and minimize the required dose since the drug is delivered directly to the conducting zone of the lungs. pulmonary route possesses many advantages over other routes of administration for the treatment of specific disease states, particularly lung associated large protein molecules which degrade in the gastrointestinal conditions and are eliminated by the first pass metabolism in the liver can be delivered via the pulmonary route if deposited in the respiratory zone of the lungs.[4]

1.3.1 ADVANTAGES OF PULMONARY DRUG DELIVERY

1) It is needle free pulmonary delivery.

2) It requires low and fraction of oral dose.

3) Pulmonary drug delivery having very negligible side effects since rest of body is not exposed to drug.

4) Onset of action is very quick with pulmonary drug delivery.

5) Degradation of drug by liver is avoided in pulmonary drug delivery.[4]

The devices currently available for pulmonary drug administration of pharmaceutical aerosols in clinical therapy include nebulizers, pressurized metered dose inhalers (pMDIs), and dry powder inhalers (DPIs). However, much effort is put into the development of new inhaler devices and formulations to optimize the pulmonary delivery system for local or systemic drug targeting.[5]

1.4 Metered Dose Inhaler

The pMDI was once termed "the most complex dosage form used in medicine today,"[6]

Metered-dose inhalers have been available for nearly 50 years and have come to be regarded as the preferred method of delivery for many important drugs intended to treat obstructive airway diseases, such as asthma, emphysema, and chronic bronchitis. MDIs represent a reliable, convenient dosing device for delivery of medications to the lungs.[7]

The MDI is a pocket-sized, hand-held, pressurized multiple-dose inhalation delivery system. It delivers small, precisely measured therapeutic doses, greatly minimizing the risk of adverse side effects. It is portable and convenient to use. MDIs, the energy source are the high pressure of the propellants. The patient has to breathe slowly and deeply, at the right moment, in order to create an air flow that draws the aerosol cloud deeper into the lung.[8]

MDI's were first developed in 1955 by Riker Laboratories, now a subsidiary of 3M Healthcare. By 1956 Riker had developed two MDI based products, the Medihaler-Ept containing epinephrin and the Medihaler-Iso containing Isoprenaline. Both products are agonists which provide short term relief from asthma symptoms and have now largely been replaced in asthma treatment by salbutamol which is more selective.[9]

In the United States starting from December 2008 inhalers containing chlorofluorocarbons, as a form of propellant to deliver the medication, will be discontinued for hydro-fluoroalkane-pressurized metered dose inhalers (HFA pMDI's). As governed by the 1987 Montreal Protocol on Substances that Deplete the Ozone Layer, all inhalers that contain CFCs are being discontinued with the target year 2010 under the auspices of the UN Environment Programme.[10]

Press-and-breathe pMDIs have recently improved their ecological appeal, can be used in every clinical and environmental situation, their dosing is convenient and highly reproducible.[30] Moreover, MDIs are capable of systemic delivery, included proteins and

peptides, and are also developed for nasal and buccal drug delivery. Diseases currently targeted for pulmonary or buccal drug delivery include, among others, diabetes, Alzheimer's, influenza, multiple sclerosis, pain disease, cystic fibrosis and osteoporosis.

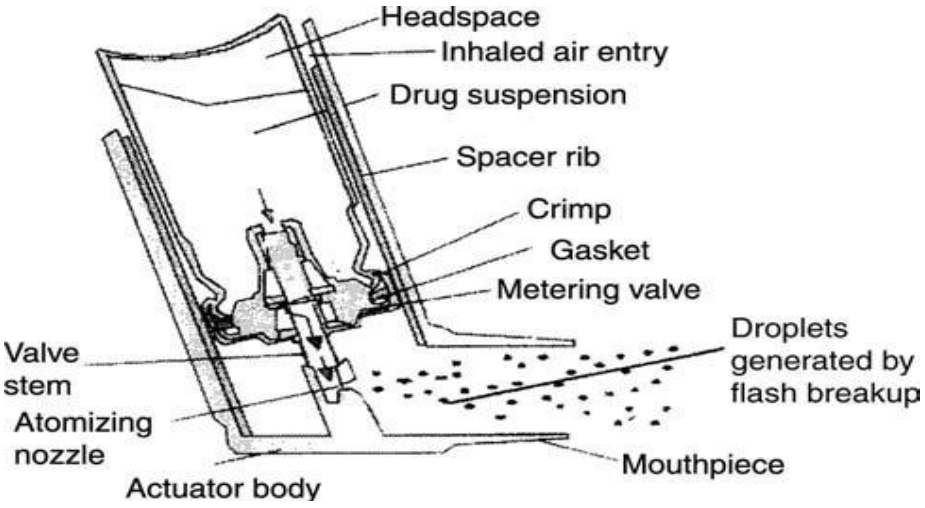

Fig. 1.1: Sectional view of a metered dose inhaler.[10]

1.4.1 Components of Metered Dose Inhaler

The device conventionally consists of five components which have an interdependent effect on drug delivery. These are the container. the propellant, the drug formulations, the metering valve and the actuator. the other significant factor or efficacy of drug delivery are patient technique and lung pathology, desirable function of the MDI can be considered to be.

- Accurate and reproducible dosing.
- Efficient atomization of the aerosol to deliver the drug to the required site,
- Retention of pressurized component.
- Protection of contents from external ingress.
- Convenient dimension for user handling and potentiality.
- Multiple dose device includes an indicator of dose availability.
- Co- ordination of dose actuation with breath inspiration.
- Acceptable organoleptic properties.[11]

1.4.2 Container

The essential requirements of containers used for MDIs are that they are compatible with the formulation, have an ability to withstand internal pressures up to 1500 kPa, and can be manufactured with reproducible quality. The most widely used containers for MDIs are made from an aluminum alloy, although glass bottles have also been used. Aluminum containers

(cans) are preferred due to their light weight, strength, break resistance, compactness, and ability to provide light protection. Different materials are used for the manufacture of aerosol containers. The materials must be inert, non-toxic and must withstand pressure as high as 140 to 180 psig at 130ºF.[3]

1.4.3 Propellant

Liquefied propellants are gases that exist as liquids under pressure. Because the aerosol is under pressure the propellant exists mainly as a liquid, but it will also be in the head space as a gas. As the product is used up as the valve is opened, some of the liquid propellant turns to gas and keeps the head space full of gas. In this way the pressure in the can remains essentially constant and the spray performance is maintained throughout the life of the aerosol. The propellant is an essential element in the formulation.[12]

Liquefied compressed gases are preferred over non-liquefied compressed gases such as nitrogen, carbon dioxide.

The use of hydrocarbons such as isobutene is common in general consumer aerosols. However, their odor and flammability have deterred their use in medical aerosols although purer grades, which are odorless, are now available. Dimethylether (DME) is used but would require expensive modification of facilities for the manufacture, storage, and transportation of MDIs. Flame extension studies have shown that the flammability of these propellants is unlikely to present a significant risk during inhalation use due to the small metered volumes. Another challenge in the use of both hydrocarbons and DME as propellants in suspension MDI formulations may be their low density, compared with most drug substances, which would give rise to poor suspension stability leading to the potential for inconsistent dose delivery. The alternatives identified, the hydrofluoroalkanes (HFAs) or HFCs were targeted for development as replacements for the CFCs in MDIs.[10]

CFCs are made up of carbon, chlorine, and fluorine atoms. The 3 common CFCs used in MDIs are CFC-11 (CCl_3F), CFC-12 (CCl_2F_2), and CFC-114 (CCl_2F_4). The CFCs are remarkably simple molecules and they exhibit great stability. The carbon-chlorine and carbon-fluorine chemical bonds are very strong. it is this very stability that causes the problem with the ozone layer. That is, the CFCs are so stable that they are able to reach the stratosphere intact. The atmospheric lifespan of the CFCs is 50–500 years. The CFCs contain chlorine, which is the atom responsible for their ozone-depleting potential.

Hydrofluorocarbons (HFAs) are made up of carbon, fluorine, and hydrogen atoms. The 2 major alternative propellants are HFA-134a ($C_2H_2F_4$) and HFA-227 (C_3HF_7). but their main feature is that they do not contain chorine and thus they have no potential to deplete the ozone layer.[13] HFAs are "greenhouse gases," which could lead to future restrictions on their use, although their contribution to global warming is likely to be very small. Dimethyl ether, propane, or butane could be considered as propellants, but propane and butane are likely to be ruled out because of their flammability.[6]

1. 4.4 The Metering Valve

MDI valves contain a large number of components made from a wide variety of materials that include plastics, rubbers, and metals and are required to accurately and precisely deliver a metered dose typically between 80 and 200 times over the life of the product. A typical valve will have a valve stem (plastic or metal), gaskets (rubber), o-ring (rubber), spring (metal), metering chamber (metal), and fill cup (metal or plastic). Two gaskets form the seal around the valve stem. The lower gasket seals between the metering chamber and the outside atmosphere, and the upper gasket seals between the metering chamber and the bulk formulation in the canister. An o-ring forms the seal between the canister and the valve assembly.[14]

Compatibility of the formulation with the valve components is essential. Elastomeric seals can swell because of solubility in CFCs, but this effect may be less marked in HFAs, so that the valve elastomers that function well with CFCs may not do so with HFAs. This has required the development of new elastomeric systems for use with HFAs. Valve elastomers must also be selected to ensure low concentrations of extractables and leachables into the formulation. Many newly designed valves appear to function adequately without the need for surfactants to lubricate the valve stem.[6]

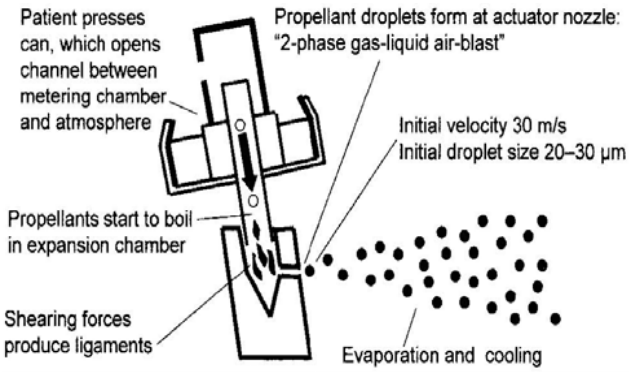

Fig. 1.2: Sectional view of a metered dose inhaler.

1. 4.5 Actuator

An actuator is utilized to activate the valve and direct the aerosol toward the patient's mouth. The shape of the actuator can affect the spray pattern and droplet/particle size of the aerosol and should be designed for optimum performance. Due to the high velocity of the emitted dose and interpatient variability observed during actuation, a spacer may be incorporated to improve performance of the device, thereby improving clinical efficacy. The actuator, also referred to as the "button," "spray-head," or "spray-tip," is the component which represents the point of exit of the spray stream. there are a number of dimensions that may be altered to influence the spray. Two of these dimensions are the length and taper of the channel leading to the exit orifice of the actuator. The plastic leading to the exit orifice can be molded as a straight channel, or the channel can be tapered, or even reverse-tapered. Each of these configurations has an effect on the resultant particle size. Furthermore, some actuators are designed to accept inserts, which serve to provide additional control over the spray.[15]

1.5 DRUG FORMULATION

MDI formulations can take the form of either suspensions or solutions. Traditionally the preferred route has been to formulate a suspension of the micronized drug substance in the liquid propellant (CFC or HFA). In some cases, additional excipients (e.g., surfactants and/or cosolvents) have been added to improve the quality of the dispersion. HFA propellants have low inhalation toxicity and high chemical stability but are poor solvents for APIs, which necessitates formulation of suspensions rather than solutions in most cases. Combinations of HFA-134a and HFA-227 can be used to provide better solubility, appropriate aerosol velocity and density of the suspension (i.e., suspension settling).[16]

Most drug suspensions undergo destabilization over time (eg, flocculating, settling out, or creaming [movement to the surface]), even when surfactants are used to form the suspension. Metering valves used in pMDIs operate by sampling a volume of suspension from the bulk, which is retained in the metering chamber of the valve when the patient actuates the pMDI, this volume of suspension in the metering chamber exits the inhaler through the valve stem and actuator into the patient's mouth (or nose). At the same time as the dose is released, the metering chamber refills with the next dose. In suspension formulations of pMDIs, the suspension must remain stable between the time when the patient shakes the inhaler before taking a dose and the time when the patient releases the valve after actuating the pMDI. This could be 10 seconds or more depending on the individual patient's inhaler technique and

whether they use a spacer. If the suspension is not stable for that time, the volume sampled into the metering chamber may not be homogenous; therefore, the next dose delivered to the patient may be either too low or too high, depending on the nature of the suspension instability.[17]

More recently, other (less volatile) organic modifiers, e.g., glycerol, have been added to solution-based HFA MDIs to modify the particle size distribution so that it more closely resembles that of the originator suspension product. HFA MDI suspension formulations there are a number of possible approaches to a suspension-based formulation. A micronized drug can simply be suspended in an HFA propellant or a mixture of HFA propellants. The principal advantage to a formulation of this type is that it is simple and contains no additional excipients with their inherent toxicological implications. The performance of a formulation of this simplicity will be dependent on the inherent properties of the drug substance and the propellants used. For Ex. if the drug substance is significantly denser than the propellant(s) is, then rapid sedimentation of the suspension is likely to occur following agitation. This could create issues in terms of the valve sampling homogeneously from the bulk container contents. Further differences between the drug and propellant in terms of relative hydrophobicities and hydrophilicities can also result in rapid flocculation immediately post shaking or a tendency for the drug to deposit on the MDI container walls and valve components.[10]

Porous particles possess excellent stability in HFAs, as the propellant can penetrate inside the particles, leading to improved density matching of the particles with the propellant, and also a reduction of the vander Waals forces between the particles. Particles with a high degree of surface roughness can also be used to improve physical stability of the formulation by reducing the area of contact between particles. Some results related to efforts in the development of novel (solid) suspension-based pMDI formulations.[17]

1.6 Advantages Disadvantage and Limitations of the pMDI

1.6.1 Advantages

- Convenient
- Easy to Use/Immediate Use
- Controlled Application
- Compact
- Portable
- Long Lasting

- Uniform Spray
- Protected from the ingress of both moisture and pathogens.[6]

1.6.2 Disadvantage

- The lung does not absorb a drug very efficiently (you'll be shocked to know that only about 10–15% of what is delivered is absorbed by the lung!).
- Your breathing pattern could create a problem (recall that with certain inhalers you may have to inhale slowly and deeply, something you're not likely to do when you are having an attack).
- Some folks have trouble pressing the device and breathing at the same time (difficulty with hand-breath coordination).
- Some folks simply don't know how to use them correctly.
- There are so many different types of devices that we get confused with how each works.
- There is a lack of standard technical information.[18]

1.6.3 Limitations of the pMDI

The limitations of pMDIs have also been recognized for decades. Drug delivery is highly dependent on the patient's inhaler technique. Reports of inhaler misuse are commonplace in the literature, and failure to coordinate or synchronize actuation with inhalation is said to be the most important problem patients have with pMDIs. Some patients suffer the so-called cold-Freon effect (Freon is the registered trademark of CFCs from DuPont), in which the arrival of the cold propellant spray on the back of the throat causes the patient to stop inhaling. The misuse of pMDIs can result in a suboptimal or even zero, lung deposition. Misuse of corticosteroid pMDIs is associated with decreased asthma stability, especially when misuse involves poor coordination. Another problem with CFC pMDIs and some HFA pMDIs is that even with good inhaler technique they deposit only 10–20% of the dose in the lungs, with most of the dose being deposited in the oropharynx. High oropharyngeal deposition of glucocorticosteroids can cause localized adverse effects (dysphonia and candidiasis) and systemic adverse effects. Poor lung deposition and high oropharyngeal deposition have been partly addressed by some recent HFA pMDI products that better target inhaled drugs to the lower respiratory tract. The drug-delivery characteristics of standard press-and breathe pMDIs bear on the possible uses of pMDIs. Low lung deposition and dependence on inhaler technique can be accepted in the case of drugs for asthma and COPD, where the patient can simply take another dose as required. But those limitations may not be

acceptable for targeted therapies that have narrow therapeutic windows, such as inhaled peptides for systemic action, where a very precise and reproducible dose may be needed.[6]

2. MTERIALS AND METHODS

2.1: Various materials and equipments used in the formulations are listed in Table 2.1 and 2.2 respectively.

Table 2.1: List of Ingredients.

Sr. No.	Ingredient	Specification	Functional Category	Source
1	Salbutamol Sulphate	BP	Active	Neuland Lab, Mumbai.
2	Oleic Acid	BP	Surfactant and Valve Lubricant	M/s Croda.
3	Ethanol	BP	Co-solvent	M/s Hayman.
4	Polyethylene Glycol 1000	USP NF	Surfactant and Valve Lubricant	M/s Vasuda. Chemical ltd.
5	Sorbitan Trioleate	BP	Surfactant and Valve Lubricant	M/s Croda.
6	HFA 134a (1,1,1,2 Tetrafluoro Ethane)	BP	Propellant	Dupont / Ineous Flour.
7	19 ml Aluminium Anodised Canister	----	Packaging	Presspart, UK.
8	50 mcl metered valve (Nitrile)	---	Packaging	Valois, France.
9	PP Adaptor (0.58 mm)	----	Packaging	Valois, Mumbai.

Table 2.2: List of Equipments.

Sr. No.	Name of Equipment	Make
1.	Pressure Mixing vessel (with homogéniser) SS	Pamasol, Spain.
2.	Product Recirculation Multilobe Pump	Pamasol, Spain.
3.	Crimper X02002-0043	Pamasol,Nashik.
4.	Weighing Balance 1.2 kg (Accuracy 10 mg)	Sartorious,Nashik.
5.	Propellant Filling Pump P2008/12	Pamasol, Spain.
6.	Diaphragm Propellant Filler P2079	Pamasol, Spain
7.	Ultrasonicator (1.5L)	Pci

2.2 PREFORMULATION STUDIES

Prior to the development of any dosage form, it is necessary that certain fundamental properties of drug molecule and other derived properties of drug powder are determined. Preformulation testing is the first step in the rational development of dosage forms of a drug substance. It can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. The overall objective of pre formulation

testing is to generate information useful to the formulator in developing stable and bioavailable dosage forms that can be mass produced.

2.2.1 Study of Physicochemical properties of drug[19]

- ***Identification*:** Identification of drug was carried out using IR method
- ***Description:*** Drug was observed for color and crystalline/amorphous nature.
- ***Solubility*:** Solubility of Salbutamol was determined in propellant along with different surfactants, excipients and co-solvent.
- ***Particle size (By Malvern):*** Particle Size of drug was determined to increase lung deposition of the drug.
- ***Assay:*** Assay for drug was carried out using HPLC method.

$$\% \text{ Drug Assay} = \frac{\text{Test response x standard dilution potency}}{\text{Standard response x Test dilution x label}}$$

2.2 .2 Drug- Excipient Compatibility study[19]

A stable and effective liquid dosage form depends on the careful selection of excipients that are added to facilitate administration, promote the consistent release and bioavailability of the drug and protect it from degradation. Related substances analysis can be used as the simplest method to predict any physiochemical interaction between the components in a formulation and can therefore be applied for selection of suitable chemically compatible excipients. Following combinations of Drug and Excipient in different ratios were kept at varying conditions of temperature as 40°C/75% RH for 15 days and 40°C/75% RH for 30 days to predict the compatibility of drug and excipients.

Table 2.3: Compositions for Drug-Excipients Compatibility study.

Sr. No.	Drug + Excipient	D: E Ratio	Weight (mg)
1	Salbutamol	__	100
2	Salbutamol + Oleic Acid	1:10	(100 + 1000)
3	Salbutamol + PEG 1000	1:10	(100 +1000)
4	Salbutamol + Sorbitan trioleate	1:10	(100 + 1000)
5	Salbutamol + HFA 134a (1,1,1,2 Tetrafluoro Ethane)	1:20	(100 + 2000)

2.3 MANUFACTURING PROCEDURE

2.3.1. Procedure For Drug Solution Preparation

- **Step-I**: Co-Solvent was weighed and filtered through 0.22 µ filter and transfer into mixing vessel.
- **Step-II**: It was homogenized at 300-400 RPM for 5 min ± 1 at 25°C.
- **Step-III**: Weighed Surfactant was added into mixing vessel (Step-I) and stirring was continued for 5 min ± 1.
- **Step- IV**: API was accurately weighed on weighing scale and transferred into mixing vessel (maintain vessel Temp at 10°C-15°C) and stirred at 600-800 RPM continue for 20 min ± 2 min.
- **Step- V**: Set the filling pressure 5.5 Bar in the Solution Filling m/c X02039 then set for desired weight.

2.3.2. Procedure For Aerosol Filling

- **Step-I**: The above drug solution was filled into canister.
- **Step-II**: It was Crimped with 50 mcl metered valve at Crimping Pressure 6.5 Bar.
- **Step-III**: Charged with propellant HFA 134a.

Quantity to be filled per canister

Concentrate: 0.409 g (Limit 0.395 g – 0.415 g)

Propellant: 16.87 g (Limit 16.65-17.00 g)

Total Net content per canister =17.30 g (Limit 17.00-17.50 g)

The gross weight of individual canister should be checked and the unit which falls out of range were rejected.

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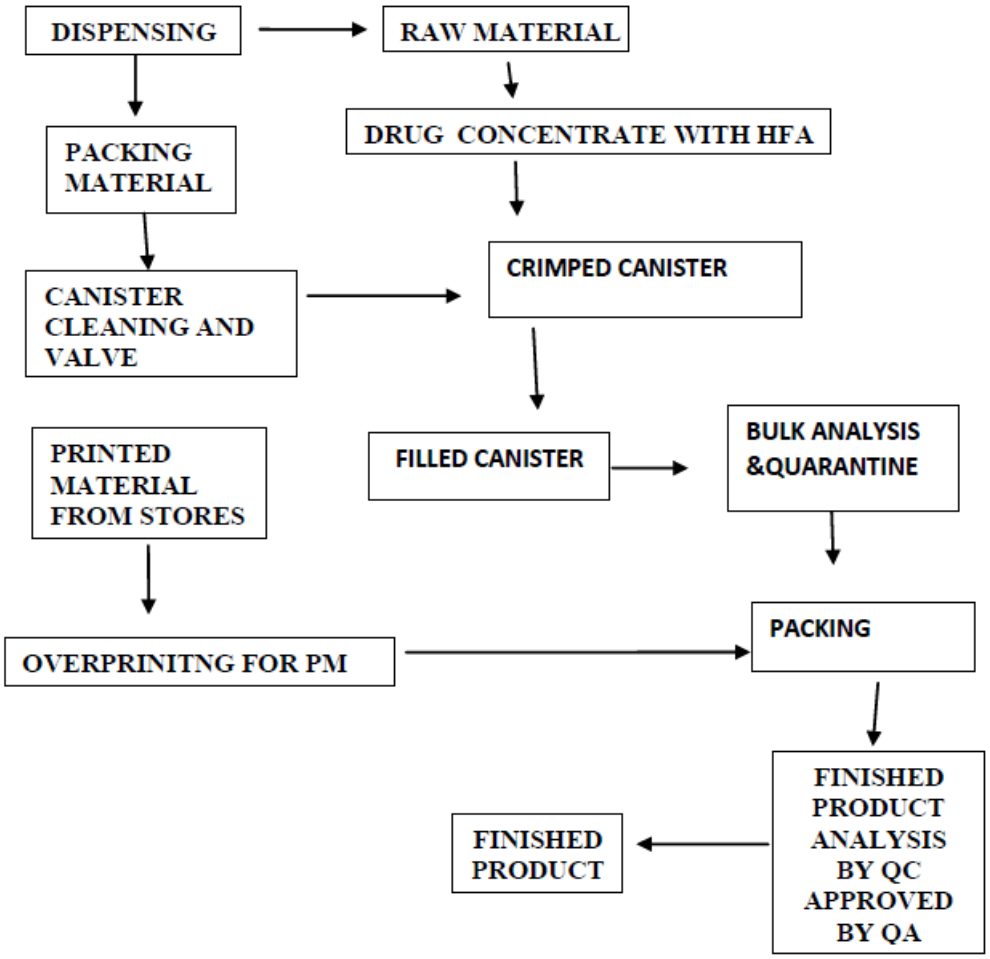

Fig 2.1: General Manufacturing Procedure For pMDI.

2.4 FORMULATION DEVELOPMENT

2.4.1 Salbutamol Sulphate Pressurised Metered Dose 100 MCG

Table 2.4 Compositions of Formulation Trial Batches 1-8.

Sr. No.	Ingredients	Composition in mg							
		1	2	3	4	5	6	7	8
1	Salbutamol Sulphate	28.92	28.92	28.92	28.92	28.92	28.92	28.92	28.92
2	Oleic Acid	--	0.20	--	--	0.45	0.60	0.85	0.9
3	Ethanol	34.60	34.60	34.60	34.60	34.60	34.60	34.60	34.60
4	Polyethylene Glycol 1000	-----	----	1.44 (0.01 %)	-----	-----	-----	-----	-----
5	Sorbitan trioleate	-----	-----	7.2 (0.05 %)	-----	- ----	-----	-----	-----
6	Propellant HFA134a (g)	16.87	16.87	16.87	16.87	16.87	16.87	16.87	16.87

Formulation

- Formulation batches **1 & 2** are based on the comparison of the product characteristics of formulation without surfactants and formulation containing Oleic Acid (As per IIG limits) using 0.5 mm orifice pp adaptor, metered valve (50 µm) and 19 ml aluminium anodized canister.
- Formulation batches **3 & 4** are based on the comparison of the product characteristics of formulation containing Polyethylene Glycol 1000 and Sorbitan trioleate (As per IIG limits).
- Batches **5-8** are aimed at comparing the product characteristics of formulation containing Oleic Acid concentrations 0.45 %, 0.6 %, 0.85 %, and 0.9 % respectively.
- Batch **5** was reproducible batch taken with Oleic Acid concentration of 0.45% to provide physical stability to the formulation.
- Batch are kept in different stability conditions like 30°C/75% RH, & 40°C/75% RH and also observed for physical stability.

2.4.2 Evaluation of Formulations[19]

2.4.2.1 Physical Characterization

- ***Description***

An aerosol filled in a suitable pressurized aluminum canister fitted with a metering valve provided with oral inhaler actuator.

- ***Solubility***

Solubility of Salbutamol sulphate was determined in propellant along with different surfactants, excipients.

- **Number of deliveries per inhaler[20]**

Take one finished product inhaler canister and discharge the contents to waste, actuating the valve at intervals of not less than 5 seconds. Record the number of deliveries so discharged. The total number of deliveries so discharged from the inhaler is not less than 200 deliveries.

- **Net Content**[20]

Weigh the canister and tare the weight (W_1). Discharge the whole canister by actuating the valve. Again weigh it (W_2). Calculate the net content by taking its difference.

Calculate the net content as follows.

Net Content = W_1-W_2 in mg

- **Valve Delivery**[20]

Weigh the canister and take the weight. Shake well and prime the canister for 10 times, shaking the canister at every priming. Weigh the canister and calculate the valve delivery. Also the above test can be done by priming the canister for 50 or 25 times and at the last i.e. before emptying the canister count the no. of actual doses discharged.

2.4.2.2 Chemical Characterization[21]

- Water Content (By Coulometric titration).
- Assay of Salbutamol sulphate (by HPLC).
- Deposition of the emitted dose of Salbutamol Sulphate.
- Deposition of the Fine Particle Fraction of Salbutamol sulphate.

2.4.2.3 Stability studies[22]

Stability of a drug has been defined as the ability of a particular formulation, in a specific container, to remain within its physical, chemical, therapeutics and toxicological specifications.

The stability studies were performed on the most promising pMDI formulation. The purpose of stability testing is to provide evidence on how the quality of a drug substances or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, and enables recommended storage conditions and shelf lives to be established.

The conditions and time duration for these studies as per ICH Q1A (R2) guidelines are given in the table.

Table 2.5: Conditions for stability according to ICH-guidelines.

Study	Storage conditions	Minimum time period covered by data at submission.
Long term	25 ± 2°c / 60 ± 5% RH or 30 ± 2°c / 65 ± 5% RH	12 months
Intermediate	30 ± 2°c / 65 ± 5% RH	6 months
Accelerated	40 ± 2°c / 75 ± 5% RH	6 months

In present study, stability study was carried out at 40±2°c/75±5% RH and 30 ± 2°c/65±5% RH for specific time period 3 month for developed formulation. Samples withdrawal schedule was initial, 1 month, 2-month, 3 month. pMDI were analysed for, Number of

delivery per inhaler, Net Content, Valve Delivery, Water Content, Related Substances, FPF, MMAD, by the method described previously.

3. RESULTS

3.1 PREFORMULATION STUDIES

3.1.1 Study of physicochemical properties of drug

It can be seen that Salbutamol sulphate was found that pass all the physicochemical test parameters as per COA.

Table 3.1: Physicochemical properties of drug.

Sr.No	Tests Applied	Results of Analysis	Inferences
01	Description	White or almost white Crystalline powder	White micronized powder
02	Solubility	Practically soluble in water, slightly soluble in ethanol.	Complies
03	Identification	By IR:IR Spectrum of sample dispersed, shall be concordant with that of the working standard.	Complies
04	Loss On Drying	NMT 0.50 %	0.20 % w/w
05	Relative substances	Total impurities= NMT 0.5	Complies
06	Assay by HPLC	Between 97.5 % and 102.0% w/w	99.07 %
07	Particle size (By Malvern)	D90 between 4-5 micron D97 less than 10 micron	4.03 micron 5.66 micron

3.1.2: Particle Size Determination

Particle size important for drug deposition to the lower respiratory tract. Particle size analyzed by wet method using Malvern Mastersizer instrument.

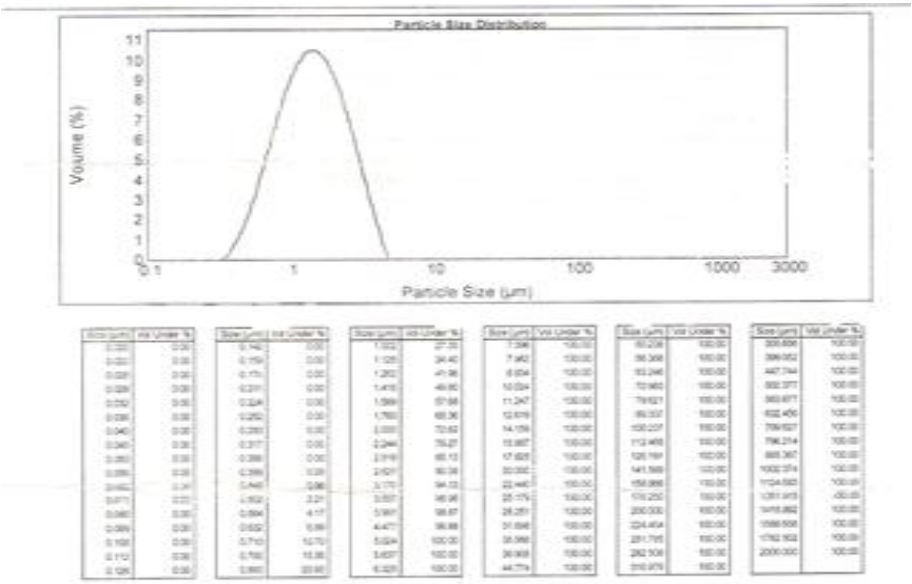

Figure 3.1 Particle Size determination of Salbutamol sulphate.

3.1.3: Infrared Spectroscopy

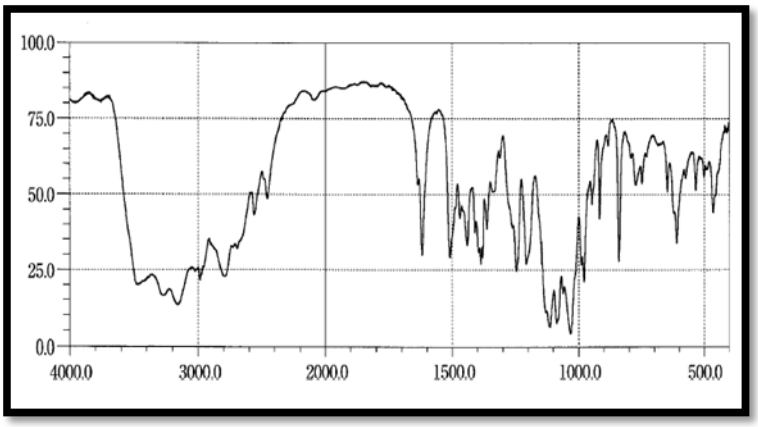

Figure3.2: FT-IR spectrum of Salbutamol Sulphate.

3.1.4 Solubility Studies

To develop a pMDI system for water soluble drug like Salbutamol sulphate, suitable surfactants, and propellant need to be selected. Surface active compounds or "surfactants" are used in MDI formulations to aid in the dissolution or suspension of the drug in the propellant. The surfactants also serve to improve valve function by virtue of their lubricating properties. In order to achieve these objectives, the surfactant must be dissolved in sufficient conc. For example, surfactant should ordinarily be at approximately 0.01-5% weight in volume (w/v). Often, the surfactant is incorporated at about 1/l0th the concentration of the drug in the MDI formulation. Solubility of drug was checked in different combination of surfactant, Propellant and solvent, the observations are noted in Table 3.2.

Table 3.2: Solubility of drug.

Sr no	Particulars	Observations
1.	Surfactant (PEG) 0.1% + 0.1g Ethanol	Sparingly Soluble
2.	Surfactant (oleic acid) 0.15 % +0.1g Ethanol	Very soluble
3.	Surfactant (Sorbitan trioleate) 0.05 % + 0.1g Ethanol	Sparingly Soluble
4.	Surfactant (PEG) 0.2% + 0.1g Propellant HFA 134a	Freely soluble
5.	Surfactant (PEG) 0.5% + 0.1g Propellant HFA 134a	Freely soluble
6.	Surfactant (PEG) 1.0% + 0.1g Propellant HFA 134a	Freely soluble
7.	Surfactant (oleic acid) 0.01g +Ethanol13.5% + HFA 134a (qs)	Soluble
8.	Surfactant (oleic acid) 0.1g+Ethanol13.5% + HFA 134a (qs)	Soluble
9.	Surfactant (oleic acid) 1.0g+Ethanol13.5% + HFA 134a (qs)	Soluble
10.	0.1 g Ethanol in < 0.1g HFA	Very Soluble)
11.	0.1 g ethanol in 0.1 -1g HFA	Freely Soluble)
12.	0.1 g Ethanol. in 1 -3g HFA	Soluble
13.	0.1 g Ethanol in 3 -10g HFA	Sparingly Solubl
14.	0.1 g ethanol in 10 -100g HFA	Slightly Soluble
15.	0.1 g ethanol in 100 -1000g HFA	Very Slightly Soluble

3.1.5 Drug-Excipients Compatibility Studies: Compatibility studies were carried out for related substances level at 40°C/75% RH for 15 days and 40°C/75% RH for 30 days and analysed by HPLC method.

Table 3.3: Drug-Excipient compatibility study.

DRUG + EXCIPIENTS	CONDITIONS	IMPURITIES	
		Single Max. Imp.	Total Imp.
Salbutamol sulphate (API)	Initial	0.09	0.21
	40°C /75% RH (15 days)	0.08	0.27
	40°C /75% RH (30 days)	0.11	0.32
Salbutamol sulphate + Polyethylene Glycol 1000	Initial	0.12	0.38
	40°C /75% RH (15 days)	0.18	0.49
	40°C /75% RH (30 days)	0.29	0.56
Salbutamol sulphate + Oleic Acid	Initial	0.08	0.18
	40°C /75% RH (15 days)	0.11	0.24
	40°C /75% RH (30 days)	0.17	0.30
Salbutamol sulphate + Sorbitan trioleate	Initial	0.07	0.13
	40°C /75% RH (15 days)	0.35	0.67
	40°C /75% RH (30 days)	0.30	0.54
Salbutamol sulphate + HFA 134a (1,1,1,2 Tetrafluoro Ethane)	Initial	0.14	0.35
	40°C /75% RH (15 days)	0.23	0.56
	40°C /75% RH (30 days)	0.38	0.77

3.2. Evaluation of formulations

Batch no.1 shows the decreased the assay result and batch no.**2-4,** using various surfactants and the result shows Oleic Acid provided better result as compare to other surfactants. Batch no.**5-8,** formed good pMDI showed good result but due to minimum concentration of surfactant in batch no.**5** was selected. Whereas Batch no. **8,** formed good pMDI, showed good assay value but were found to small variation in % of emitted dose.

- **3.2.1** FPF and MMAD of the formulation is determination by Cascade Apparatus.

- **3.2.2. MMAD and GSD Analysis Results:** Aerodynamic particle size was determined by Anderson Cascade Impactor (Apparatus D) most of the drug distributed in stages 3 and 4, the diameter of stages are 3.3-4.7 and 2.1-3.3 respectively. On the basis of stages result calculated MMAD, GSD by using fusion AE software US and result was found to be 3.3462 µm and 1.6942 µm. The FPF result was found to be 39.29 %, conclusion was found over the studies Oleic Acid show better effect in MDI formulation.

Table 3.4: MMAD and GSD Analysis Results of Batch no.5.

Mass Median Aerodynamic Diameter	3.3462 µm
Geometric Standard Diameter	1.6942 ----

➢ **3.2.3 Chromatographs of samples used for calculating the drug content by HPLC system:** A content was found be within the range of 80-120 %. Conclusion was found to be on result the drug is consistently delivered from the container as per label claim.

Table 3.5: Assay results of batch no. 5.

Stages	Retention time	Assay
Initial	3.012	99.98%
Middle	3.121	99.72%
End	3.019	99.79%
Average		**99.83%**

➢ **3. 2. 4. Chromatographs of samples used for calculating the Emitted Dose by HPLC system:** The emitted dose was analysed by using (Twin Glass Impinger). The emitted dose test is carried out on the basis of determined the percentage of fine drug particle Dose deposited into the lungs. The percentage drug deposition of formulation was found to be 45.60 %. The conclusion was found on the basis of above result by using Oleic Acid are properly dispersed drug in propellant. To provided a more drug deposition into the lungs. Results noted in table 3.6.

Table 3.6: Emitted dose results of batch no. 5.

Sr. no.	Stages	Drug deposition (%)
1	Valve	1.58 %
2	Actuator	11.43 %
3	Stage I	39.07 %
4	Stage II	45.60 %
	Mass Balance	**98.68 %**

➢ **3.2.5 Valve delivery (Dosage test):** Valve delivery or dosage test studied on performance of 50 µl Nitrile Valve. To check the efficiency of nitrile valve for delivered a dose per actuation. In above table showed the result of 50 mcl metered valve to delivered dose at desired rate & desired amount from the container. The conclusion of the study showed Oleic Acid is improving the valve function like reduces drug friction.

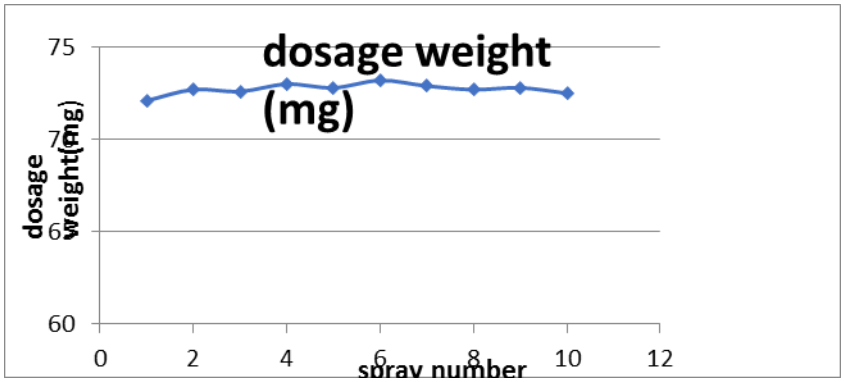

Fig.3.3: Spray number v/s dosage weight plot for 50 µl valve.

➢ **3.2.6. Stability Studies:** There was no significant change in physical and chemical properties of the pMDI of Batch No. 5 after Initial, 1 Month, and 2 Month. Parameters quantified at various intervals were shown in table. 3.7 and 3.8 in two different condition.

Table 3.7. Stability compilation sheet of batch no.5. (Temp.30°C/ RH 65 %)

Salbutamol sulphate Pressurised Inhalation (100 mcg per actuation)								
Batch No.	**Stage**	**Assay**	**ED (Limit NLT 35%)**	**MMAD (µm)**	**FPF (Limit NLT 15 %)**	**RS single/ Total**	**No. of Doses (NLT 200 nos.)**	**Valve Delivery (Limit 53 - 62 mg)**
5	Initial	99.83 %	45.60 %	3.3462 µm	39.22 %	0.07/0.36	238	72.7
	1 M	99.71 %	44.54 %	3.3142 µm	38.45 %	0.09/0.39	239	72.2
	2 M	99.44 %	46.96 %	3.3554 µm	37.89 %	0.11/0.52	232	73.6
	3 M	99.58 %	46.43 %	3.2725 µm	39.53%	0.14/0.58	234	72.3

Table no.3.8 Stability compilation sheet of batch no. 5. Stability Condition (Temp. 40°C/ RH 75 %)

Salbutamol sulphate Pressurised Inhalation (100 mcg per actuation)								
Batch No.	**Stage**	**Assay**	**ED (Limit NLT 35 %)**	**MMAD (µm)**	**FPF (Limit NLT 15 %)**	**RS single/ Total**	**No. of Doses (NLT 200 nos.)**	**Valve Delivery (53-62 mg)**
5	Initial	99.83 %	45. 60 %	3.3462 µm	39.22 %	0.07/0.36	238	72.7
	1 M	99.76 %	48.04 %	3.1197 µm	37.62 %	0.08/0.41	230	73.1
	2 M	99.30 %	46.33 %	3.4755 µm	38.10 %	0.12/0.47	233	72.3
	3 M	99.65 %	45.54%	3.3271 µm	38.08 %	0.21/0.61	235	71.8

4. DISCUSSION

4.1. Preformulation studies

➢ **4.1.1 Study of physicochemical properties of drug:** Salbutamol sulphate was found that pass all the physicochemical test parameters as per COA.

- **4.1.2 Particle Size Determination:** To require efficient deposition of drug in the lungs of D (90%) should be in between 2-5 micron. The D (90%) was found to be 2.81 micron. Particles in excess of 10 micron will deposit in the oro-pharynx. D (50%) was found to be 1.420 micron. These particle sizes are providing better result in formulation
- **4.1.3: Infrared Spectroscopy:** Salbutamol sulphate sample were analyzed by FTIR spectroscopy (Bruker P Alpha) to elucidate the probable structure. The spectrum is plotted by using the OPUS software. The Salbutamol sulphate was characterized by IR spectra which show the wave number at 3400, 3200, 2700-2900, 1600-1700 and 1180-1360.To observed the spectrum and interpretation of Salbutamol sulphate the conclusion was found to the spectrum of Salbutamol sulphate are similar with standard spectrum. And the group are observed in spectrum are sufficient for elucidate the structure of Salbutamol sulphate.
- **4.1.4 Solubility Studies:** The aim of this work was to examine the interaction of oleic acid, PEG and sorbitan trioleate with Ethanol and PEG dispersed in HFA 134a as a model propellant system. The objective of this work is to provide MDI formulations which utilize HFA-134a as the sole propellant with a pharmaceutically acceptable surfactant for suspending, solubilizing, wetting, emulsifying, lubricating. According to the Study, it has been found that; Oleic Acid can be used effectively in MDI formulations.
- **4.1.5 Drug-Excipients Compatibility Studies:** To develop a pMDI various co-solvents are available. They can be included to increase the solvent capacity of formulation for drug. Ethanol is a powerful solubilizing agent used in several dosage forms on account of its ability to solubilize many drugs. The MDI formulations employing HFA 134a and the surfactant will be formulated in approximately the same proportion (e.g. greater than 90% propellant, less than 5% surfactant and most preferably less an 1% micronized drug (usually less than 5 microns in diameter), less than 5% surfactant and most preferably less than 2% surfactant), Drug-Excipient combinations are compatible. No significant increase in the impurity has been observed at storage condition 40°C/75% up to 30 days.

4.2. Evaluation of formulations: Batch no. **5,** is reproducible batch for study and kept for physical stability for 3 months

- **4.2.1 MMAD and GSD Analysis Results:** On the basis of stages result calculated MMAD, GSD by using fusion AE software US and result was found to be 3.3462 µm and 1.6942 µm. The FPF result was found to be 39.29 %, conclusion was found over the studies Oleic Acid show better effect in MDI formulation.

- **4.2.2 Chromatographs of samples used for calculating the drug content by HPLC system:** The assay results of innovator sample was found to be between 99.72% to 99.98%. A content was found to be within the range of 80 – 120 % as per limit. The result shows the drug is consistently delivered per actuation as per the label claim.
- **4.2.3. Chromatographs of samples used for calculating the Emitted Dose by HPLC system:** The emitted dose was determined by using (Twin Glass Impinger). The emitted dose test is carried out on the basis of determined the percentage of drug deposited into the lower chamber. The percentage drug deposition of innovator sample was found to be 45.60 %. The conclusion was found on the basis of above result by using Oleic Acid are properly dispersed drug in propellant. To provided a more drug deposition into the lungs.
- **4.2.4 Valve delivery (Dosage test):** Valve delivery or dosage test studied on performance of 50 µl Nitrile Valve. To check the efficiency of nitrile valve for delivered a dose per actuation. In above table showed the result of 50 mcl metered valve to delivered dose at desired rate & desired amount from the container. The conclusion of the study showed Oleic Acid is improving the valve function like reduces drug friction.
- **4.2.5 Stability Studies:** The stability studies were carried out for period of 3 months as per ICH guidelines, there is no significant change was observed in FPF & ED results and other parameters of the reproducible formulation no. 5 were results in acceptable limits.

The final selected batch was found to be batch no. 5, as this batch was found to be highly stable as compared to rest of the batches and it shows much better results compared to that of the innovator product.

Table no. 4.1: Finish Product Specifications.

Sr. No.	Tests	Specifications	Results 40°C/ RH 75 % / 30°C/ RH 65 %
01	Description	An Aerosol suspension filled in an Anodized Aluminum Canister fitted with meter valve provided with oral inhalation actuator.	Complies
02	Assay	80 - 120 %	3 Month- 99.65 % / 99.58 %
03	Fine Particle Fraction	NLT 15 %	3 Month- 38.08 % / 39.53 %
04	Emitted dose	NLT 35 %	3 Month- 45.54 % / 46.43 %
05	Mass Median Aerodynamic Diameter (MMAD)	NLT 3 µm	3 Month- 3.3271 µm/ 3.2725 µm
06	Water content	NMT 500 ppm	3 Month- 374 ppm / 392 ppm

07	No. of Doses	NLT 200 nos.	3 Month- 235 / 230
08	Net Content	Limit 16.47-17.92 g	3 Month- 16.85 g
09	Avg. Valve Delivery	Limit 68.1– 78.3 mg	3 Month- 72.07

5. CONCLUSION

The purpose of the present research work was to develop a robust and physicochemically stable pMDI formulation for pulmonary delivery of a bronchodilator agents, the-Salbutamol. From the literature review, it was found that the absence of detectable concentrations of Salbutamol in the plasma following oral administration is predictable from its very high clearance, which would be expected to result in a high first pass metabolism. Therefore targeting Salbutamol as pMDI form as spray formulation for the management of Asthma & COPD is a rationale approach.

The Drug-Excipient compatibility studies for 30 days at 40°C/75%RH did not show any significant change in physical properties. The Related substances limits were also at par. These preformulation studies ensured the compatibility of Salbutamol with various excipients. Therefore mentioned proportions of drug and excipients can be used to formulate a stable pMDI spray as an alternative route to oral delivery. Hence, based on the literature review and results of preformulation study, excipients were selected and formulation trials were designed.

Salbutamol was formulated by pressure filling technique as MDI formulation. Different approaches were practiced to make a stable dosage form which can be delivered into the lungs.

Approach-I included the use of different surfactant forming good suspension with drug, propellant. Different surfacatants and/or combinations thereof were employed in Approach-II with In IIIrd Approach, batches were carried out with different surfactants concentration with propellant. Final manufacturing formula and method had been selected on the basis of these approaches for the development of Salbutamol pMDI. Hence, the formulation was developed successfully by these approaches.

Salbutamol pMDI 100 mcg was evaluated for different parameters like identification of pMDI type, physical, chemical and packaging characterizations.

From the physical observations of optimized batches, batch no. **5** was found to be more stable batches**.** Hence the studied suspension for pulmonary delivery was found to be physically stable at 30°C/65%RH, 40°C/75%RH for 3 months.

Stability studies were carried out on optimized batches at 30°C/65%RH, 40°C/75%RH for 3 months in final container with 19 ml plain base Anodised aerosol can with 50 µl valves with actuator.

Valves of 50µl spraying capacity having actuator systems were found to encompass acceptable results for dosage test or pump delivery.

Hence it was concluded that pressurised based MDI formulation in an attempt to develop pulmonary administrable product of Salbutamol was found to be stable and robust with desired attributes of packaging requirements.

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