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FROM MOLECULE TO MARKET: PREFORMULATION MANUFACTURING AND EVALUATION OF SALBUTAMOL

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ABSTRACT

Asthma is a chronic inflammatory respiratory disorder characterized by airway hyperresponsiveness, bronchoconstriction, and increased mucus secretion, leading to symptoms such as wheezing, coughing, and shortness of breath. The condition arises from complex interactions between genetic and environmental factors, including allergens, infections, pollution, and lifestyle triggers. This paper presents a comprehensive overview of asthma, including its types, etiology, pathophysiology, and clinical manifestations. Special emphasis is given to the pharmacological management of asthma using antiasthmatic drugs, particularly bronchodilators. Salbutamol, a short-acting β_2-adrenergic agonist, is discussed in detail with respect to its mechanism of action, pharmacokinetics, therapeutic uses, and side effects. The study further explores the preformulation parameters essential for developing effective inhalation dosage forms, such as particle size, solubility, and drug-excipient compatibility. Additionally, the formulation and manufacturing process of a salbutamol metered dose inhaler (MDI) is described, along with its components, working mechanism, and evaluation tests to ensure quality, safety, and efficacy. Overall, the paper highlights the importance of optimized drug delivery systems in improving asthma management and patient outcomes.

KEYWORDS: Bronchodilator, Metered Dose Inhaler (MDI), β_2-adrenergic agonist,astma Bronchoconstriction, Preformulation studies, Aerosol drug delivery,

INTRODUCTION

Asthma, also referred to as bronchial asthma, is a condition wherein there is increased responsiveness of bronchial smooth muscle to various stimuli resulting in narrowing of the airways (constriction of bronchi). It is characterized by difficulty in breathing(dyspnea), cough, wheezing (abnormal sound during wheezing) accompanied with increased mucus secretion and increased respiratory rate(tachypnoea).

Types of asthma

Types of asthma include:

- **Allergic asthma**: when allergies trigger asthma symptoms
- **Cough-variant asthma**: when your only asthma symptom is a cough
- **Exercise-induced asthma**: when exercise triggers asthma symptoms
- **Occupational asthma**: when substances you breathe in at work cause you to develop asthma or trigger asthma attacks [1,2,3]

PATHOPHYSIOLOGY

On exposure to antigen, antibodies are generated by B cells.

↓

On further exposure, IgE binds to mast cells where antigen–antibody (Ag–Ab) complexes form.

↓

Mast cell synthesis is mediated inside it.

↓

Degranulation of mast cells occurs with release of leukotrienes (LTs) and prostaglandins (PGs) due to rupture of mast cells.

↓

Mediators bind to receptors.

↓

This causes bronchoconstriction.

↓

Leads to asthma.

Fig:1 Pathophysiology of asthma. [1,2]

Asthma signs and symptoms include:

- Shortness of breath
- Chest tightness or pain
- Wheezing when exhaling, which is a common sign of asthma in children
- Trouble sleeping caused by shortness of breath, coughing or wheezing
- Coughing or wheezing attacks that are worsened by a respiratory virus, such as a cold or the flu

ETIOLOGY

Asthma is caused by combination of complex and incompletely understood environmental and genetic interactions. These influence both its severity and its responsiveness to treatment it is believed that the recent increased rates of asthma are due to changing living environment Asthma that starts before age 12-year-old is more likely due to genetic influence, while onset after age 12 is more likely due to environmental influence: Genetic,Respiratory infections,Air pollutions,Smoking,Stress, Chemicals and perfumes, Certain medications.

ANTI-ASTHMATIC DRUGS

Drugs used to treat asthma are known as antiasthmatic drugs.These drugs are given by inhalation, oral, or by parenteral routes. They are very effective and safe when inhaled (due to their deposition in the lungs)

CLASSIFICATION

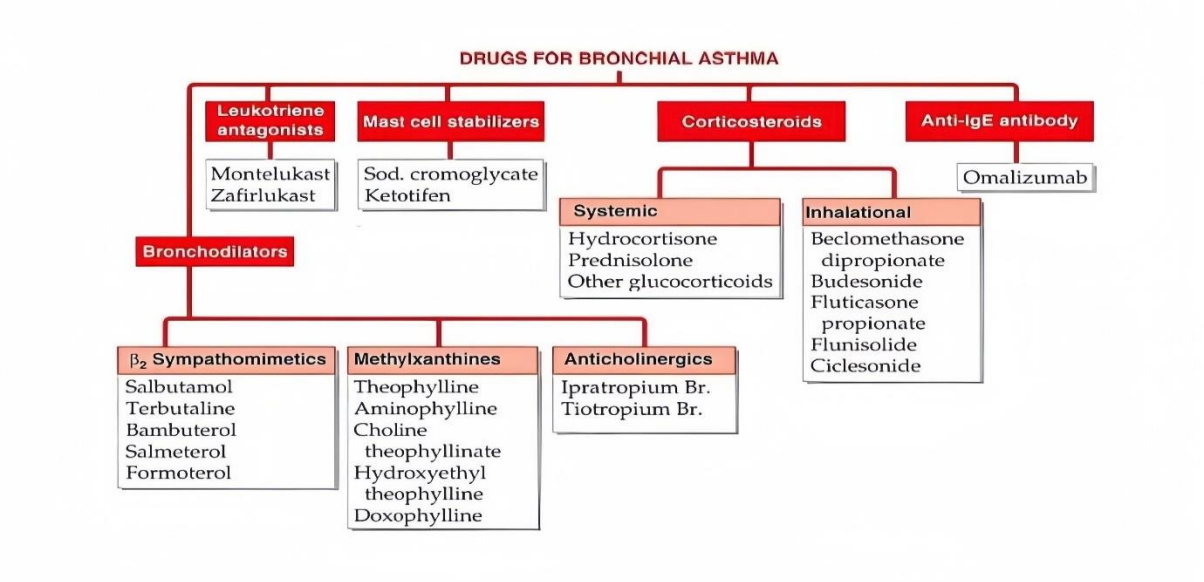


Fig 2: classification of antiasthmatic drugs.

SALBUTAMOL (ASTHALIN)

Salbutamol (also known as **albuterol**) is a short-acting β_2-adrenergic receptor agonist primarily used for the rapid relief of bronchospasm in patients with asthma and chronic obstructive pulmonary disease (COPD).[2,3,4]

MECHANISM OF ACTION[1,2,4]

Salbutamol selectively binds to beta-2 rather than beta-1 receptors.

↓

Beta-2 stimulation result in activation of Gs

↓

Which in turn stimulates G-protien coupled receptor

↓

Resulting in inbcreased cAMP levels

↓

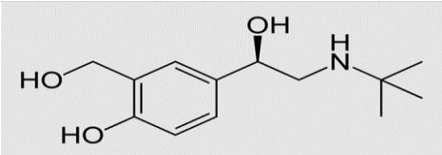
Which relaxes bronchial smooth muscles by reducing calcium dependent coupling of actin and myosin filaments.

↓

Thus,salbutamol induced beta-2 stimulation result in **bronchodilation.**

Fig 3:Mechanism of action salbutamol.

DRUG PROFILE

Physical properties **Organoleptic properties**	• **Colour-white almost cystalline powder** • **Odour-odorless** • **Taste-slightly bitter**
Chemical properties Chemical structure Molecular formula Molecular weight Melting point Solubility Pka pH	 • $C_{13}H_{21}NO_3$ • 231.31g/mol • 155-160˚c • Solubility-freely soluble in water and slightly soluble in Ethanol/alcohol • 5.9 • 4.0-5.0
Pharmacokinetic	• Absorption:Rapid inhalation and oral route • Onset:5 minutes • Peak effect:1-2 hours

	• Duration:4-6 hours • Metabolism:hepatic • Excretion:Mainly in urine
Side effect	Palpitation, increased bp, tremor
Therapeutic uses	• Used in COPD • Effective in the treatment of mild to severe asthma • Used in hyperkalemia especially in patient with renal failure. • Has prominent broncho dilatory effect • Safe cduring pregnancy • Short acting
Available dosage form	
Storage	Store below 25˚c;protect from light and moisture.

DOSAGE FORM	MARKETED FORMULATION
Inhalation aerosol	Cipla asthalin inhaler
Nebulizer solution	Ventolin respirator solution
Drypowder inhaler	Ventolin diskus
Oral tablet	Ventolin 2mg/4mg tablet
Oral syrup/Liquid	asthalin
Injection	Ventolin injection

PREFORMULATION STUDIES OF SALBUTAMOL

Preformulation studies of Salbutamol for inhalation dosage forms are conducted to evaluate its physicochemical and aerodynamic properties to ensure efficient pulmonary drug delivery. These studies help in selecting suitable carriers, optimizing particle size, maintaining stability, and ensuring uniform dose delivery in devices such as dry powder inhalers (DPIs), metered-dose inhalers (MDIs), or nebulizers.

1. Organoleptic Properties: A small quantity of Salbutamol powder is spread on a clean white surface and observed under natural light to determine its color and appearance. The odor is checked by gently wafting air above the powder toward the nose. The texture is examined to determine whether the drug is crystalline or amorphous. These observations assist in preliminary identification and purity assessment.

2. Determination of Particle Shape and Particle Size: Particle size is a critical parameter for inhalation formulations. A thin layer of Salbutamol powder is placed on a glass slide and examined under a calibrated microscope to determine particle shape and morphology. At least 100 particles are measured to calculate average particle size and distribution. Laser diffraction analysis is performed for accurate particle size measurement. For effective lung deposition, the particle size should be in the range of 1–5 µm. Particles larger than 5 µm deposit in the upper respiratory tract, while particles smaller than 1 µm may be exhaled.

3. Determination of Solubility: An excess amount of Salbutamol is added to distilled water and simulated lung fluid and shaken for 24 hours at room temperature. After filtration, the dissolved drug concentration is determined using UV spectrophotometry. Good aqueous solubility ensures rapid dissolution in lung fluids after deposition.

4. Determination of Melting Point: A small quantity of Salbutamol is filled into a capillary tube sealed at one end and placed in a melting point apparatus. The temperature at which the drug melts completely is recorded. This confirms purity and thermal stability.

5. Determination of pKa and pH: A solution of Salbutamol is titrated with a strong acid or base while continuously monitoring the pH using a calibrated pH meter. The titration curve is plotted to determine the pKa value. This study helps predict ionization behavior and solubility at physiological lung pH.

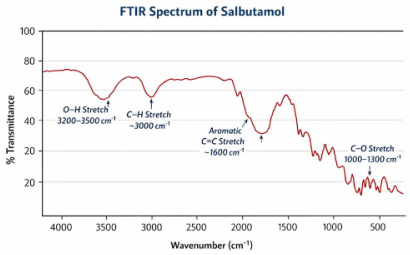
7. Drug–Excipient Compatibility Studies: Salbutamol is blended with commonly used inhalation carriers such as lactose in a 1:1 ratio and stored at 40°C/75% RH for 1–4 weeks. Samples are analyzed using FTIR, DSC, or PXRD to detect any chemical interaction or physical changes. Compatibility studies ensure formulation stability and consistent aerosol performance.

FTIR (Fourier Transform Infrared Spectroscopy) Study:FTIR analysis is performed to identify functional groups and confirm the identity and purity of Salbutamol. A small quantity of the drug is mixed with potassium bromide (KBr) and compressed into a thin pellet or analyzed directly using ATR technique. The sample is scanned over a range of 4000–400 cm^{-1}.

9. Moisture Content and Hygroscopicity: Salbutamol powder is exposed to controlled humidity conditions to determine moisture uptake. Moisture content is measured using Loss on Drying (LOD) or Karl Fischer titration. This study is important because moisture can cause particle agglomeration and reduce aerosol efficiency. [5,6,7]

RESULT

Organoleptic properties	White almost white crystalline powder; odorless, slightly bitter taste
Particle shape and particle size	Crystalline particles ;irregular shape;
Solubility	Freely soluble in water; slightly soluble in ethanol; practically insoluble in chloroform and ether
Meting point	155-160°c
Pka and pH	9.3(amine group); aqueous solution is slightly acidic to neutral(pH-3.5-6 depending on the salt

FTIR study	 • Broad peak around 3200-3500 cm^{-1} due to O–H stretching • Peak near 3000 cm^{-1} due to C–H stretching • Peak around1600 cm^{-1} due to aromatic C=C stretching • Peaks between 1000–1300 cm^{-1} due to C–O stretching
Moisture content	Low moisture content, slightly hygroscopic; typically<1%

FORMULATION OF METERED DOSE INHALER.

Salbutamol Meterd Dose Inhaler

INGREDIENT	QUANTITY
Salbutamol sulphate	120mcg per actuation
HFA-134a(propellent)	10-12g per canister
Ethanol(anhydrous)	0.5-1g
Oleic acid	0.01-0.02g
Aluminium canister	1 unit
Meterfing valve	1 unit
Plastic actuator	1 unit
Dust cap	1 unit

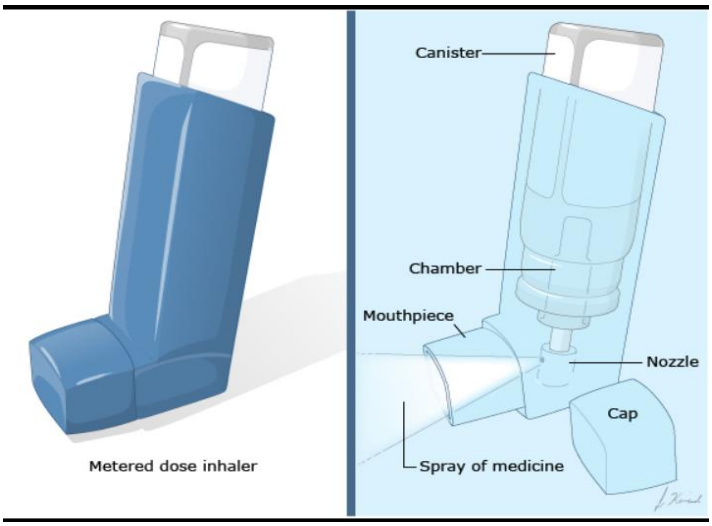


Fig 4:External view and internal parts of a Metered Dose Inhaler.

METHOD OF PREPARATION[8]

Manufacture / Preparation of a Metered Dose Inhaler (MDI)

Procedure

1.Preparation of formulation: The required amount of Salbutamol sulfate (API) is weighed accurately. Excipients such as ethanol and surfactant (e.g., Oleic acid) are added. The mixture is dissolved or dispersed properly to obtain a uniform solution/suspension.

2.Filling of concentrate: The prepared drug concentrate is filled into clean, dry aluminum canisters using a precision filling machine.

3.Crimping of metering valve: A metering valve is placed on the mouth of the canister. The valve is sealed tightly by crimping to ensure airtight closure.

4.Addition of propellant: The propellant such as 1,1,1,2-Tetrafluoroethane (HFA-134a) is filled into the canister under pressure through the valve.

5.Shaking and mixing: The filled inhaler is shaken mechanically to ensure uniform distribution of the drug in the propellant.

6.Quality control testing: Each inhaler is tested for dose uniformity, leakage, spray pattern, and pressure.

7.Assembly and packaging: The pressurized canister is fitted into the plastic actuator (mouthpiece). A dust cap is placed and the finished inhaler is labeled and packed.

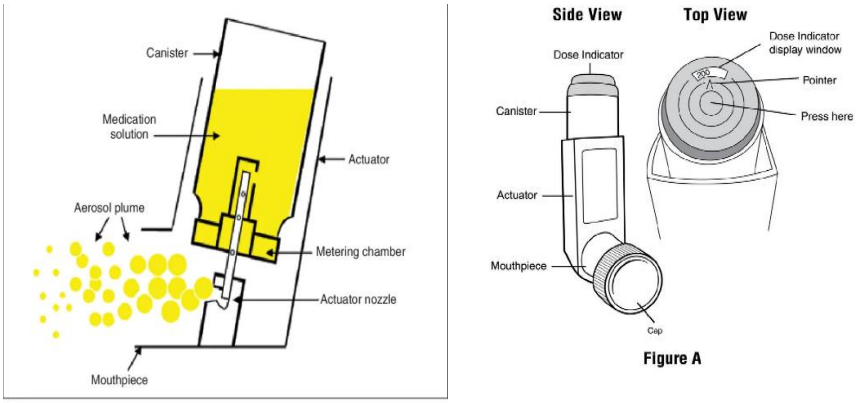


Fig 5: Structure of a Metered Dose Inhaler (MDI) with a dose indicator.

Parts and Components of a Salbutamol Metered Dose Inhaler (MDI)

A Salbutamol Metered Dose Inhaler (MDI) is a pressurized device that delivers a fixed dose of medication to the lungs as an aerosol spray. It mainly contains three core components: canister, metering valve, and actuator.

PART/COMPONENTS	FUNCTION
Canister	Measures and releases a fixed dose of medication with each press.
Propellent	Connects the metering valve to the actuator and allows the drug to pass through.

Metering valve	Measures and releases a fixed dose medication with each press
Valve stem	Connect the metering valve to the actuator and allows the drugs to pass through
Actuator	Plastic body that holds the canister and directs the spray
Spray nozzle/orifice	Convert the liquid formulation to fine aerosol spray
Mouthpiece	Part where the patient inhales the medication.
Dust cap(mouth piece cover)	Protects the mouthpiece from dust and contamination.
Dose indicator(in some inhalers)	Shows the remaining number of doses.

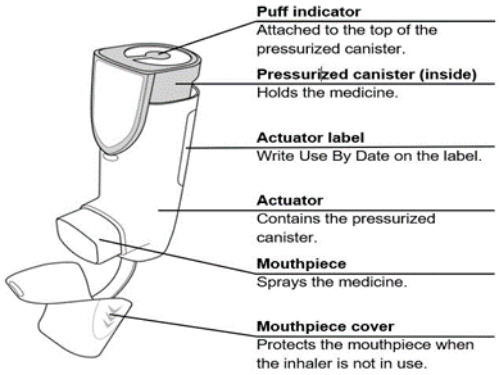


Fig 6: Parts of metered dose inhaler.

Working Mechanism of a Salbutamol Metered Dose Inhaler (MDI)

1. **Pressing the inhaler**: When the user presses the canister, the **metering valve** releases a fixed dose of the drug formulation containing **Salbutamol sulfate** and propellant.
2. **Formation of aerosol**: The pressurized propellant such as **1,1,1,2-Tetrafluoroethane (HFA-134a)** rapidly expands when released from the canister. This converts the liquid formulation into a **fine aerosol spray**.
3. **Inhalation into lungs:** The patient inhales through the mouthpiece at the same time the inhaler is pressed. The aerosol particles travel through the **mouth → trachea → bronchi → lungs**.
4. **Drug action:** The released **salbutamol** acts as a **β_2-adrenergic agonist**, relaxing the bronchial smooth muscles.
5. **Relief of bronchospasm**: The bronchioles widen (bronchodilation), improving airflow and relieving symptoms such as **wheezing, coughing, and shortness of breath**. [5,6,7]

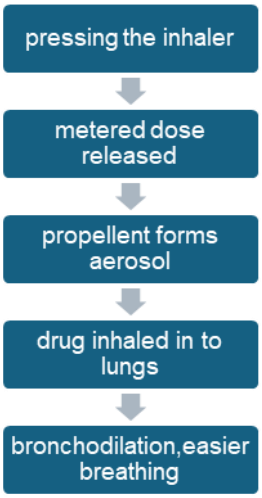


Fig 7: Working mechanism of metered dose inhaler.

EVALUATION OF METERED DOSE INHALER[9]

Evaluation tests ensure the quality, safety, and proper performance of the inhaler containing Salbutamol sulphate.

1.Dose Uniformity Test: Shake the inhaler well. Actuate the inhaler into a collection apparatus or dose collection tube several times. The collected drug is analysed to determine the amount of Salbutamol sulphate in each actuation. The results are compared to check if each dose is uniform. Each actuation of the inhaler should deliver the same amount of drug. This test checks whether the metering valve releases a consistent dose every time the inhaler is pressed.

2.Spray Pattern Test: The inhaler is actuated onto a suitable surface such as filter paper or glass plate. The pattern of the spray is observed. The spray should be symmetrical and uniform.The spray produced by the inhaler is examined to ensure it forms a proper and uniform aerosol pattern for effective delivery to the lungs.

3.Particle size distribution: The size of aerosol particles is measured. Proper particle size is important because very large particles remain in the mouth and throat, while very small particles may be exhaled**.** The inhaler is actuated onto a suitable surface such as filter paper or glass plate. The pattern of the spray is observed. The spray should be symmetrical and uniform.

4.leakage test: The inhaler is checked for any leakage of drug or propellant such as 1,1,1,2-Tetrafluoroethane to ensure the container is properly sealed. The filled inhaler is weighed initially. It is stored under specified conditions for a certain period. The inhaler is weighed again to check any weight loss due to leakage of propellant such as 1,1,1,2-Tetrafluoroethane.

5.Net Content Test: The inhaler is weighed before and after releasing all doses. The difference in weight indicates the amount of formulation present in the container. This test determines whether the inhaler contains the correct amount of formulation as specified on the label.

6.Number of Actuations per Container: The inhaler is tested to confirm that it provides the correct number of doses (for example, about 200 puffs per inhaler). The inhaler is actuated continuously until it becomes empty. The total number of puffs delivered is counted and compared with the labelled number of doses.

7.Valve Performance Test: The metering valve is repeatedly actuated.

Its functioning, dose accuracy, and smooth operation are evaluated. These tests ensure the metered dose inhaler provides accurate, safe, and effective drug delivery to the lungs.[6,10]

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