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REVIEW

Update on the Efficacy of Aerosol Therapy Delivered to Obstructive Lung Disease Patients

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ABSTRACT

The distribution of many medications to the body via the respiratory tract system is crucial. This route has emerged as one of the most crucial techniques for the delivery of locally acting medications that can be used to treat a variety of respiratory conditions, including asthma and chronic obstructive pulmonary disease (COPD). The advantages of this focused drug delivery to the lungs over systemic administration methods include an improved therapeutic effect, a faster onset of action, and fewer systemic side effects.

Many formulations as suspension and solutions, such as bronchodilators, corticosteroids, and antibiotics have been recommended in a wide area as aerosolized medications and therapy for different pulmonary diseases. An aerosol drug is one that consists of solid or liquid particles of a specified size suspended in a gas. A variety of aerosol delivery devices are available in the marketplace which can be used for this purpose.

However, the pulmonary architecture poses a significant problem for aerosol drug delivery since it evolved to keep foreign chemicals from entering the lung periphery. Therefore, the site and degree of deposition in the respiratory tract, as well as the pharmacology of the utilized inhaled medications, all play a role in how well inhalation treatment works. As a result, in addition to the devices required for the release of aerosols and the facilitation of their distribution to the lungs, aerosols must also satisfy a number of parameters for inhaled medicine delivery to be successful. Due to this, parenteral and oral drug delivery by inhalation are more complicated.

Keywords: Aerogen ultra, Holding chamber, Aeogen solo, Vibrating mesh nebulizer, Total inhalable dose

1. Introduction

Deposition of aerosolized pharmaceuticals is the movement of the aerosol's particles toward the airway surfaces, which can only have an impact after passing through the oropharynx and coming into contact with them after being inhaled into the respiratory system [6].

The lung is divided into two distinct areas, referred to as the conducting zone and the respiratory zone respectively, as shown in Fig. 1 [8]. The respiratory zone, which has 7 generations from the 17th to the 23rd generation of airways, is where gas exchange between air and blood takes place. The conducting zone, which has 16 generations of airways, is exclusively engaged in the conduction of inhaled air. In order to manage the volume of air that enters the lungs, smooth muscle in the bronchi and bronchioles of the respiratory tract can contract and relax [7].

Many aerosolized medications that aim to work systemically, such as chemotherapy and insulin, are thought to enter the body through the lung. It should be directed toward alveolar region which provide optimal systemic absorption. The lung is the exclusive

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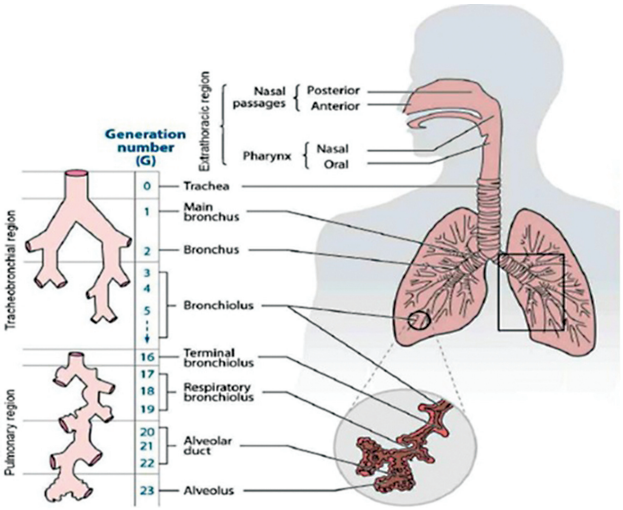

Fig. 1. Airway geometry and depiction of 23 generations of airways separated into conducting and respiratory zones [8].

organ that receives all of the cardiac output. Additionally, there are between 200 million and 600 million alveoli, resulting in a large surface area with an epithelium that has a single, extremely thin cellular layer with a thickness of between 0.2 and 0.7 μm.

Drug bioavailability is increased 10–200 times more than that of nasal and gastrointestinal absorption due to a thin diffusion layer (alveolar vascular permeable barrier) with a sluggish surface clearance and a comparatively low enzymatic controlled environment [9, 10].

To be successful, inhaled medication must reach the specific lung areas where drug receptors are situated and deposit a sufficient amount of drug. While $\beta 2$ receptors are found in the lower respiratory tract as the medium and small airways with more than 90% in the alveolar wall, muscarinic and histaminic receptors are mostly found in the large and medium sized airways [11]. This indicates that anti-muscarinic and anti-histaminic medications can be administered via the conducting airways, whereas $\beta 2$ agonists need to be administered via the periphery, specifically the medium and small airways, to have any therapeutic impact at all. When delivered to patients with mild or severe asthma, monodisperse β-adrenergic aerosols (such as salbutamol and ipratropium bromide) of 2.8 μm were found to cause greater airway dilation than equivalent doses of these aerosols of 1.5 or 5 μm, as measured by forced expiratory volume in 1 second (FEV_1) and maximum expiratory flow [12].

The varied spatial distributions of deposited particles may be to blame for the variation in bronchodilator responsiveness between aerosol sizes. The size of 2.8 μm was found to be optimal for aerosol deposition in the targeted medium and small airways and less in the alveolar region. The smaller the particle size, the better the penetration [13]. In addition, it was found that inhaled anti-inflammatories can be beneficial medications when distributed throughout the lung in inflammatory conditions like asthma due to the presence of inflammatory cells, such as lymphocytes, macrophages and eosinophils which distribute throughout the lung [14, 15].

On other hand, when aerosol is targeted toward systemic absorption like insulin in diabetes mellitus disease, it should be directed toward alveolar region that produce optimal systemic absorption. Antibiotic treatment which can be used in cystic fibrosis (CF) for example may require prolonged residence of the drug in the lungs to have the best possible therapeutic outcome. Therefore, it could be important to use a formulation like liposomes that is kept in the lungs for the required amount of time [9].

2. Mechanisms of aerosol deposition in the respiratory tract

Aerosolized drugs can only perform their effects as they contact the air surface after passing the oropharynx following inhalation. Transport or deposition of inhaled particles towards these surfaces depends on forces acting on inhaled particles and the balance between these forces [5]. Gravitational, diffusional, and inertial impaction forces, as well as to a lesser extent interception, turbulent flows, and electrostatic precipitation, are the main types of forces or mechanisms that cause particle deposition in the respiratory tract as shown in Figs. 2 and 3 [16, 17]. Deposition through sedimentation, or the settling of particles under the influence of gravity, is the first category of forces [21]. The particles which are greater than 0.5 μm in diameter are liable to this process. Since sedimentation is a time-dependent process and suggests

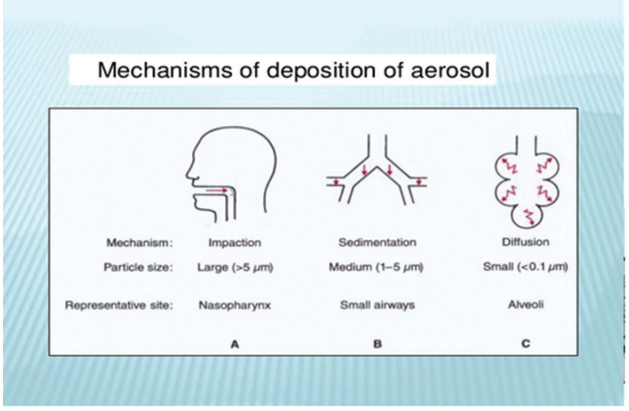

Fig. 2. Mechanisms of deposition of aerosol [21].

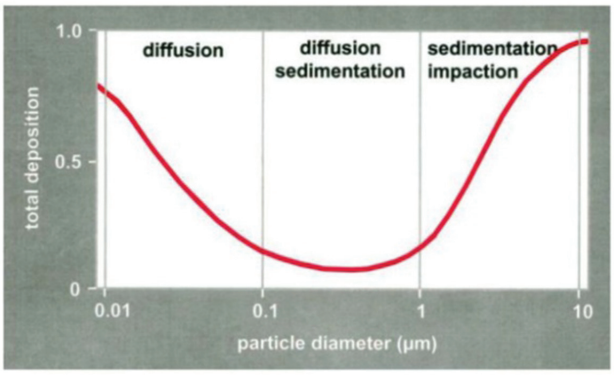

Fig. 3. Total deposition of inhaled drug in the human respiratory tract [20].

that the particles deposit higher by sedimentation when they reside in an airway duct longer time, this mechanism appears in the peripheral airways (such as small conducting airways and alveoli) when both the air velocity is low and the residence time is high [18, 19]. The second method that can be utilized for inhaled medication deposition is known as diffusion, also known as Brownian motion. This mechanism involves the random movement of particles inside a gas as a result of collisions with the gas molecules. Diffusion mechanism occurs with very fine particles which are smaller than 0.1 μm as this process increases with the decrease in particle diameter. Like sedimentation mechanism; diffusion is a time-dependent process. Therefore, deposition by diffusion primarily occurs in the peripheral airways; however, some very fine particles may be exhaled more frequently than they are deposited due to a reduction in the deposition probability that can be caused by the respiratory particles' short residence times in combination with their erratic movements [20].

Particles with velocities above 30–50 L/min and a diameter larger than 5–10 μm can be deposited in the throat via inertial impaction at bends and airway bifurcations where the air velocity is high and the airflow turbulent, as shown in Fig. 3 for the upper airways, which include the first 10 generations of the lung. As the probability of impaction occurrence increases with the particle density, particle velocity and the square of the particle diameter [5, 19].

On the other hand, interception mechanism can be referred to the mechanism that based on the shape and the size of particles and it was found that the elongated particles as the fibers for example, can be deposited by interception, unlike the spherical ones [22].

Aerosol particle deposition in the major airways and upper respiratory tract is impacted by turbulent flow or mixing. It can be described as an irregular mixing or fluctuations that the fluid experiences in a turbulent zone that causes the fluid's speed and consequently the particle trajectories to continuously fluctuate in magnitude and direction until they eventually deposit on the walls of the airways. While inertial impaction deposition is dependent on mean flow, turbulent mixing deposition of particles can come from flow fluctuations [17].

Electrostatic participation is exerted when the charged particles have charges near to airway surface, this mechanism can be stimulated [17].

3. Aerosol deposition in healthy lungs

By counting the number of inspired and exhaled particles in each breath using photometer techniques, for instance, one can assess the amount of particles deposited in the human lung. Therefore, it is possible to examine the impact of breathing patterns and particle size on the deposition of particles in a systematic way [17]. It was shown that raising the tidal volume while maintaining a constant flow rate enhanced residence time and the penetration of the aerosol in the lung. All observations demonstrated that when particles are larger than 0.5 m in diameter, deposition increases with particle size due to increased gravitational and inertial transport, whereas deposition increases with particle size for particles smaller than 0.5 m in diameter due to increased diffusive transport [23].

As a result, as the depth of inhalation and residence time increase, more particles are deposited, reflecting increased deposition by gravitational sedimentation for large particles and by Brownian diffusion for small particles. This is explained by the fact that both of these mechanisms are time-dependent and most effective in the lung periphery because the air velocities are low and the dimensions are small [24, 25].

4. Aerosol deposition in diseased lungs

Usually, lung diseases are accompanied with mucus clogging, changes in lung compliance, and airway constriction. These elements impact the distribution of inhaled medicines and their pattern of deposition. Due to the decreased airway cross-section in the diseased lung, deposition of inhaled particles is higher in obstructive lung disease patients, particularly in asthma and COPD, than in healthy people. Higher velocities in the constricted and narrower airways, such as turbulent flow and inertial impaction, are the mechanisms that cause the enhanced deposition in patients with lung diseases [26].

Additionally, compared to a healthy lung, the diseased lung exhibits more diverse deposition patterns of inhaled particles. Due to the increased deposition during expiration in airways with flow limitation, airway blockage reduces the ability of the inhaled aerosol to penetrate and hence deposit in the central regions of the lungs, leading to poorly ventilated subtended lung regions [27].

5. Factors affecting the aerosolized medications delivery to the lungs

The effectiveness of medication delivery to ensure the maximum amount of drug reaches the lung is affected by a number of variables. The patient's age, the patient-device interface, the patient's physical and cognitive ability, the patient's inhalation pattern, the clinical condition of the patient's lungs, and the patient's lung clearance mechanisms are some examples of these factors. They may also include the type and design of the aerosol delivery devices being used (such as a nebulizer), as well as the physicochemical properties of the inhaled drugs (such as the particles size) or the aerodynamic characteristics of The impact of the medications' physicochemical characteristics on inhalation [28, 29].

5.1. The effect of the physicochemical properties of the inhaled drugs on inhalation: Aerodynamic characters

The particle size, density, and shape of the medicine that is inhaled are some of its physical characteristics that influence deposition. These are influenced by the aerosol drug's formulation, which refers to the substance's chemical and physical makeup, the solvent used, and the effectiveness of the aerosol generator [23].

As the aerodynamic diameter refers to the diameter of a sphere with a unit density and having the same terminal settling velocity in still air as the particle in question, it is one of the most crucial properties that should be established during aerosol medication delivery. For this purpose, many cascade impactors such the Andersen Cascade Impactor, Next Generation Cascade Impactor, and Multi-Stage Liquid Impinger can be employed. The fundamental principle underlying these sizing methods is the inertial impaction of particles travelling through an air stream [30].

The mass median aerodynamic diameter (MMAD), which is used to indicate particle size and can be defined as the aerodynamic diameter below which 50% of the emitted mass is confined, is one of many metrics that can be used to express aerodynamic characteristics. MMAD is a measure or indicator of central tendency as a result; however it does not provide information regarding the dose's conversion to aerosol [31].

In most cases, inhalation can be safely performed with particles having an aerodynamic diameter between 1 and 5 μm. Aerosol particles with size more than 5 μm MMAD are unable to enter the lung and can pass through the mouth, nose, pharynx and larynx via the impaction mechanism and if the particles had a diameter less than 5 μm. These particles are known as respirable or in the fine particle fraction (FPF), and it was discovered that they had been deposited in the lower respiratory tract as the bronchioles and alveolar region. While if the particle size was less than 2 μm MMAD, they can traverse through the artificial airway like the endotracheal tube and can be concentrated in the alveoli through gravitational sedimentation mechanism. However, as they are deposited in the extrathoracic area, such as the mouth and throat, if the particles were larger than 12 m, they had been considered unsuitable for pulmonary delivery. Because the particles were less dense and smaller, they were more likely to infiltrate the distal lung regions [5, 19].

5.2. The effect of the patient himself

Each individual is different from the other in aerosol drug deposition. This variation can be attributed to the random differences in the airway geometry which has an effect on sedimentation and the impaction probabilities [17].

5.3. The effect of the physical and cognitive ability of the patient on inhalation

The patient's physical capacity determines his or her capacity to use a certain device, which may be influenced by things like inspiratory volumes and flows, hand-breath synchronization, or the capacity to utilize a mouthpiece. The patient's capacity to comprehend how and when to utilize the inhalation device and medications is determined by their cognitive ability [32].

5.4. The effect of interface

5.4.1. Mouthpiece and facemask

The response of bronchodilator medication appears similar with either mouthpiece or facemask interface Figs. 4 and 5, [36] but sometimes the selection of patient interface can be based on patient preference [33]. Although, the face mask produces more mouth leak control, the mouthpiece has many advantages

Fig. 4. Mouth piece.

Fig. 5. Aerosol face mask [36].

as they may not require headgear and has very little dead space unlike the aerosol mask which increases the dead space [34, 35].

5.5. The effect of the age of the patient on inhalation

Different age groups can use any aerosol generators but a special recommendation should be taken in the consideration to young children because they may unable to complete the difficult steps which are required for aerosol drug delivery. The patients who are more than 3 years can use the mouthpiece but the less; it is hard to use it. Patients should be aware of how to properly seal their lips over the mouthpiece and provide enough flow for their used inhaler, regardless of their age [37, 38].

6. Inhalation pattern

It was approved that the changes in the inhalation pattern of the patient have an effect on the relationship between the site of particles deposition and particle size. The site of deposition within the respiratory system is determined by how the aerosol is inhaled (the patient's breathing pattern). The inhalation speed (inhaled flow rate) also is considered an important factor. Slow, steady breathing allows more particles to enter the peripheral region of the lung (such as tiny conducting airways and alveoli), but rapid intake increases the deposition potential in the oropharynx and large conducting airways by impaction. However, the breathing pattern has no effect on the site of deposition of particles if they are smaller than 1 μm [18]. More ever, more aerosol particles are capable of penetrating into the bronchial tree when the inhaled volume (tidal volume) increased. After completion of inhalation, a period of breath holding allows the particles entered the lung periphery to deposit on the airways under gravity [39].

6.1. Lung conditions

Airway narrowing, lung compliance changes and/or mucus plugging usually accompany lung diseases. These changes identified in lung diseases can significantly affect the inhaled drug distribution and hence their deposition pattern [17].

Patients suffering from obstructive lung diseases show higher aerosol deposition than healthy subjects. Of note, in comparison with healthy volunteers, the bronchial deposition is elevated over alveolar deposition in both asthmatic and chronic bronchitis patients. This might be caused by the patients' lungs' reduced airway cross-section.

Consequently, after bronchoconstriction, the central to peripheral ratio of aerosol deposition in the lungs noticeably increases [19, 40]. Additionally, when using bronchodilators, an increase in FEV_1 results in an increase in the depth of aerosol penetration into the lung [41].

7. Lung clearance mechanisms

After being deposited in the lungs, inhaled particles are either removed by mucociliary clearance, taken in by the bloodstream, or broken down by drug metabolism as shown in Fig. 6 [45]. Through mucociliary clearance, particles that have been accumulated in the conducting airways are eliminated. The upward migration of mucus produced by the metachronous

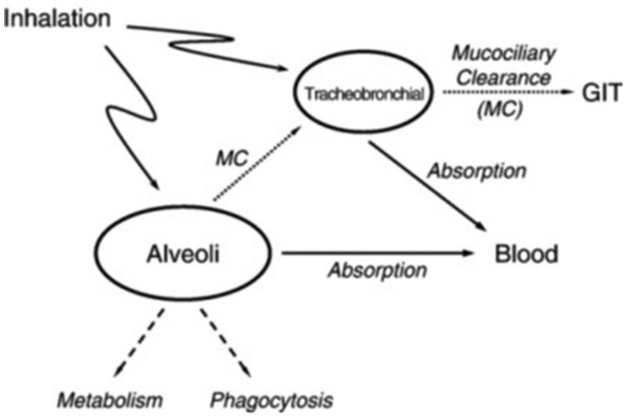

Fig. 6. Lung clearance mechanisms [45].

beating of cilia traps insoluble particles in the mucus gel layer and transports them through the pharynx and ultimately to the gastrointestinal tract [42]. In addition to the clearing provided by the mucociliary system, absorptive processes in the conducting airways are also capable of removing soluble particles. In respiratory disorders like asthma, cystic fibrosis, and immotile cilia syndrome all contribute to a reduction of mucociliary clearance [43, 44].

Alveolar macrophages have the ability to remove drugs that have accumulated in the alveolar region or to absorb them into the bloodstream. The lung contains all of the liver's metabolizing enzymes, albeit to a reduced level (CYP450 enzymes are 5–20 times less abundant in the lung than in the liver and can be found throughout the conducting airways and alveoli). However, macrophages and inflammatory cells create proteases that hydrolyze proteins and peptides, and the lung appears to be a poor site for sulphation.

7.1. The effect of aerosol devices on drug deposition

There are three main types of aerosol devices which are used in drug delivery to different patients with respiratory disorders: (1) Metered dose inhalers (MDIs) (2) Nebulizers and (3) Dry powder inhalers (DPIs) [46].

In addition, soft mist inhaler is a new development of inhalation devices.

People need to use these aerosol medicine delivery systems properly. Aerosol drug delivery devices with effective drug delivery and new features have emerged in recent years as a result of technical advances in areas like materials of manufacture, breath actuation, dose tracking, portability, patient interface, combination therapies, and systemic delivery [47].

7.2. Choosing the appropriate inhaler device

Important correlations to establish when prescribing an inhaled drug product include how the patient will interact with the inhaler device. Proper inhaler preparation and use are essential for achieving the desired therapeutic effect in the lungs [48].

For all devices, there is a large percentage of patients have been observed to use their devices in an incorrect manner leading to suboptimal therapy. These proportions may increase if patients use multiple and different types of devices. Therefore, it is necessary to, if at all possible, minimize the patient's exposure to a variety of devices [5, 48].

The choice of aerosol device is a very important aspect depended on the requirements of patients and the intent of the physician. They should be aware of the various characteristics of the used inhalers products that suit the ventilatory differences and the disease states. As the conditions of specific disease with certain inhalation patterns stimulate the performance of the inhaler device and at the same time may induce adjustments in the inhaled drug delivery device to increase the aerosol deposition in airways. Furthermore, training and regular checks of the patient's technique are required in this regard [47].

8. Aerosol drug delivery system (ADDS)

8.1. A-Nebulizers

Nebulizers are the devices which responsible for converting liquids to aerosols in a size easy to be inhaled into the lower respiratory tract. Nebulization is a one of the most important methods which can be used in delivering of the aerosols medications to the respiratory tract for treating different respiratory disorders including asthma, COPD and cystic fibrosis for many years [49]. Fortunately, nebulizers are beneficial for elderly, paediatric, ventilated and non-conscious patients or those who face a problem in using either pMDIs or DPIs as they do not need coordination between inhalation and actuation. Nebulizers are capable of delivering drugs in higher doses when compared with other aerosol generators but this will be translated into longer administration times [5, 50].

8.2. Factors affecting the efficiency of nebulizers: Nebulization time

Nebulization time refers to the time which is required to deliver a dose of medication. It can be adjusted by the volume of drug to be delivered and the flow of the driving gases into the nebulizer [51].

9. Dead volume (VD)

Dead volume or residual volume can be defined as the volume of the drug remained inside the nebulizer and can't be inhaled. If the fill volume was increased, the amount of medication trapped in the nebulizer (dead volume) was decreased and the amount delivered to the patient was increased [52]. However, the nebulizer output has been increased with a greater fill volume; this may lead to an increase in nebulization time. For jet nebulizers for example, DV was higher, and considering both factors (DV and nebulization time), an initial nebulizer fill volume of 3 to 6 mL was typically used [53].

9.1. Humidifiers

It was found that humidifying the inhaled gases has an important role to resist the mucosal dryness which may lead to a decrease in the benefits of bronchodilator medication. However, during humidification, the lost amount of nebulized drug may be increased as the amount of inhaled drug delivered to the lung of the patient was decreased [54, 55].

These effects can be overcome by increasing the inhaled dose of the drug and bypassing the humidifier during nebulization of very expensive drugs in a short time not exceed 10 minutes to prevent mucosal dryness. So, the accurate humidification of the inhaled gas would increase the patient comfort and increase the effect of bronchodilator therapy in patients [56, 57].

9.2. Gas density

The gas density has an observed effect on the performance of the nebulizer. If the density of gases used were lower than of air, it would increase the percent of medication delivered to patients [53].

9.3. Disadvantages of nebulizers

Their main limitations includes mainly bulkiness, costs, time consuming and the requirement of an electrical source [58].

10. Types of nebulizers

Nebulizers are divided into three types:

(1) Jet nebulizers (JNs)
(2) Ultrasonic nebulizers (UNs)
(3) Vibrating mesh nebulizers (VMNs).

Fig. 7. Jet nebulizer [59].

10.1. Jet nebulizers (JNs)

The JN as shown in Fig. 7 [59] is the one that operated through a 2 to 10 L/min of compressed gas source which may be a compressor or hospital pressurized gas to convert the liquid into aerosols [38].

JNs are the traditional nebulizers used in most of Egyptian hospitals for the treatment of respiratory diseases [9]. JN operates according to Venturi's principle stating that when the fluid passes through narrow sectional area, its pressure decreases. Aerosolization of liquid occurs in JN when a fast-moving air stream passes through a narrow capillary tube, lowering the pressure at the top of the tube. After that high velocity air stream carrying the droplets would hit baffles which are placed in different positions and numbers based on the exact design of the nebulizer. Large droplets that impacted on these baffles have two fates either to be broken into smaller droplets that can leave the nebulizer or to be retained in the device in order to be re-nebulized till their size enables them to leave the nebulizer [60, 61].

The JN have an advantage in the price as they are inexpensive nebulizers, especially if they are compared with VMN or Ultrasonic nebulizers. Consequently, they have been commonly used as an aerosol drug delivery system in different cases of respiratory tract disorders [28, 62].

There are four types of JN: JN attached with reservoir, breath-actuated one, breathe enhanced nebulizer and JN with collection bag. Since the JN with reservoir tube produces an aerosol continuously during the breathing cycle, it is the most popular choice [50].

10.2. Disadvantages of JN

The Contamination is the most important problem can be resulted during the administration of JNs due

to the position of them as its reservoir is in a dependent position to and in direct connect with the used holding chamber device leading to accumulation of pathogens and fluids in condensate which drain into the reservoir causing contamination to the medication which is delivered to the patient [63].

Other problem can be associated with the use of JN is the need for a compressor in order to generate the aerosol which may be a source of inconvenience due to the noise generated by it and the drop that occur in the temperature of the liquid due to evaporation [39].

In addition, an actual amount of drugs which placed in JN remains in the reservoir and cannot be reached to patients due to the large residual volumes of JN beside the long times for preparation and cleaning (Johnson et al. 2008). It was reported by Lewis that 66% of solution was retained in the apparatus tubing, 20% exhaled, 12% was retained in the lungs and 2% deposited in the mouth [64].

10.3. Ultrasonic nebulizers (UNs)

The UNs as shown in Fig. 8 usually operated through acoustic waves which are high frequency pulses that produced from a vibrating piezoelectric element (produce oscillatory mechanical movement from electric signals) to the drug solution [68]. These waves create crests which break the liquid into relatively small droplets. Obviously; ultrasonic nebulizers require an electric supply for charging so they are considered non portable devices [46]. The amount of drug produced is proportional to the amplitude of the crystal's vibrations, whereas the size of the droplets produced is inversely related to the frequency of the vibrations. The high aerosolization flow in a short time is considered an important advantage to it [65].

Fig. 8. Ultrasonic nebulizer [68].

There are two categories of nebulizers that use ultrasonic technology: large volume and small volume. While small volume nebulizers are used to administer inhaled drugs, large volume nebulizers are often utilized to administer hypertonic saline for producing sputum [66]. If comparing UNs to JNs, UNs are more efficient than JNs due to higher nebulization rate at shorter time [67]. However, aerosol particle size was larger than that of JNs [55].

10.4. Disadvantages of UNs

The UNs are not recommended to be used due to their expensiveness and bulkiness; in addition, they produce more heat than any other aerosol generators leading to instability and degradation to materials which are heat sensitive like thermolabile peptides or DNA [67]. They also are unsuitable to use for the suspension or viscous medications as the particles are smaller than suspension, leading to a decrease in the output of the drug which may be not observable [69]. They are like to JN in producing the contamination which drains into the reservoir [70].

10.5. Vibrating mesh nebulizers (VMNs)

The VMNs are small size, portable and less noisy nebulizers. In addition, they are able to generate constant particles with optimal diameter based on micro pump technology as they force medications in liquid form through aperture plate or multiple apertures as shown in Fig. 9 [74]. They are operated by using the electricity or battery [71].

VMNs are either "passively vibrating" or "actively vibrating" nebulizers. To disperse medication into the air, passively vibrating nebulizers employ a piezoelectric crystal coupled to a transducer horn. Aerosol particle size and flow rate are determined by the exit diameter of the aperture hole, but actively vibrating nebulizers use a micro-pump (perforated plate with about 1,000 tapered funnel- shaped holes) containing vibrating element that vibrates in response to electric current and generates aerosol [72, 73].

Fig. 9. Micro-pump technology of active VMNs [74].

Fig. 10. SOLO nebulizer [74].

Fig. 11. Pro nebulizer [78].

There is no contamination can be occur unlike the JN due to their superior position to the holding chamber used during the administration and the separation of the reservoir from the used device by the mesh membrane. In addition, during the administration of VMN, the temperature don't change unlike ultrasonic nebulizers, consequently, there is no risk of denaturation of the aerosolized drug [75].

Mesh nebulizers offer many advantages including consistent and improved efficiency of aerosol generation, increased output efficiency, short treatment times, minimal residual volume and the capability to nebulize low drug volumes [65, 76].

The most common apparatuses of VMN can be commercialized for patients are Aeroneb® Solo and the Aeroneb® Pro (Aerogen Inc., CA, and USA) as shown in Figs. 10 and 11 [78]. The Aeroneb Solo: it is a single patient use.The Aeroneb Pro: It can be operated by the Aeroneb® controller which generates continuous aerosolization, in addition, it can be sterilized and reused [50, 77].

10.6. Disadvantages of VMNs

The VMNs have many advantages than other types if they are compared with JNs or UNs, but their high cost is a large drawback as being 20-fold higher than JNs [70].

In addition, the membrane of VMN may become obstructed during the administration of viscous or very concentrated solutions. Also, cleaning of mesh nebulizers can be difficult [73].

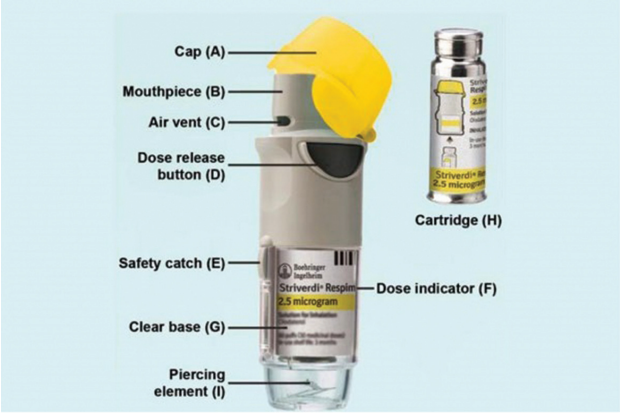

Fig. 12. Soft mist inhaler [81].

11. The Soft Mist Inhaler (SMI) respimat®

It is a development of inhalation devices, it is similar to VMN, as it disperses the solution of the active ingredient into fine droplets as shown in Fig. 12 [81]. It is a handheld, portable device powered by a mechanical spring, unlike regular nebulizers [48, 79].

The instantaneous aerosol generation resembles a pMDI, hence correct actuation-inhalation is needed. However, it takes 1.5 s to make the complete aerosol (compared to 0.21–0.36 s for pMDI) and emits it as a slow-moving mist, permitting substantial lung deposition [80].

12. Pressurized metered dose inhalers: (pMDIs)

pMDI as shown in Fig. 13 consists of a canister with a nozzle, a metering valve, and an actuator [84]. The canister contains drugs, propellants, and excipients which releases an accurate amount of the medication and propellant with each actuation. All of these factors contribute to the creation of the spray and ultimately determine how much of the aerosol is inhaled. Additionally, spacers or holding chambers may be connected to the actuator mouthpiece [72, 82].

Shaking the canister, activating the device at the beginning of inhalation, an inspiratory flow rate (IFR) of 60 $l.min^{-1}$, and a 10-second breath hold at the end of inspiration are all recommended for inhaling

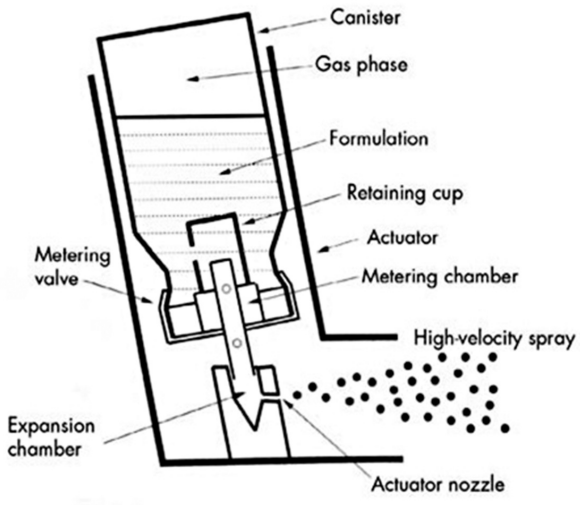

Fig. 13. Standard components of pMDI [84].

pMDI aerosols for maximum particle deposition on the periphery of the lung [83].

It can be used as in Fig. 14, as the mouthpiece of the actuator usually is open to the atmosphere [86]. The adapter or spacer is positioned between the pMDI and the mouth to spread out the aerosol medicament, reducing its velocity and allowing the propellant to evaporate. Consequently, there is a decrease in the particle size and an increase in drug delivery to the airways [85]. For reproducibly delivered dose, the patient should prime and shake the pMDI canister every use [47].

Newer pMDIs provide an aerosol in a lower flow velocity due to the use of hydrofluoroalkane (HFA) propellant instead of the previously used chlorofluorocarbon (CFC). Hence, the patients who may experience a coordination problem to inhale the drug, can benefit from the decreased delivered velocity [87].

The efficiency of pMDI in aerosol drug delivery depended on design, shape and size of the spacer or adapters which attached to MDI, in addition, its position as the pMDI should be in a proximal position to the airway of the patient [88].

Spacers are classified as extension or add on devices that can improve pMDIs efficacy especially in patient with a coordination difficulty by retaining the aerosol dose for a definite period of time [47, 89] therefore, by the use of a spacer with pMDIs, a fine aerosol will be emitted with smaller particle size and slower movement resulting in reduced oropharyngeal aerosol deposition and hence systemic drug absorption, better lung penetration and improved patient response [90].

Drug deposits may accumulate on holding chamber and plastic spacer walls due primarily to electrostatic charge. Holding chambers made from non-electrostatic materials are more effective in keeping aerosols in suspension for extended periods of time. A delay of 2 to 5 seconds during inhalation is possible without significant drug loss to the walls of metal or non-conducting spacers. By washing the spacer in mild detergent and then rinsing it in water to avoid breathing in dried detergent particles, the electrostatic charge in plastic spacers can be significantly reduced [91].

12.1. Disadvantages of MDI

The major limitations of the conventional (press and breathe) pMDIs has always been the need for co-ordination between aerosol generation and patient inhalation, high oro-pharyngeal deposition [82]. Another practical problem facing patients using pMDIs is the inability to determine the number of the remained doses in the device as the propellant can release aerosol containing little or eventually no drug after the labelled actuation number, a phenomenon known as tail-off [92].

The restricted number of pharmaceuticals that can be administered by pMDIs, the Cold Freon effect (early breath cut off due to a cold sensation caused by CFC in the pharynx), and the difficulty of administering drug combinations [87].

Fig. 14. The steps of pMDI use [86].

Fig. 15. Different forms of Dry powder inhaler [97].

13. Dry-powder inhalers (DPIs)

The DPIs are another type of devices used for the delivery of inhaled dugs. They are classified on the basis of many variables, including the number of doses carried by the device, the contribution of the patient to convert the powder into an aerosol or the mechanism of dispersion of the powder. Therefore, there are many forms as single dose inhalers (eg; Rotahaler), and Multi-dose inhalers (eg; Diskhaler) [39, 93].

Generally, they produce consistent and efficient dose,very portable and quick and be easy to use in a correct manner. These advantages make the patient more compliance and increase the treatment efficacy [94]. As shown in Figs. 15 and 16 [97, 98], it is an

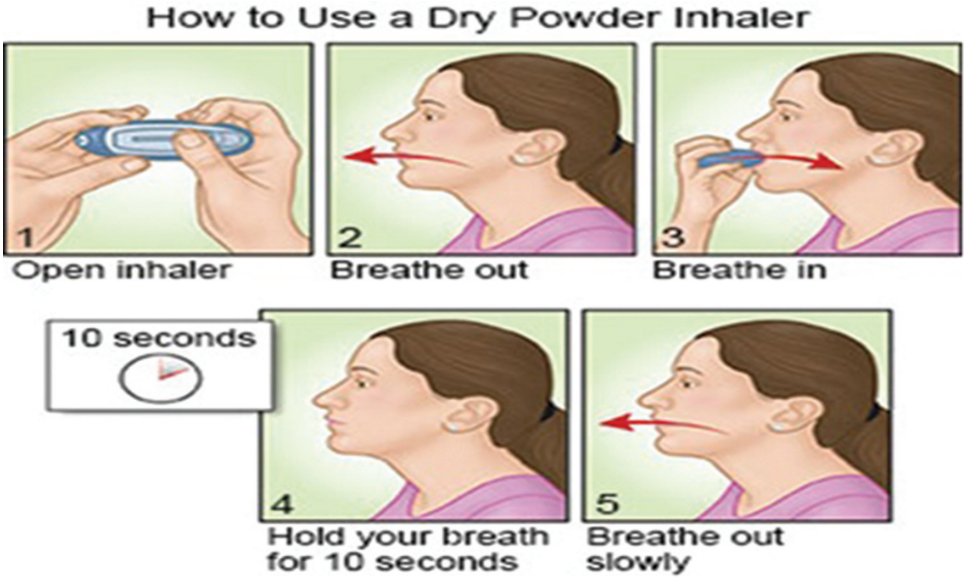

Fig. 16. The steps of dry powder inhaler use [98].

example of diskhaler that consists of DPI device with or without a cartridge, and a medication containing an active ingredient for respiratory tract delivery [95].

The DPIs are usually used for patients more than 5 years old and who have adequate inspiratory flow, sufficient lung volume and are able to use the device in appropriate method [96].

13.1. Disadvantages of dry powder inhaler

DPIs are the devices that have been depended on the energy released during the inspiration of the patients to draw a dose of medication into his lung [99], therefore this disadvantage is considered a great limitation in the treatment of patients having low inspiratory flow rates, especially patients with severe COPD.

Another limitation is seen with the Rotahalers, for example, that require individual loading of single doses into the inhaler directly before use This does not permit direct dose counting and is uncomfortable for patients. In addition, the inhalation should be repeated till emptying the capsule, which may result in an increase in the variability of dose [100].

14. Connections (add on devices)

14.1. Aerogen ultra adapter

It is a novel holding chamber can be used with different aerosol drug delivery devices such as Solo nebulizer. This gadget does more than just creating "space" between the mouth and the medicine. It also traps the medication, allowing for a moment to take a slow, deep breathing. This permits complete inhalation of the medication (Lung 2018). Its structure as shown in Fig. 17 [101] includes an adapter chamber which is 170 mm by 46 mm, with an internal volume of 125 mL. When there is no oxygen being provided, the oxygen nipple will be covered by a one-way flap valve that is located on the chamber inlet. This will prevent any leaking occurrence. It can be used with mouthpiece or facemask. The mouthpiece has a one-way expiratory flap valve. The Aerogen Ultra is a single patient use device [101].

The valved system of the device's innovative design regulates the airflow within the aerosol chamber. When the user takes a breath in, air is sucked through the inlet valve located at the bottom of the device, which then starts a flow of air or oxygen through the apparatus. This removes the aerosol from the aerosol chamber and administers the medication to the patient using the mouthpiece. The mouthpiece's exhalation valve opens and the inlet valve closes as the patient exhales. This enables the patient to exhale through the mouthpiece port while the Aerogen Solo refills the aerosol chamber [101].

A more than 30% inhaled dosage is available for successful aerosol therapy due to its holding chamber. At various stages of patient care, it can be utilized to administer suspensions, solutions, proteins, and peptides. It is not only available with spontaneously breathing patients using mouthpieces

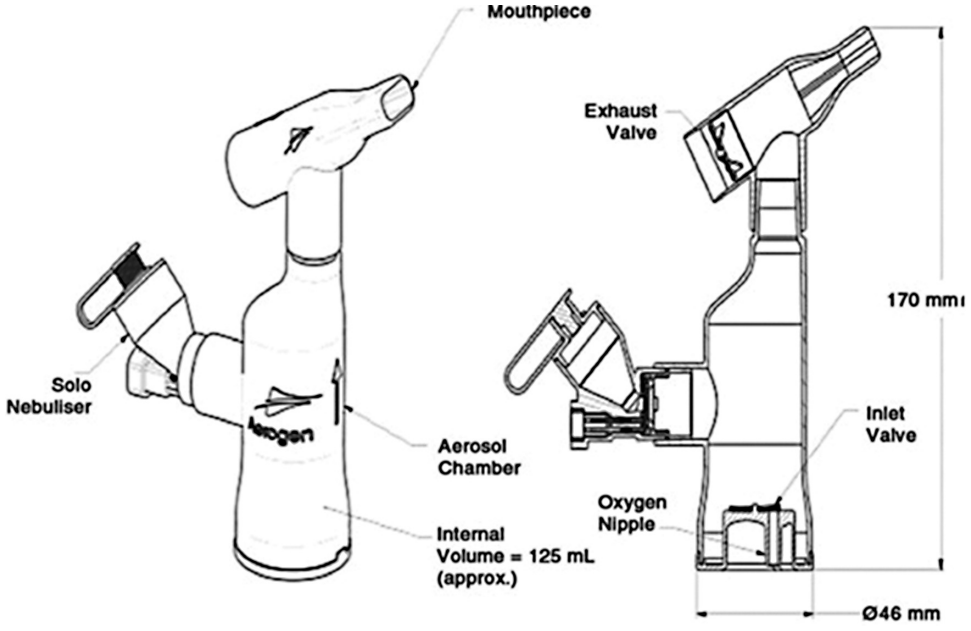

Fig. 17. Schematic diagram indicating the structure of Aerogen Ultra adapter [101].

and masks throughout the acute care system, but it may also be employed during both invasive and non-invasive ventilation. It makes it possible for pediatric (those aged 29 days or older) and adult patients to get supplementary oxygen by continuous or intermittent nebulization. (Aerogen 2017; Tri-anim 2018).

14.2. Instructions for aerogen ultra use: (Aerogen 2017)

1. Insert the nebulizer firmly into its position on holding chamber Aerogen Ultra.
2. Put the mouthpiece to Aerogen Ultra.
3. If additional oxygen is needed, connect the oxygen tubing to the Aerogen Ultra's oxygen nipple. Flow rate of oxygen is set at 6 L/M.
4. Add the prescribed medication (1 ml salbutamol) to nebulizer and connect cable to it.
5. Turn on Aerogen Ultra and detect if there are any visible aerosols.
6. Introduce Aerogen Ultra to volunteer and observe aerosol flow to in

15. Oxygen therapy

Maintenance the adequate oxygenation and improvement in alveolar ventilation are the most important targets of any respiratory support can be used during different respiratory disorders, therefore, supplemental oxygen is the commonest drug prescribed used for hypoxemic respiratory failure [102].

The inhaled concentration is affected by many variables both from the patient as well as the device itself such as the flow rate of administered oxygen, the characteristics of the devices used in drug delivery and the breathing pattern of the patient. There is a variety of devices by which oxygen can be administered at different concentrations. The amount of oxygen (FIO_2) that was delivered was dependent on a number of variables, including the harmony between the patient's inspiratory and expiratory flow rates, the presence of a reservoir during entrainment, the presence of an expiratory pause, which causes a pharyngeal reservoir of oxygen to build up, and the method used to deliver the oxygen, such as a face mask, mouthpiece, or nasal cannula. The inspiratory flow rate of the patient is based on the respiratory rate and tidal volume [103].

There are different classifications to oxygen delivering systems as low, intermediate and high flow devices. Depending on the oxygen flow rate, the peak inspiratory flow of the patient, and the parameters of the device, the fraction of inspired oxygen (FIO_2) delivered by low flow devices like nasal cannulas, non-rebreathing masks, and bag valve masks might vary. The entrainment ports in a mask allow ambient air to be mixed in with the pressurized oxygen that is being delivered via the mask at a steady flow rate. While high flow devices provide a fixed FIO_2 which means FIO_2 will be known at all times [102, 104].

Low-flow supplemental oxygen has been characterized that it is free of serious side effects, but local irritation in the nose and eyes usually observed. Some retention of carbon dioxide may be reported in some patients used higher oxygen flow. And can be avoided by adjustment of the flow rate of supplemental oxygen to maintain the PaO_2 between 60 and 65 mm Hg [102] (Nishimura 2016).

15.1. Salbutamol

Salbutamol drug (albuterol) is usually manufactured and distributed in the market as the sulfate salt salbutamol sulfate like farcoline or ventolin [105].

It belongs to the short acting bronchodilator which is usually used for relieving the bronchospasm in respiratory system diseases as asthma, COPD and cystic fibrosis [106].

15.2. Mechanism of action

It works on beta 2 receptors in the lung, leading to stimulation adenylate cyclase enzyme causing an increase in the production of cyclic adenosine monophosphate which results in the relaxation of the smooth muscle, so, producing bronchodilation [107].

15.3. Medical uses

Due to its relaxation effect on the muscles in small airways walls; In diseases like asthma and COPD, it is used to treat bronchospasm [108]. It can be used to treat hyperkalemia because of its ability in stimulation the flow of the potassium into the cells so, decrease potassium level in the blood [109].

15.4. Route of administration

Salbutamol is available in many dosage forms for inhalation include; conventional pMDIs which is the most commonly used, dry powder inhalation capsules or discs delivered by DPIs, respirable solutions for nebulization through different types of nebulizers, oral formulations (syrup and tablet), IV formulations for slow injection of continuous infusion, subcutaneous and intramuscular injections. Salbutamol is utilized in aerosol inhalers as the base or sulfate, and in other preparations as the sulfate [110].

15.5. Pharmacokinetics

The onset of action of inhalation forms of salbutamol occurs 1–5 min and is slightly delayed with oral preparations [111]. The duration of action of salbutamol lasts 2–6 hr. after using inhalation forms and 4–8 h after oral administration. Salbutamol's plasma half-life has been estimated to be 4 to 6 hours after inhalation and 6 hours after oral dosing [112]. Inhaling salbutamol causes 10 to 20% of the dose to reach the lower airways, where it is rapidly absorbed. The percentage of a drug that is systemically bioavailable is the amount that is either not lost throughout the delivery process or is swallowed and absorbed in the stomach [113].

Salbutamol systemic bioavailability is only 50% due to extensive pre-systemic metabolism. The liver and potentially the intestinal wall undergo first-pass metabolism of salbutamol, with the inactive sulfate conjugate produced via sulfate conjugation of the phenolic hydroxyl group representing as the major metabolite [114].

It is excreted, mainly in the urine, as unchanged salbutamol and the inactive phenolic sulfate, in addition, a little amount is excreted in the feces [115].

16. Methods for identifying pulmonary salbutamol deposition post inhalation

More than 20% of the inhaled dose reaches the lungs after inhalation but the major part is swallowed. The proportion of the dose which is delivered to the lung is cleared by two ways, by the mucociliary clearance or by absorption into the systemic circulation through the airway wall. The latter is the dose fraction which is responsible for the clinical effects The basic methods for identifying pulmonary drug deposition are pharmacokinetic (PK) and gamma-scintigraphy techniques [19, 113].

16.1. Pharmacokinetic method

Pharmacokinetic method or it is called "indirect method" because it depends on the measurements of the urine or serum. This method cannot differentiate between the drug distributions into different zones of the lung but it provides an indicative measure of the quantity of the inhaled dose which produces the desired action in the lung by estimating the data about total lung dose from urinary recovery and/or plasma concentrations [116]. Hence, it has an advantage in comparing the equivalence of different inhaled products or estimating the differences between inhalation techniques via comparing urinary drug excretion or the data of the area under the curve [113]. It was found that urinary salbutamol concentrations are much higher than plasma concentrations; therefore, urinary salbutamol samples can be used in the bioavailability determinations after inhalation [116].

16.2. Gamma-scintigraphy techniques

These techniques have advantage over pharmacokinetic indirect methods as they have the ability in the quantification of total lung deposition as well as differentiate between drug depositions in various zones of the lung. There are two and three-dimensional gamma scintigraphy techniques. Two-dimensional gamma-scintigraphy was firstly used as it gives an image for inhaled drugs delivery, then it was developed to tridimensional imaging technologies as positron emission tomography (PET) and single photon emission computed tomography (SPECT) which they have been used for giving a more accurate image on drug deposition in the airways [19].

16.3. Side effects

Common side effects which are produced after administration of salbutamol include: headache, muscle cramps, anxiety, tremor, palpitation and dry mouth. Rare side effects include arrhythmia, tachycardia, disturbances of sleep and myocardial ischemia [117].

High doses of salbutamol may lead to Hypokalemia and hyperglycemia therefore; potassium level should be monitored with renal failure patients and those receiving diuretics which have an effect on potassium level.

16.4. Drug interaction

Salbutamol may interact with many drugs as aminophylline, certain diuretics (e.g., furosemide and hydrochlorothiazide), digoxin, tricyclic antidepressants (e.g., amitriptyline and desipramine), other bronchodilators (e.g., terbutaline and salmeterol), dopamine, beta-receptor blocking drugs because these medications counteract salbutamol's bronchodilator action, and others [118].

Additionally, those who have diabetes mellitus, hypertension, hyperthyroidism, cardiac arrhythmia, convulsive disorders, or hyperthyroidism should use it with caution.

16.5. In pregnancy and lactation

It is a pregnancy category C drug. During pregnancy, it used only in necessary [119]. There is no

any adverse effects have been documented in breast feeding babies during their mothers receiving salbutamol although it may excreted in human milk [120].

17. Conclusions

Aerosol has been in the field of healthcare for long period and it is upgrading contentiously. So caution should be taken for the selection of such treatment. Also, update of the information about aerosol device, solutions, and medication should be done to be sure that the best medication is prescribed to lung obstruction patients. Such patients require to have a very efficient treatment with the least side effect. The present review article describes the most updated information about such treatment. We recommend a contentious update of such information to help the healthcare provider to receive the most updated information about inhalation devices and aerosol in a very simple way or the guidelines of obstructive lung disease incorporate such information in their yearly report.

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