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Review Article

A Concise Overview on Recent Advances in Pharmaceutical Aerosols and Their Commercial Application

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Abstract: -

For the treatment of various pulmonary disease such as asthma, chronic abstractive disease, pneumonia, bronchitis, and cystic fibrosis, localized drug delivery to the respiratory system has shown to be an increasingly effective and crucial approach. The global market for respiratory inhaler device is being propelled in large part by the increasing prevalence of respiratory disease. The main objective of this article is to present various aspect of pharmaceutical aerosol, including their various types, components, in-process and finished product quality control, and their commercial applications.

Aerosol also known as a pressurized device work by continuously or metered applying a small mist spray to activate a suitable valve system. Aerosol is not only used for the treatment of asthma and chronic obstructive pulmonary disease but also used to treat a wide range of other conditions including diabetes, cancer, angina pectoris, bone disorder, and acute lung injury, bone disorders, and tuberculosis. The therapeutic efficacy of pharmaceutical aerosol is affected by wide range of factors, such as the types and characteristics of propellant, active ingredient, container, valve, actuator, spray pattern, valve crimping efficiency, and aerosol particle size.

Key words: -

Aerosol, types, metered dose inhaler, dry powder inhaler, nebulizers, commercial applications.

Introduction: -

Aerosol: -

What is an aerosol? An aerosol, also known as pressurized packages or pressurized dosage forms, is considered the most effective novel-delivery drug system (NDDS) for distributing the active pharmaceutical ingredient(s) to both the systemic circulation and for local action. ‘’An aerosol is specifically defined as a dispersed system in which the majority of fine solid drug particles and/or liquid droplets are dispersed into a relevant propellant (gas), which acts as a continuous phase’’.

OR

An aerosol is a system that expels or activates the contents from the container based on the pressure generated by compressed or liquefied gas [(1)].

Pharmaceutical inhalation aerosols are a sophisticated form of medication that enables the administration of therapeutically active drugs to the respiratory system. These aerosols offer a high concentration of medication in Broncho-alveolar fluids and other lung tissues when used as oral inhalation products.

Components of aerosol: -[(2)]

1] Propellant

2] Container

3] Valve

4] Actuator

5] Product concentration

1] Propellant: -

The container undergoes a pressurization process, whereby propellants such as compressed gases like carbon dioxide or nitrogen, as well as liquified gases like methane or ethane, can be utilized. It is noteworthy that compressed gases are not frequently employed. In contemporary times, pharmaceutical aerosols employ propellants such as trichloro-fluor-methane, dichloro-difluoro-methane, dichloro-tetrafluoro-ethane, and difluoro-ethane.

The substances for propellant may solid or liquid form. They may be soluble in the propellant or they may not dissolve completely. Additionally, the formulation includes various additives, such as solvents, antioxidants, surface active agents, and flavouring agents. All of these components, including the propellants, medicaments, and additives, are then filled into an aerosol container.

2] Container: -

In pharmaceutical aerosol packaging, the containers are manufactured using various materials including metal (such as tin-plated steel, aluminium, and stainless steel), glass, and plastic. These containers possess the ability to endure high pressure.

3] Valve: -

It should be simple to open and close the valves that are used. Additionally, the content should be sent in the desired format. Thus, there are three types of valves in use today:

i) valve-The medicament is expelled continuously

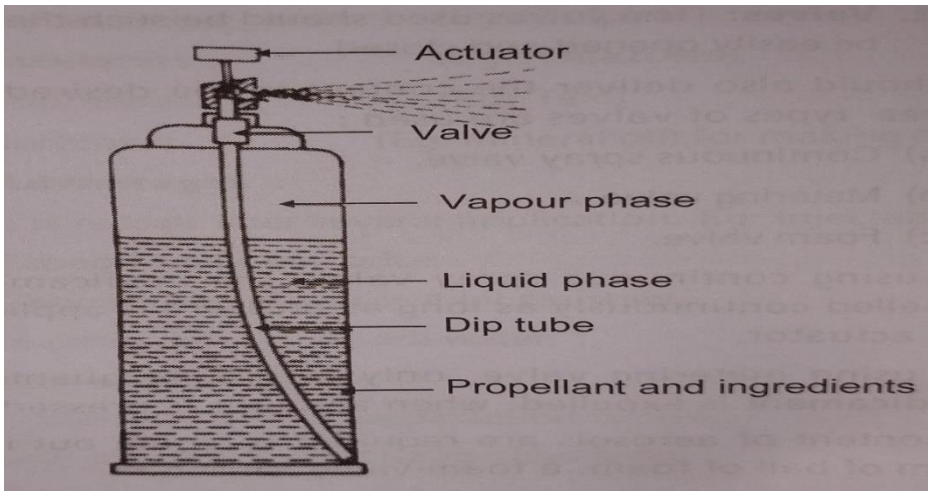
ii) The expulsion of the medicament occurs only when the actuator is pressed, thereby defining the quality of the medicament through the metering valve.

iii) A foam valve -The required content is come out in the form of ball of foam.

4] Actuator: -

The valve stem is equipped with an actuator. When necessary, it facilitates the simple opening and closing of the valve. Actuators come in a variety of forms and can generate foam, fine mist, or spray.

5-Product concentration Product concentration of an aerosol in which the active ingredient together with appropriate excipients can be supplied in three different liquid forms: as an emulsion, solution, or semisolid



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Metered dose inhaler (MDI):

It is also called as MDI. It is hand hold device used to deliver mattered dose to the lungs. The drug exists within the propellant in either a dissolved or suspended state [3]. MDIs are widely used inhalers for the treatment of localized respiratory ailments like asthma and COPD. It is an inhaler that administers medication

through a propellant spray in a pressurized manner. The MDIs administer a minimal portion of the medication dosage to the respiratory system. Generally, only 10-20% of the emitted dose is deposited in the lungs [4]. The initial MDI was created in 1956 by Riker Laboratories, which currently operates as a division of the 3M corporation. It contains two emerging technologies, namely the chlorofluorocarbon (CFC) propellant and the Mesh burg metering valve [5]. The late 1970s witnessed a notable enhancement in drug delivery through MDIs with the advent of spacer devices. These devices were specifically designed to minimize oesophageal deposition and enhance the penetration of drugs deep into the lungs [6]. Metered dose inhalers provide several benefits, including their portability, independence from external power sources, and delivery of a fixed dose formulation [7].

Instructions for Using the MDI [8,9,10,11]: -

To properly use the MDI, follow these steps:

1] Shake the inhaler well before use, giving it 3 to 4 shakes.

2] Remove the cap.

3] Breathe out, away from the inhaler.

4] Bring the inhaler to your mouth and place it between your teeth, closing your mouth around it.

5] Begin to breathe in slowly, pressing the top of the inhaler once and continuing to breathe in slowly until you have taken a full breath.

6] Remove the inhaler from your mouth and hold your breath for approximately 10 seconds before exhaling.

Advantages [12]: -

1] A specified dose is administered by it.

2] It possesses a compact size, making it easily transportable and convenient for usage.

3] It generally offers a more affordable option in comparison to dry powder inhalers and nebulizers.

4] Quick and easy to use

5] The contents remain safeguarded against contamination from pathogens.

6] It possesses a multi-dose capability, providing over 100 available doses.

Disadvantages [12]: -

1] Using pMDI to administer large doses is challenging.

2] Precise coordination between dosage actuation and inhalation is necessary.

3] A patient's technique affects how a drug is delivered.

Components of pMDI [13,14,15,16]: -

The components of pMDI formulation are propellant, mattering valve, actuator and container. Thay are all play important role in formulation of pMDI. Other ingredients used in formulation of pMDI are co-solvents, surfactants, stabilizers, lubricants, bulking Agents, etc. The active component utilized in MDI aerosol should possess therapeutic efficacy at a low dosage and should not cause irritation to the respiratory tract. Additionally, it must exhibit stability and compatibility.

Propellant: -

One of the key elements of an MDI is its propellant, which is a liquefied gas with a vapour pressure exceeding atmospheric pressure (14.7 Psia) at a temperature of 105ºF. The propellant plays a crucial role in generating the appropriate pressure within the container and expelling the product when the valve is opened. By supplying the necessary pressure within the aerosol system, propellants perform the essential function of expelling the material from the container. To achieve the desired delivery and spray characteristics of aerosol, mixtures of propellants are often utilized. Given that propellants typically constitute over 99% of the delivered dose in MDIs, it is the properties of the propellant that exert the greatest influence, surpassing any other individual factor.

Depending upon their chemical nature there are different types of liquified gas propellant as follow

- Fluorinated Hydrocarbon
- Hydrofluoroalkane
- Hydrocarbon
- Semiflurinated alkane

Fluorinated Hydrocarbon [17]: -

It is also called as Chlorofluorocarbons (CFCs), these substances serve as the preferred propellants for oral inhalation and nasal aerosols. Notable propellants in this category encompass trichloromonofluoromethane (P-11), dichlorodifluoromethane (P-12), and dichloro-tetrafluoroethene (P-114).

Hydrofluoroalkane [18, 19]: -

It is also called as non-chlorofluorocarbons (non-CFCs), such as HFA-134a, HFA-152a, and HFA-227, are alternative propellants that are free of chlorine and possess no potential for ozone depletion.

Hydrocarbon: -

Topical pharmaceutical aerosols utilize hydrocarbons such as propane, butane, and isobutane as propellants due to their affordability and eco-friendliness. Despite these benefits, their flammability and explosiveness pose a potential hazard.

Container [20]: -

Pharmaceutical aerosols have been utilizing containers composed of glass, stainless steel, and aluminium due to their pleasing appearance and exceptional drug compatibility. These containers must be able to endure pressures of up to 180 Psig at 130ºF. The majority of pMDI formulations are filled into canisters made of aluminium.

Metering valve [21]: -

The metering valve plays a crucial role in regulating the flow of active ingredients and propellant from the container, thereby determining the spray characteristics of the aerosol. It is imperative that the valve is constructed using materials that are inert to the contents of the aerosol. The primary function of the valve is to accurately and repeatedly meter small volumes of liquid containing the drug, while also ensuring that the pack is sealed against any undue leakage of propellant vapor. The valve is a complex assembly comprising of at least seven component parts, each made from different materials.

Actuator [22, 23]: -

The actuator is an essential component of MDI, facilitating the effortless opening and closing of the valve. Specifically designed for oral inhalation, the actuator (adaptor) incorporates a discharge orifice known as a spray nozzle, as well as a socket that engages and forms a seal with the metering valve stem. The expansion chamber plays a crucial role in determining the physical characteristics of the spray, ensuring that the active ingredients are delivered within the appropriate particle size range. Additionally, the actuator must effectively restrict any lateral movement of the container during actuation to minimize stress on the valve stem, which could potentially lead to inaccurate metering or leakage between the valve stem and actuator. Furthermore, the actuator should provide sufficient air ducting to the mouthpiece, ensuring a low flow resistance that allows for comfortable inhalation.

Technological advances of pressurized metered dose inhalers (MDIs): -

New pMDIs can be classified as either breath-actuated or coordination devices. Breath-actuated pMDIs, such as the Airbreather, were specifically designed to address the issue of poor coordination between inhaler actuation and the patient's breathing. These mechanical devices are activated when they detect the patient's breath and release the prescribed dose accordingly [24, 25]. On the other hand, coordinated pMDIs were developed to synchronize the patient's inhalation with the discharge of the dose from the inhaler. The actuator ensures that the inhalation flow rate is coordinated, allowing the patient sufficient time to reliably actuate the pMDI during inhalation [26].

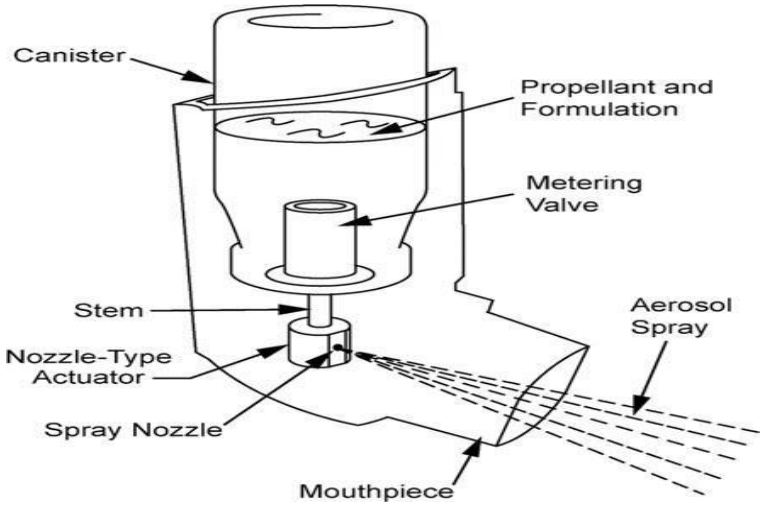


Fig- Mattered Dose Inhale

Kelkar and Dalby proposed a clever method to decrease the size of droplets released from pMDIs. This involves adding dissolved CO2 to a blend of HFA-134 and ethanol. When the dose is activated, the CO2 bubbles burst, creating an effervescent effect within the emitted HFA/ethanol droplet. As a result, the generated droplets break up into smaller ones. The objective of this approach is to enhance the respirable fraction emitted from a conventional pMDI [27].

The targeting of the lungs is dependent on the size of the particles, which ranges from 1 to 7 μm [28]. Pulmonary drug delivery offers a non-invasive alternative to subcutaneous and intravenous injections [29]. Clinical evidence suggests that any of these devices can be effective in most situations, including exacerbations and outpatient treatment [30]. The selection of the device should be based on inter-patient variability and environmental factors [31,32]. Dry powder inhalers (62.8%–88.5% of patients) and pressurized metered dose inhalers (18.9%–35.3% of patients) are the most commonly prescribed inhalers for asthma and COPD maintenance therapy [33]. An example of a pressurized metered dose inhaler is Flovent HFA, which consists of a metering valve attached to an aluminium canister. Flovent HFA contains fluticasone, an inhaled corticosteroid suitable for administration [34].

New technologies to improve patient's inhalation with MDI :-

One such technology involves the use of spacers, which are devices designed to improve the patient's ability to coordinate their inhalation with the timing of the aerosol puff. Both adults and children often struggle with this coordination, leading to inconsistent inhalation techniques [35,36].

Flow gate valve technology in spacers: -

Certain companies in the market offer a spacer that is free from static. This spacer is equipped with a valve mechanism that enhances the delivery of medication to the lungs. The valves open during inhalation and close during exhalation, ensuring that the remaining dose is retained within the spacer for future inhalations [37].

Dry powder Inhaler (DPIs):

Dry powder inhalation utilizes bolus drug delivery devices to administer medication in a dry powder format through the pulmonary route, resulting in both local and systemic effects [38]. Inhalers known as DPIs do not utilize propellants and depend on the patient's inhalation rate to determine the amount of medication delivered. DPIs were initially introduced in 1967, with the spin inhaler being the first inhaler to achieve commercial success. This inhaler was designed for the administration of sodium cromoglycate, a stabilizer for mast cells [39]. The turbo inhaler was the first modern multidose DPI, utilizing a dosing disc to regulate the amount of medication dispensed [40]. A variety of DPI devices are currently accessible in the market, include single- or multiple-dose devices, breath-activated devices, and power-driven devices [41-44]. However, these devices have certain limitations such as inadequate drug deagglomeration, low respirable fraction, flow dependency rate for breath-actuated devices, and high complexity for power-driven DPIs. As a result, more sophisticated DPIs have been developed [45].

Based upon dosage form of drug the DPI are classified into two types: -

1] Single dose DPI: Single-dose powder inhalers consist of a holder where a capsule containing powder is inserted. The device is opened and the powder is inhaled from within the capsule. This system is reloaded.
It consists of,

A] Spinhaler

B] Rotahaler

A) Spinhaler: - The mechanism of action is same as to a rotahaler, with the exception that the outer sleeves are moved downwards to puncture the capsule, allowing the propellant to disperse the drug.

Advantages:

1) It is very safe device to use.

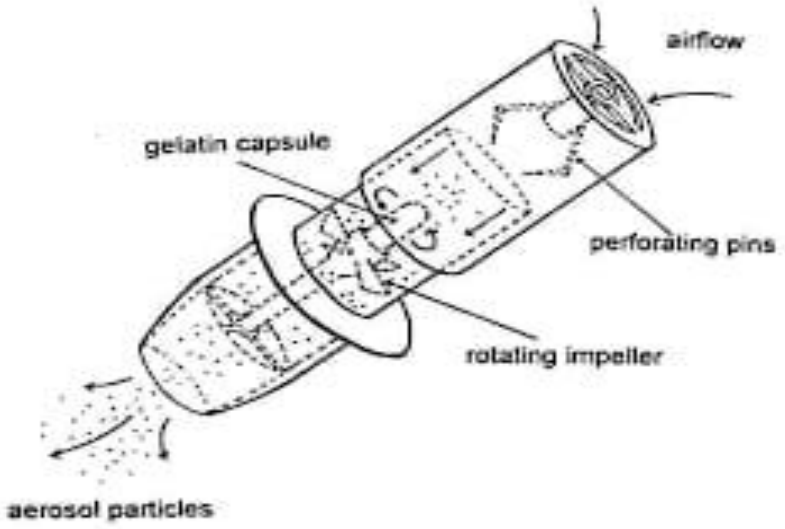
2) The Spinhaler allowed for easier patient use and enabled manufacturers to create powders with improved shelf-life stability. This was achieved by reducing the need for precise coordination on the part of the patient.

Disadvantages:

1) The device needs to be loaded before each use since it is designed to deliver a single dose.

2) Certain patients may experience difficulties in administering Spinhaler formulations and may have an intolerance towards its use

Fig: Spinhaler



b) Rotahaler: -

Place the capsule into the rotahaler with the coloured end facing inward, rotate the rotahaler to rupture the capsule. Inhale deeply to allow the powder to enter the airway. Multiple breaths may be necessary, and there is no need for coordination with the aerosol.

Advantages:

1) It possesses a compact and user-friendly design, suitable for the majority of patients.

2) Breath coordination is not required.

Disadvantages:

1) Each dose must be loaded on every occasion.

2) Loading the rotahaler can be challenging for individuals with limited finger or hand mobility.

3) Due to its high inspiratory flow rate requirement, it may not be suitable for individuals of all age groups.

4) Humidity can occasionally impact the effectiveness of the capsules

Table1: DPI administered through Rotahaler

Drug	Strength	Brand
Beclomethasone dipropionate	200mcg, 400 mcg	Bacoside rotahaler
Salbutamol	200mcg	Ventolin rotahaler

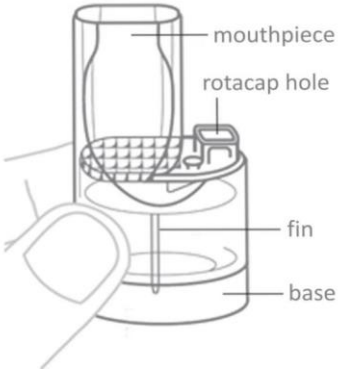


Fig-Rotahaler

2] <u>Multidose DPI: -</u>

Multidose devices use a circular disk with four or eight powder doses, which can last for one to two days. The doses are kept in separate aluminium blister reservoirs until just before inspiration. This device is a true multidose device, with 60 doses in a foil-foil aluminium strip that is opened only at the point just prior to patient inspiration.

It consists of,

a) Turbohaler

b) Disk haler

a] Turbohaler: -

The dry powder inhaler is conveniently accessible for easy to use, effectively eliminating the requirement for a carrier and the loading of individual dose.

Advantages:

1] Shaking before use is not necessary, unlike pMDI's.

2] The device will release all the powder when the patient inhales the first 200 ml of air.

3] The device is user-friendly, compact in size, and should be used according to the provided instructions.

4] Breath coordination is not required.

5] The device has the ability to hold multiple doses.

6] An attached whistle adapter allows for the assessment of adequate inspiratory flow.

Disadvantages:

1] The complete emptiness of the inhaler lacks a definitive guide.

2] It is not appropriate for individuals of all age groups.

3] Failure to maintain an upright position during the loading process of the turbohaler may result in the incorrect delivery of the prescribed dosage.

Table 2: DPI administered through Turbohaler

Drug	Strength	Brand name
Budesonide	100,200,400 mcg	Pulmicort
Terbutaline sulphate	500 mcg	Bricanyl
Formoterol fumarate	612 mcg	Oxis
Salbutamol sulphate	50,100 mcg	---

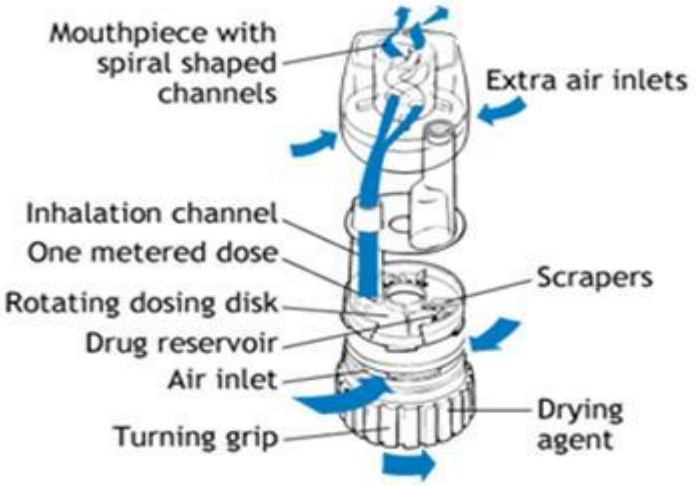


Fig-Turbohaler

b) Disk haler: -

The Disk haler, manufactured by GlaxoSmithKline, is a multiunit dose DPI device that serves as an alternative to the Rotahaler24. It comprises a medication disk, hinged lid, piercing needle, and dose indicator. The disk is inserted into a cartridge unit and then inserted into the outer body. The piercing needle punctures

the blister, allowing the medication to be inhaled through the mouthpiece. Additionally, a coarse mesh is included to induce turbulence in the airflow, promoting de-aggregation.

Advantages:

1] It is more use in comparison to pMDI's25.

2] It is convenient in size and design, making it effortless to use.

3] Breath coordination is not required.

Disadvantages:

1] Limited dosages for every disk.

2] More than one inspiration can be needed for each dosage.

3] Not appropriate for all ages and needs strong

Table 3: DPI administered through Disk haler

Drug	Strength	Brand
Salbutamol	200,400 mcg	Vento disks
Beclomethasone Dipropionate	100,200,400 mcg	Bicodisk
Salmeterol xinafoate	50 mcg	Servant
Fluticasone propionate	50,100,250 mcg	Flixotide

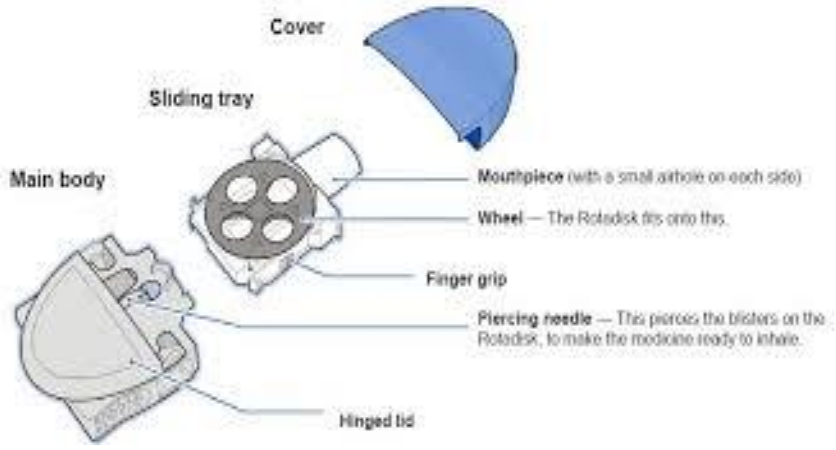


Fig-Disk haler

The patient's dose from the DPI or inhaler is determined by a number of factors [46-48]

1) The patient's inspiratory flow rate

2) The formulation's flow properties

3) the drug carrier interaction and particle size.

4) the inhaler device's performance, including aerosol generation, delivery, and inhalation method.

Need of advancement in DPIs:

The patients' efforts, which are determined by the DPI's internal resistance, are essential in achieving sufficient inspiratory flows for a uniform and effective dose distribution. Individuals who have severe airway blockage discover High resistance is undesirable since it takes more work to produce the Ventilatory flow [49]. As patients with respiratory problems typically have low inhalation flow rates, the dependence of DPIs on inspiratory flow rate is a cause for concern [50].

Loading capsules into single unit DPI devices is necessary for the inhalation process to commence. However, the high dose variability caused by the inhalation process can persist until the capsule is completely empty. Additionally, the capsules may become soft due to high temperatures, which can make them challenging to perforate [51].

Turbuhaler and other multidose DPI devices have some problems with patient feedback because the inhaled particles are not tasted or felt by the patient. Variations between devices and doses are high, and the device cannot be filled again. Particle agglomeration causes the amount of drug released from the DPI devices to decrease in high humidity [51,52].

Recent advances in dry powder inhaler:

DPIs are strong competitors to pMDIs due to their ability to administer multiple doses of medication over an extended period. DPIs are equipped with an indicator that alerts users when the drug supply is running low [53]. Unlike pMDIs, DPIs do not require coordination between inhalation and actuation, as the medication automatically follows the path of the inhaled air. The majority of DPIs on the market based on the patient's inhalation effort to lift the powdered medication from the reservoir. This inhalation effort also aids in breaking down the powder into smaller particles that can effectively reach the patient's lungs. The performance of DPIs is primarily influenced by the patient's inspiratory flow rate and the design of the inhaler [54]. In DPI many recent advances have been seen. Research is currently being conducted to enhance the effectiveness of drug delivery from DPIs by modifying formulation technology, developing new drugs, carriers, and devices. The primary goals in the development of new DPIs are to reduce reliance on high inspiratory flow rates and enhance the dispersion of drug particles for more efficient systems.

Agertoft and Pedersen demonstrate that DPIs are superior to pMDIs in the management of asthma. When patients transitioned from nebulizers to Turbohalers, the dosage was decreased [55].

Improvements in DPI performance can be achieved through changes in device design or powder formulation. The particle-particle interactions in agglomerates and the forces involved in deagglomeration play a significant role in this process. Recent developments in powder formulation aim to reduce adhesive and cohesive forces between particles to increase the FPF. Supercritical fluid technology is used to improve the surface properties of the drug substance, while large porous particles with reduced inter-particulate forces and improved aerodynamic behaviour are claimed to reduce phagocytosis in the alveoli. Smaller porous particles have also been used to improve deagglomeration and lung deposition. New device developments focus on increasing deagglomeration forces during inhalation, with active and passive devices available. Passive devices rely on the kinetic energy of the inhalation flow generated by the patient, while active devices apply impaction forces for aerosol generation [56].

The characteristics of the advanced DPIs are displayed in Table-4

Table-4 Various characteristics of advanced DPIs

Device name	Characteristics	Drug used in study
Novolizer	Multidose breath actuated by DPI. The airflow is generated by Multiple supply channels, producing Cyclones during inhalation. Dosage stop system released dose only when previous dose was correctly inhale.	Budesonide Salbutamol formoterol
Airmax	A multi dose dry powder inhaler That has similar mechanism of novolizer and is more efficient than turbohaler. It is easier to uses control air pressure for measuring the drug dose by internal pump.	Salbutamol Budesonide
Exubera	Energy is used as a key factor for the particle deagglomeration Process. An air chamber is activated by pressure. It is designed by aerosolizing insulin	Insulin

Microdose	Battery operated, low cost, handled, Usable, multiunit dose device which operate use in vibrating piezoelectric element to generate aerosol mist. These are highly efficient at inspiratory flow rate	Insulin corticosteroid Long and short actin agonist Beta agonist and anticholinergic.
Spiros	Battery-powered electrically driven Systems, operates at very low inspiratory flow rates. Lungs deposition of 40.5% was observed with beclomethasone at flow rate 15 /min.	Corticosteroid (Beclomethasone).

Nebulizer: -

A nebulizer is a medical instrument utilized for delivering medication in the form of a mist that can be inhaled into the lungs through a mouthpiece or mask. Nebulization is a widely employed technique for generating aerosols, and it is used worldwide by both adults and children for emergency treatment of acute illnesses and long-term management of pulmonary conditions like asthma and COPD [(57)]. The word ‘’nebulizer’’ was derived from the Latin word ‘’nebula’’ means ‘’mist’’ and it was first introduced in 1872[(58)]. These devices produce a moist mist that can penetrate deep into the respiratory system and quickly relieve bronchial muscle tension. Nebulizers employ compressed gas or a compressor (electric/battery-operated) to transform the medication from a solution into an aerosol form, generating tiny droplets that can effectively reach the alveolar region. Typically, a gas flow of around 6-8 L/min is necessary to operate the nebulizer. The nebulizer utilizes oxygen, compressed gas, or ultrasonic power to disperse the drug solution and administer the therapeutic dosage directly into the lungs [(59)]. Bronchodilators are frequently utilized in nebulized format, although numerous other medications can also be administered via nebulization, including steroids and antibiotics. Nebulizers are experiencing a decrease in usage, although there are still certain patients who prefer them. Nebulizer solutions are composed of drug solutions that are combined with excipients in order to attain the intended objective. Sodium citrate is a frequently employed excipient in nebulizer formulations, serving as a buffer component. Polysorbate 80 acts as a surfactant, while disodium edentate functions as a chelating agent for cations, enhancing stability. Sodium chloride is used for isotonicity adjustment, and sodium hydroxide, hydrochloric acid, and sulphuric acid are employed for pH adjustment or to maximize drug

stability. Nitrogen is utilized for headspace sparging to reduce oxidation, and calcium chloride is included to facilitate the biological activity of DNase. The existing nebulizer solutions are sterile and are packaged as unit-dose-form vials to ensure the prevention of anti-microbial agents from entering [60].

Types of Nebulizers:

A) Jet nebulizer

B) Ultrasonic nebulizer

A] Jet nebulizer:

It is also called as ‘’atomiser’’ [61] or ‘’pneumatic nebulizer ‘’ and it is widely used in paediatric and adult patients [62]. The initial technological advancement in producing aerosol was the development of the jet nebulizer. The medication is drawn up through a capillary tube from the nebulizer reservoir using 2 to 10 L/min of pressurized gas in these nebulizers. This creates a wide range of particle sizes that are blasted into one or more baffles, which remove larger particles from suspension and return them to the reservoir. Formulations that cannot be delivered with pressurized metered-dose inhalers (pMDIs) or dry powder inhalers (DPIs) can be effectively delivered with jet nebulizers. Jet nebulizers can be used to administer antibiotics, mucolytics, liposomal formulations, and recombinant products like Pulmozyme Inhalation Solution, among other medications. On the other side, jet nebulizers Can be difficult to use because of their need for compressed gas and additional tubing. Their inefficiencies in medicine delivery have been shown by many research studies [63-65]. These factors have resulted in the development of new kinds of jet nebulizers over time.

The jet nebulizers are based on the Bernoulli’s theorem, which states that the formation of aerosol is caused by a high-velocity air stream from the pressurized source [66] . The main parts of jet nebulizers are compressors, nebulizer chambers, mouthpieces, or facemasks. Jet nebulizers also use baffles as they serve a surface for the collision of aerosol droplets, where the droplets aggregate and return to the reservoir. Large particles are divided into smaller particles that follow the airflow when they collide with one or more baffles.

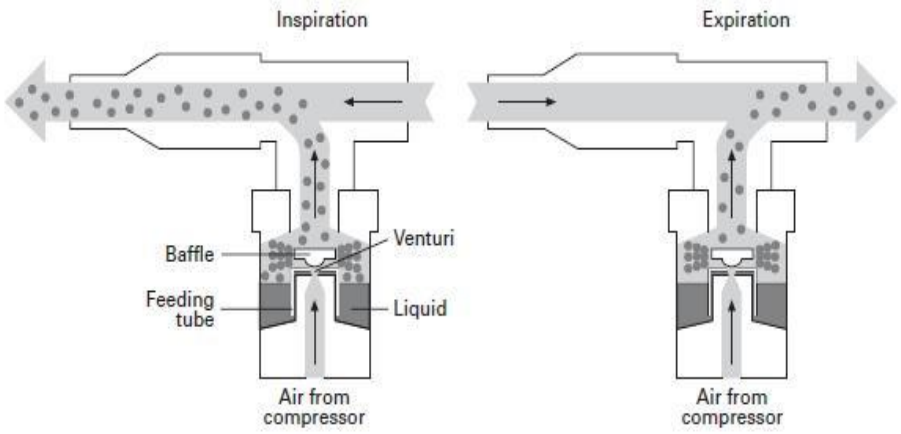


Fig- Jet Nebulizer

Jet nebulizers are divided into four types:

(1) jet nebulizers with a Corrugated tube.

(2) jet nebulizers with a collection bag.

(3) breath enhanced jet nebulizers.

(4) breath-actuated jet nebulizers.

1] Jet nebulizer with a corrugated tube –

Conventional constant-output nebulizers that produce continuous aerosol during inspiration, expiration, and breath-hold are jet nebulizers with a corrugated tube. While the jet nebulizer's corrugated tube acts as a reservoir, this kind of nebulizer still experiences significant drug loss during expiration. These nebulizers' restricted portability, need for compressed air or gas sources to function, and variation in nebulizers are further drawbacks [67-69]. Although corrugated tube jet nebulizers have a number of drawbacks, they are simple to use and have an excellent record of promoting patient adherence to therapy [70].

2) Jet nebulizer with a collecting bag: -

A jet nebulizer that has a collection bag is known as a dosimetric nebulizer because it only releases aerosol when inhaled. Through a one-way valve that is situated between the mouthpiece and the collection bag, aerosols produced during expiration are collected and given to the patient with the subsequent inspiration. One example of this kind of nebulizer is the Circulaire (Westmed INC, Tucson, AZ). When used on patients admitted to the emergency room because of bronchospasm, it improves peak expiratory flow, heart rate, and respiratory rate, making it a better clinical profile than jet nebulizers with corrugated tubing [71]. Further, by reducing the quantity of medication that leaks into the surroundings, the Circulaire protects caregivers from exposure [72-73] and enhances the delivery of aerosol drugs to patients' airways [72-74].

3) Breath enhanced jet nebulizer: -

Breath-enhanced jet nebulizers have one-way valves in the mouthpiece that allow more aerosol to be released during inhalation. Through the use of a negative pressure produced by the patient's inspiratory effort, they produce aerosols. Breath enhanced jet nebulizers include the PARI LC Plus (PARI, Midlothian, VA), PARI LCD (PARI, Midlothian, VA), and NebuTech (Salter Labs, Arvin, CA). It should be highlighted that while breath-enhanced nebulizers are more efficient than jet nebulizers with corrugated tubing, different breath-enhanced nebulizers have varying residual volumes and particle sizes [75-77].

4) Actuator jet nebulizer: -

Aero Eclipse (Monoghan/Trudell Medical International, London, Ontario, Canada) is an example of a breath-actuated jet nebulizer (BAN) that senses the patient's inspiratory flow and only delivers aerosol on inspiration. As a result, while these nebulizers reduce medication waste during aerosol therapy, they may lengthen the course of treatment [(78)]. The top portion of the Autoclips nebulizer has a green button that moves up and down to indicate to the patient when the nebulizer is activated. When the patient inhales, the actuator button descends and the aerosol is produced. During expiration, the actuator returns to its closed position, stopping the production of aerosol until the patient takes a breath. It releases aerosol in reaction to the patient's inspiratory maneuver, meaning that there is little medication lost to the surroundings. The Aero Eclipse is user-friendly and linked to a decreased frequency of unfavourable events [(79)]. A recent clinical study found that in patients experiencing an acute exacerbation of chronic obstructive pulmonary disease (COPD), the breath-actuated nebulizer was more effective in reducing respiratory frequency and lung hyperinflation [(80)].An in vitro study showed that breath-actuated nebulization produced a lower lung dose and longer treatment time in a simulated spontaneously breathing 2-4 year old child, despite a lack of studies evaluating the effectiveness of the devices in paediatric patient populations [(81)].

How to use jet nebulizer? [(82)]

It's so easy to use a jet nebulizer that kids can give themselves a treatment. Take these actions:

1) To stop the medication from getting contaminated, wash your hands.

Make sure the hose is firmly attached to the air compressor.

2) Pour your prescribed medication into the medicine cup; always double-check that the medication is correct.

3) Make sure the connection is tight by attaching the hose and mouthpiece to the medication cup.

4) Put the mouthpiece inside your lips.

5) To ensure that all of the misted medication enters your lungs, make sure to breathe deeply. Treat the patient until all of the medication is gone from the medicine cup.

6) After using the machine, turn it off.

B) Ultrasonic nebulizer: -

Since ultrasonic nebulizers can produce more than air jet nebulizers, they are typically chosen for aerosol therapy. High frequency ultrasonic waves are used to create aerosolized particles, and a piezo-electric crystal with a vibration frequency between 1.2 and 2.4 MHz is needed. The liquid formulation receives the vibration mechanism, which further creates a fountain of liquid drug made up of larger and smaller droplets. The liquid medication reservoir receives the larger droplets. The patient inhales the nebulizer's chamber, which contains the smaller droplets [(83)].

are categorised into two types,

1) large volume ultrasonic nebulizer.

2) Small volume ultrasonic nebulizer.

1) large volume ultrasonic nebulizer: -

The most popular application for large-volume ultrasonic nebulizers is the delivery of hypertonic saline for sputum induction.

2]Small player ultrasonic nebulizer: -

Inhaling medicine requires the use of small-volume ultrasonic nebulizers. As Compared to jet nebulizers, ultrasonic nebulizers have a lot of limitations. For example, they degrade heat-sensitive materials and have large residual volumes and cannot aerosolize viscous solutions. As a result, they must not be used with proteins or suspensions [84,85,86,87].

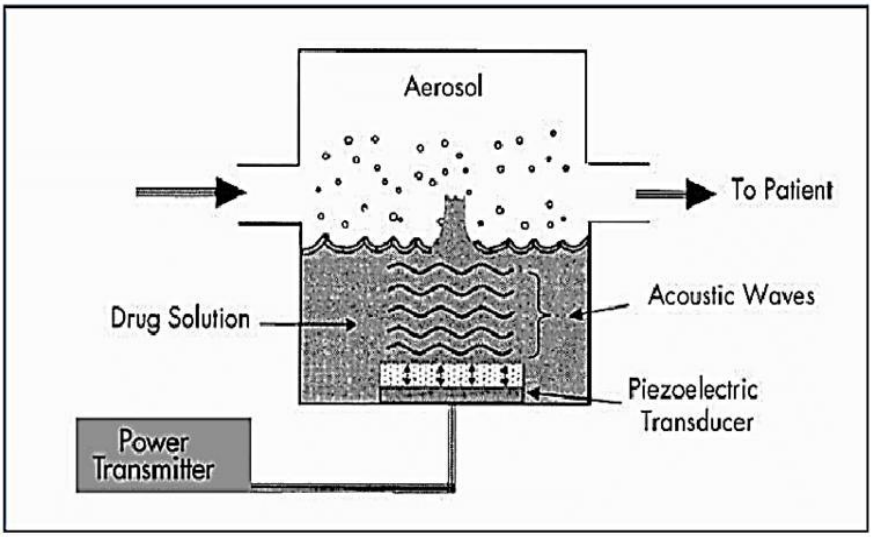


Fig: - Ultrasonic nebulizer

C) Mesh nebulizer: -

Mesh nebulizers that use micropump technology to produce aerosols are the result of recent advancements in nebulizer technology. To create aerosol, they press liquid drugs through several holes in a mesh or aperture plate. They are compact, lightweight, battery- or electricity-powered nebulizers with reduced residual volume, silent operation, quick treatment times, and enhanced output efficiency [66,70,88-90]. Mesh nebulizers have low residual volumes, a primarily fine-particle fraction that reaches the peripheral lung, consistent and improved aerosol generation efficiency, and the ability to nebulize when the dosage is low. The aerosol and the pore size Chamber, the reservoir, and the mesh natural barrier output rate can be modified for various medications to maximize aerosol Delivery of drugs to patients [89]. Mesh and ultrasonic nebulizer comparisons showed comparable medication delivery in patients who were simulated to be ventilator-dependent [91,92]. Mesh nebulizers can give patients larger doses of medication and are more effective than jet

nebulizers. While there are few human studies on mesh nebulizers, in vitro research showed that lung deposition with mesh nebulizers was roughly two to three times greater than that of jet nebulizers [93].

Mesh nebulizer can be classified into two types:

1) Active mesh nebulizer
2) Passive mesh nebulizer

1)Active mesh nebulizer: -

In order to create aerosol, active mesh nebulizers vibrate a precisely drilled mesh in contact with the medication using a piezo element that contracts and expands when an electric current is applied. Example of active nesh nebulizer is the Aeroneb (Aerogene, Galway, Ireland) and the eFlow (PARI, Starnberg, Germany)

2)**Passive mesh nebulizer :-**

In order to create aerosol, passive mesh nebulizers use a transducer horn to create passive vibrations in a perforated plate with 6000 tapered holes.

Example of passive mesh nebulizer is Micro air NE-U22 (Omron, Bannockburn, IL)

Table-Advantages and disadvantages of different types of nebulizers

NEBULIZERS	ADVANTAGES	DISADVANTAGES
Jet nebuliser with corrugated tube	• Cheap • Easy to use • Effective than pMDI and DPIs for administering medication	• Inefficient • Difficult to clean • Need to compress gas
Breath -actuator and Breath-enhanced Jet nebuliser Ultrasonic nebuliser	• Easy to use • Less loss of medication • More effective than Jet nebuliser with tubing • Delivery of drug only during inhalation • Easy to use	• More expensive • Take longer time to deliver drug • Need sufficient flow to start the drug delivery prosses • Large residual volume • Degradation of heat sensitive materials

	• More effective than jet nebuliser	• Not able to aerosolised the viscous solution
Mesh nebuliser	• Easy to use • More efficient than other nebulisers • Fast, Quiet, Portable • Sel contain power source	• More expensive • Difficult to clean • Not compatible with viscous liquids or those crystallize the on drying

References: -

1.Composition and Aerosol Spray Dispenser for Eliminating Odors in Air US patent, 20,070,194,040 A1, 2007

2.A book of pharmaceutics by prof R.M Mehta, 6th edition,2019, Page no:

3.Thiel CG. How can we describe the respirability of pharmaceutical aerosols? J Aerosol Med 1997;10(3):2–4.

4.3 Newman SP, Clarke SW. Inhalation devices and techniques. In Asthma, 3rd edn, eds Clark TJH, Godfrey S, Lee TH. London: Chapman & Hall, 1992; 469–505.

5. Clark AR. Medical aerosol inhalers: past, present, and future. Aerosol Sci Technol. 1995;22: 374–91.

6. Hardy JG, Jasuja AK, Frier M, Perkins AC. A small volume spacer for use with a breath-operated pressurised metered dose inhaler. Int J Pharmaceut. 1996;142(1):129–33.

7.M. Ibrahim, R. Verma, L. Garcia-Contreras, Inhalation drug delivery devices technology update, Med. Devices Auckl. (Auckl) 8 (2015) 131

8.Paul J. Atkins and Timothy M. Crowder. The Design and Development of Inhalation Drug Delivery Systems. Modern Pharmaceutics by Marcel Dekker, P.1-31.

9.Hindle M and Byron Pr. Dose Emissions from Marketed Dry Powdered Inhalers. Int J Pharm. 1999;116–169., Dehradun-248001, Uttarakhand, India

10.Tangri and S. Khurana DIT-Faculty of Pharmacy, Mussoorie Diversion Road, Bhagwantpura

11. Basavaraj K, Nanjwade, Sagar A. Adichwal PDA journal of pharmaceutical science and technology vol.65 no. 5 513-534

12. SR Thorat, SM Meshram “Formulation and product development of pressurised metered dose inhaler: An overview.” Vol. 3, Issue 9 magazine.pharmatutor.org pp 53-64

13. Federico Lavorini, "The Challenge of Delivering Therapeutic Aerosols to Asthma Patients." Hindawi Publishing Corporation ISRN Allergy, Volume 2013, 17 pages.

14.Dowing R. C., "Theory and practice of aerosols", In: Aerosol: Science and Technology; Shepherd H. R. (Ed.), 213, pp. 17-29 (1961).

15.June D, Miller N. ET. Al, "Conceptual mode for the development of pressurized metered dose aerosols", Pharm. Tech., 18: 44 (1994).

16.Evans R. M., Farr. S. J. ET. Al, "Formulation and in-vitro evaluation of pressurized inhalation aerosols containing isotropic systems of lecithin and water", Pharm. Res., 8: 629-630 (1991).

17. Molina M. J., Rowland F. S. ET. Al., "Stratospheric sink for chlorofluoromethanes: chlorine atom-catalysed destruction of ozone", Nature; 249: 810-812 (1974).

18.Manzer L. E., "The CFC-Ozone issue: Progress on development of alternatives to CFCs", Science; 249: 31-35 (1990).

19.C Tsagogiorgas, J Krebs, M Pukelsheim, G Beck, B Yard, B Thweisinger, M Quintel T Luecke "Semiflurinated Alkanes A new Class of excipients suitable for pulmonary drug delivery." European Journal of Pharmaceutics and biopharmaceutics (EJPB) Vol 76 issue 1 Sep 2010 page 75, 76 (2010).

20. Wiley J, Bekker M., "Pressurized containers", In: Encyclopedia of Packaging Technology; pp. 548-549 (1986).

21. Sciarra J., "Aerosol suspensions and emulsions", In: Pharmaceutical Dosage Forms- Disperse Systems; Liberman H. A., Rieger M. M. (Eds), 10th Ed., Marcel Dekker Inc., Vol. 12, pp. 49- 492 (1990).

22.Cooper D. and Sethachutkul K., "Effect of actuator design on MDI plume particle size", Pharm. Tech.; 16: 84-86 (1992).

23.Crompton GK. Breath-activated aerosol. Br Med J. 1971;2(5762):652–653.

24. Lenney J, Innes JA, Crompton GK. Inappropriate inhaler use: assessment of use and patient preference of seven inhalation devices. EDICI. RespirMed. 2000;94(5):496–500.

25. Newman SP. Principles of metered-dose inhaler design. Respir Care. 2005;50(9):1177–1190.

26.Kelkar MS, Dalby RN. Effervescent aerosols: a novel formulation technology for pressurized metered dose inhalers. In: Dalby RN, Byron PR, Peart J, Suman JD, Farr S, Young PM, editors. Respiratory Drug Delivery. River Grove, IL: Davis Healthcare International Publishing, LCC; 2014:669–672

27.M.L. Everard, Role of inhaler competence and contrivance in "difficult asthma" Paediatr. Respir. Rev. 4 (June (2)) (2003) 135–142.

28.B.K. Nanjwade, S.A. Adichwal, K.R. Gaikwad, K.A. Parikh, F.V. Manvi, Pulmonary drug delivery: novel pharmaceutical technologies breathe new life into the lungs, PDA J. Pharm. Sci. Technol. 65 (September (5)) (2011) 513–534.

29. D.E. Geller, comparing clinical features of the nebulizer, metered-dose inhaler, and dry powder inhaler, Respir. Care 50 (October (10)) (2005) 1313–1322.

30. A. Ari, J.B. Fink, Guidelines for aerosol devices in infants, children and adults: which to choose, why and how to achieve effective aerosol therapy, Expert Rev.Respir. Med. 5 (August (4)) (2011) 561–572.

31. F. Lavorini, M.L. Levy, C. Corrigan, G. Crompton, The ADMIT series-issues in inhalation therapy. 6) Training tools for inhalation devices, Prim. Care Respir. J. 1 (November (4)) (2010) 335.

32. B. Ding, M. Small, G. Scheffel, U. Holmgren, Maintenance inhaler preference, at-tribute importance, and satisfaction in prescribing physicians and patients with asthma, COPD, or asthma–COPD overlap syndrome consulting for routine care, Int.J. Chron. Obstruct. Pulmon. Dis. 13 (2018) 927.

33. PRODUCT MONOGRAPH PR FLOVENT® HFA fluticasone propionate inhalation aerosol 50, 125, and 250 mcg/metered dose PR FLOVENT® DISKUS® fluticasone propionate powder for inhalation 100, 250, and 500 mcg/blister.

34. Paul J. Atkins and Timothy M. Crowder, Paul J. Atkins and Timothy M. Crowder, "The Design and Development of Inhalation Drug Delivery Systems", modern pharmaceutics by Marcel Dekker p.1-31.

35. Manfred Keller, "Innovations and perspectives of metered dose inhalers in pulmonary drug delivery", international journal of pharmaceutics 186 (199) 81-90.

36.www.cipladoc.com

37.Franklin W, Lowell FC, Michelson AL, Schiller IW. Aerosolized steroids in bronchial asthma. J Al-lergy. 1958;29(3):214–21.

38.Bloomfield P, Crompton GK, Winsey NJ. A tube spacer to improve inhalation of drugs from pressurised aerosols. Br Med J. 1979;2(6203):1479.

39.Smith IJ, Parry-Billings M. The inhalers of the future? A review of dry powder devices on the market today. Pulm Pharmacol Ther. 2003;16(2):79–95.

40.Srichana T, Martin GP, Marriott C. Dry powder inhalers: the influence of device resistance and powder formulation on drug and lactose deposition in vitro. Eur J Pharm Sci. 1998;7(1):7380.

41.Crompton GK. Dry powder inhalers: advantages and limitations. J Aerosol Med. 1991;4(3):151–6.

42. Zeng XM, Martin GP, Tee SK, Ghoush AA, Marriott C. Effects of particle size and adding sequence of fine lactose on the deposition of salbutamol sulphate from a dry powder formulation. Int J Pharm.1999;182(2):133–44.

43.Louey M, Stewart P. Particle interactions involved in aerosol dispersion of ternary interactive mixtures. Pharmaceutical Research. 2002;19(10):1524–31.

44.Islam N, Gladki E. Dry powder inhalers (DPIs)—a review of device reliability and innovation. Int J Pharm. 2008;360(1–2):1–11

45.Atkins PJ. Dry powder inhalers: an overview. Respir Care. 2005;50(10):1304–12.

46. Hess DR. Metered-dose inhalers and dry powder inhalers in aerosol therapy. Respir Care. 2005;50(10):1376–83.

47. Chan HK. Dry powder aerosol delivery systems: current and future research directions. J Aerosol Med. 2006;19(1):21–7.

48. Colthorpe P, Voshaar T, Kieckbusch T, Cuoghi E, Jauernig J. Delivery characteristics of a low-resistance dry-powder inhaler used to deliver the long-acting muscarinic antagonist glycopyrronium. J Drug Assess 2013;2(1):11-6.

49.Ashurst II, Malton A, Prime D, Sumby B. Latest advances in the development of dry powder inhalers. Res Focus 2000;3(7):246-56.

50.O'Connor BJ. The ideal inhaler: Design and characteristics to improve outcomes. Respir Med 2004;98 Suppl A: S10-6.

51.Burnell PK, Small T, Doig S, Johal B, Jenkins R, Gibson GJ. Ex-vivo product performance of Diskus and Turbuhaler inhalers using inhalation profiles from patients with severe chronic obstructive pulmonary disease. Respir Med 2001;95(5):324-30.

52.Garg T, Chanana A. Dry powder inhalers- recent trends. Indo-global Res J Pharmaceut Sci. 2012;2(4):443–9.

53. de Boer AH, Le Brun PP, van der Woude HG, Hagedoorn P, Heijerman HG, Frijlink HW. Dry powder inhalation of antibiotics in cystic fibrosis therapy, part 1: development of a powder formulation with colistin sulfate for a special test inhaler with an air classifier as de-agglomeration principle. Eur J Pharm Biopharm. 2002;54(1):17–24.

54.Agertoft L, Pedersen S. Effects of long-term treatment with an inhaled corticosteroid on growth and pulmonary function in asthmatic children. Respir Med. 1994;88(5):373–81.

55.Manfred Keller, "Innovations and perspectives of metered dose inhalers in pulmonary drug delivery", international journal of pharmaceutics 186 (199) 81-90

56.Terzano C, Petroianni A, Parola D, Ricci A. Compressor/nebulizers differences in the nebulization of corticosteroids. Eur Rev Med Pharmacol Sci. 2007;11(4):225–37.

57. Collins N. Nebulizer therapy in cystic fibrosis: an overview. J R Soc Med. 2009; 102:11–7.

58. Brocklebank D, Wright J, Cates C. Systematic review of clinical effectiveness of pressurised metered dose inhalers versus other hand-held inhaler devices for delivering corticosteroids in asthma. BMJ. 2001;323(7318):896.

59.Rakesh Pahwa P, Manisha S, Mona P, Avneet Kaur L. Nebulizer therapy: a platform for pulmonary drug delivery. Der Pharmacia Sinica. 2012;3(6):630–6

60.Finlay WH. The Mechanics of Inhaled Pharmaceutical Aerosols An Introduction Academic Press: London; 2001.

61.Terzano C, Petroianni A, Parola D, Ricci A. Compressor/nebulizers differences in the nebulization of corticosteroids. Eur Rev Med Pharmacol Sci. 2007;11(4):225–37.

62. Hess D, Fisher D, Williams P, Pooler S, Kacmarek RM. Medication nebuliz-er performance. Effects of diluent volume, nebulizer flow, and nebulizer brand. Chest 1996; 110: 498-505.

63. Zainudin B, Biddiscombe M, Tolfree SE, Short M, Spiro SG. Comparison of bronchodilator responses and deposition patterns of salbutamol in-haled from a pressurised metered dose inhaler, as a dry powder, and as a nebulised solution.

64.Smith EC, Denyer J, Kendrick AH. Comparison of twenty-three nebulizer/compressor combinations for domiciliary use. Eur Repir J 1995; 8: 1214-21.

65.Hickey AJ. Pharmaceutical inhalation aerosol technology, Second Ed. Marcel Dekker, NY, USA. 2004.

66.Ari A, Hess D, Myers TR, Rau JL. A guide to aerosol delivery devices for respiratory therapists. 2nd ed. Dallas, Texas: American Association for Respiratory Care; 2009.

67. Ari A, Fink J Guidelines for aerosol devices in infants, children and adults: which to choose, why and how to achieve effective aerosol therapy? Ex-pert Rev Respir Med 2011; 5: 561-72.

68. Ari A, Restrepo RD, American Association for Respiratory Care. Aerosol delivery device selection for spontaneously breathing patients: 2012. Respir Care 2012; 57: 613-26.

69. Waldrep JC, Dhand R. Advanced nebulizer designs employing vibrating mesh/aperture plate technologies for aerosol generation. Curr Drug Deliv 2008; 5: 114-9.

70. Hoffman L, Smithline H. Comparison of Circulaire to conventional small volume nebulizer for the treatment of bronchospasm in the emergency department. Respir Care 1997; 42: 1170-4.

71. Mason J, Miller W, Small S. Comparison of aerosol delivery via Circulaire system vs conventional small volume nebulizer. Respir Care 1994; 39: 1157-61.

72. Mason J, Miller W. Comparison of aerosol delivery via Circulaire nebulizer system versus a disposable nebulizer in COPD patients. Respir Care 1996; 41: 1006-8.

73. Piper SD. In vitro comparison of the circulaire and Aero Tee to a traditional nebulizer T-piece with corrugated tubing. Respir Care 2000; 45: 313-9.

74.Coates AL, MacNeish CF, Lands LC, Meisner D, Kelemen S, Vadas EB. A comparison of the availability of tobramycin for inhalation from vented vs unvented nebulizers. Chest 1998; 113:951-6.

75. Dennis J. Drug nebulizer design and performance: breath enhanced jet versus ultrasonic. J Aerosol Med 1995; 8: 277-80.

76. Ho SL, Kwong WT, O'Drowsky L, Coates AL. Evaluation of four breath enhanced nebulizers for home use. J Aerosol Med 2001; 14: 467-75

77. Rau JL, Ari A, Restrepo RD. Performance comparison of nebulizer designs: constant-output, breath-enhanced, and dosimetric. Respiratory Care 2004; 49: 174-9.

78. Arunthari V, Bruinsma RS, Lee AS, Johnson MM. A prospective, comparative trial of standard and breath-actuated nebulizer: efficacy, safety, and satisfaction. Respir Care 2012; 57: 1242-7.

79.Haynes J. Randomized controlled trial of a breath-activated nebulizer in patients with exacerbation of COPD. Respir Care 2012; 57: 1385-90.

80. Lin HL, Wan GH, Chen YH, Fink JB, Liu WQ, Liu KY. Influence of nebulizer type with different pediatric aerosol masks on drug deposition in a model of a spontaneously breathing small child. Respir Care 2012; 57: 1894-900

81.https://www.oxygenconcentratorsupplies.com/articles/what-is-a-jet-nebulizer/

82.P.G. Rogueda, D. Traini, The nanoscale in pulmonary delivery. Part 2: formulation platforms, Expert Opin. Drug Deliv. 4 (November (6)) (2007) 607–620

83. Ari A, Fink J Guidelines for aerosol devices in infants, children and adults: which to choose, why and how to achieve effective aerosol therapy? Ex-pert Rev Respir Med 2011; 5: 561-72.

84.Ari A, Restrepo RD, American Association for Respiratory Care. Aerosol delivery device selection for spontaneously breathing patients: 2012. Respir Care 2012; 57: 613-26.

85.Watts AB, McConville JT, Williams RO 3rd. Current therapies and technological advances in aqueous aerosol drug delivery. Drug Dev Ind Pharm 2008; 34: 913-22.

86. Taylor K. Ultrasonic nebulizers for pulmonary drug delivery. Int J Pharm1997; 153: 93-104.

87. Rau JL. The inhalation of drugs: advantages and problems. Respir Care 2005; 50: 367-82.

88. Dhand R. Nebulizers that use a vibrating mesh or plate with multiple apertures to generate aerosol. Respir Care 2002; 47: 1406-16.

89. Dolovich MB, Dhand R. Aerosol drug delivery: developments in device design and clinical use. Lancet 2010; 377: 1032-45.

90.Pedersen K, Handlos V, Heslet L, Kristensen H. Factors influencing the in vitro deposition of tobramycin aerosol: a comparison of an ultrasonic nebulizer and a high-frequency vibrating mesh nebulizer. J Aerosol Med 2006; 19: 175-83.

91. Ari A, Areabi H, Fink JB. Evaluation of aerosol generator devices at 3 locations in humidified and non-humidified circuits during adult mechanical ventilation. Respir Care 2010; 55: 837-44.

92. Ari A, Atalay OT, Harwood R, Sheard MM, Aljamhan EA, Fink JB. Influence of nebulizer type, position, and bias flow on aerosol drug delivery in simulated pediatric and adult lung models during mechanical ventilation. Respir Care 2010; 55: 845-51.

93. Vecellio L, De Gersem R, Le Guellec S, Reychler G, Pitance L, Le Pennec D, Diot P, Chantrel G, Bonfils P, Jamar F. Deposition of aerosols delivered by nasal route with jet and mesh nebulizers. Int J Pharm2011; 407: 87-94.