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PULMONORY DRUG DELIVERY SYSTEMS FOR ASTHMA MANAGEMENT

Yelwante Suyash R., Miss. Gawande Trupti S., Miss Bedse Yogini
Students of Rashtriya College of Pharmacy Hatnoor, Kannad, Chh. Sambhajinagar, Maharashtra, India

ABSTRACT

Due to its improved local targeting and decreased systemic side effects when administering minute drug dosages, pulmonary drug delivery has garnered a great deal of scientific and biomedical attention in recent years and has advanced significantly in the context of local treatment for lung diseases. Furthermore, a paradigm shift toward inhaled medicine for systemic usage has occurred in the 21st century due to the lung's high surface area and permeability. However, the pulmonary tract is often thought to be a very appealing and promising route for the administration of active compounds meant to treat both systemic disorders and local pulmonary conditions like asthma, chronic obstructive pulmonary disease (COPD), microbial infections, and so on. (for instance, diabetes) Recent developments in biotechnology have produced a class of innovative protein and peptide medications to

Therefore, in contrast to parenteral or gastrointestinal administration (tablets, capsules, etc.), administration to the respiratory tract appears to be preferable in order to obtain systemic delivery. Because the lungs have little metabolic activity, systemic distribution can occur without hepatic transit. Because biomolecules are especially sensitive to enzymatic degradation in the gastrointestinal tract (ventricle and intestines) as well as hepatic degradation (first-pass metabolism), the lung is therefore an ideal location for them.

Keywords : Asthma, pulmonary drug delivery system, bronchial blood circulation

Introduction

Drug:

A drug is a chemical substance with known biological effects on humans or other animals. In the pharmacology field, a drug is defined as a chemical substance used in the treatment, cure, prevention, or diagnosis of disease or used to otherwise enhance physical or mental well-being. Drugs usually affect either normal or abnormal physiological processes. Drugs may be used for a limited duration, or on a regular basis for chronic disorders.

Drug delivery systems:

Technology-based systems known as drug delivery systems are used to synthesize and store drug molecules into forms that are appropriate for administration, such as tablets or solutions. They expedite the delivery of medications to the precise targeted place within the body, optimizing therapeutic efficacy and reducing the likelihood of offtarget accumulation. There are several ways that drugs can enter the body; they include, but are not restricted to, the oral, buccal, and sublingual routes; nasal and ophthalmic; transdermal and subcutaneous; anal and transvaginal; and intravesical.

The drug's constituents are what give it its physiochemical characteristics and cause the alterations in the physiological systems that it affects when ingested. DDS has been used successfully in the last few decades to cure illnesses and enhance health because of its increased systemic circulation and ability to regulate the pharmacological action of the medicine. The concept of controlled release emerged as pharmacology and pharmacokinetics advanced and shown how important drug release is in determining the effectiveness of therapy.
Since its first approval in the 1950s, a drug's controlled-release formulation has garnered a lot of attention because of its many advantages over traditional medication. It delivers medication for a set amount of time and at a set rate. Furthermore, regulated drug delivery systems have a days-to-years lifespan since they are not impacted by physiological circumstances. Along with constant or variable release rates, it also offers spatial control over drug release. It also lessens medication toxicity and enhances pharmacological activity, target site accumulation, effectiveness, pharmacokinetic characteristics, patient acceptance, and compliance. A number of drug delivery systems (NDDS) have been created recently utilizing sophisticated technology.

for a delivery that is more streamlined, focused, and convenient. The unique characteristics of every medication delivery system dictate its release mechanism and rate. This is mostly because of the variations in their morphological, chemical, and physical properties, which ultimately influence how well-suited they are for different types of drugs. Diffusion, chemical reaction, solvent reaction, and stimulus control have been found to be the main release mechanisms in these studies. As an example, since

Since the lymphatic system and permeable blood vessels allow most cancer cells to thrive, drugs can readily pass through these gaps and enter the target regions. The term "Enhanced Permeability and Retention" (EPR) describes this. EPR is a well-studied passive diffusion mechanism that is used to administer a variety of chemotherapy drugs. Although EPR is a contentious idea, numerous studies have seen this effect in a variety of human tumor types, and this is what led to the development of nanomedicine as a cancer treatment modality. However, its lack of selectivity and higher toxicity are drawbacks. Passive targeting lacks selectivity and specificity; active targeting addresses this issue. It entails binding to certain ligands, chemicals that can bind to the carriers actively, and

the target tissues' surface. This lessens toxicity and adverse effects by preventing uptake by cells that are not the target. The complete development of actively targeted drugs is currently hampered by factors such as ligand selectivity to target cells, immunogenicity, and the likelihood of lysosomal breakdown following macrophage endocytosis. In the process of targeting responsive stimuli, these delivery systems can also reach the target cells by manipulating one or more physical or chemical properties. pH, temperature, ultrasonography, magnetic field, and electric field are some of these physical characteristics [2–3].

Any illness or disease that affects the lungs and respiratory system is referred to as lung disease. It could be brought on by fungi, viruses, bacteria, or the environment. Lung disorders are the fourth biggest cause of respiratory diseases in India, accounting for about 10.9% of all respiratory ailments, according to 2017 data from the World Health Organization. Lung cancer, interstitial lung disease, bronchitis, asthma, emphysema, pneumonia, and chronic obstructive pulmonary disease are among the major illnesses. Devices, machinery, or structures that deliver medications to the lungs for the treatment of respiratory conditions or other illnesses are

referred to as pulmonary drug delivery systems. These days, medications that can be utilized locally or regionally are delivered to the lungs through oral or nasal inhalation.

increased bioavailability, which offers the crucial advantage of allowing the medication to enter the system directly. It offers a non-invasive technique that avoids first-pass metabolism as well. Nonetheless, there are still concerns about the inhaler's efficacy and safety. 1. Pulmonary medication delivery may be a substitute for conventional drug delivery because of the special characteristics of the lung. The body's unique characteristics include. [4]

- Various Type Drug Delivery System

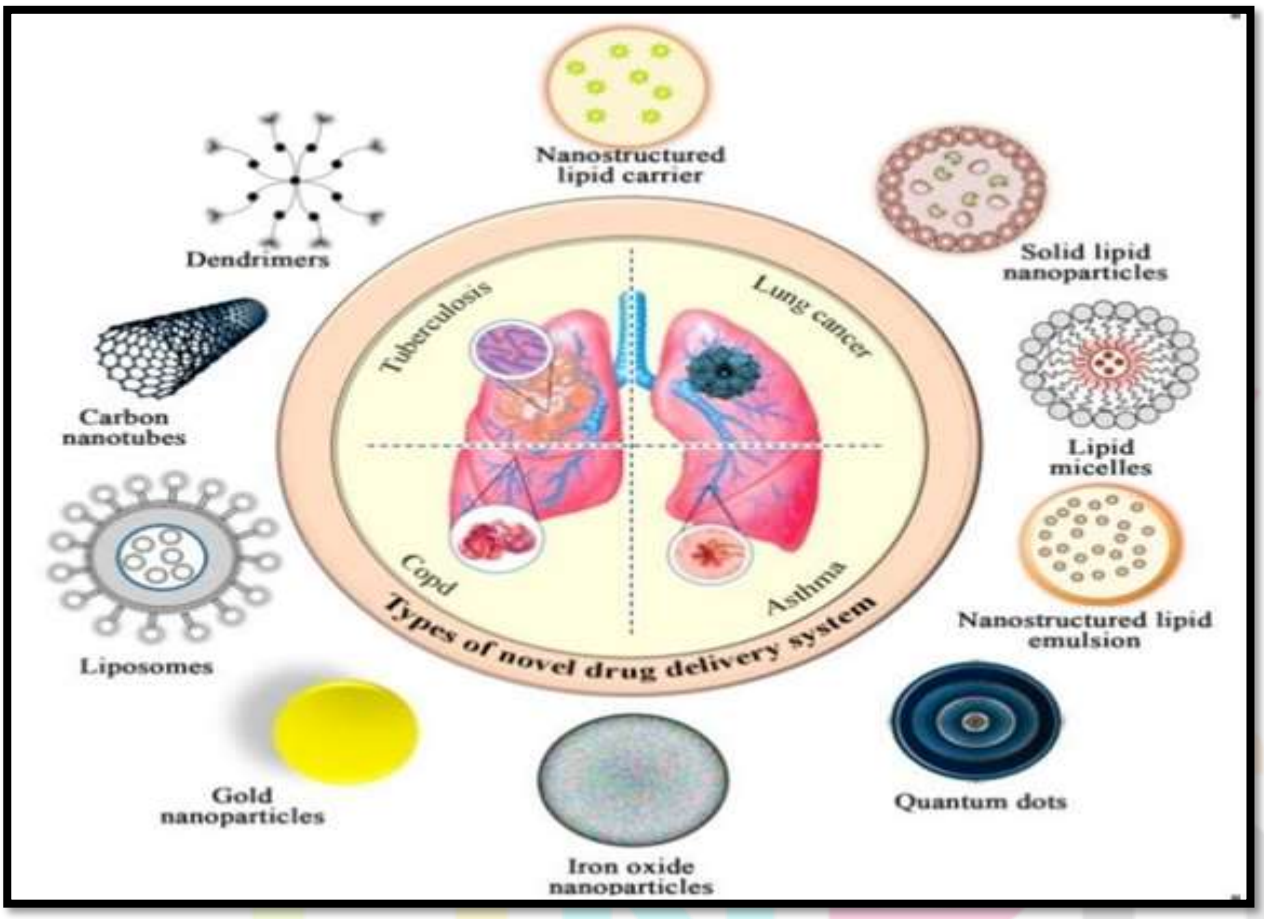

Fig.1 Various Type Of Drug Delivery System

Over time, scientists have come to understand the potential advantages of nanotechnology for significantly enhancing drug delivery techniques. Nanoparticles disguised like red blood cell membranes are a novel class of drug delivery vehicles. Red blood cells (RBCs) can be used as an effective method as a nanoparticle camouflaging material due to their nature and biological significance. Red blood cells (RBCs) are the most prevalent circulating cells in the body, and because of their extended circulating half-life, biodegradability, and lack of immunogenicity, they are a perfect medium for drug administration. An increasing number of materials are being investigated and examined to improve pharmaceuticals as science and technology continue to progress.

delivery. One of these materials is boron nitride (BN), a crystalline substance containing an equal number of atoms of boron (B) and nitrogen (N). There are several different types of this material, including wurtzite BN (wBN), rhombohedra BN (r-BN), cubic BN (c-BN), and hexagonal BN (h-BN). With sp2 hybridized B-N bonds, hexagonal boron nitride is a two-dimensional (2D) layered-dense structure. It is also known as white graphene,

and it is occasionally seen as graphite's equivalent. The carbon atoms are replaced by B–N atoms, which are kept together by a potent

Interlocking rings are formed by a covalent link. Van Dyer-Waals forces, with a bond length of 1.466 Å and an interlayer gap of 3.331 Å, hold the compound's layers together. This molecule features polar B-N bonds because of its unique feature of being somewhat ionic. As an insulator, H-BN has found extensive use in a variety of industries, including dentistry, ceramics, cement, cosmetics, and most notably, medicine as a drug carrier that resembles graphene.[4]

An inflammatory illness of the respiratory system is what is known as asthma. Airway hyperresponsiveness (wider airway narrowing) and hypersensitivity are related. Increased sensitivity to allergens and physical activity), leading to symptoms such as coughing, dyspnea, chest tightness, and wheezing. Large yet fluctuating lung airflow is typically linked to symptoms, which are frequently treated with asthma medication or reversals on a regular basis.[5] More than 300 million people worldwide suffer from chronic obstructive pulmonary disease, or asthma.

illness (COPD). 22 million people in the US suffer from asthma, one of the most prevalent chronic illnesses in the world. With an estimated 6 million children affected, asthma is the most prevalent chronic illness in childhood and a major reason for pediatric hospitalizations in the US. [6]

Review of literature:

Hatem Amin Hejaz1 and RafikKaraman In addition to A chemical compound with recognized biological effects on humans or other animals is called a medication. A chemical substance used to treat, cure, prevent, diagnose, or otherwise improve physical or mental well-being is referred to as a drug in the discipline of pharmacology. Typically, drugs have an impact on either normal or aberrant physiological systems.

Tobechukwu Christian Ezikealong with others (2023): drug delivery system advancements, difficulties, and future directions Drug delivery systems (DDS) are designed with cutting-edge technology to minimize off-target accumulation in the body and maximize therapeutic efficacy by accelerating systemic drug delivery to the precise target site. They thus have a significant impact on the management and treatment of diseases as well as the distribution of different drugs.

. **Harish Kumar, K. Rathod, VinayakA.Katekar, Yashkumar, R. Dhole .and Prashant S. Nalinde** et al. (2021–2023) Review of the pulmonary medication delivery system The pulmonary drug delivery system (PDDS) is a crucial channel for managing different medications. Concerns about the scientific and environmental benefits of treating lung disorders have grown in the lungs in recent years. One of the most popular medication delivery methods for planned or local drug rescuers is now lung delivery. Drug delivery systems are being developed for the treatment of lung illnesses because of their potential to improve localized lung function.

Harold Kim, Jorge Mazza and Associates (2014) In Canada, asthma is the most prevalent respiratory illness. Even with great advancements in the diagnosis and treatment of asthma, most Canadians still have inadequate asthma control. However, control may usually be obtained in most cases by using appropriate pharmaceutical therapies along with avoidance tactics. For most individuals, inhaled corticosteroids (ICSs) are the standard of therapy.

Sara M Tony1, Mohamed EA Abdelrahim et al.(2022*)* ***Inhalation Devices and Pulmonary DrugDelivery*** The primary application of inhaled drug delivery is the treatment of pulmonary airway disorders, as it delivers the medication directly to the site of action. This minimizes any possible negative effects and lowers the dose

needed to have a therapeutic impact. A quicker beginning of action is made possible by direct medication administration to the airways.

ND Shah, VV Shah and ND Chivate et al. (2012***) Pulmonary Drug Delivery: A Promising Approach*** Drug deposition mechanism: Brownian diffusion, electrostatic precipitation, impaction (inertial deposition), sedimentation (gravitational deposition), and interception are the ways in which particles deposit in the respiratory tract. Patterns of breathing
Since breathing volume and frequency control the mean flow rates in each respiratory tract region, which in turn influence the efficacy of each deposition mechanism, the pattern of respiration during aerosol exposure affects regional deposition.

Aim And Objective

Aim An overview of pulmonary drug delivery systems for the treatment of asthma.
The goal of this review is to thoroughly examine the state of pulmonary medication delivery devices available today for the treatment of asthma. It specifically aims to assess the viability, safety, and effectiveness of several delivery systems, such as nebulizers, dry powder inhalers, and metered-dose inhalers.

Objective:

1) Giving a thorough understanding of the pulmonary medication delivery methods utilized in the treatment of asthma is the goal of this quick review.

2) The review's objective is to assess the efficacy, safety, and patient adherence of a range of delivery systems, including nebulizers, dry powder inhalers, and metered-dose inhalers. It also aims to provide an overview of recent developments and breakthroughs in pulmonary medication delivery technology.
3) The review's goal is to provide insights into the state of asthma therapy today by combining the body of research and pointing out areas where improved pulmonary medication delivery methods may improve treatment outcomes.

4) This succinct review aims to objectively analyze the function and effectiveness of pulmonary medication delivery devices in the treatment of asthma.

5) In particular, the review attempts to assess the many formulations and delivery systems that are available for directly delivering asthma drugs to the lungs.
6) By evaluating the benefits, drawbacks, and relative efficacy of nebulizers, dry powder inhalers, and metered-dose inhalers, the review aims to give medical professionals and researchers important information about the best pulmonary drug delivery system selection and application for asthma management.
7) The review also seeks to identify new directions and areas for investigation in order to improve the efficiency and results for patients related to pulmonary medication administration in asthma treatment.

4) The purpose of this brief study is to provide a concise assessment of pulmonary drug administration techniques for the management of asthma.

Pulmonary Drug Delivery System:

Recent years have seen a rise in scientific and biomedical interest in pulmonary medication delivery. By enhancing the local target and mitigating side effects with the use of microdosing, considerable progress has been made in the local therapy of lung disorders. The lungs' vast surface area and permeability have led to a change in the use of inhaled medications. The drug's inhalation route of administration is not well understood, despite being known for a long time. Nonetheless, the use of the lungs as a delivery system for medications to treat local lung conditions (such as asthma, obstructive pulmonary disease (COPD), microbiological) as well as systemic illnesses (like diabetes). The medication is used to treat a wide range of illnesses and is primarily inhaled orally. Medications such as corticosteroids, anticholinergics, and long- and short-acting beta sympathomimetic are widely used in inhalation therapy to prevent lung infections. As a result, the respiratory route is being given greater consideration when it comes to parenteral medication delivery, namely for the delivery of inhaled insulin as well as peptide and protein treatment.[7]

Advantages

- The pulmonary delivery method is needle-free.
  A small portion of the oral dose is needed.
  Because pulmonary drug administration does not expose the rest of the body to the drug, its adverse effects are minimal.
- Pulmonary medication administration has a very rapid course of action.
  In pulmonary medication delivery, the drug is not broken down by the liver.

Disadvantages

Oropharyngeal deposition has adverse effects in the area.
Patients might experience trouble correctly using the pulmonary medication devices. It's possible that the mucus layer's physical barrier restricts drug absorption.
The repeatability of medication distribution in the lungs is influenced by a number of factors, such as pharmacological and physiological obstacles.

Delivery devices are necessary to target drug delivery, in addition to the lungs being accessible surfaces for drug delivery complexes.
the drug's stability in vivo.
specifying target accuracy.

substance toxicity and irritation.
protein immunogenicity.
The physical barrier of the mucus layer may restrict the amount of drug absorbed.
Patients may experience some difficulty correctly operating the pulmonary medication delivery devices.
Oropharyngeal deposition has adverse effects in the area. [8–9]

Anatomy and Physiology of Human Respiratory Tract:

In order to move carbon dioxide out of the body and return it to the lungs for excretion, the respiratory system collaborates with other organs to move oxygen from the lungs into the cells. Respiration is the process by which oxygen and carbon dioxide are exchanged between the air, blood, and tissues. About one pint of air is breathed by healthy lungs 12–15 times every minute. Every minute, all of the blood in the body travels via the lungs. The lungs, trachea, bronchi, and pharynx comprise the internal organs of the respiratory system, whereas the nose, nostrils, and pharynx comprise the upper respiratory system. Starting at the edge of the larynx, the trachea splits into two bronchi before continuing on its path to the lungs. Air can go from the larynx to the trachea.

The lungs' working organs, the alveoli, make room for gas exchange. To the right of the fifth thoracic vertebra, the larynx continues as the trachea, or air duct. The left and right bronchi, which together comprise the complete lungs, are split off at the carina. It is located in the middle plain in front of the esophagus and is around 10 to 11 cm long. The tissue that makes up the trachea also makes up the bronchi. The ciliated columnar epithelium covers them. Alveolar ducts, terminal bronchioles, bronchioles, and alveoli are the successive divisions of the bronchi.

In the distal bronchi, the cartilage is not at the bronchiolar level and has a poor form. There are only about 300 million tiny alveoli in each lung. Despite being tiny structures, alveoli have a sizable overall surface area (about 100 m2), which facilitates effective gas exchange. The pulmonary capillaries and alveolar area are separated by a thin blood barrier that permits

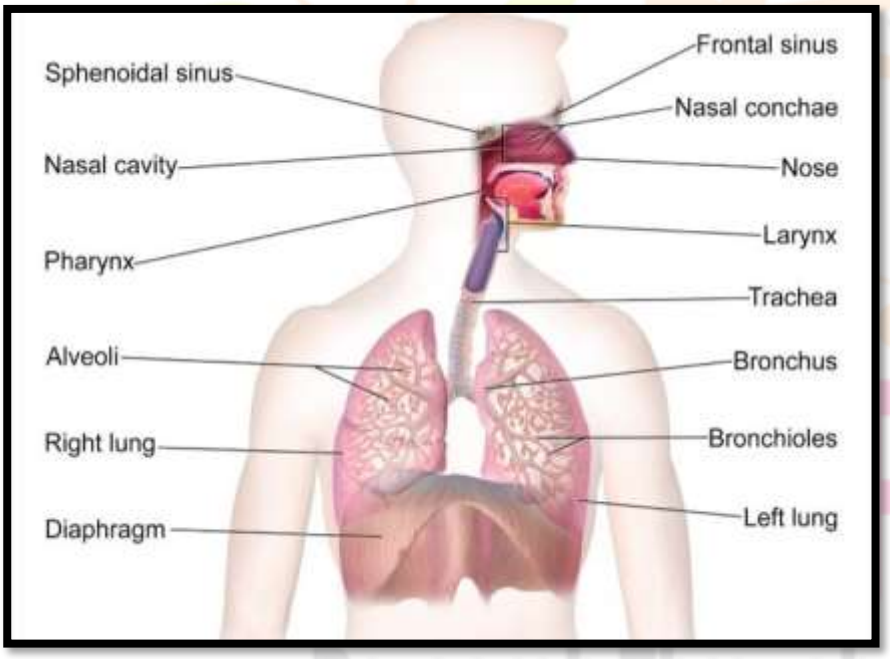

Figure 2: Human Respiratory System

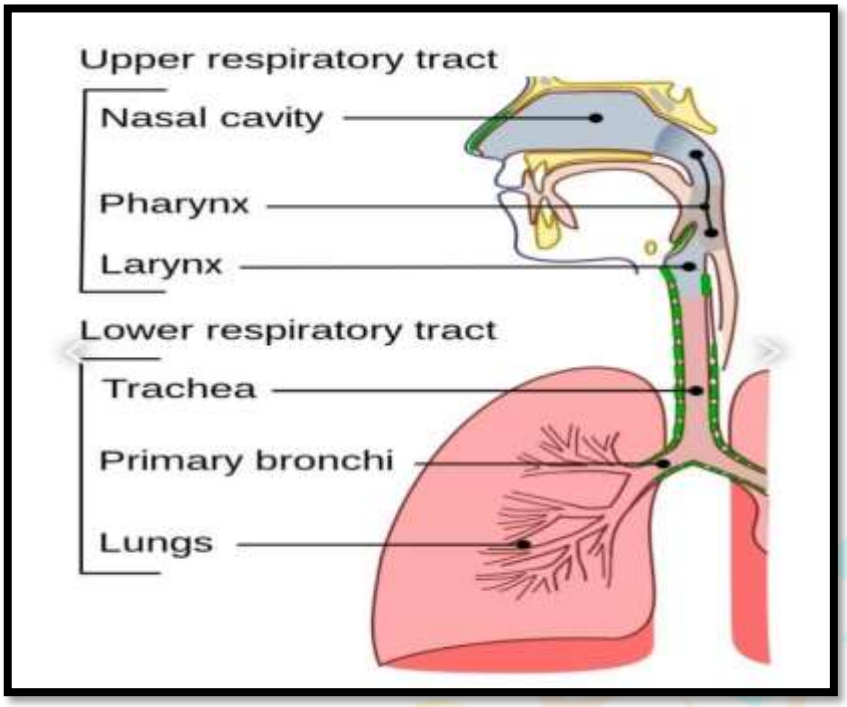

Fig3: Schematic illustration of the human respiratory system shows the upper respiratory and lower respiratory tracts [10]

Mechanisms of Particle Deposition in the Respiratory Tract:

When external particles are cleared from the airways, effective resistance mechanisms can lessen their load and potentially aid in storage. Depending on the process and formulation used to create the aerosol, therapeutic aerosols are two-phase colloidal systems in which the medication is contained in a dispersed phase. These phases can be liquid, solid, or a combination of the two. It appears that in order for a medication to be therapeutically effective, it must have entered the lung in the form of aerosol droplets or particles that settle in a particular lung location and in a quantity that was necessary. Insoluble particles may be subject to the respiratory mechanisms of resistance to mucociliary clearance and phagocytosis by macrophages. Aerosol particle dissolution may be slowed, and before the medication reaches its precise site of pharmacological action, it may then be susceptible to an enzymatic process. Aerosols from the mouth are used to deliver drugs to the lungs. The respiratory tract's particle deposition mechanism.

Inertial impaction:

For particles larger than 1 μm, this is the main mechanism of deposition in the upper tracheo-bronchial areas. When inspired air transfers bifurcations, a particle with a lot of momentum might not be able to follow the changing direction of the air, causing it to collide with the walls of the airway while continuing on its previous path.[11]

Sedimentation:

The particles may be deposited by settling under gravity. It becomes highly important for particles that reach airways where the velocity of the airstream is relatively low, e.g., the bronchioles and alveolar region. The fraction of particles deposited by this mechanism may be dependent upon the time the particles spendnd in these regions.

Brownian diffusion:

This has little bearing on particles larger than 1 μm. Smaller particles are propelled by a series of gas molecules bombarding one another, which could cause a particle collision with the airway walls. Particle size reduction enhances the opportunity for particle deposition by diffusion. Brownian diffusion is frequently more prevalent in areas with very little or no airflow, such as the alveoli. Although it might not be as effective for medication delivery, another deposition technique is significant for fibers.

Generally:

Particles bigger than 10 μm will affect the upper respiratory tract and are quickly expelled through coughing, swallowing, and mucociliary movements. Particles sized between 0.5 and 5 μm have the potential to detach from impaction in the upper respiratory tract and collect through sedimentation and impaction in the lower TB and A regions. Deposition is mostly found in the TB region if the aerosol's particle size is between 3 and 5 μm. Sufficient deposition in the A region is expected to happen if the particles are less than 3 μm.

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Interception:

When a particle meets an airway surface because of its size or shape, this is known as interception. Particles placed by interception follow their air streamlines exactly, unlike impaction. Small airways or situations where the air streamline is near an airway wall are more likely to result in interceptions. Since fibers are long and easily come into contact with airway surfaces, intercepting them is usually important. Because of this, fibers can frequently enter the smallest airway because of their extremely small aerodynamic dimensions in relation to their size. [12]

Absorption:

Many proteins and medicinal peptides, as well as small-molecule medications, can naturally pass through the pulmonary membrane. The lung's epithelium, a crucial barrier for the absorption of inhaled medications, is shown to be thick (50–60 μm) in the trachea and incredibly thin (up to 0.2 μm) in the alveoli. The transition from trachea, bronchi, and bronchioles to alveoli is characterized by a significant change in cell types and appearance. Compared to alternative entry points into the body, the lungs have a higher permeability to macromolecules. Peptides and proteins that can be breathed rather than injected are therefore the most promising therapeutic agents since they increase patient compliance. Specifically, peptides that have undergone chemical modification to block

The pulmonary route results in significantly higher bioavailabilities for peptidase enzymes. If a small molecule is strongly cationic or highly soluble, it may exhibit delayed absorption. Even though quick molecule absorption has many potential medicinal applications, there are situations in which it is desirable to slow down a tiny molecule's absorption after inhalation in order to control its body absorption or prolong its localized effects in the lung. Many insoluble molecules from the inhaled particle that slowly breakdown will remain in the lung for several hours or even days. B-amphothericin, The sluggish dissolving rate of fluticasone propionate and all-trans retinoic acid from relatively insoluble lipophilic particles contributes to their prolonged absorption from the

lungs over several hours. Controlling absorption can also be accomplished by encapsulating slow-release particles like liposomes and nanoparticles. [13]

Electrostatic Precipitation:

Electrification typically takes place during the production of aerosols. The effectiveness of particle deposition in the lungs during breathing may be significantly impacted by the unipolar charge on the particle. When condensation aerosols are utilized, the amount of particle deposition in the lungs under the same conditions is comparatively minimal. Since there are no electric charges in the condensation aerosols, the additional deposition from electrostatic forces may be the reason for the variation in fractional deposition. For submicron and micron particles with unipolar charges of up to 100 electrons, this kind of action is highly important. The electrostatic precipitation resulting from the image force between the particle and the wall is the main cause of the observed alterations.

Respiratory Patterns

Since breathing volume and frequency impact the mean flow rates in each region of the respiratory tract, which in turn improves the effectiveness of each deposition mechanism, the pattern of respiration during aerosol exposure favors regional deposition. Particle deposition is generally enhanced by turbulence, to varying degrees depending on the size of the particles. While slow, steady inhalation increases the number of particles that penetrate to the peripheral parts of the lungs, rapid breathing frequently results in increased deposition of larger particles in the upper respiratory tract. Slow breathing, with or without breath-holding, demonstrated a broad maximum deposition in the ciliated airways (tracheobronchial region).

The range of the pulmonary maximum was 1.5 μm to 2.5 μm with breath-holding and 2.5 μm to 4 μm when it wasn't. Similar tendencies were seen with rapid inhalation: the maximum in the tracheo-bronchial region decreased and shifted to a distance between 3 and 6 μm. Between 1.5 μm and 2 μm when breath-holding and between 2 μm and 3 μm when not, pulmonary deposition sharpens and takes place. The optimum situation for aerosol would be the following when the aforementioned factors are taken into account:

- Slow and steady inhalation;
- Aerosol AD less than 5 μm, to minimize oropharyngeal deposition
- A moment of holding one's breath after inhaling fully. [14]

Pulmonary Clearance:

Maintaining the respiratory surfaces of the alveoli clean and prepared for respiration is the main purpose of the pulmonary defensive reaction to inhaled particles. As a vital defensive mechanism, the removal of particles lodged in the lower respiratory tract stops potentially harmful interactions between aerosols and lung cells. There are multiple, as yet poorly understood, routes by which insoluble particles are cleansed. These routes are hypothesized to be dependent on the type of substance delivered and are known to be compromised in certain disorders. The first sequence associated with clearance mechanisms functioning in the naso/oropharynx and tracheobronchial tree is present in swallowing, expectoration, and coughing.

. The mucociliary escalator is a key route of clearance for inhaled particulate matter deposited in the conducting airways, while alveolar macrophage absorption is primarily observed in the alveolar region. Apart from these

routes, the breakdown of soluble particles and their subsequent absorption from the lower respiratory tract can also remove them. There are differences in the rate at which particles are cleared from certain areas, and if this process is prolonged, it may lead to lung disorders that are caused by the inhaled compounds' hazardous effects. The lungs are known to be a location of absorption, accumulation, and/or metabolism of various endogenous and/or foreign substances.

. Though in reduced quantities, the lung has all of the liver's metabolizing enzymes. The rate of medication clearance and absorption from the respiratory tract is primarily determined by the dynamic interaction of multiple variables.

• Rate of mucociliary clearance
• Location of the deposits near the airways

• Drug release rate; • Biopharmaceutical variables (drug in solution versus particles); • The drug's physicochemical characteristics, including molecular weight, charge, and partition coefficient. [15]

Pulmonary Absorption:

Many therapeutic proteins and peptides, as well as small-molecule medications, can naturally pass across the pulmonary membrane. The lung's epithelium, which acts as a major barrier to the absorption of medications breathed, is thick (50–60 μm) in the trachea and incredibly thin (0.2 μm) in the alveoli. Transitioning from bronchi, trachea, and bronchioles to alveoli involves a fairly drastic change in cell types and morphology. The lungs have greater macromolecule permeability.

than any other entrance point into the body. The ideal range of aerodynamic particle sizes for macrophage absorption in the alveolar region is thought to be 0.5–5 μm (500–5000 nm). Drug molecules are lost during the process of phagocytosis in carrier particles. The effective method for long-term medication release in the lungs is quick phagocytosis targeting. Lung barriers in drug absorption through the pulmonary route include the epithelial lining fluid thickness of 0.05 μm in alveoli and 10 μm in central airways, the heterogeneous composition of cell types in the endothelium and epithelium, the basement and interstitial membrane drained by lymphatic vessels and the lymphatic system, the surfactant secreted by type II cells, the mucocilliary clearance from the trachea to the bronchioles, mucus production, and pathophysiological

alterations such as epithelium disruption, hypersecretion, and inflammation. Hydrophilic substances cause paracellular diffusion, transcellular diffusion, and passive diffusion (lipophilic compounds). Pulmonary absorption involves the occurrence of many transport processes, including vesicle-mediated transcytosis, carrier-mediated transport, and efflux transporters. The lung has a very thin barrier, a huge surface area, and greater medication absorption due to its increased systemic bioavailability. As a result, the lung experienced quick absorption upon inhalation. The problem lies in the formulation's need to remain in the lung's local site of action and release the drug for an extended duration. When comparing the absorption qualities of polar medicines in the gastrointestinal system and the lungs, the former have lower metabolisms and faster absorption rates. Lung metabolism rates are naturally lower, while lung and liver esterase expression are comparable.

Phase I activity in the lung is typically 10% of that in the liver. When inhaled, small proteins and peptides are absorbed much more quickly than when injected subcutaneously. Since the lung has far lower amounts of drug efflux transporters and metabolizing enzymes than the gastrointestinal tract, inhaling other tiny molecules is a quick way for them to enter the body. Lipophilic tiny compounds absorb quickly—t1/2 absorption takes around a minute or two. Small compounds that are soluble in water are absorbed quickly; their t1/2 absorption is appropriately 65 minutes. If a small molecule is strongly cationic or highly soluble, it may show delayed absorption.

There are situations in which it may be desirable to slow the absorption of a tiny molecule that has been breathed, either to allow it to act locally in the lung for a longer period of time or to control its absorption into the body, despite the fact that rapid molecule absorption has numerous potential medical applications. For several hours or even days, very insoluble chemicals that gradually disintegrate from the inhaled particle can remain in the lung.

The slow dissolution rate of amphotericin B, fluticasone propionate, and all-trans retinoic acid from relatively insoluble lipophilic particles contributes to their absorption from the lungs over several hours. Controlling absorption can also be accomplished by encapsulating slow-release particles like liposomes and nanoparticles. [16]

Mechanism of drug accumulation (deposition) in pulmonary airways:

The lungs are the site of three primary drug-deposition processes. We refer to the first mechanism as inertial impaction. It is the most typical method by which particulates accumulate in the upper respiratory tract. The particle with increased momentum (velocity x mass) in the upper respiratory system appears unable to adjust to the changed inspired air track. The lungs' internal airway walls become impactful due to this high velocity. Particles that are larger, move faster, or have a higher density will exhibit more impaction since the chance of impaction is related to the particle's momentum.

Another way that drugs might accumulate is through sedimentation. Gravity causes the particles to settle downhill when the airflow velocity drops. When the bronchioles and alveoli's airflow is constricted, this occurs. The fraction of particles deposited by this method depends on how long the particles stay in these areas. Breathing deeply after inspiration prolongs the duration of the particles in these areas, leading to increased drug deposition in the lungs. [17]

ASTHMA :

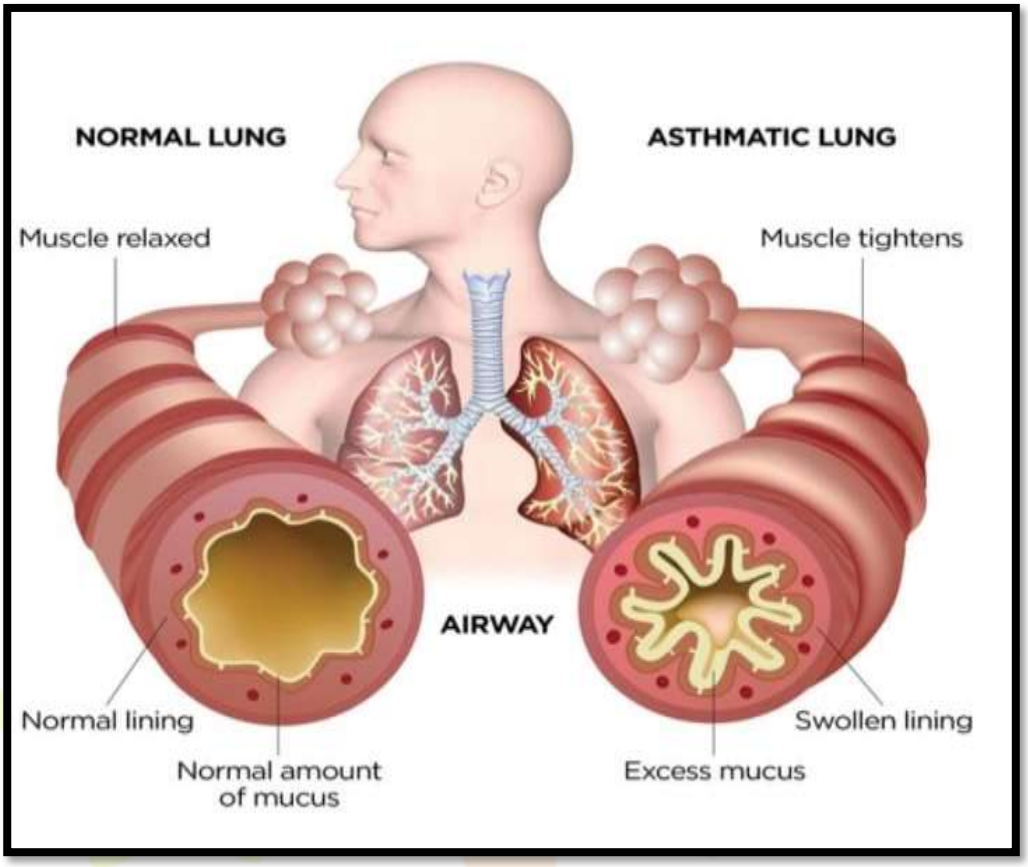

Fig.4 Asthma

Up to 300 million people worldwide, of all ages, races, and ethnicities, are thought to have asthma, and the condition is becoming increasingly common in both children and adults. Growing urbanization is frequently associated with an increase in asthma prevalence [19]. Worldwide, asthma is thought to be the cause of 250,000 fatalities annually, the majority of which can be avoided [20]. According to estimates, 8.2% of Americans (24.6 million people) have asthma, with prevalence rates slightly higher in children than in adults and in females than in males.

Asthma is becoming more common in the US; each year, asthma symptoms result in 10.6 million medical visits and 444,000 hospital admissions. The Centers for Disease Control and Prevention estimate that asthma affects 16.4 million people (7.3%) and seven million children (9.4%) in the US and that it is the cause of approximately 4000 fatalities per year [21]. Optimizing asthma control has been identified as the main objective of asthma care, according to international consensus recommendations and guidelines [22]. In a

The Global Initiative for Asthma (GINA) recommendations suggest monitoring control through the assessment of exacerbations, lung function, nighttime awakenings and symptoms, the need for rescue medication, and daytime symptoms in an effort to enhance asthma management. Similar to this, the joint task force report from the American Thoracic Society and the European Respiratory Society (ATS/ERS) assesses the patient's level of control by considering the risk of future adverse events, such as loss of control, and the degree to which the patient can perform activities of daily living and achieve optimal quality of life.

exacerbations, a quicker reduction in lung function, and medication side effects. The basic objectives of asthma treatment are to achieve effective asthma control and reduce the patient's future risk of exacerbations with minimal side events and cheap cost, notwithstanding modest variations in definitions among asthma control

guidelines [23]. This article focuses on the role of asthma triggers, which are defined as substances or events that cause an abrupt start or worsening of asthma symptoms lasting many hours or days [24, 25]. While many factors undoubtedly contribute to asthma control or lack thereof, this article focuses on the function of asthma triggers. Certain triggers have been linked to the need for an intensive care unit (ICU) and severe asthma exacerbations.

admissions [26]. As part of asthma control care, doctors, authoritative authorities, and patient education programs typically help patients identify asthma triggers and offer recommendations for methods to reduce exposure to triggers [27, 28]. Results from a sizable retrospective cohort study revealed that 30% of patient clinic visits included advice on trigger management, and 85% of visits included discussion of triggers [29]. Patients' views of triggers and actions taken to handle triggers in the real world were investigated in a recent US focus group study. The findings showed that asthma patients can name a wide range of common asthma triggers in their surroundings, such as indoor and outdoor allergens,

The frequency and intensity of asthma symptoms are thought to be influenced by a variety of factors, including environmental pollutants and irritants, strong scents, meals, weather, exercise, sinusitis and respiratory infections, stress, drugs, and strong emotions [30]. According to this study, patients adjust their lifestyles, either permanently or temporarily, to stay in control when triggers are present. This literature review aimed to collect empirical data on trigger management to support evidence-based practice and patients' perceptions of high trigger burden and lifestyle modifications made to avoid such triggers in their daily lives, given the focus on trigger education and avoidance as a way to optimize asthma control for asthma patients.

scientific investigation on the best approaches to handling triggers through education, medication therapy, information, or any combination of these. The adult and pediatric asthma trigger literatures are distinct from one another, according to early searches of the literature, and more conclusive empirical research about pediatric asthma trigger therapy has been published. The evidence regarding adult asthma patients' avoidance of triggers is the main topic of this review. The literature review's particular goals were to [19] examine policies and instructional materials in order to give the most recent ideas on trigger definitions and the best practices on current approaches to clinical trigger management; [20] collect data on global asthma trigger types and increase awareness of typical triggers patients face in their daily lives; and [21] compile empirical data from the scientific and medical literature to support guidelines on suggested trigger management practices. With the aim of enhancing trigger management in clinical practice and pinpointing opportunities for future research, these study objectives were designed to better understand the function of triggers in asthma control.

Bronchial Blood Circulation:

The right and left bronchial arteries' branches supply the bronchial walls and minor air channels, whereas the bronchial veins primarily carry the venous return. They empty into the superior intercostal vein on the left and the azygos vein on the right. The lung is the body's most frequently used organ since it receives all of the cardiac output. But the pulmonary circulation only supplies the alveolar area and respiratory bronchioles. The systemic circulation supplies larger airways (trachea to terminal bronchioles), which receive about 1% of the cardiac output. The bronchial circulation's function

It is uncertain how aerosolized medications are distributed to parts of the lung that are not ventilated or far from the original location of deposition. Through the bronchial veins and right atrium, the endobronchial circulation is recirculated to the lung parenchyma and peripheral airways. In conditions like bronchiectasis, bronchial blood flow is increased from 1% to 30% of cardiac output. In sheep, bronchoconstriction caused by histamine and antigen resulted in an increase in bronchial blood flow. It is theoretically possible for inhaled medications that enter the bloodstream through the tracheobronchial areas to be re-distributed peripherally and downstream of airway blockages. lung regions that are difficult to reach that could improve the medication's effectiveness. As of

now, The significance of bronchial circulation in the lung distribution of inhaled drugs and its impact on their efficacy have not been studied experimentally in people. [7]

Pathophysiology

T-helper cell type-2 (Th2) resistive responses, which are typical of other atopic illnesses, are linked to asthma. A variety of non-allergic (diseases, tobacco smoke, cold discussions, exercise) and adversely susceptible (clean bugs, cockroach accumulation, furred critters, molds, dust) triggers set off a chain reaction of immune-mediated events that eventually aggravate the aircraft route. Increased Th2 cell counts along aircraft routes release specific cytokines, such as interleukin (IL)-4, IL-5, IL-9, and IL-13, which exacerbate eosinophilic inflammation and stimulate the production of immunoglobulin (IgE) by pole cells. Consequently, IgE production sets off the release of

fiery mediators that result in bronchospasm (contraction of the smooth muscle in the airways), edema (swelling), and increased mucous secretion (mucous hypersecretion), which are the hallmark symptoms of asthma. Examples of these mediators are histamine and cysteinyl leukotrienes. The early phase of an immunological response to an instigating allergen releases mediators and cytokines, which set off a subsequent inflammatory reaction known as the late-phase asthmatic response. This response results in increased airway inflammation and bronchial hyperreactivity. There is evidence to show that asthma may have a hereditary predisposition to develop. Numerous chromosomal areas have been linked to the development of airway hyperresponsiveness, the generation of IgE antibodies, and the susceptibility to asthma. mediators of inflammation. To identify the precise genes linked to asthma and the gene-environment interactions that can result in the disease's manifestation, more research is necessary. [31–32]

Clinical Presentation

The history, clinical characteristics, and objective proof of reversible airway obstruction are used to make the diagnosis of asthma [33]. Breathlessness, coughing, wheezing, chest tightness, and deteriorating exercise tolerance are all common symptoms of asthma exacerbations, but none of these are sensitive or specific enough to be diagnosed (Table 3) [34]. Episodes of aggravation caused by infection, environmental irritants, cold air, exercise, or other allergens disrupt the periods without symptoms. Patients frequently experience tightness or weight in their chests during severe exacerbations. The sensitivity and specificity for each type of asthma symptom are listed in Table 1. The sensitivity and specificity of the diagnosis are only increased to 60% and 66%, respectively, when the various symptoms are used in combination [35]. Consequently, having a thorough history is essential for

the assessment and diagnosis of asthma. Table 2 lists the signs. Symptoms that suggest alternative diagnoses other than asthma. Evidence of airflow limitation can be measured by a decline in peak expiratory flow rate (PEFR) or forced expiratory volume in the first second (FEV1), and often an increase in symptoms [36, 37]. Exacerbations, just like symptoms, are caused by a variety of triggers depending on the endotype of the asthmatic (i.e., classic eosinophilic or Type 2 vs. non-eosinophilic or Type 1). Triggers and risks for severe exacerbation of asthma are innumerable, of which viral upper respiratory infections have been reported to be the most common (rhinovirus, coronavirus, and influenza) [38]. Allergen exposures, including dust mites, pollen, and animal dander, are well-known environmental factors that can precipitate asthma [40, 34, 38, 39]. Specific populations are at risk for more profound exacerbations and should be within the first-contact healthcare providers' radar. Pregnancy, a lower socioeconomic level, and people of African or Puerto Rican heritage not only have greater rates of exacerbations, but they also wait to be hospitalized until their symptoms worsen [38, 41]. A higher prevalence of hospitalizations and asthma exacerbations has been linked to residential location and

air quality, particularly in children [42, 43]. As a result, demographic analysis may be useful in predicting asthma control and the need for hospitalizations due to severe exacerbations in the future. Co- Along with the asthma exacerbation, other morbid conditions such as obesity, mental illness, smoking, rhinosinusitis, environmental or food allergies, LPR, and GERD should also be appropriately handled [38, 41]. In addition to complicating the diagnosis of asthma, many of the potential diagnoses shown in Table 4 can exacerbate episodes of the condition. As a result, an asthma exacerbation should be assessed for a hospitalized patient who has been diagnosed with something else.

Table3: Sensitivity and specificity of common symptoms during asthma exacerbations.

Symptom	**Sensitivity**	**Specificity**
Cough	16-66%	26-64%
Wheezing	9-76%	34-87%
Dyspnea in adults	11-73%	33-71%

Table 4: Differential diagnoses for asthma exacerbation

Symptoms	**Diagnosis**
A prominent cough without changes in lung function	Chronic cough syndrome, Paroxysmal vocal cord dysfunction, angiotensin converting enzyme inhibitors or angiotensin receptor blocker intake.
Dizziness/light-headedness/peripheral tingling	Hyperventilation syndrome (dysfunctional breathing disorder)
Prominent nasal symptoms without changes in lung function	Rhinitis
Postural and/or food-related symptoms	Gastro-esophageal reflux disease Laryngopharyngeal reflux
Orthopnea*/paroxysmal nocturnal dyspnea*/ edema/known cardiac disease	Decompensated heart failure, obstructive sleep apnea*
Fine crackles on auscultation	Pulmonary fibrosis
Smoking >30 pk/yrs, symptom onset >35 years of age	Chronic obstructive pulmonary disease
Chronic productive cough without wheezing or breathlessness	Bronchiectasis, inhaled foreign body, obliterative bronchiolitis
New onset weight loss or systemic symptoms /hemoptysis	Lung cancer or sarcoidosis

Diagnosis:

A comprehensive medical history, physical examination, and objective measurements of lung function—spirometry is preferred—are necessary for the diagnosis of asthma (see Table 1). The diagnosis of asthma may also benefit from bronchoprovocation challenge testing and monitoring for indicators of airway inflammation, especially in cases where objective lung function tests are normal but symptoms of the condition are present. [44, 45, 46]

Diagnosing Asthma

The following are typical indications and symptoms: wheezing, coughing

• Chest tightness; breathing difficulties; deterioration of symptoms at night; deterioration of symptoms in cold air; problems during exercise; and symptoms following allergen exposure
Additionally, it's a good idea to be aware of any medical issues that may interfere with managing asthma, like

Medical history:

Patients who have shortness of breath, chest tightness, coughing fits, or wheezing frequently may have asthma. Asthma is strongly suggested by symptoms that are unpredictable, worsen at night, arise after exposure to allergens or irritants, and respond to proper asthma therapy [44, 46]. Excluding chronic obstructive pulmonary disease (COPD), bronchitis, chronic sinusitis, gastroesophageal reflux disease, recurrent respiratory infections, and heart disease are among the alternative explanations for suspected asthma symptoms. A personal history of atopic disorders or a positive family history of asthma or other atopic diseases

in particular allergic rhinitis, can be useful in diagnosing asthmatic patients. Examining potential asthma triggers, such as dust mites, cockroaches, animal dander, molds, pollens, exercise, and exposure to cold air or tobacco smoke, is equally crucial during the history-taking process. Inhaling chemicals from the workplace might potentially trigger asthma attacks. Details of work exposures and improvements in asthma symptoms over the holidays should be investigated if a link between job-related asthma and asthma is suggested. Examining for concomitant conditions such as allergic rhinitis, sinusitis, obstructive sleep apnea, and gastroesophageal reflux syndrome is especially crucial because these conditions can exacerbate asthma symptoms [46]. When When asthma is diagnosed in young children, it is often more challenging because spirometry is often unreliable in kids under the age of six, and episodic wheezing and coughing are common in this patient population. In young children, a trial of short-acting bronchodilators and inhaled corticosteroids (ICSs) is a helpful way to confirm the diagnosis. Asthma diagnosis is supported by significant clinical improvement during treatment and worsening after therapy discontinuation [44, 47, 48].

Physical Examination

Patients with suspected asthma often have unremarkable physical examinations because asthma symptoms can vary widely. Usually, physical findings are only noticeable when the patient exhibits symptoms. Therefore, a diagnosis of asthma cannot be ruled out in the absence of physical signs. Wheezing during auscultation is the most frequent abnormal physical finding that indicates the existence of airflow limitation [44]. In addition, doctors must check the skin and upper respiratory tract for indications of coexisting atopic disorders such as dermatitis or allergic rhinitis [46].

Objective measurements of lung function

The ideal objective measure for determining the presence of reversible airway obstruction—that is, a quick improvement in lung function following the inhalation of a rapid-acting bronchodilator—and validating an asthma diagnosis is spirometry. All patients who are able to do so and who are older than six should have their lung function tested [44, 46]. Spirometry needs to be done in accordance with the right guidelines. Although primary care offices can also perform it, pulmonary function laboratories are the usual setting. The patient is directed to inhale as deeply as possible during spirometry and to expel as forcefully and completely as feasible into the mouthpiece of the

respirometer. Spirometry measures the forced expiratory volume in one second (FEV1) and the forced vital capacity (FVC), which is the greatest amount of air that can be expelled. A measure of airflow restriction is provided by the FEV1 to FVC ratio. When an inhaled rapid-acting bronchodilator is administered and the FEV1 improves by at least 12% and 200 mL within 15–20 minutes, or when an anti-inflammatory medication is administered and the FEV1 improves by at least 20% and 200 mL within two weeks, the diagnosis of asthma is confirmed. Generally speaking

Since the FEV1/FVC ratio in the general population is typically greater than 0.80 (and probably greater than 0.90 in children), any results below these indicate airflow limitation and therefore lend credence to the diagnosis of asthma. Patients with asthma may not always display reversible airway obstruction during visits due to the diversity of asthma symptoms. Spirometry should therefore be repeated in order to increase sensitivity, especially in cases where patients are symptomatic [45, 46]. When spirometry is not available, peak expiratory flow (PEF) monitoring is a suitable substitute that can also be helpful. for identifying occupational asthma and/or tracking the effectiveness of asthma medications. PEF is typically measured twice a day, in the morning and at night. Asthma is indicated by a diurnal fluctuation in PEF of greater than 20%, an improvement of at least 60 L/min, or a minimum of 20% following inhalation of a rapid-acting bronchodilator [46]. PEF is less accurate than spirometry, despite being easier to use. As a result, as was already noted, spirometry is the recommended way to record airflow restriction and validate the asthma diagnosis.

Allergy skin testing

Additionally, allergy skin testing is advised to ascertain the patient's allergy status and pinpoint potential asthma triggers. Usually, the allergens pertinent to the patient's location are used for testing. While there have been suggestions to replace skin testing with allergen-specific IgE tests, which assess a patient's specific IgE levels against specific allergens in vitro, these tests are less sensitive and cost more money [44, 45].

Treatment

In order to prevent exacerbations—a sudden, abrupt worsening of asthma symptoms that frequently necessitate immediate medical attention and/or the use of oral steroid therapy—and lower the risk of morbidity and mortality, the main objective of asthma management is to attain and maintain control of the disease. Using Table 2's criteria, the level of asthma control should be evaluated at every visit, and treatment should be customized to bring the condition under control. Most asthma patients can be brought under control with a combination of pharmaceutical therapies and avoidance techniques. Pharmacologic treatments that are frequently used to treat asthma can be divided into two categories: controllers, which are long-term, daily medications that primarily reduce inflammation, and relievers, which are short-term, daily medications that essential foundation for prompt symptom and bronchoconstriction alleviation). ICSs, leukotriene receptor antagonists (LTRAs), long-acting beta2-agonists (LABAs) taken in conjunction with an ICS, and anti-IgE treatment are examples of controller drugs. Long-acting beta2-agonists (LABAs) combined with an ICS, anti-IgE treatment, and rapid-acting inhaled

beta2agonists and inhaled anticholinergics (LTRAs) are examples of drugs used as relievers. Fast-acting inhaled beta2-agonists and inhaled anticholinergics are examples of relief drugs. Most people with allergic asthma may also be candidates for allergen-specific immunotherapy, but doctors who are knowledgeable about treating allergies must recommend it. Acute asthma exacerbations may also need to be managed with systemic corticosteroid therapy.

Table 2 Criteria for Assessing Asthma Control [44,46]

1.	No exacerbations
2.	Fewer than 3 doses per week of a rapid-acting beta2-agonist bronchodilator
3.	Daytime symptoms < 3 days per week
4.	No nighttime symptoms
5.	Normal physical activity

Following asthma management, continuous monitoring is necessary to determine the lowest maintenance doses needed to keep asthma under control. But because asthma is a fluctuating illness, it might be necessary to periodically modify medication in response to a loss of control (as shown by a failure to achieve the control requirements in Table 2) [44]. Encouraging all asthma sufferers to participate actively in their own treatment is also essential. This can

be achieved by teaching patients about the nature of their illness, the function of drugs, the significance of following controller therapy, and the proper use of inhaler devices, as well as by giving them a specific written action plan for disease management [46].

Pulmonary Delivery Devices:

For thousands of years, the lung has been used as a medication administration route. The history of inhaled treatments dates back 4,000 years to India, where the Atropa belladonna plant's leaves were smoked to treat cough suppression. To relieve the symptoms of their ailment, asthmatics smoked cigarettes infused with stramonium powder and tobacco in the late 19th and early 20th centuries. The advancement of two types of tiny portable devices, the metered-dose inhaler (MDI) and the dry powder inhaler (DPI), as well as the improvement of the nebulizer, can be classified into three distinct groups in the development of modern inhalation devices. Each system's benefits and drawbacks are covered in detail below and summed up. More thorough evaluations of breathing technologies

Nebulizers:

For many years, people with asthma and other respiratory conditions have been treated with nebulizers. Nebulizers come in two primary varieties: jet and ultrasonic. By allowing compressed gas (air or oxygen) to pass through a small opening and creating an area of low pressure at the liquid feed tube's exit, the jet nebulizer operates according to the Bernoulli principle. As a result, the medication solution is forced into the gas stream from the fluid reservoir and breaks up into droplets. The ultrasonic nebulizer creates a liquid fountain in the nebulizer chamber by vibrating a piezoelectric crystal at a high frequency (about 1-3 MHz); the greater the

frequency, the smaller the droplets that are created. Most medication solutions can be aerosolized using constant-output jet nebulizers, which also offer

Nebulizers can be time-consuming, but they are also ineffective, wasting a lot of medication (nebulizers that run continually lose 50% of their contents). Although these disposable nebulizers are cheap, the oxygen or air supplied by the compressors is not. With nebulization, the majority of recommended drugs never make it to the lungs. An inhaler's medication is directly inhaled into the airways. As a result, a far smaller dosage is required than when the medication is taken orally as a tablet or liquid. Inhalation is a convenient, quick, and patient-friendly method of administering medications that have a systemic effect or that are intended to act locally on the lungs.

Fig.5 Nebulizers inhalers

Metered-dose inhalers: The most popular aerosol delivery device on the market today, the MDI, was a ground-breaking technology that solved the drawbacks of the hand-bulb nebulizer and was the first portable outpatient inhalation device. Through a nozzle, the MDI releases a drug aerosol at a high velocity (> 30 m/s), propelled by propellants such as hydrofluoroalkanes (HFAs) and, more recently, chlorofluorocarbons (CFC). Only a small portion of the medication dose is delivered to the lung by MDIs. Usually, the lung absorbs only 10–20% of the dosage that is released.

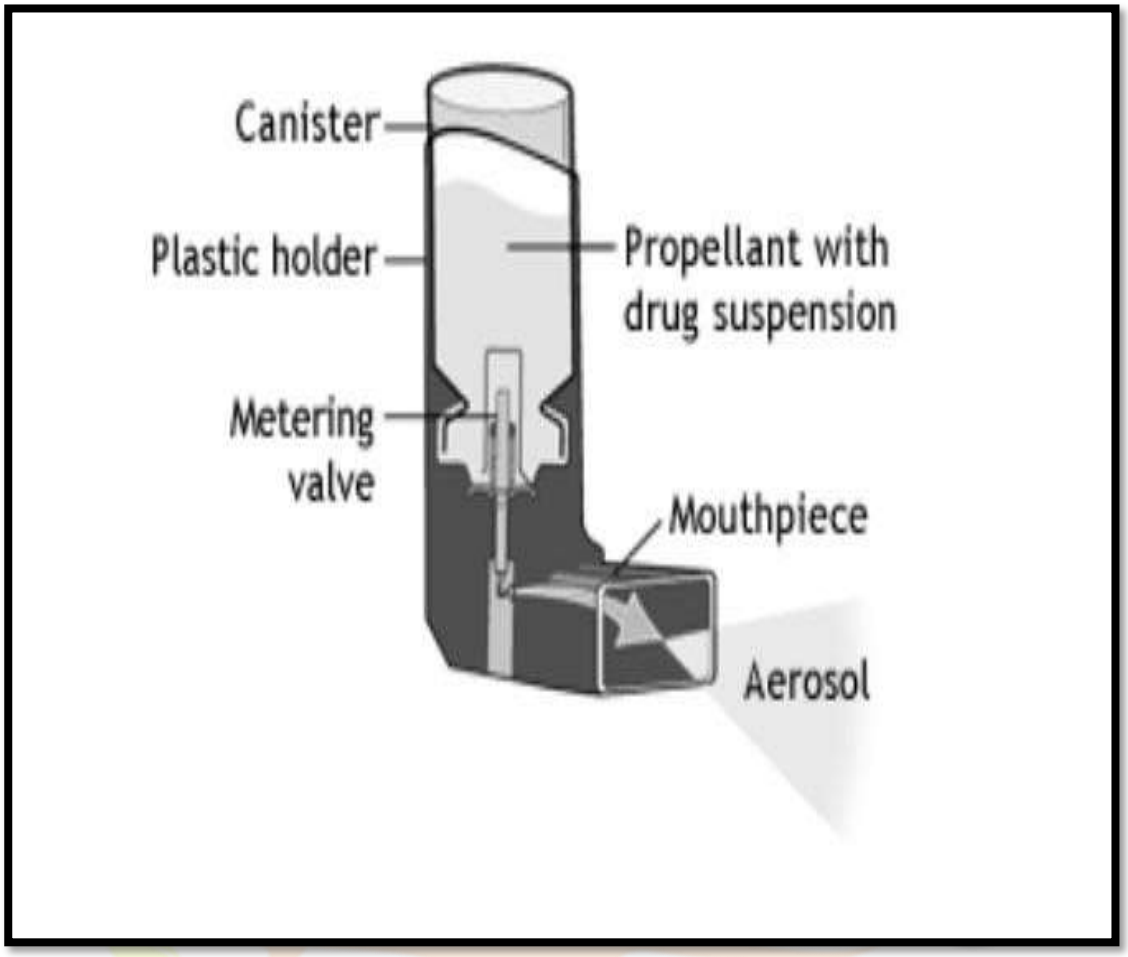

Fig 6 Metered-dose inhalers

Pressurized metered-dose inhalers: It is challenging for doctors to prescribe the same kind of device for a variety of inhaled medications because the pMDI is not accessible for all substances or dosages. The practice of many pharmaceutical companies not to release newer inhalation medications as part of the pMDI program exacerbates this. The CFC propellant PMDI design necessitates both initial and ongoing priming. A significantly lower dose than recommended is administered when the device is not primed. Regrettably, frequent priming often results in drug waste entering the atmosphere.

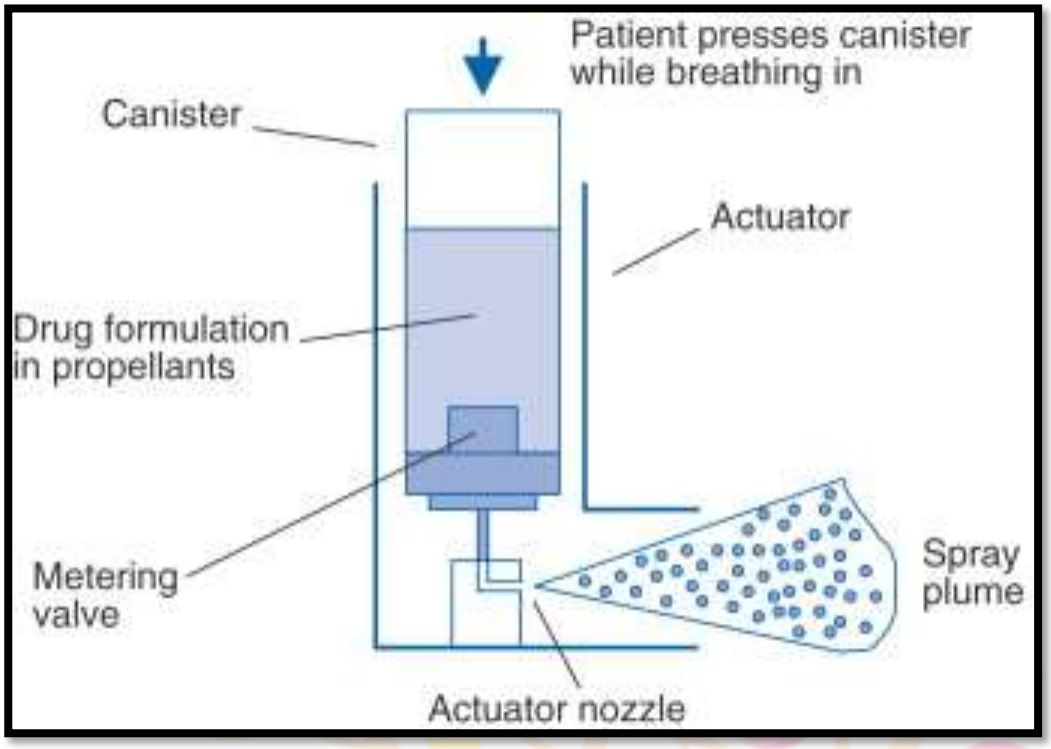

Fig 7 Pressurized metered-dose inhalers

Dry powder inhalers: In recent years, there has been an increased interest in drug delivery to the lung by DPIs due to their effectiveness, efficiency, and environmental friendliness. One of the main challenges in creating solid-state aerosols, or DPIs, is controlling the permanent and transient pressures present in powder beds. In fact, controlling these particulate forces—for instance, through particle engineering methods—is currently thought to be essential to the development and manufacturing of effective DPI. [48]

Fig 8 Dry powder inhaler

Result & Discussion:

Using Pulmonary Medication to Treat Asthma: A Conversation Without a doubt, pulmonary medication administration revolutionizes the treatment of asthma. Let's explore more and talk about its benefits, drawbacks, and fascinating developments. Straight Hit Drugs directly target the irritated respiratory tract, resulting in quicker relief from wheezing and dyspnea. Reduced Adverse Effects: Because inhaled pharmaceuticals avoid the digestive system, they have a lower risk of side effects than oral prescriptions.

bloodstream to a significant degree. Convenience Champions: Because inhalers and nebulizers are lightweight and easy to use, discreet and practical symptom treatment is possible even on the go. Findings We Observe: Breathable Relief: By lowering inflammation and widening airways, inhaled drugs facilitate better lung function and make breathing easier. Symptom SOS: When used consistently, asthma symptoms are greatly reduced, enabling patients to lead more active lives without being concerned about having an asthma attack.

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