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A NOVEL APPROACHAND ADVANCEMENT IN RESPIRATORY DRUG DELIVERY SYSTEM

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ABSTRACT: The respiratory drug delivery system (RDDS), which delivers drugs straight to the lungs for quicker effect and better bioavailability, is essential for treating respiratory disorders. It works particularly well for treating lung infections, COPD, and asthma. Metered-dose inhalers (MDIs), dry powder inhalers (DPIs), nebulizers, and sophisticated aerosol formulations are examples of technology that are part of RDDS and maximize medication delivery to the lungs. Particle size, the drug's physicochemical characteristics, and patterns of deposition within the respiratory system are some of the variables that affect how effective RDDS is. For example, smaller particles enhance therapeutic benefits by reaching deeper parts of the lungs. To ensure effective medication deposition while reducing adverse effects, the delivery system's composition and design are essential. New developments in formulation science, nanotechnology, and inhaler design have propelled recent advances in RDDS. By improving treatment's portability, accuracy, and convenience, these advancements are increasing patient adherence. Modern inhalers, for instance, provide improved particle accuracy and dosage control, increasing the treatment's total efficacy. With its potential to revolutionize the treatment of respiratory disorders, RDDS is becoming more and more important in contemporary pharmacology. It is anticipated that RDDS will become increasingly more important in boosting patient care, improving treatment results, and transforming the management of respiratory diseases as long as technology developments continue.

INTRODUCTION: The respiratory system is an essential network of organs and tissues that facilitates gas exchange, enabling the body to release carbon dioxide and absorb oxygen into the blood. Air is first filtered, warmed, and moistened in the nose and mouth before passing via the pharynx and larynx and into the trachea. The two main bronchi that emerge from the trachea then split into smaller bronchioles inside the lungs. The exchange of carbon dioxide and oxygen takes place in tiny air sacs called alveoli at the end of the bronchioles.

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Breathing is made easier by the diaphragm and intercostal muscles, which contract and expand the chest cavity. Because it supports the body's need for oxygen and the elimination of metabolic waste gases, efficient respiration is essential for cellular metabolism and general health. The respiratory system is essential for preserving homeostasis because it controls blood pH and makes sure there is enough oxygen in the blood for cellular processes.

The upper respiratory tract, which includes the pharynx and nasal cavity, filters and humidifies the air that is inhaled. The voice box, also known as the larynx, serves as a conduit to the lower respiratory tract and contains the vocal cords. The trachea is a strong tube that branches into the left and right bronchi before entering the lungs. It is held up by cartilage rings. The bronchi further divide into

smaller bronchioles inside the lungs, leading to the alveoli, which are microscopic, balloon-like structures that allow oxygen to diffuse into. Treatment for respiratory diseases like asthma and COPD can be improved by directly administering drugs to the lungs through a pulmonary drug delivery system. Through the use of nebulizers or inhalers, medications are dispersed into tiny particles that can be inhaled and enter the alveoli and bronchi. Compared to oral drugs, these systems offer quicker, more localized drug action and less systemic side effects because they target the lungs specifically. Metered-dose inhalers (MDIs), dry powder inhalers (DPIs), and nebulizers are important medical equipment. Precise dosages are delivered straight to the site of action through efficient pulmonary drug delivery, which improves patient compliance and therapeutic effectiveness.

Respiratory System: The respiratory system is a biological system that connect the external environment to the internal environment or we can say that there is a network of organ and tissues that helps to exchange the gases i.e. inhalation of oxygen and exhalation of carbon dioxide **Fig. 1** [1]. Because the respiratory system is by necessity directly connected to the environment and therefore potentially vulnerable to pathological contaminants, the airway between the lungs and the environment is uniquely adapted to prevent airborne infections. The airway between the nose and the lungs is called the conduction zone or dead air space. This route contains special cells that secrete mucous membranes and collectively eliminate most air pollutants before reaching the lungs. This respiratory route is damp, warms the air and distributes oxygen in the blood better [2].

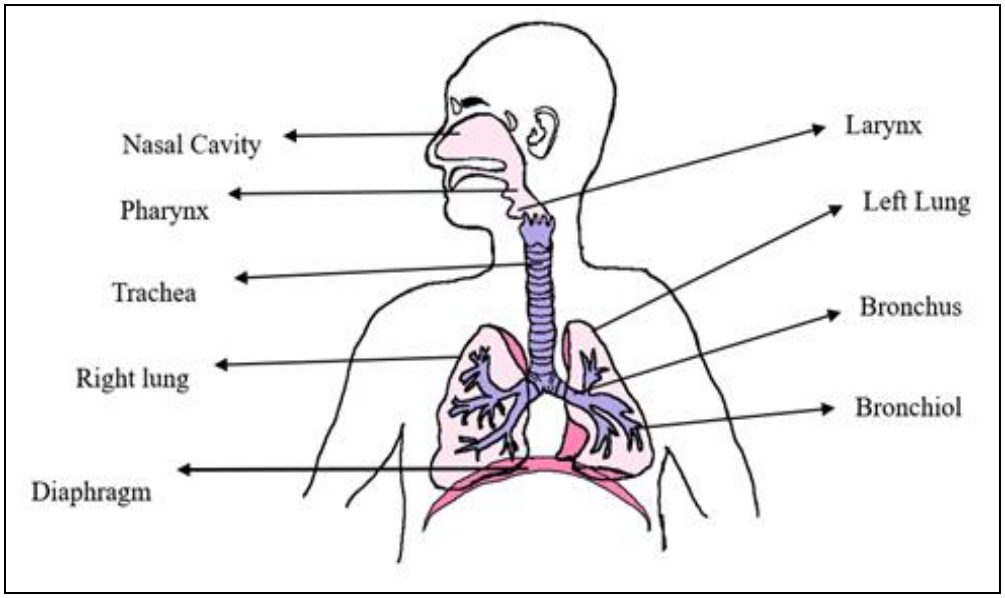

FIG. 1: HUMAN RESPIRATORY SYSTEM

The Steps Involved in Respiration:

1. **Pulmonary Ventilation:** it is normally said as breathing its mainly function is to exchange the air from the atmosphere to the alveoli of the lungs or simply inhalation and exhalation of oxygen and carbon dioxide respectively
2. **Externa Respiration:** in this the exchange of gases between the alveoli of the lungs and the blood vessels can takes place
3. **Internal Respiration:** in this the gaseous exchange can take place in blood vessel and the tissue cells

Functions of Respiratory System:

1. **Provides the Gas Exchange:** supply of oxygen from atmosphere to the body cells and removal of carbon dioxide from body cells to the atmosphere
2. Helps to regulate blood pH level in the body
3. Contains receptors for sense of smell, filter inspired air, produces vocal sounds (phonation) and excretes same amount of water and heat
4. Helps to regulate the body temperature

5. **Endocrine Functions:** release ACE [3].

Normal Respiratory Rate at Different Age:

1. **New Born:** 30-60 per min
2. **Early Childhood:** 20-40 per min
3. **Late Childhood:** 15-25 per min
4. **Adult:** 12-16 per min.[4]

Phases of Respiration:

1. **Inspiration:** Phase when the air enters the lungs from atmosphere.
2. **Expiration:** phase when the air moves outwards or leaves the lungs.

Note: during normal breathing inspiration is an active process and expiration is a passive process [1].

Components of the Respiratory System: Structurally the respiratory system consists of two parts:

1. Upper respiratory tract
2. Lower respiratory tract **Fig. 2.**

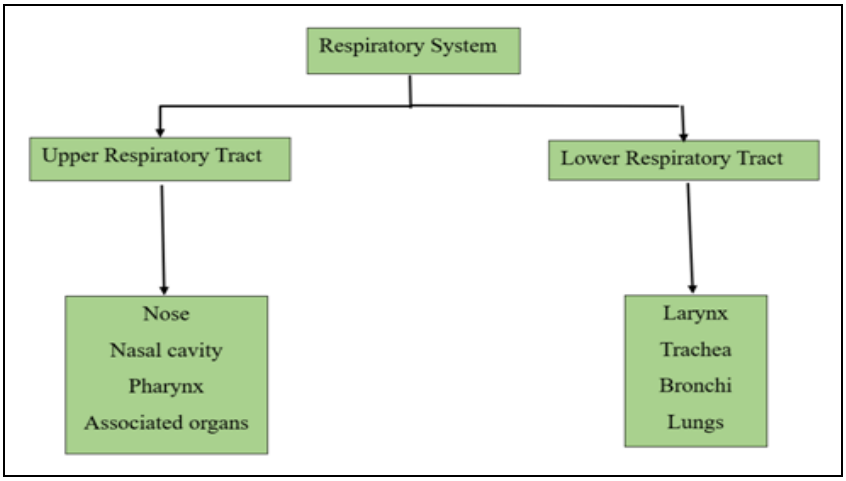

FIG. 2: FLOW CHART SHOWING OF THE RESPIRATORY SYSTEM ON THE BASIS OF STRUCTURAL

The respiratory system is divided into two functional components:

1. Conducting zone
2. Respiratory zone **Fig. 3.**

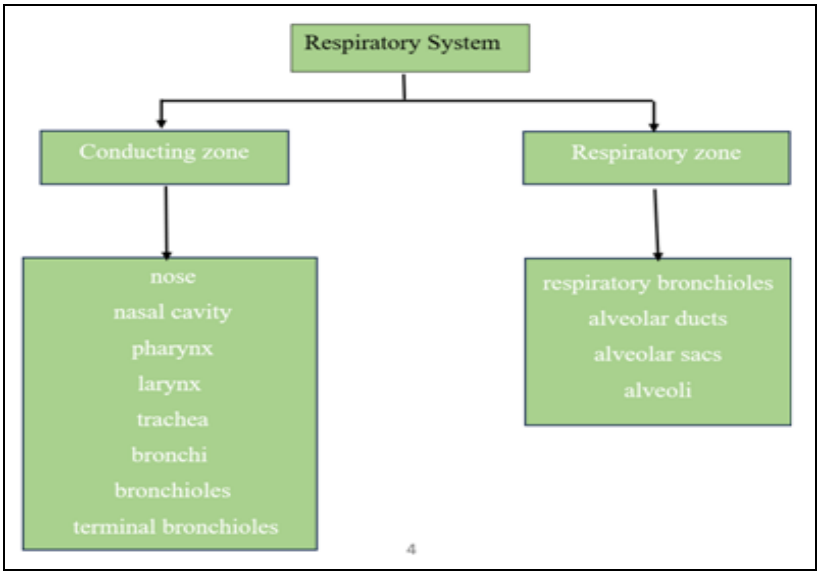

FIG. 3: FLOW CHART SHOWING OF THE RESPIRATORY SYSTEM ON THE BASIS OF FUNCTION

The branch of medicine that deals with the diagnosis and treatment of ear, nose, and throat (ENT) diseases is called otorhinolaryngology [1].

The Upper Respiratory Tract:

Nose and Nasal Cavity: The nose is a special organ at the entrance of the respiratory system with visible external parts (outer nose). Inside of the skull called the nasal cavity (inner nose). The external nose is the part of the nose visible on the face and consists of a supporting frame of bone and hyaline cartilage, covered by muscle and skin and lined with mucosa. The frontal bone, nasal bones and upper jaw form the bony framework external nose [5].

Cartilaginous structures are the respiratory structures of the head and neck. The outdoor nose is composed of several parts of the connected ghost cartilage A specific bone of the skull using a Fiber -like connection.

The internal structures of the external nose have three functions:

1. To warm, humidify, and filter the incoming air
2. Tto detect olfactory stimuli
3. To alter sound vibrations as they pass through a large, hollow resonating chamber. The nasal cavity (internal nose) is a large cavity at the front of the skull, located below the nasal bones and above the oral cavity. It is lined with muscles and mucous membranes [6].

Pharynx: The pharynx is a conductive structure located in the midline of the neck [7]. The pharynx is divided into three sections, arranged from superior to inferior: the oral pharynx, which is behind the oral cavity opening, the laryngeal pharynx, which is behind the laryngeal inlet (opening), and the nasal pharynx, which is behind the posterior nasal apertures (choanae). First off, air travels through the nasal pharynx from the nasal cavities, which is the only way it is connected to the respiratory tract. Additionally, on the lateral surface of the back of the nasopharynx, there are two openings, one on each side, known as the auditory tubes (also known as the pharyngotympanic or Eustachian tubes), which are encircled by mucous membrane elevations known as tubal elevations. These tubes, which attach posteriorly to the tympanic cavities of the middle ears, are primarily used to balance pressure and make it easier for the secretions of the middle ears to drain. Second, the oral pharynx passes the bolus to the laryngeal pharynx below. It is an extension of the oral cavity [8].

The soft palate muscles tighten as the bolus exits the mouth cavity, sealing the choanae and preventing food from entering the nasal cavity. In order to stop food from entering the airways, the epiglottis, a single cartilage at the top of the larynx, is simultaneously pushed interiorly to close the laryngeal inlet. Finally, the bolus is passed from the oral pharynx to the laryngeal pharynx, where it is processed by the oesophagus. Air enters the larynx through the nasal and oral cavities in the upper pharynx [9].

Division of Pharynx:

1. **Nasopharynx:** The nasopharynx reaches the soft palate from the base of the skull.
2. **Oropharynx:** It extends from the soft palate to the upper margin of the epiglottis.
3. **Laryngopharynx:** The laryngopharynx, which extends below the hyoid bone to the oesophagus, is the lower portion of the pharynx, situated below the larynx (voice box). It acts as a conduit for food and air, sending food down the oesophagus and air to the larynx [10].

The Lower Respiratory Tract:

Larynx: The respiratory tract's cartilaginous larynx is situated in the anterior aspect of the neck. In humans and other vertebrates, the larynx's main job is to keep the lower respiratory tract safe from food particles that might enter the trachea during breathing. Along with housing the vocal cords, it serves as a voice box for making sounds, i.e. phonetics.

The laryngeal skeleton has nine cartilages:

1. Thyroid cartilage
2. Cricoid cartilage
3. Epiglottis

4. Arytenoid cartilage
5. Corniculate cartilage
6. Cuneiform cartilage.

The first three are unpaired cartilages, and the latter three are paired cartilages [11].

Trachea: The trachea is a U-shaped structure with smooth muscle, the tracheal is, forming the posterior border, and anterior and lateral walls made of hyaline cartilage [12]. Beginning with the mucosa and ending with the submucosa, the tracheal wall's layers are composed of areolar connective tissue, followed by hyaline cartilage and adventitia [1].

Bronchi: The bronchi trachea, also referred to as the "windpipe," is where the bronchus originate. The tracheobronchial tree of the lungs is made up of these two structures together **Fig. 4.**

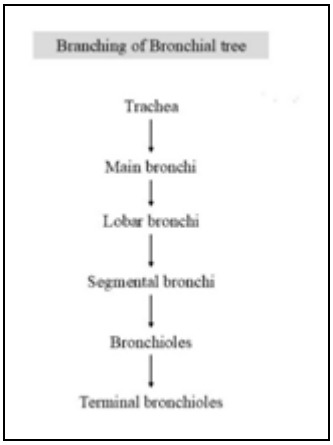

FIG. 4: THE SYSTEMATIC FLOW CHART OF BRANCHING OF BRONCHIAL TREE

Lungs: Exchange of carbon dioxide and oxygen between inhaled air and blood cells occurs in the lung, the organ of outward breathing. The aviation pathways are designed in a way that expedites their evacuation while effectively blocking the entry of foreign airborne particles, including bacteria [13].

Within the thoracic cavity are two conical-shaped organs called the lungs. They are separated from each other by the heart and other structures of the mediastinum, which divides the thoracic cavity into two anatomically distinct chambers [14]. The superficial layer, called the parietal pleura, lines the wall of the thoracic cavity; the deep layer, the visceral pleura, covers the lungs themselves.

The pleural cavity, which lies between the visceral and parietal pleurae, is a tiny area where a tiny quantity of lubricating fluid secreted by the membranes is found. During breathing, the membranes can more easily glide over one another because of the pleural fluid, which lowers friction between them [15].

The lungs rest against the ribs on both the anterior and posterior surfaces, extending from the diaphragm to a point just superior to the clavicles. The base, which is the broad inferior part of the lung, fits over the diaphragm's convex area and is concave.

The apex of the lung is the narrow superior portion. The hilum, a region on the mediastinal (medial) surface of each lung, is the entrance and exit point for bronchi, pulmonary blood vessels, lymphatic vessels, and nerves [16].

These structures form the lung's root and are kept together by the pleura and connective tissue. The apex of the heart rests in the cardiac notch, a concavity located medially in the left lung **Fig. 5.**

The left lung is approximately 10 percent smaller than the right due to the area taken up by the heart. Because the diaphragm is higher on the right side to accommodate the liver, which is located inferior to it, the right lung is somewhat shorter than the left lung despite being thicker and broader overall [17].

The pleural cavity in this location is not entirely filled with the lungs. Thoracentesis, a procedure that involves inserting a needle anteriorly through the seventh intercostal space, can be used to remove excess fluid from the pleural cavity without harming lung tissue. The pleural cavity in this location is not entirely filled with the lungs.

Thoracentesis, a procedure that involves inserting a needle anteriorly through the seventh intercostal space, can be used to remove excess fluid from the pleural cavity without harming lung tissue. The intercostal nerves and blood vessels are protected by passing the needle along the superior border of the lower rib. The diaphragm is at risk of being punctured inferior to the seventh intercostal space [18].

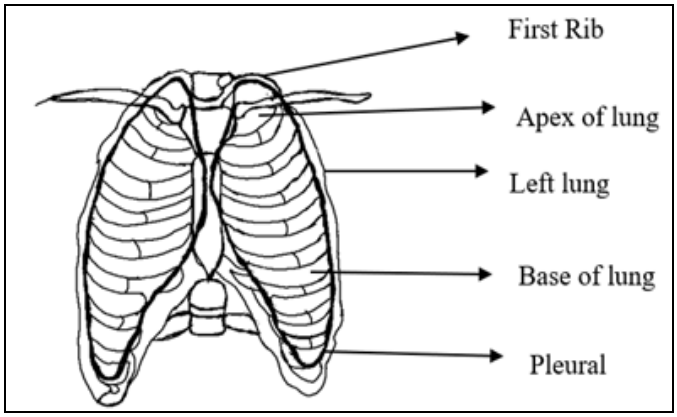

FIG. 5: ANTERIOR VIEW OF LUNGS AND PLEURAE IN THORAX

Alveoli and Alveoli Sac: According to traditional descriptions, alveoli resemble clusters of grapes, with each alveolus existing independently of the others around it. Recent histologic studies, however, have shown that the true structure is considerably more intricate and distinct. There are many connections between alveoli, which leads to a complicated airflow system in the distal airways. Instead of being spherical, alveoli have flat, polygonal shapes, and each one has a common wall with its neighbor. Rather than balloons, they probably resemble foam or froth [19]. The inter-alveolar septum is the wall that two adjacent alveoli share. Alveolar epithelial cells make up a single layer, accompanied by capillary endothelial cells and a diversity of interstitial tissue.

There are Three Distinct Types of Alveolar Epithelial Cells:

1. Type I pneumocytes
2. Type II pneumocytes
3. Alveolar macrophages

Type I Pneumocytes: About 95% of the surface area of alveoli is made up of type I pneumocytes, which offer an ideal region for gas exchange.

Type II Pneumocytes: As will be covered later in the text, type II pneumocytes generate surfactant, an essential chemical that lessens the effects of surface tension. In addition, after lung damage, they serve as stem cells that develop into both kinds of alveolar cells [20].

Alveolar Macrophages: The alveoli are home to mononuclear phagocytes. Blood monocytes are the source of them. The microtubule network in these cells allows the cell membranes to change form during phagocytosis or chemotaxis [21].

Function of Alveoli:

1. Facilitate gas exchange
2. Maintain ion and fluid balance within the alveoli
3. Communicate with type II pneumocytes to secrete surfactant in response to stretch. .
4. Produce and secrete pulmonary surfactant - surfactant is a vital substance that reduces surface tension, preventing alveoli from collapsing.
5. Expression of immunomodulatory proteins that are necessary for host defense
6. Transepithelial movement of water
7. Regeneration of alveolar epithelium after injury [22].

Blood Supply to the Lungs: The pulmonary and bronchial arteries are the two sets of arteries that supply blood to the lungs. The pulmonary trunk, which splits into the left pulmonary artery, which enters the left lung, and the right pulmonary artery, which enters the right lung, carries deoxygenated blood. The lungs receive oxygenated blood through the bronchial arteries, which emerge from the aorta. The muscular walls of the bronchi and bronchioles are primarily perfused by this blood. Although there are connections between the bronchial and pulmonary artery branches, the majority of blood returns to the heart through the pulmonary veins. Certain blood flows into the azygos system's bronchial veins and then returns to the heart through the superior vena cava [23].

Pressure Exchenge in Pulmonary Ventilation:

1. Alveolar pressure and atmospheric pressure are equal when the diaphragm is relaxed, resulting in no airflow. This is known as rest.
2. Both the external intercostals and the diaphragm contract during inhalation. As a result of the expansion of the chest cavity, the alveolar pressure falls below atmospheric

pressure. In reaction to the pressure gradient, air enters the lungs and causes the lung volume to expand. Deep breathing causes the chest to expand even more due to the contraction of the sternocleidomastoid and scalene muscles, which increases the alveolar pressure drop.

3. The external intercostals and the diaphragm both relax during exhalation. The alveolar pressure rises above atmospheric pressure, the chest and lungs recoil, and the chest cavity contracts. In reaction to the pressure gradient, air escapes the lungs, causing the lung volume to drop. The internal intercostals and abdominal muscles tighten during forced exhalations, further contracting the chest cavity and raising alveolar pressure at the same time [24].

Lung Volume and Lung Capacity: There are different amounts of air that enter and exit the lungs during inhalation and expiration.

There are two categories into which the various air amounts can be divided:

1. Lung Volumes
2. Lungs Capacities

Lung Volumes:

1. **Tidal Volume:** A healthy adult breathes 12 times per minute on average, bringing 500 mL of air into and out of the lungs with each breath. The term "tidal volume" (VT) refers to the volume of one breath.
2. **Inspiratory Reserve Volume:** You can breathe in much more than 500 mL by taking a very deep breath. An adult male's inspiratory reserve volume (IRV) is approximately 3100 mL, while an adult female's IRV is approximately 1900 mL.
3. Along with the 500 mL of tidal volume, you should be able to push out a lot more air if you inhale normally and then exhale as forcefully as you can. The additional 1200 milliliters for men and 700 milliliters for women is known as the expiratory reserve volume (ERV) [25].

Lung Capacity:

1. Inspiratory capacity (IC) is the sum of tidal volume and inspir atory reserve volume (500 mL + 3100 mL = 3600 mL in males and 500 mL + 1900 mL = 2400 mL in females).
2. Functional residual capacity (FRC) is the total of the expiratory reserve volume and residual volume (1200 mL + 1200 mL = 2400 mL for men and 1100 mL + 700 mL = 1800 mL for women).
3. Vital capacity (VC) is the sum of inspiratory reserve volume, tidal volume, and expiratory reserve volume (4800 mL in males and 3100 mL in females).
4. Total lung capa city (TLC) is the sum of vital capacity and residual volume (4800 mL + 1200 mL = 6000 mL in males and 3100 mL + 1100 mL = 4200 mL in females) [26] as we see in **Fig. 6.**

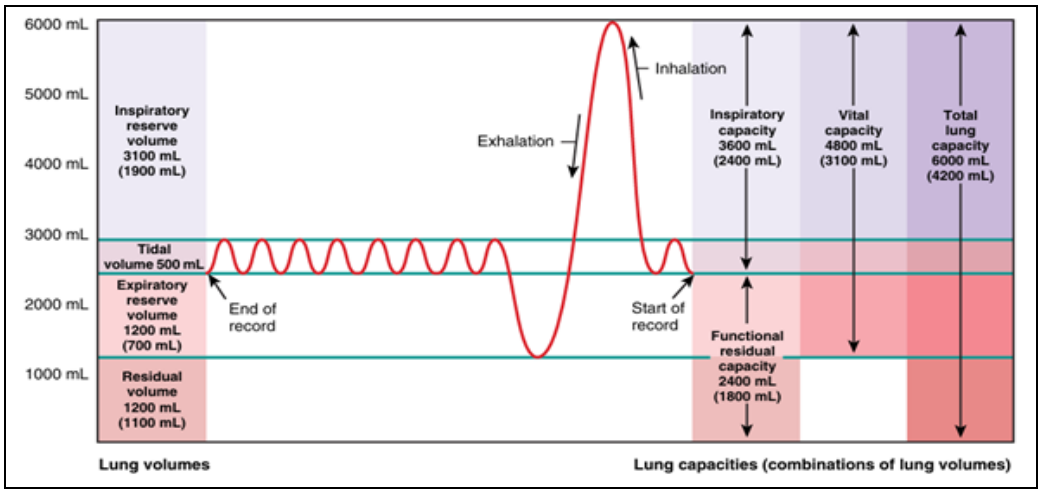

FIG. 6: THE GRAPHICAL REPRESENTATION OF LUNG VOLUME AND CAPACITY

Exchange of Oxygen and Carbon Dioxide: Dalton's law and Henry's law, two gas laws that describe the behavior of gases, control the passive diffusion process that transports oxygen and carbon dioxide from alveolar air to pulmonary blood.

Henry's Law: Clarifies the relationship between a gas's solubility and diffusion.

Dalton's Law: Is crucial for comprehending how gases diffuse down pressure gradients [27].

Diseases Associated with Respiratory System:

Cronic Obstructive Pulmonary Disaeses (COPD): A reduction in the lungs' elasticity causes air trapping and other symptoms, such as difficulty breathing. Chronic and irreversible obstructive respiratory disease, COPD is characterized by this. Because smoking causes alveolar macrophages, endothelial cells, and epithelial cells to die through apoptosis, smoking is the most common cause of COPD. Patients are more vulnerable to lung infections when there is a disruption in the function of alveolar macrophages, which prevents them from phagocytozing bacteria. High quantities of cytokines are also released by alveolar macrophages, which encourage inflammation and draw neutrophils and monocytes, which in turn cause inflammation-related lung damage [28].

Asthma: Another long-term obstructive respiratory condition is asthma, which is treatable as opposed to COPD. Inflammation and airway hyperreactivity are hallmarks of this illness. Since alveolar macrophages control both pro- and anti-inflammatory reactions in the lungs, it's plausible that these cells contribute to asthma [29].

Cystic Fibrosis: An autosomal recessive condition marked by the malfunctioning of the type II pneumocyte and other body areas' cystic fibrosis transmembrane conductance regulator (CFTR). The production of mucus, digestive juices, and sweat is attributed to the CFTR protein. In particular, the CFTR protein's loss of function in the lungs results in thicker rather than thinner mucus lining the alveoli. Furthermore, there is a rise in alveolar macrophage counts, which causes an increase in inflammation. Breathing difficulties, coughing, and pulmonary infections can be brought on by thick mucus and inflammation that clog the airways [30].

Pulmonary Fibrosis: Fibrosis and inflammation of the alveoli are the hallmarks of pulmonary fibrosis, a disease that restricts the respiratory tract. This disease process, which begins with pulmonary injury, can be brought on by immune or allergic reactions, environmental particles, infections, ormechanical damage. Airway inflammation follows the initial insult. The ability to expand alveoli is diminished and fibrosis results from subsequent tissue contraction and repair. Type II pneumocytes undergo hyperplastic transformation, multiply, and undergo haphazard differentiation in an effort to replace damaged alveolar epithelium [31].

Pneumoconioses: Interstitial lung diseases known as pneumoconioses are brought on by the inhalation of both organic and inorganic particles, which alveolar macrophages phagocytize. They then release cytokines into the lungs, which lead to inflammation. Certain illnesses are brought on by this process, including asbestosis, silicosis, and pneumoconiosis in coal miners. It is known as ferruginous bodies within the cytoplasm, which have a dumbbell-like shape, when asbestosis is engulfed by alveolar macrophages [32].

Tuberculosis: When alveolar macrophages phagocytize the bacteria Mycobacterium tuberculosis, tuberculosis (TB) results. *M. tuberculosis* has evolved defense mechanisms to evade eradication after phagocytizing and gathering in alveolar macrophages.

Alveolar macrophages also form multinucleated giant cells, also known as Langerhans giant cells, in an effort to enclose the infection and wall it off. T cells surround them, and a granuloma is formed by the T cells' interaction with the alveolar macrophages *via* TNF-alpha and IFN-gamma. It's crucial to remember that harm to these alveolar macrophages brought on by an additional infection can release *M. tuberculosis* and result in recurrent tuberculosis [30].

Sarcoidosis: Sarcoid is a disorder where patients' lungs develop non-caseating granulomas as a result of alveolar macrophages uniting in an effort to obstruct the infectious process. Sarcoidosis-related hypercalcemia is facilitated by the secretion of vitamin D by alveolar macrophages [32].

Acute Respiratory Distress Syndrome (ARDS): Non-cardiogenic pulmonary edema brought on by an inflammatory illness that compromises ca pillary endothelial integrity. Although the fluid eventually goes away, some patients might still have fibrous tissue [33]. Due to incomplete surfactant secretion by their type II pneumocytes, premature infants experiencing respiratory distress are unable to overcome the collapsing surface tension of their alveoli.

Bronchioloalveolar or Alveolar Carcinoma of the Lung: Approximately 5% of lung cancers are bronchoalveolar or lung alveolar carcinomas. Apart from Clara cells and bronchial mucous cells, type II pneumocytes can also give rise to alveolar carcinoma [34].

Influenza Pneumonia: When the influenza virus infects alveolar epithelial cells directly, it can lead to influenza pneumonia, which damages and inflames alveoli. This pneumocyte defense against influenza virus damage is facilitated by alveolar macrophages [35].

Pneumonia: Inflammation of the lung parenchyma, pneumonia frequently manifests as pleuritis and bronchiole inflammation.

Clinical signs and symptoms include elevated heart rate, altered breathing pattern and depth, coughing, abnormal auscultation breath sounds, and, in the majority of bacterial pneumonias, toxaemia [36, 37].

TABLE 1: THE TABLE SHOWING THE ACTIVE PHARMACEUTICAL INGRETIENT AND DOSAGE FORM TO TREAT THE RESPIRATORY DRUG DELIVERY SYSTEM [38, 39]

ActivePharmaceutical Ingredient	Dosage Form	Diseas Consideration
Aminophylline	Oral Intravenous	Chronic Bronchospasm Acute Severe Bronchospasm
Bambuterol	Oral	Persistant Reversible Airway Obstruction
Beclometasone	Aerosol Inhaler	Asthma prophylaxis
Betamethasone	Oral Intramuscular Parentral	Allergic Inflammatory Disorder
Budesonide	Inhalers	Asthma COPD
Cromoglicic Acid	Oral Nasal Inhaler	Food Allergy Mastocytosis Asthma Prophylaxis
Doxophylline	Oral	Bronchial Asthma COPD
Dextromethorphan	Oral	Non Productive Cough
Ethambutol	Oral	Tuberculosis
Ethionamide	Oral	Tuberculosis
Fluticasone	Inhaler	Asthma Prophylaxis
Formoterol	Inhaler	ProphylaxisExercise Induced Asthma COPD
Isoniazide	Oral Intramuscular Parentral	Pulmonary Tuberculosis Latent TB Infection
Ipratropium Bromide	Inhaler	Asthma COPD
Montelukast	Oral Inhaler	Chronic Asthma Cough and Cold
Phenylephrine	Oral	Allergic Rhinitis Cough Nasal Congestion
Pseudoephedrine	Oral	Nasal Congestion
Pyrazinamide	Oral	Tuberculosis
Rifampicin	Oral Intravenous	Tuberculosis
Salbutamol	Oral Inhaler Intravenous Parentral	Bronchospasm Prophylaxis of Exercise Induced Bronchospasm
Salmeterol	Inhaler	Chronic Asthma COPD
Terbutaline	Oral Inhaler Parentral	Bronchospasm
Theophylline	Oral Intravenous	Bronchospasm
Tiotropium Bromide	Inhaler	Asthma COPD
Sodium Chloride	Nasal	Nasal Congestion
Mometasone	Nasal	Seasonal Allergic Rhinitis Perennial Allergic Rhinitis
Oxymetazoline	Nasal	Nasal Congestion
Azelastine	Nasal	Allergic Rhinitis
Xylometazoline	Nasal	Nasal Congestion

Absorption of Particles in Respiratory Tract: The pulmonary membrane is naturally permeable to a number of therapeutic peptides and proteins as well as small molecule drugs. The lung epithelium acts as a broad barrier to the absorption of drugs inhaled. Its thickness drops to 0–2 μm

in the alveoli from its dense (50–60 μm) state in the trachea [40]. Changes in cell types and shapes are observed when moving distally from the trachea, bronchi, and bronchioles to the alveoli. There is no other bodily entry site where macromolecules are as sensitive as the lungs [41]. By the pulmonary route, a small number of peptides have shown exceptionally high bioavailability, particularly those that have undergone chemical modification to inhibit peptidase enzymes. Small molecules may exhibit prolonged absorption if they are highly cationic [42].

While rapid molecular absorption in the lungs has many therapeutic uses, there are situations in which reducing the rate at which inhaled small molecules absorb energy is required, either to maintain the molecules' local action in the lungs or to control their distribution throughout the body. For hours or even days, very insoluble molecules that gradually dissolve from an inhaled particle may remain in the lungs [43].

Throughout the respiratory tract, the rate and amount of drug absorption vary. Absorption in distinct regions, for instance, affects different areas of each region (roughly 140 m2 of alveolar surfaces compared to 2 m2 of conducting airways) [44]. the cell populations and thickness of the epithelium vary in the alveolar and airway regions. The alveolar surface is coated with a surfactant layer, and the airway epithelium is covered with a mucus gel [45]. Macrophages are primarily responsible for drug clearance from the deep lung, whereas ciliated cells and mucus primarily mediate drug clearance from the trachea and bronchi [46]. Macrophages are essential for deep lung clearance, while ciliated cells and mucus together form an important pathway for drug clearance from the trachea and bronchi [47].

The overall therapeutic efficacy of an aerosol determines how much medication is deposited and diffused inside the lungs. Aerosolized drug delivery to the airways is physically impeded by these processes. Lung anatomy and physiology must be thoroughly understood in order to fully explain the function of each physiological zone regarding ultimate pharmaceutical absorption [48]. There are two types of pneumocytes that line the surface of the alveoli: type II pneumocytes, which are larger cuboidal cells that produce lung surfactant and are more diffuse than type I cells, and type I pneumocytes, which are thin squamous cells that play a significant role in the capillary gas exchange barrier [49].

Approximately 3 percent of the cells in the alveolar region are alveolar (phagocytic) macrophages, which scavenge and move particulate matter to the lymph or mucociliary escalator [50]. Impaction causes larger particles (5–10 μm) to deposit in the larynx and oropharyngeal area. Typically, particles with a diameter between 1 and 5 μm are observed in the tracheobronchial tract. Gravitational sedimentation deposits particles with a diameter of 0–1 μm in the alveoli and narrow conducting airways. When exhaling, particles larger than 0 point1 μm are deposited and expelled, while smaller particles are not deposited [51].

Previously, studies have evaluated regional drug deposition in the airways while concurrently calculating the clinical response in order to explore the science of bronchodilator particle size effects. The target effect or cells are transmitted to inhaled lung regions by means of a system that employs différentes particle sizes [52].

Mechanism of Drug Absorbtion: The lung has many of the same absorption mechanisms as other administration routes that occur in organs. Onaverage, drugs inhaled may be absorbed transcellularly or paracellularly. The paracellular space between lung epithelial cells is where paracellular absorption takes place through the use of close junctions, claudine, and occludine integral proteins [52].

Additionally, studies have revealed that the degree of cell tightness is indicated by the apical to basal trans-epithelial electrical resistance, which decreases from the tracheal area to the distal airways before increasing again in the alveolar region. As a result, the distal bronchioles are most likely to experience paracellular absorption. Numerous hydrophilic medications with comparatively low molecular weights, like insulin (Mol. What?: 5808 Da), which are known to be taken up by the lungs via paracellular transport [44]. Additional techniques exist to enhance drug transport through paracellular pathways.

One such technique involves the reversible administration of compounds like chitosan, which loosen paracellular junctions and permit larger molecules to pass through. A significant component of transcellular transport is the requirement that the drug diffuse into the cells in order for it to be absorbed [52]. Transcellular transport, in which the medication must diffuse into the cells to be absorbed, forms a major part of drug absorption through the lungs [53]. Expression of transporter molecules on the surface of the cell membrane is often necessary for transcellular transmission. Few details are known about lung transporters compared to those related to the intestine, liver, and kidney. Because most other studies on transporter expression were conducted *in-vitro*, it may not be possible to precisely characterize the level of expression or distribution of transporters *in-vivo*. Moreover, the degree to which these transporters influence the absorption kinetics of various medications remains unknown. Two important transporters present in lung cells are the ATP binding cassette transporter and the solute carrier [54].

The solute carrier can move organic cationic or anionic molecules through organic cation transporters and organic anion transporters. Depending on where these receptors are expressed on the basolateral side facing the endothelium of the blood capillaries or on the apical side at the airway lumen they can either improve or obstruct the absorption of the drugs. Because these transporters have such a wide variety of substrates, these receptors are a significant issue to take into account when calculating dosage. Another possible absorption mechanism is vesicular transport, which entails the formation of invasions in the cellular plasma membrane that subsequently split into individual vesicles that engulf the particles inside [55]. Caveolin- or clathrin-mediated vesicular transport is possible, depending on the size of the particles. Larger particles, measuring 150–200 nm, are transported by clathrins, whereas particles smaller than 120 nm are typically transported by caveolin-mediated transport [56].

Pulmonary Drug Delivery System: The delivery of drugs through the lungs is not a novel concept; in the past, it was a commonly recognized method for treating lung and other respiratory ailments. Certain medications that are easily absorbed by alveoli and go straight into the systemic circulation were used in 19th-century inhalation therapy to treat tuberculosis. Large doses can be delivered into the lungs thanks to these sophisticated pulmonary delivery devices [57].

Some medications have been available for sale for the past ten years in formulations that can be used to create drug dispersions for pulmonary delivery to treat a variety of human ailments. In particular, lung-associated large protein molecules that break down in gastrointestinal conditions and are removed by the liver's first pass metabolism can be delivered using a pulmonary drug delivery system, which has many advantages over other methods of administration for the treatment of particular disease states. Large molecules like insulin, interferon-b, or an a1 proteinase inhibitor were first delivered systemically using this cutting-edge technology [58]. Particle size is one of the crucial factors to take into account when creating a pulmonary drug delivery system. For the medication to be targeted to the lungs, the particle size must be at its ideal. They will exhale if the particle size is too small, and they may damage the larynx and oropharynx if it is too large. Carriers such as liposomes, cyclodextrins, microparticles, nanoparticles, etc. can be used to deliver the medication [59].

Advantages of Pulmonary Drug Delivery System:

1. Pulmonary delivery without the use of needles.
2. Given that the rest of the body is not exposed to the drug, the side effects are extremely minimal.
3. The action starts very quickly.
4. Drug degradation by the liver is prevented.
5. It needs a small amount of oral medication.
6. Avert the metabolism of first pass.
7. It is possible to lower the dosage required to have a pharmacological effect.
8. Long- term therapy is vital for asthma and diabetes, and pulmonary drug delivery offers

the highest level of safety by minimizing exposure to the rest of the body.

9. Gastrointestinal distress is prevented through this strategy.

10. The bioavailability of smaller drug molecules is notably increased in this method.

11. Absorption enhancers can be used to boost the bioavailability of larger drug molecules.

12. This method is more patient-friendly in terms of long-term therapy, compared to parenteral medication [58].

Disadvantage of Pulmonary Drug Delivery System:

1. Using the wrong dosage.

2. Drug stability *in-vivo*.

3. Certain medications can cause toxicity and irritation.

4. Producing the ideal particle size is difficult.

5. Certain medications may be difficult to remove from the lungs after they are retained there.

6. Focusing on precision.

7. Challenging to transport.

8. Uneasy to use

9. Mucus layer barrier function may be a physical barrier to drug absorption [59].

Pulmonary Diseases: A few of the lung diseases that have been linked to a wide range of persistent pulmonary conditions such as:

1. Chronic obstructive pulmonary disease (COPD)

2. Cystic fibrosis

3. Extreme progressive pulmonary hypertension

4. Pulmonary tuberculosis

5. Bacterial and fungal pulmonary infections

6. Lung cancer

7. Asthma

8. Idiopathic pulmonary fibrosis (IPF)

9. Multiple interstitial pulmonary diseases [60].

It takes longer to treat diseases because they are chronic and occasionally fatal. No therapy has been found to be completely successful in fully restoring lung functions, and none of them have fully recovered. The most common type of IPF, accounting for 45% of cases, is idiopathic pulmonary fibrosis. Despite sensitivity to common environmental risk factors, the frequency of COPD and IPF increases with age [61]. Asthma, IPF, and COPD are common diseases that affect an estimated 300 million and 210 million people worldwide, respectively.[62]Still, with 10 million new cases of TB worldwide in 2018 and over 3 million deaths from the disease, pulmonary tuberculosis continues to be the world's leading irreversible executioner [63]. Based on the types of clinical agents used, there are several types of conventional medication for chronic lung conditions. Numerous genetic compounds, peptides, antibodies, and chemical medications have been used to treat chronic lung diseases (e.g. g. including shRNA, miRNA, and siRNA) [64].

Drug Delivery to Pulmonary System: Encasing the medication to be supplied in microparticles with a size range of 0.5 to 10 microns ideally between 2 and 5 microns was the technique of drug administration to the pulmonary system. A drug-releasing substance with a pH greater than 6.4 produced these microparticles [65]. Making microparticles that are either stable at pH values below 6 pH or unstable at pH values above 6 pH, or stable at both basic and acidic pH but unstable at pH values between about 6 pH and 8, is a favored variation of the drug delivery mechanism. Many other types of components can also be used, such as proteins, alginate, polymers of mixed poly (hydroxy acids), amino acids (proteinoids), and biodegradable natural and manmade polymers. Only after the microparticles had reached the targeted cells were they altered in a new form to accomplish targeting to particular cell types and release. The pulmonary effects of ultrafine particles in urban air may be more detrimental than those of fine or coarse particles, according to epidemiological data [66]. Research has already assessed medication deposition in the airways

while simultaneously determining clinical response to gain a better understanding of the science underlying bronchodilator particle size effects. To use the various particle sizes to provide the desired impact or cells to the lung regions that are inhaled **Fig. 7** [67].

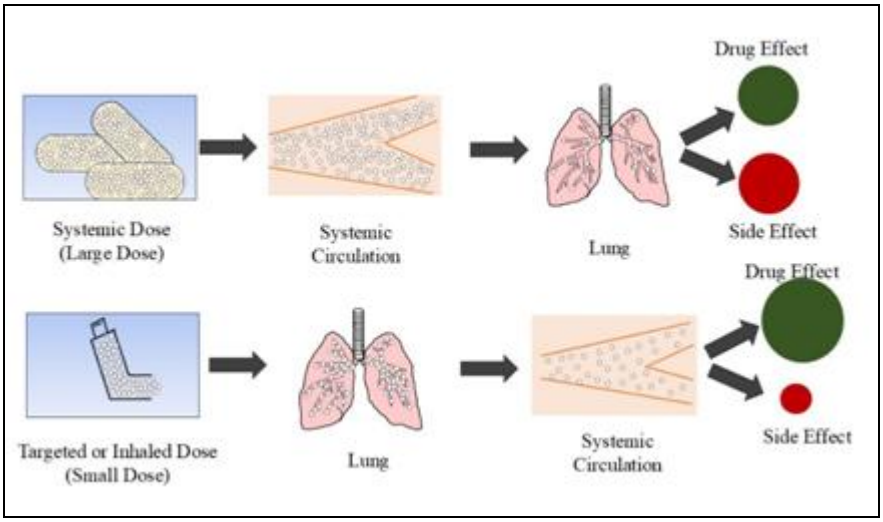

FIG. 7: COMPARISON OF THE CONVENTIONAL DOSAGE FORM FROM THE INHALED DOSAGE FORM

Drug Dellivery Devices:

Meter Dose Inhaler: The most popular delivery method for medicine aerosol delivery is the pressurized metered dose inhaler, also known as a metered dose inhaler. Metered dose inhalers have several benefits, including portability, the ability to formulate a fixed dose, and the lack of a need for an external power source [68]. Medication such include anti-inflammatory drugs, steroids, bronchodilators, and anticholinergics can be administered with this preferred device, pMDIs. The pMDIs make it feasible for medicine to be aerosolized efficiently. A pressurized system, a pMDI is made up of a mixture of flavorings, surfactants, preservatives, propellants, and active drug, which makes up about 1 percent of the total contents. When the mixture is released from the delivery device through a metering valve and stem that fit into the design of an actuator boot, the drug is delivered through the pMDIs. The pressurized metered dose inhaler's aerosol properties and output can be impacted by minor modifications to the actuator design **Fig. 8** [69].

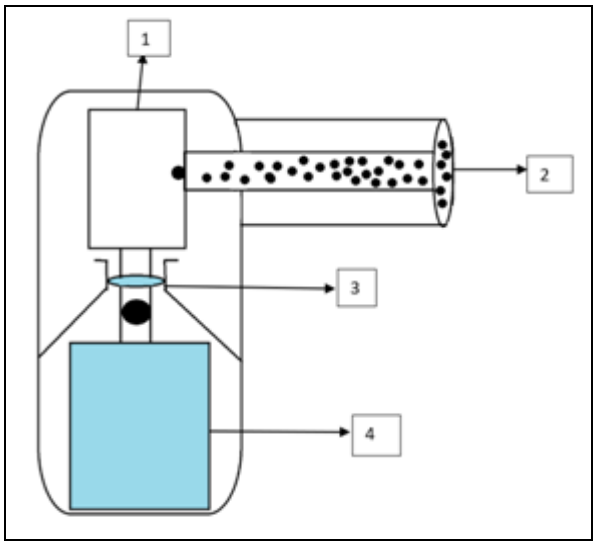

FIG. 8: SYSTEMATIC REPRESENTATION OF METERED DOSE INHALER, (1) THE AEROSOLIZED DRUG DELIVERY IS ACTUATED BY THE ACTUATOR IN THE EXPANSION CHAMBER, (2) MOUTHPIECE: RELEASE OF AEROSOL PARTICLES AT A HIGH SPEED, (3) THE METERING VALVE IS RESPONSIBLE FOR SUPPLYING THE ACTUATOR WITH THE NECESSARY DOSE, (4) THE PROPELLANT THAT ACTIVATES THE FORMULATION IS PRESENT IN THE LIQUID FORMULATION [70]

Dry Powder Inhaler: With minimal synchronization between the patient's breathing and the device's activation, the dry powder inhaler delivers medicine into the lungs as dry powder. The dry powder inhaler's formulation, which is subjected to greater dispersion forces to break down into individual particles, delivers the aerosolized drug powder. The Clickhaler, Multihaler, and Diskus are just a few of the devices that have been designed. They are able to feed powder into a high-speed airflow that splits the aggregated particles, obtaining the respirable particles. The Spinhaler and Turbuhaler devices rely on the deagglomeration mechanism caused by the impaction of particles on the device surfaces [71]. The equilibrium between the inhaler resistance and flow rate in the device is a limitation in the design of dry powder inhalers. A higher fine particle fraction can be achieved in dry powder inhalers by stronger impactions and faster airflow, which is required to increase particle deagglomeration. On the other hand, rapid airflow can decrease the amount of drug powder that reaches the lungs and raise the likelihood of deposition in the oropharynx **Fig. 9** [72].

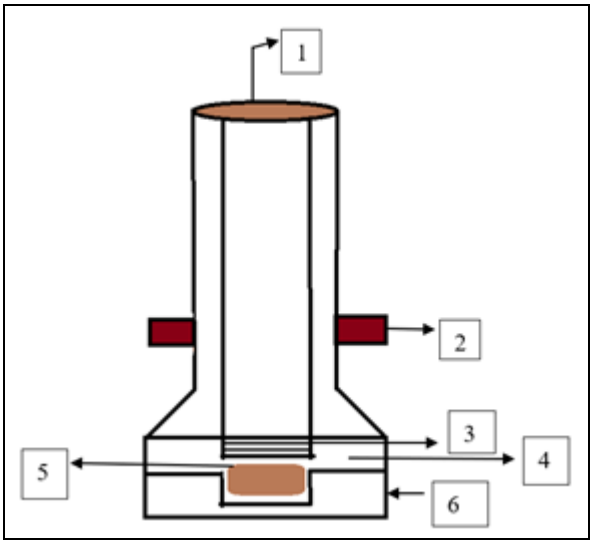

FIG. 9: SYSTEMATIC REPRESENTATION OF DRY POWDER INHALER, (1) THE DRUG DELIVERY DEVICE'S MOUTHPIECE ACTS AS AN AIR OUTLET, (2) BUTTON: DESIGNED TO OPERATE THE APPARATUS, (3) FILTER/GRID: THIS DEVICE HANDLES VARIATIONS IN INTERNAL FLOW RESISTANCE, (4) CAPSULE CHAMBER: THIS PART OF THE DEVICE HOLDS THE CAPSULE, (5) CAPSULE: THE DOSAGE IS ADMINISTERED FOLLOWING THE CAPSULE'S COMPRESSION THROUGH THE DEVICE'S MOUTHPIECE, (6) THE AEROSOLIZATION OF THE POWDER BASED ON CARRIERS IS GREATLY IMPACTED BY THE AIR INTAKE TABLE 2 [72].

TABLE 2: VARIOUS DRY POWDER INHALER KINDS ACCORDING TO THE DOSE FORM [70]

Parameters	Single dose DPIs	Multidose DPIs	Multi-dose Reservoir
Dose	Individual capsules are used to provide the dosage.	The dosage is provided in a sealed, factory-metered container.	When the device is activated, the dose is delivered individually in the form of bulk powder.
Dose delivery capability	The dosage is administered all at once.	The dosage is given in numerous doses.	The method of individual dosages each actuation determines the dose.
Reusable or Non-reusable	It can be further divided into reusable and disposable categories.	It can be further divided into catridges, replaceable disks, and foil-polymer blister packing.	It is based on the mechanism in the device that releases the dosage with each actuation; this mechanism has not yet been created in the newer devices.

For systemic and oral drug delivery additionally, single-use dry powder inhalers have been developed, which are cost-effective to use.

This was the first time capsule-based DPI technology was employed for medicinal reasons, with the introduction of the Aerohaler® in the middle of the previous century to administer antibiotics. The third DPI to be launched at the end of the 1960s was the Spinhaler®, which was the first to use a powder formulation of bronchoactive

drugs in a gelatine capsule that could be loaded into the device before the patient administered it. Since then, as technology has advanced, DPI systems' performance has been updated often. Larger carrier particles, often lactose, are mixed with tiny powder medicines (less than 5 μm in particle size) to create the bulk of DPIs now available on the market. Lactose is added before the medicinal formulation is aerosolized to improve the flow of the powder. All of the research' results suggested that powder formulations might be carried via the airways and land in the specific lung areas that need more activity.

Breezhaler® is a contemporary example of a DPI that is based on capsules. This single-dose DPI system features improved Aerolizer technology with redesigned parts for improved device management and appearance [73].

DPI systems are classified into two categories.

1. Turbuhaler
2. Diskus TM

Turbuhaler: The most sophisticated nebulizers are those that administer the formulation at the nanoscale, while there are other varieties as well. The creation of new, smarter drug carriers is a result of advancements in nanotechnology and sophisticated liquid nebulization techniques that allow for the administration of these intelligent aerosolized particles. Diskus TM is less effective than Turbuhaler.

Diskus TM: An inhaler that uses dry powder, the Diskus inhaler has the following features: A. Connected cover: The device's cover is what keeps it small; B. Grip to improve the gadget's compatibility; C. doses counter: the part of the device that maintains a steady dosage.; D. mouthpiece: for inhaling the medication; E. dosage releaser: The dosage is released from the dose counter bysliding it [70].

Nebulization Systems: Nebulizers are the tools used to create aerosols from solid or liquid solutions or suspensions. The inhalation devices called nebulizers are used to administer medications to the lower respiratory tract. The insufflation devices and formulation have a major impact on the pulmonary bioavailability. Nebulizers have been used for many lower respiratory tract illnesses for decades [74].

The nebulization system is further classified into different category:

1. Air-jet nebulizers
2. Ultrasonic nebulizer
3. Vibrating-mesh nebulizer

Air-jet Nebulizer: The earliest kind of nebulizers are called air-jet nebulizers, and they are made by a wide range of manufacturers. Through the Bernoulli effect, an aerosol is produced by all air-jet nebulizers. That is, when air velocity rises in a certain area, pressure decreases. When compressed air passes through the air-jet nebulizer, a volume of liquid is pulled up from a liquid reservoir into a region of strong shear forces. After the liquid has been firmly separated into droplets, the patient's breathing often produces a mild stream of carrier air that transports the liquid out of the nebulizer **Fig. 10.**

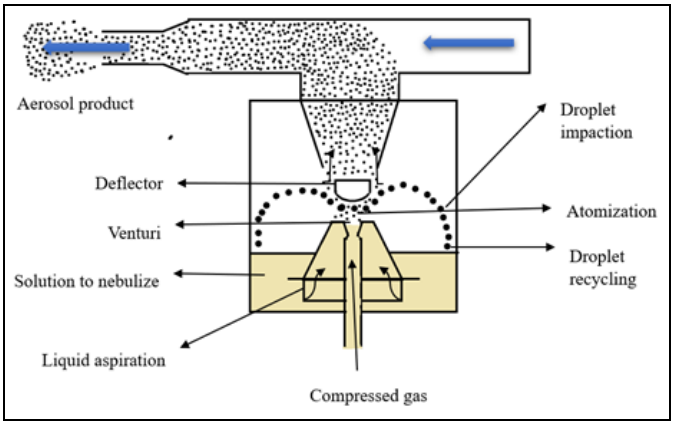

FIG. 10: SYSTEMATIC REPRESENTATION OF AIR JET NEBULIZER

Ultrasoni Nebulizer: These nebulizers have a piezoelectric crystal built into the bottom of the medication reservoir or cup. This crystal vibrates mechanically at a high frequency when it is subjected to an electric field. The crystal's vibrations create shockwaves that move through the liquid-filled reservoir, creating turbulence on the surface and cavitation in the liquid to create droplets at the liquid's surface. Cavitation is the process by which voids in a liquid develop and subsequently collapse due to crystal vibrations.

The resulting droplets form a soft aerosol cloud above the liquid reservoir. Although usually less dispersed than for air-jet systems, the aerodynamic particle size distribution of aerosols is likewise polydisperse due to the turbulent liquid surface environment. The aerosol cloud can then be coupled with inspiratory airflow to deliver medications to the lungs **Fig. 11.**

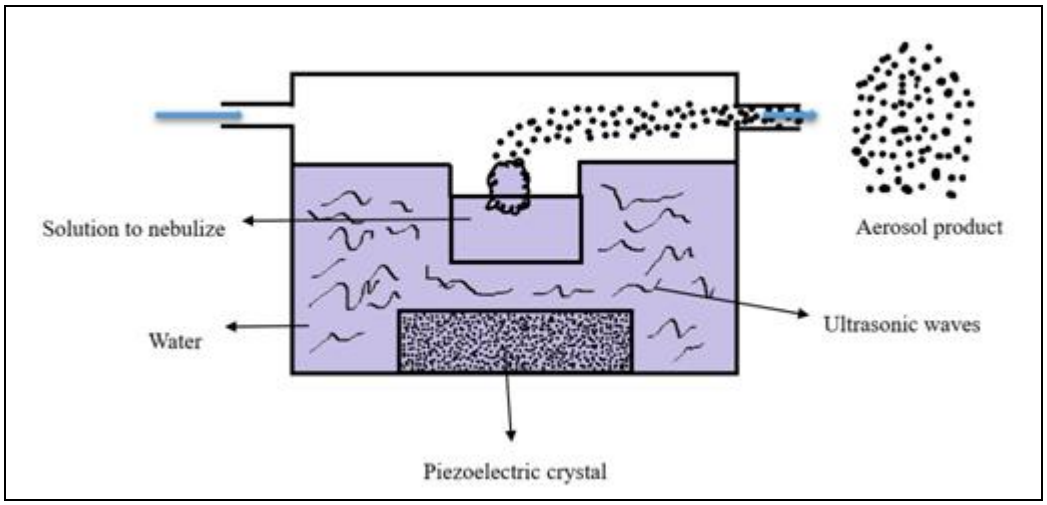

FIG. 11: SYSTEMATIC REPRESENTATION OF ULTRASONIC NEBULIZERS

Vibrating-mesh Nebulizer: The vibrating-mesh nebulizer is a relatively recent nebulizer technology designed to have more uniform aerosol particle size distributions and function with a wider variety of formulations. These nebulizer devices attach a piezoelectric crystal to a laser-drilled metal mesh at the bottom of a medicine cup or reservoir. When the crystal is subjected to an electric field, the metal mesh rapidly oscillates, forcing the drug liquid through the pores in the mesh. Then, a mild aerosol with a consistent aerodynamic particle size distribution is produced due to the uniformity of the laser-drilled holes in the metal membrane. This aerosol can be administered to the patient via a face mask, mouthpiece, or in-line junction for patients on mechanical ventilation **Fig. 12** [75].

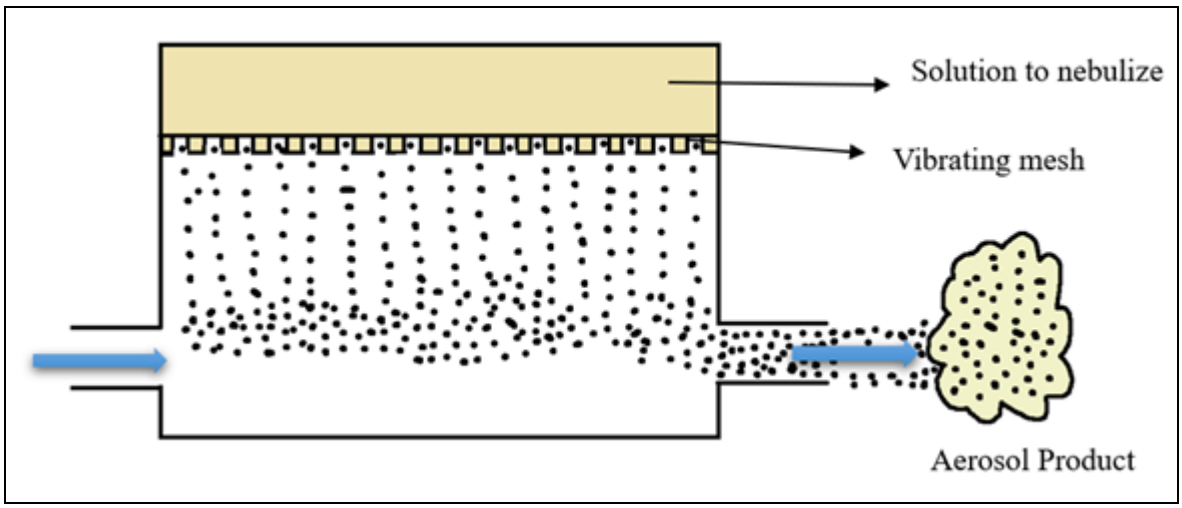

FIG. 12: A SYSTEMATIC REPRESENTATION OF VIBRATING MESH NEBULIZER

CONCLUSION: It has been shown that treating pulmonary infectious diseases with antibiotics administered inhaled through the pulmonary route is effective. However, because inhaled forms require strict control over the size distribution of aerosol particles as well as their aerodynamic behavior and surface properties to ensure optimal deposition at the target infection site, they are regarded as complex dosage forms that are challenging to develop. For the pulmonary route, nebulizers are the most recommended method of drug delivery. The nebulizer's construction and design have a significant impact on the performance of the inhaler dispersion or device

retention. A great nebulizer should provide accurate and consistent dosages to the patients' targeted respiratory systems while maintaining the stability of the aerosolized drugs. In order to assess the clinical effects of different inhalers, examine the clinical result in the juvenile population, and customize treatment to meet the needs of patients with asthma and chronic obstructive lung disease, clinical manifestations were employed. In light of this, the conclusion section states that, even though nebulizers are the most effective therapy for pulmonary conditions, they should be updated regularly to better suit patient convenience and compliance.

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