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NEBULIZED DRUG DELIVERY: AN OVERVIEW

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ABSTRACT: Inhaled Pharmacological therapy is key to treatments for patients with asthma and COPD. People who suffered from COPD died every year in low- and middle-income countries. The primary reason for COPD is tobacco smoking or second-hand smoke. Another risk factor is air pollution, dust, and fumes. Current guidelines endorsed inhaled pharmacology therapy as the favorable route of administration for treating COPD. Bronchodilators (β_2 agonists and antimuscarinics) are the anchor of the pharmacology therapy in patients with COPD, with long-acting approved for patients with ordinary to serious symptoms or those who are at higher risk for COPD aggravations. Dry powder inhaler (DPI) pressurized metered dose inhaler (pMDI) is the frequently used drug delivery devices, but they may be sparse in various clinical scenarios. There are a lot of drugs become available in solutions; suspensions form to treat patients suffered from COPD with nebulized drug delivery, which supplies benefits similar to drugs delivered by the conventional delivery system and better quality of life. A successful pulmonary administration requires a harmonic interaction between the drug formulation, the inhaler device, and the patient. However, the biggest major problem for lack of desired effect or adverse outcomes is the improper use of the inhaler device due to lack of training in how to use the device or how to coordinate actuation and inhalation. This review describes the operational and mechanical features of nebulizer delivery devices concerning mechanisms of aerosol generation, their use with different formulations, and their advantages and limitations.

INTRODUCTION: Aerosol therapy is defined as drug administration in the form of an aerosol into a patient's airways or lung. Its efficiency depends on the type of drug used and the aerosol's physical and chemical properties, the aerosol device as well as the patient's breathing pattern, lung anatomy and physiology. Currently, inhalation therapy is the best option for lung diseases like asthma, cystic fibrosis, and chronic obstructive pulmonary disease (COPD) [1].

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These local therapies allow the use of smaller doses and reduce systemic side effects. Devices used to deliver therapeutic agents as aerosols are based on one of the three platforms: nebulizers, a pressurized metered-dose inhaler (pMDI), and dry powder inhalers (DPIs) [2, 9].

'Nebulizers' is a device that converts liquids into aerosols that can be inhaled into the lower respiratory tract. 'Nebulizers' used in aerosol drug delivery produce a polydisperse aerosol where the drug delivered in the particles size range 1–5 µm in diameter. Most Nebulizers use compressed air for atomization, but some use ultrasonic energy. 'Nebulizers' are generally used for the treatment of cystic fibrosis, asthma, COPD and other respiratory diseases or disorders [2, 3].

Chronic obstructive pulmonary disease (COPD) reason for significant morbidity and mortality worldwide in the elderly and it has been estimated to become the third exorbitant cause of death worldwide by 2020. Majorly prescribed inhalation devices worldwide, are pressurized metered dose inhalers (pMDIs), dry powder inhalers (DPIs), slow mist inhalers (SMIs), and 'nebulizers,' have similar efficacious in patients with COPD, provided they have used adequately [2]. Dry powder inhalers (DPI) and pressurized metered dose inhalers (pMDI) are the frequently used devices and endorsed for long term treatment in the wide majority of patients. Global Initiative for Chronic Obstructive Lung Disease (GOLD) states that 'nebulizers' are for specific patient populations like those having low respiratory rate and they could get better advantages to compare to DPIs and pMDIs [2]. GOLD proposed that the benefits of nebulizer treatment typically simpler, cheaper and cost-effective [3]. Patients and their caretakers are becoming increasingly contented with nebulized drug delivery and benefits are comfort, effortless and improved quality of life [4].

Chronic Obstructive Pulmonary Disease and Asthma: 'COPD' a typical averted and curable disease, is distinguished by ongoing perpetual airflow obstruction that is allied with upgrade inflammatory response to noxious particles or gases in the lung and airways. It is characterized by such respiratory signs like a wheeze, shortness of breath, chest tightness and cough. These symptoms can be varied by the intensity and expiratory airflow limitation [5]. These variations are often triggered by factors like exercise, allergen or irritant exposure, weather change and different respiratory infection [6]. COPD is a leading disease which causes death in the United States of America (USA), affected 16 million and more millions who don't know they suffered from it [7]. There are more than 65 million people around the world suffered from moderate or severe COPD; this number would be increased over the next 50 years [8]. There are more than 90% of people who suffered from COPD died every year in low- and middle-income countries. The primary reason for COPD is tobacco smoking or second-hand smoke.

Another risk factor is air pollution, dust and fumes [9]. Air pollution can affect the infants and represent a risk factor for developing COPD later in life [10]. Some genetic and environmental factors also influence the risk of COPD. The researcher showed that gene study would recruit 10000 who smoke and who don't smoke to identify the genetic factors that investigate why some people develop COPD, and others don't [11]. Asthma is a heterogeneous disease usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time in intensity, together with variable expiratory airflow limitation [12, 13, 31].

Pharmacological Therapy for COPD: Pharmacology therapy is a mainstay therapy in patients who suffered from COPD. Patients those having high intensity of COPD and a higher risk of COPD exacerbations (according to GOLD guideline) and different categories of patients. Long-acting bronchodilators are better than short-acting bronchodilators to improve symptoms, exercise tolerance, improved quality of life and reduce the risk of exacerbations [13, 37]. It depends on several factors like availability of drug, / device pairings, cost, and patient inferences and satisfaction [14]. GOLD guidelines recommend a long-acting beta$_2$ agonist as initial treatment and inhaled corticosteroids only for patients with more severe disease. As a result, long-acting bronchodilators (LABA) with or without inhaled corticosteroids (ICS) or long-acting antimuscarinic agent (LAMA) are the alternative drugs for the majority of patients with COPD [15, 37].

Basically, three categories of drugs used in asthma; (1) Bronchodilators (SABA and LABA), Muscarinic agonists, methylxanthines) (2) Anti-inflammatory agents (steroids, slow anti-inflammatory drugs, release inhibitors) (3) Leukotriene antagonists (lipoxygenase inhibitors, receptor inhibitors) and drugs used in COPD (1) Bronchodilators (2) Anti-inflammatory agents (steroids) (3) Leukotriene antagonists [33].

Inhalation Delivery Device: Inhaled dosage form, or medicines that you breathe directly into the lungs, are an important or essential part of treatment for chronic lung disease. When inhaled, the medicine quickly reaches the lung airways, and less is absorbed into the systemic circulation [33, 34,

[40]. Aerosol particle size majorly affect the deposition pattern of a drug in the lungs, and the optimal particle size range for deep lung deposition is 1 to 5 μm. The choice of inhaler device depends upon cost-effectiveness and the patient's preference and ability to use it correctly. Several inhalation device types are available, including metered-dose inhalers (MDIs), dry-powder inhalers (DPIs), soft mist inhalers (SMIs), and small volume nebulizers (SVNs) [35]. Each of these devices has a unique feature to consider when selecting treatment for a specific patient. Nebulizers are vital for the treatment of chronic lung disease, including asthma and COPD. Metered dose inhaler (MDIs) and Dry powder inhaler (DPIs) formulations are more difficult to administer, peculiarly to the young and elderly who are most ordinarily the patients in need of such therapy. It is much more difficult to get the proper dosage with an inhaler because a person suffering from COPD patient cannot inhale with great force. Hence, the majority of the drug deposit in their mouth (where it does no good), rather than in their lungs. The nebulizer provides a far superior delivery method for a patient with COPD [36, 37, 38].

A combination of inhaled medications or alone along with selected inhalation device can be used for some chronic lung diseases, including asthma and COPD. Each of the delivery devices those are available in the market for administration of drugs to patients with COPD and asthma (*e.g.*, pMDI, DPIs, SMIs, and Nebulizers) has advantages, and disadvantages all are described in **Table 2**.

TABLE 1: TREATMENT GUIDELINE OF ASTHMA AND COPD IN PATIENTS [31, 32, 34]

Diagnosis	Diagnosis
COPD with Asthma	Intermittent symptoms – SABA If persistent symptoms (*i.e.*, using SABA >3 times a week) or exacerbations – SABA plus LABA/ICS combination If continuing exacerbations – SABA plus LABA/ICS plus LAMA or consider referring to a specialist
COPD frequent exacerbations and breathlessness:	Intermittent exacerbations – SABA plus LAMA or LABA If persistent exacerbations – SABA plus LAMA/LABA Combination: If continuing exacerbations – SABA plus LABA/ICS combination + LAMA or consider referring to a specialist
COPD and breathlessness (but no asthma):	Intermittent breathlessness – SABA If persistent breathlessness – SABA plus LAMA or LABA If still getting persistent breathlessness – SABA plus LABA/ LAMA combination

TABLE 2: ADVANTAGES AND DISADVANTAGES OF AEROSOLIZED FORMULATIONS [14, 39]

Aerosolized formulations	Advantages	Disadvantages
DPI	Ease of use, lack of additives, no propellent or vehicle, controlled treatment	Inspiratory flow required to actuate DPI
pMDI	Reliable aerosol generation until canister empty, wide dose range potentially available per actuation from 10 μg to 5 mg., totally self-contained power source	Most devices are not breath actuated the unaided MDI deposits 75% of the drug in URT. It may convict local or systemic effects
SMI	Multiple dosing, high lung deposition, portable, no propellants	Multiple steps involved and lack of availability in most countries

Nebulizer and Nebulizer Types: Nebulizer is a device that transforms liquid formulations and suspension into a medical aerosol by pneumatically converting a bulk liquid solution or suspension formulation into small droplets is called atomization [41]. Even though the first choice of an aerosol generator for the delivery of bronchodilators and steroids is the metered dose inhaler (MDIs), nebulizers remain useful for several reasons. The physiologic aids of metered-dose inhalers and nebulizers are almost equivalent, and the choice of device is often based on the clinical outcome of a nebulizer or patient preference rather than clear superiority of one approach over the other. Nebulizers do not require patient synchronization between inhalation and actuation; thus they are useful for pediatric, elderly, ventilated, non-conscious patients, or those who are

unable to use pMDIs or DPIs. Nebulizers have the ability to deliver larger doses compared to the other aerosol devices even though this will require longer administration times [27, 43, 44]. There are majorly three types of nebulizers available namely jet Nebulizers, which can nebulize all drugs both in the form of solution and suspension and it can be disposable; ultrasonic nebulizers, which are silent but can only nebulise aqueous solutions and may produce heat during nebulization process; and mesh Nebulizers, which can be used to nebulise aqueous solutions, but can be less efficient in nebulising suspensions formulation [39, 45].

(A) Jet Nebulizers: Jet nebulizers are applicable for acute and domiciliary treatment of various respiratory diseases, pediatric and adult medical practices. These types of nebulizers required 2-10 L\min withdraw medication a capillary tube from the reservoir of the nebulizer. It may cause generate a wider range of particles which blasted into one or more baffles (to convert larger particles to smaller particles) out of suspension and return them to nebulizer [15]. These types of nebulizers are working on Venturi's principle. Venturi's principle assumed that fluid pressure decreases when it passes through a narrow gap or sectional area, so air moves through a small capillary tube at high velocity and low pressure; that drives the liquid converted to aerosolized form up to capillary tube[16]. There are four types of jet nebulizers: (A) jet nebulizers with a corrugated tube (B) jet nebulizers with a collection bag (C) breath-enhanced jet nebulizers and (D) breath-actuated jet nebulizers.

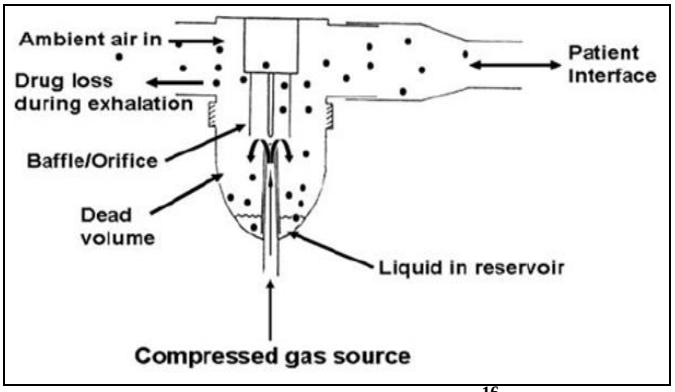

FIG. 1: JET NEBULIZER [16]

Jet Nebulizers with a Corrugated Tube: These types of nebulizers are conventional and constant output nebulizers. They produce continuous aerosol during respiration (inspiration-expiration) and breath hold. In this corrugated nebulizer tube attached to jet nebulizer which acts as a reservoir. The limitation of this nebulizer is that significant loss of drug during expiration with this nebulizer [17]. Some other limitations of this nebulizer are that limited portability, requirements for compressed air/gas sources for operation and it may vary from the nebulizer to nebulizer's types of nebulizers are easily handling and better profile on patients [18].

Jet Nebulizers with a Collection Bag: Jet nebulizers with collection bag is also known as Dosimetric nebulizer which releases aerosol during respiration [19]. This nebulizer produces aerosol that stored in a collection bag during expiration and the patient can take during the next inspiration. It contains one valve situated between the mouthpiece and collection bag [20].

Common example of this type of nebulizer is circular. It's having more advantages compare to jet nebulizers with corrugated tubing: enhances peak expiratory flow, improve heart rate and respiratory rate who suffered from bronchospasm during admitted in the emergency department. Circulaire decreases the loss of drug into the environment and gives less exposure to caretakers during aerosol drug [21].

Breath-Enhanced Jet Nebulizers: This nebulizer commode that the side stream of the nebulizer to air flow of the patient. In this type of nebulizer, patient can breathe easily during inspiration; which improves the nebulizer output [22]. When a patient exhales than one-way valve directly flows away from the chamber of the nebulizer. Many scientists assumed that greater pulmonary deposition compares to conventional nebulizer [23]. The efficacious advantages of this nebulizer are that improved respiratory flow and increase Nebulizer output [16].

Breath-Actuated Jet Nebulizers: These types of nebulizers embellished to improve drug delivery *via* generating aerosol during inspiration. The anchor advantages of these types of nebulizers are that loss of medication during expiration reduced and improved the inhaled dose, greater efficiency and optimum dosing time [24]. The limitation of this nebulizer is that it requires sufficient flow to trigger drug delivery and expensive.

(B) Ultrasonic Nebulizers: Ultrasonic nebulizers incorporate a piezoelectric crystal vibrating at high frequencies (1-3 MHz) to produce an aerosol. Ultrasonic nebulizers work on the principle that converts electrical energy to high-frequency vibrations using a transducer [25]. This nebulizer generates vibrations which are transferred to solution surface that would create waves, and those waves produce aerosol; we can say that these types of nebulizers are large volume nebulizers to deliver hypertonic saline for sputum inductions [26, 27]. They have large residual volumes, an inability to aerosolize viscous solutions, and degradation of heat-sensitive materials. Therefore, they should not be used with suspensions and proteins. The major limitation of ultrasonic nebulizers is that they will generate heat which may cause disrupting proteins and peptides [43, 44, 45].

(C) Mesh Nebulizers: Recent improvements in nebulizer technologies have led to the development of mesh nebulizers using micropump technology for aerosol production. Mesh nebulizers contain apertures or aperture plate; when we applied force, it will generate aerosol [30, 31]. They force liquid medications through multiple apertures in a mesh or aperture plate to generate aerosol. Comparisons of mesh and ultrasonic nebulizers demonstrated similar drug delivery in simulated ventilator-dependent patients. Mesh nebulizers are more efficient than jet nebulizers and can provide higher drug doses to patients. Although human studies with mesh nebulizers are limited, *in-vitro* studies demonstrated approximately 2-3 times higher lung deposition with mesh nebulizers when compared to jet nebulizers [32, 33, 34].

Either battery or electricity empower these nebulizers. The advantages of these nebulizers are that short treatment time, increased output and low residual volume [36, 38]. The efficiency of mesh nebulizers affected by various factors like size of the pore, aerosol chamber, and reservoir. These nebulizers designed to reduce the adverse effects due to an overdose of medication [39, 45].

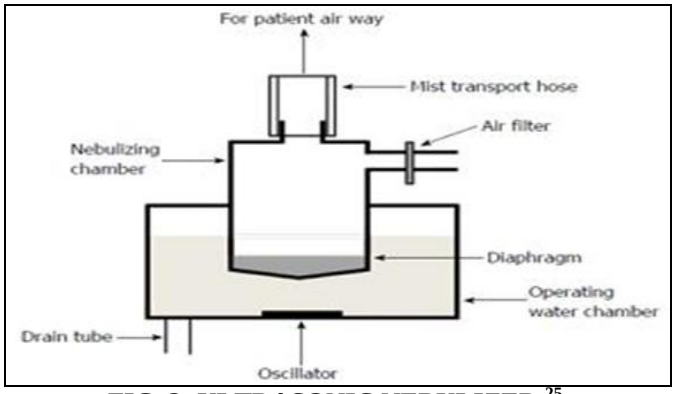

FIG. 2: ULTRASONIC NEBULIZER [25]

FIG. 3: MESH NEBULIZER [29]

TABLE 3: COMPARISON OF THREE DIFFERENT NEBULIZERS

S. no.	Nebulizers	Working principle	Advantages	Disadvantages
1a)	Jet nebulizers with a corrugated tube	Bernoulli's principle	Cheap, easy to use, Effective in delivering the drugs that cannot be delivered with pMDIs and DPIs	Inefficient, difficult to clean, Need compressed and additional tubing
1b)	Breath-actuated and breath enhanced jet nebulizers	Bernoulli's principle	Drug delivery only during inhalation, easy to use, less medication wasted, more efficient than JNs with tubing	Need sufficient flow to trigger drug delivery, Takes longer to deliver the drug, Not ventilator-enabled expensive
2	Ultrasonic nebulizers	Piezoelectric crystal vibration at high frequencies	Easy to use, more efficient than jet nebulizers	Large residual volume Inability to aerosolize viscous solutions. Degradation of heat sensitive materials
3	Mesh nebulizers	Contraction and expansion of vibration	A fast, quiet, portable, self-contained power source, optimize particle size for specific drugs, more efficient than other nebulizers, easy to use	More expensive, cleaning can be difficult, medication dosage must be adjusted, not compatible with viscous liquids or those that crystallize on drying

Marketed Formulations of Nebulizer: Some of the marketed formulations of nebulizers are given below:

TABLE 4: MARKETED FORMULATIONS OF NEBULIZER [40, 41, 42, 43, 44]

S. no.	Brand name	Drug	Innovator name
1	Accuneb®	Albuterol sulphate	Mylan
2	Xopenex®	Levalbuterol HCl	Oak Pharmaceuticals
3	DuoNeb®	Ipratropium bromide, Albuterol sulphate	Mylan
4	Performist®	Formoterol fumarate	Mylan
5	Cayston®	Aztreonam	Gilead life sciences
6	Aeronab®	Albuterol sulphate and Ipratropium bromide	Nectar therapeutics
7	Micro air NE U-22	Albuterol sulphate and Ipratropium bromide	Omron health care
8	Bethkis®	Tobramycin	Chiesi
9	Brovana®	Arformoterol tartrate	Sunovion Pharma
10	Pulmicort	Budesonide	AstraZeneca

CONCLUSION: The structure and design of inhaler have a major impact on the aerosol deposition to the lungs. An ideal inhaler should deliver precise and consistent doses to a targeted region in the lungs and maintain the stability of the delivered drugs. It is also required that devices are small and simple to be used easily by patients. Nebulizers delivery device has been used clinically for many years. Some factors affect nebulizer performance, and these should be considered by clinicians who use these devices. In patients those suffered from COPD, nebulizers are an alternative inhalation device to pMDI and DPIs for providing an inhaled remedy, rendered the drug is available and chemically stable in liquid form.

Despite some drawbacks associated with nebulizers (*e.g.*, pliably long treatment times and daily cleaning), contemporary affirmation proposed that the efficacy of treatments administered to patients with moderate to severe COPD via nebulizers is similar to that observed with pMDIs and DPIs. Nebulized therapy is best, effective and less patient compliance and improves quality of life.

Nebulizers can vary significantly droplet size, nebulization time and drug output from the nebulizer, and residual volume. Selection of nebulizer is critical, mesh Nebulizers can be used to nebulize aqueous drugs, but, for suspensions, there may be a reduction in performance in terms of aerosol output rate and inhaled mass so far, there are no relevant published studies evaluating the bioequivalence between marketed mesh Nebulizers and current jet Nebulizers.

In the future, marketed mesh Nebulizers should be tested *in-vivo* to determine bioequivalence and clinical equivalence, and new optimal mesh nebulizers could be developed for a known drug formulation. The number of inhaler devices available in the market for inhaled therapies has increased significantly in the past decade. However, they have made modest differences in clinical outcomes.

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