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Inhalation Devices and Pulmonary Drug Delivery

Sara M Tony[1], Mohamed EA Abdelrahim[2]*

[1]Beni-Suef Specialized Hospital, Beni-Suef, Egypt

[2]Clinical Pharmacy Department, Faculty of Pharmacy, Beni-Suef University, Beni-Suef, Egypt

***Corresponding author:** Mohamed EA Abdelrahim, mohamedemam9@yahoo.com

Abstract: Inhaled drug delivery is mainly used to treat pulmonary airway disorders by transporting the drug directly to its targeted location for action. This decreases the dose required to exert a therapeutic effect and minimizes any potential adverse effects. Direct drug delivery to air passages facilitates a faster onset of action; it also minimizes irritation to the stomach, which frequently occurs with oral medications, and prevents the exposure of drugs to pre-systemic metabolism that takes place in the intestine and liver. In addition to that, the lung is regarded as a route for transporting medications throughout the entire body's blood circulation. The type of medication and the device used to deliver it are both important elements in carrying the drug to its target in the lungs. Different types of inhalation methods are used in inhaled delivery. They differ in the dose delivered, inhalation technique, and other factors. This paper will discuss these factors in more detail.

Keywords: Pulmonary drug delivery; pMDI, DPI; Nebulizer

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1. Mechanism of drug accumulation (deposition) in pulmonary airways

Three main mechanisms for drug deposition occur in the lungs. The initial mechanism is termed inertial impaction. It is the most common mechanism by which particles deposit in the upper airways. When air passes through the upper respiratory tract, the particle that gains elevated momentum (velocity x mass) seems incapable of coping with the altered track of inspired air. This high velocity causes impaction on the airway walls inside the lungs. Since the probability of impaction is proportional to the particle's momentum, particles that are larger and moving at a greater speed or have a higher density will exhibit more impaction. Sedimentation is another mechanism for drug accumulation. Once the airflow velocity decreases, particles are deposited downwards due to gravity. This happens when airflow is restricted in the bronchioles and alveoli. The duration the particles spend in these locations determines the percentage of particles deposited by this mechanism. Holding one's breath after inspiration increases the time the particles remain in these locations, resulting in higher drug deposition in the lungs [1].

"Brownian diffusion' is the third deposition mechanism. This is most common mechanism for particles smaller than 1 μm because particles smaller than this move by the random bombardment of gas molecules. The likelihood of deposition through diffusion increases when the particle size is smaller, and it is also more common in areas with low or no airflow, such as the alveoli. This mechanism promotes deposition by holding one's breath after inspiration. **Figure 1** is a diagram of the three mechanisms outlined above [1].

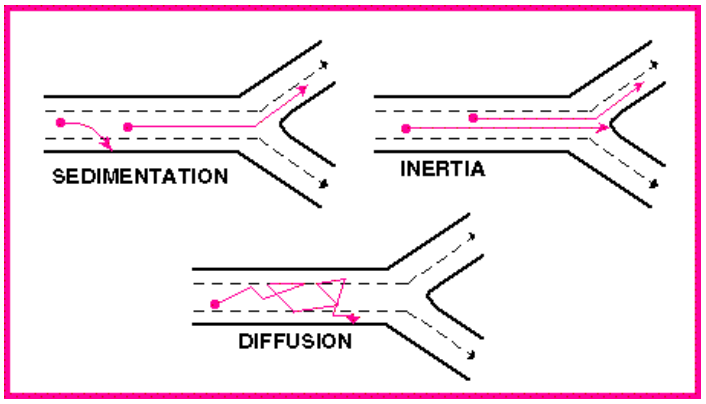

Figure 1. Mechanisms of particle deposition in the airway

As shown by the three mechanisms above, the anatomy of the lungs has an influence on particle deposition since large particles are forced to settle inside upper respiratory airways instead of gliding. Increased inspiratory flow alters particle deposition by increasing turbulence and the impaction in the broncho-tracheal zone's primary branches, especially in the glottis and windpipe. Impaction will improve much more as a result of this. The impact of inhalation flow rate on drug accumulation or deposition from devices that use inspiration energy to make drug aerosol (such as DPIs) is more complicated since increasing inhalation flow nearly always results in the formation of smaller particle size aerosol.

Increased inspiratory volume allows aerosol particles to penetrate deeper into the lungs, thus increasing the likelihood of depositing in the alveolar region. Breath-holding improves pulmonary drug delivery by increasing sedimentation and diffusion throughout the time that the particles dwell in the lungs [2].

Pharmaceutical parameters such speed of aerosol, distribution of particle size generated by the aerosol, particle form, density, and also stability may have an impact on deposition. The required diameter of particles is 5 μm, in order to achieve successful drug sedimentation in the airways, but all particles should preferably be within the range of 2 to 3 μm in individuals who suffer from obstructive lung diseases [3].

2. Inhalation devices

Although there are several new asthma medications that can be taken orally (targeted medications) or by injection (monoclonal antibodies), they are unlikely to be as successful as inhaled B2-agonists or corticosteroids. As a result, inhaled therapy is still the preferred treatment for asthmatic patients [4].

An ideal inhaler would have the following features from a pharmaceutical standpoint: simplicity of manufacturing, zero propellant (environmentally friendly), consistent dosing throughout its life, little risk of contamination, and long shelf life [1]. From a clinical standpoint, an acceptable inhaler must meet the requirements outlined in **Figure 2** [5], in order to provide consistent clinical control. For both patients and physicians, the most significant characteristics include successful transportation of aerosolized medication into the lungs and its ease of use.

The majority of inhalers are primarily used for delivering medications effectively to their site of action, such as anti-asthmatics. An aerosol is a colloidal substance made up of finely dispersed and compacted material inside a container. When this substance is atomized, it forms a mist of microscopic droplets that can be inhaled to transport drug particles. These medication-carrying droplets must be smaller than 5 μm in size to be effective. Nebulizers, metered-dose inhalers (MDIs), and dry powder inhalers (DPIs) are the three main types of aerosol generators used in inhaled therapy.

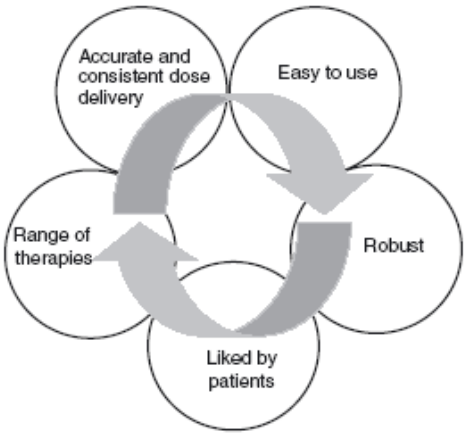

Figure 2. Features of an ideal inhaler

2.1. Nebulizers

Nebulizers are appliances that turn liquid or micronized medication suspension into aerosolized form, which can be inhaled. Because nebulizers have the ability to transport relatively large volumes of medication, they are frequently utilized with medications that cannot be properly formed into MDI or DPI devices, or if the medication dose is too large to be delivered using another approach [6,7]. High-velocity air stream dispersion, ultrasonic energy dispersion, and vibration energy dispersion are the three main processes by which energy is generated in vibrating mesh nebulizers. The solutions in nebulizers are strenuous liquids. Aliquots are removed from those solutions and then diluted prior to application. Since preservatives and antioxidants in some concentrated solutions might cause bronchoconstriction, the standard method is to use respules that have been liberated from preservatives and antioxidants. viscosity and surface tension characteristics of a nebulized solution, have notable influence on commission of nebulizer gadget [7,8].

2.1.1. Air-jet nebulizer

Jet nebulizers turn liquid solution into its sprayed form by the aid of condensed air or by using oxygen [9]. A thin venturi nozzle is used to pass accelerated gas jet either tangentially or throughout via the co-axial mechanism. As shown in **Figure 3** [6], a zone of negative pressure where the air jet exits causes liquid to be sucked upwards from the liquid reservoir to the feed tube. Then, a portion of the resulting aerosol is transported directly into the air flow by the nebulizer. The remaining large, non-respirable particles that collide with the nebulizer chamber's baffles are converted back into fluid in the reservoir. The concentration of the aerosol is reduced by ambient air before being inhaled through a face mask or mouthpiece. The filtering action of the jet nebulizer's baffles, along with droplet aggregation, solvent evaporation, and condensation drastically alter the droplet size of the aerosol inside the nebulizer. The solution tends to become concentrated in the nebulizer [6,10]. The cooling of reservoir solution occurs during nebulization, which, along with vapour loss, leads to drug solution concentration. This results in crystallisation and consequent gadget blockage, as well as an alteration in size of the aerosol particles [1,7]. The aerosol product of a jet nebulizer is a mixture of drug solution plus solvent vapour that saturates outgoing air [11]. This raises the concentration of solutes over time [11], resulting in a 10-15°C decline in temperature of the liquid being nebulized [12,13]. Air-jet nebulizers are commonly used in hospitals.

The diameter of aerosolised particles excreted from jet nebulizers is mostly affected by the rate of gas flow causing atomization. In a diffraction analysis of four jet nebulizers by using laser, a study conducted in 1983 found that increasing the flow from four to eight litres per minute results in a 50% decrease in the mass median aerodynamic diameter (MMAD). This is associated with a linear elevation in exposure of

droplets smaller than 5 μm and an increase in aerosol polydispersity [13]. Since energy is needed to resist forces from viscosity and form a new surface, viscosity and surface tension are capable of altering the output characteristics of nebulizers. According to atomization theory, when viscosity rises, so does the mean diameter of aerosol droplets [14].

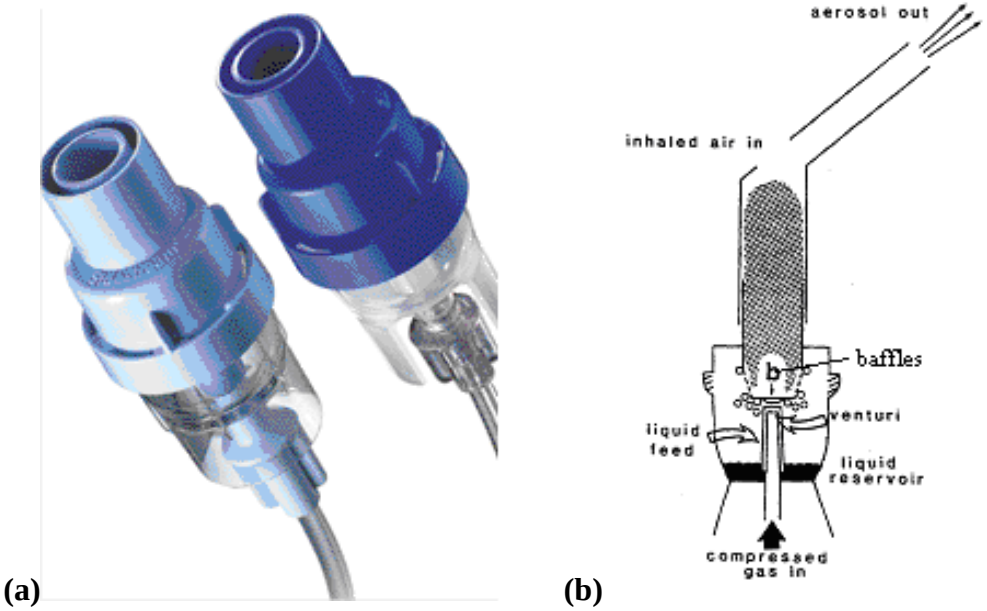

Figure 3. (a) Side stream jet nebulizer; (b) Jet nebulizer

This is the sort of nebulizer that is indicated for suspensions such as corticosteroid formulations (AstraZeneca's Pulmicort Respules) [6]. Recombinant human deoxyribonuclease has been successfully atomized using jet nebulizers [15]. When jet nebulizers are utilised, the enzyme's activity and structural rigidity are conserved. Many variable models of nebulizers and compressors are present in commercial markets. These devices are in no way comparable. For example, the aerosols created by MMADs in the range of 0.9 to 7.2 μm in a study of 18 jet nebulizers available on the market that are operated according to the manufacturer's specifications [16]. Clearly, the localized deposition of aerosols created by such devices in the lungs will differ greatly. Variations may occur not only among various types of nebulizers, but also between single nebulizers of the same type [17]. Frequent usage of a particular nebulizer causes variability due to deflector wear and assembly variety [18].

2.1.2. Ultrasonic nebulizer

An ultrasonic nebulizer utilizes a piezoelectric crystal converter to create energy inside the liquid of the nebulizing gadget. The capillaries in the vertical position split up to produce aerosol when the magnitude of the applied energy is enough (**Figure 4**) [19]. Since the temperature of the nebulized solution rises while using an ultrasonic nebulizer, its use should be avoided when thermolabile medications are indicated, such as proteins. Despite their reasonable size, which makes them easier to transport, they are less popular than jet nebulizers.

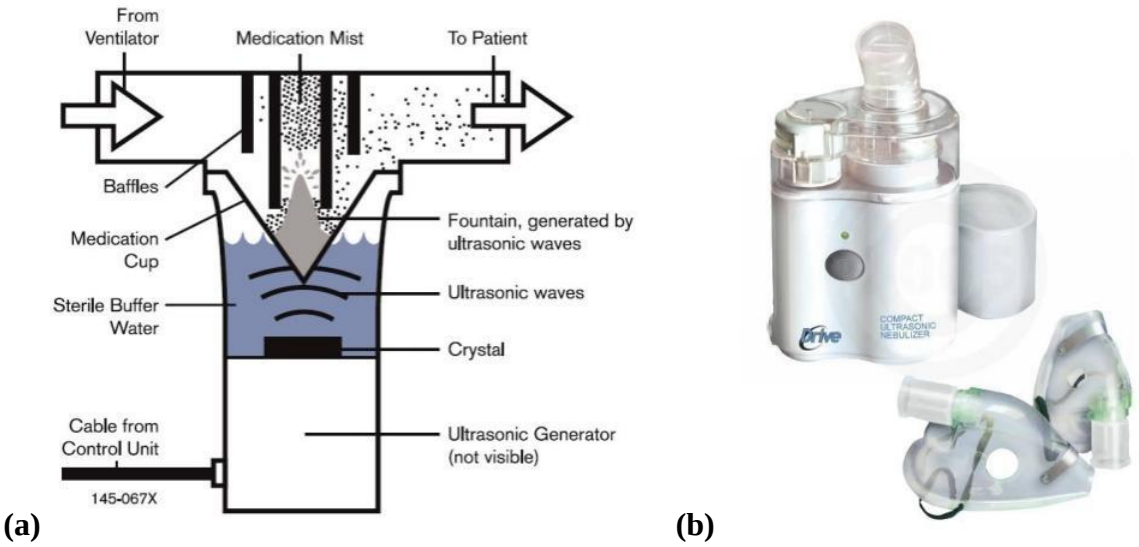

Figure 4. (a) Mechanism of ultrasonic nebulizer; **(b)** Ultrasonic nebulizer diagram

2.1.3. Vibrating mesh nebulizer

Nebulizers with vibrating mesh have been developed lately. The disadvantages of classic nebulizers are as follows: they are not liable; they are low efficiency; they have performance differences among various brands [20]. Recent advances in technology have resulted in the creation of gadgets that have the ability to overcome the disadvantages of classic nebulizers. Vibrating mesh nebulizers transport drugs to the lungs with far improved efficiency, precision, and consistency compared to classic ultrasonic nebulizers. In order to create a liquid mist, this recent generation of nebulizers uses a plate with numerous openings (vibrating mesh). These devices include Aerogen aerosol generator, PARI's gadget, Omron's vibrating mesh, and ODEM's TouchSpray Technology (**Figure 5**).

Some vibrating mesh nebulizers have been manufactured to be used during mechanical ventilation [21]. These devices produce aerosol in a continuous manner, so that aerosol can be produced at time of inhalation. Aerogen Pro is three to five times more accurate than standard jet nebulizers or ultrasonic nebulizers in terms of drug transport to the lungs [22-24]. As a result, with a vibrating mesh nebulizer, identical therapeutic benefits can be produced with lesser nominal drug doses than with classic nebulizers [22-24].

Figure 5. Examples of nebulizers under the vibrating mesh category; **(a)** eFlow nebulizer; **(b)** Aerogen Pro nebulizer; **(c)** NE-U22 nebulizer

As shown in **Figure 6**, aerosol generator is mainly operated with a vibrating element and a dome-shaped perforated plate that is powered by an alternating battery pack, which can be recharged. Approximately one thousand holes are formed electrically in the hole-containing plate. The drug is located towards the wider end, while the atmosphere is located towards the narrower end. The medication is kept inside the pool that is located either above the hole-containing plate (Aerogen Pro) or below the hole-containing plate (eFlow). When electricity is applied, the ceramic vibrating element expands and then contracts, which drive the perforated plate to move a few micrometres forward and downward, creating a micro-pump effect that ejects drug in the direction of the holes to generate aerosol [21].

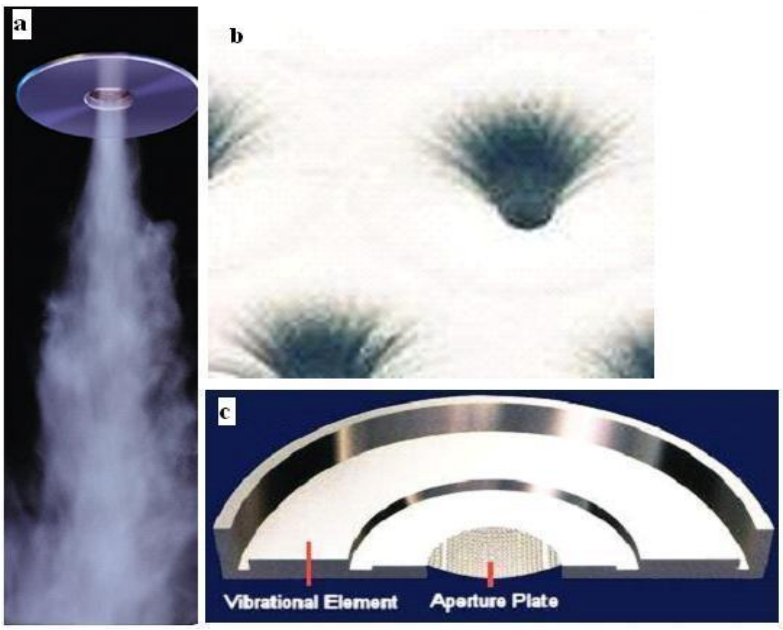

Figure 6. (a) Aerogen aerosol generator; **(b)** microscopic view of the perforated plate; **(c)** components of the aerosol producer

The size of the holes in the perforated plate determines the size of the aerosolized particles and their flow. These can be tweaked to meet specific clinical requirements. These nebulizers nebulize within a velocity of 0.3 to 0.6 ml/min. Its nebulization period is often lower when compared to classic nebulizers [25]. Since these devices do not demand pressurized gas flow or strong vibration power for aerosol production, they are considered quite silent. Furthermore, the amount of liquid left in such devices after treatment is negligible. Since the energy demanded to carry out nebulization is applied to the aerosol generator's vibrating element rather than the nebulized solution, the temperature of the solution during the process is kept to a minimum [19]. As a result, there is no risk of proteins or peptide denaturation or lowered antibiotic action during the aerosolization process.

Drug particles can obstruct the minute apertures, especially when solutions are aerosolized. Hence, these devices must be cleaned on a regular basis to avoid accumulation of deposits in the apertures.

2.2. MDIs and their accessory (add-on) gadgets

When patients are outdoors, MDIs are efficient and convenient. They are the cornerstone in treating airway obstruction because they provide reliable and repeatable production of drugs. They do not require any exerting effort from the patient, and these devices protect the content from moisture and bacteria. They are portable and cost effective. They are considered the most adaptable delivery systems when linked with add-on accessories.

2.2.1. Pressurized metered dose inhalers (PMDIs)

The most often used aerosol therapy device is the MDI. About 70 million people utilize pMDI around the world, whether alone or with a spacer device. Since its first production, pMDI has remained largely unchanged [3].

Figure 7 shows a pMDI, which is a remarkable tiny spray that consistently produces nearly similar aerosol dosages from the start until the end of the canister load [26].

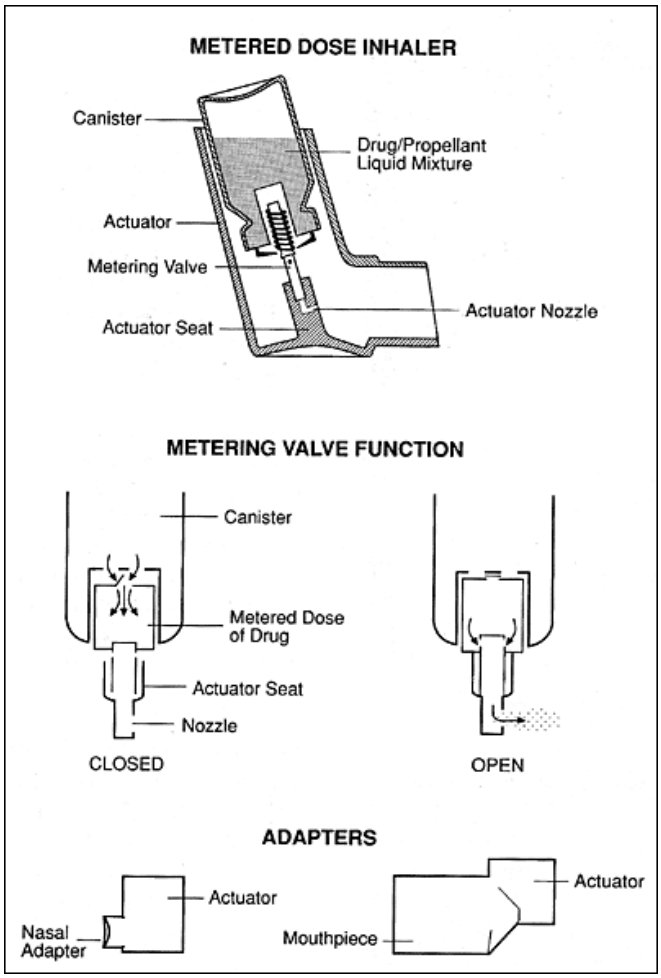

Figure 7. Constituents of pMDI

The pMDI is made up of a container encompassing a metering valve that carries medication in the form of suspension, in addition to surfactants, propellant, and lubricants, all at a pressure. The pMDI actuator (operator) is a plastic brace that holds the container upturned. Metered medication dose is discharged by striking the bottom of the container. When the container is forced down, liquid propellant holding the medication material is pumped into the actuator, causing flashing. As particles of drug solution depart through the actuator opening, the resultant gas under high pressure drives the propellant, additives, and medication together, forming an aerosol mist. The aerosol cloud is made up of a heterodisperse spray, which has a particle size ranging from around 1 µm to 35 µm. They erupt at a highly elevated velocity. As large particles have more inertia, they tend to accumulate in the tongue and oropharyngeal region. From 100 µm of medication, only about 10 µm remain in the actuator and mouthpiece, with 10 to 15 grams arriving at the site of action in the lungs.

Despite the fact that the pMDI delivery technique is ineffective in general, this dose is sufficient to achieve the highest level of bronchodilation in case of stable, mild and moderate asthmatic patients [27].

Several factors affect the size of the particles transported by pMDIs, including pressure within the canister, propellant characteristics, concentration and quantity of medication used, delivery port design, mouthpiece, as well as delivery port hygiene [27]. The time it takes for the propellant to evaporate and the distance it must travel from the discharge port are used to calculate the particle size. The aerodynamic diameter of the medication particles should be less than 5 µm, in order to reach effective particle deposition in the lower respiratory tract [28]. However, all particles should have a diameter of 2 to 3 µm, especially in case of patients with obstructive lung disease [29].

Until recent times, companies have been chlorofluorocarbons (CFCs) during production of MDIs. In 1974, Molina and Rowland discovered that large amounts of CFCs were being released into the atmosphere, thus destroying the ozone layer [30]. In 1987, the use of CFCs was prevented; this included those used in MDIs. This effort was implemented to keep the ozone layer away from further damage [31]. Drug companies have modified pMDIs with HFA propellants that do not disrupt the ozone [32].

The incapacity to perform the steps properly while using an inhaler, in particular a good coordination between the release of the aerosolized drug and the beginning of inhalation, is a fundamental restriction in using pMDI. According to several studies, approximately 25% of people who have been trained to use pMDIs in chest clinics [33] and 75% of elderly patients [34] may be unable to perform the correct inhalation technique. According to a recent study, only 7.5% of asthmatics had the correct approach in using pMDIs [35]. The primary issues associated with the use of pMDIs are shown in **Table 1**. Previously, the evaluation process of the inhalation technique has placed a strong emphasis on timing the dose discharge with the start of inhalation. However, investigations have found that as long as the patient is inhaling with a slow inspiratory flow rate when the dose is discharged [36], the coordination between releasing the dose and inspiration is unnecessary. The slow inspiratory flow rate through pMDI promotes deposition in the lungs more than a quick inspiratory flow rate [29].

Table 1. Problems arising from the use of pMDIs

The canister is not shaken vigorously before using.
The cap of the mouthpiece is still intact.
Inhalation begins either prior to or following the release of dose or from the nose.
Exhalation at time of inhalation or prior to completion of inhalation.
Patient releases multiple successive doses without allowing time between them.
The inspiratory flow rate is higher than required.
Patient stops inhaling upon feeling a chilling effect (cold sensation in the patient's mouth and pharynx due to CFCs)

The 2Tone Trainer device resembles a MDI; however, it does not have a canister. This device was developed to aid patients in practising the maintenance of a slow inhalation rate. The 2Tone Trainer helps adult asthmatics to remember the correct inhalation technique after verbal counselling [35].

Autohaler is gadget that produces metered aerosolized drug dose. It is operated once loaded throughout the optimum inspiratory flow rate, resulting in aerosol delivery. The mechanism is triggered when patient begins inhaling, and a dose is immediately discharged into the airway.

Breathe-actuated inhalers can increase drug sedimentation inside the lungs of patients who are unable to use their inhalers properly [29]. For patients who have poor inhalation technique, these devices are significantly easier and better. Autohaler is simple to use for children above the age of seven [37]. These devices can aid patients with poor coordination to reach a satisfactory degree of drug accumulation in the lungs, but they do not increase the deposition of medication in individuals who are able to use pMDI with proper inhalation technique [38]. The utilisation of spacers was found to decrease drug deposition in the

oropharyngeal region in healthy individuals by 80% [39]. The Optimiser spacer captures the bulk of non-respirable medication while retaining the small particles of the Easi-Breathe inhaler [39].

Neohaler and Tempo use new technologies in order to delay the cloud of aerosolized drug before it is released from the actuation nozzle [40,41]. Gentlehale and Spacehaler were the previous names for Neohaler. This device eliminates the majority of non-respirable medication, so that it minimises oropharyngeal drug accumulation, and either increases or maintains the deposition in lungs [40,42].

Figure 8 shows a Neohaler device, which resembles a pMDI device but with a slightly extended mouthpiece.

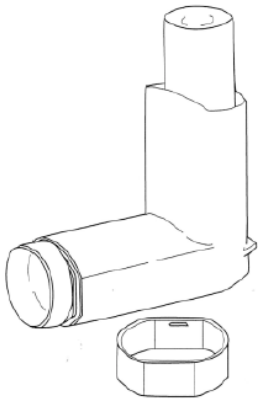

Figure 7. Neohaler

2.2.2. Spacer

In the 1970s, spacer devices were first developed as an extension accessory tube connected to the pMDI mouthpiece to address the coordination problem while using pMDI. **Figure 9** shows a spacer. A spacer is a container that has a hole on one of its two ends for linking a MDI; however, a spacer mask or spacer mouthpiece can also be connected to other side. Patients usually inhale through the mask or mouthpiece after releasing a dose inside the spacer. As previously stated, about 25% of adults and almost all paediatric patients have trouble coordinating when actuating their MDI while inhaling [33]. These spacer devices connected to pMDIs can assist in overcoming this problem and enhancing the inhalation technique.

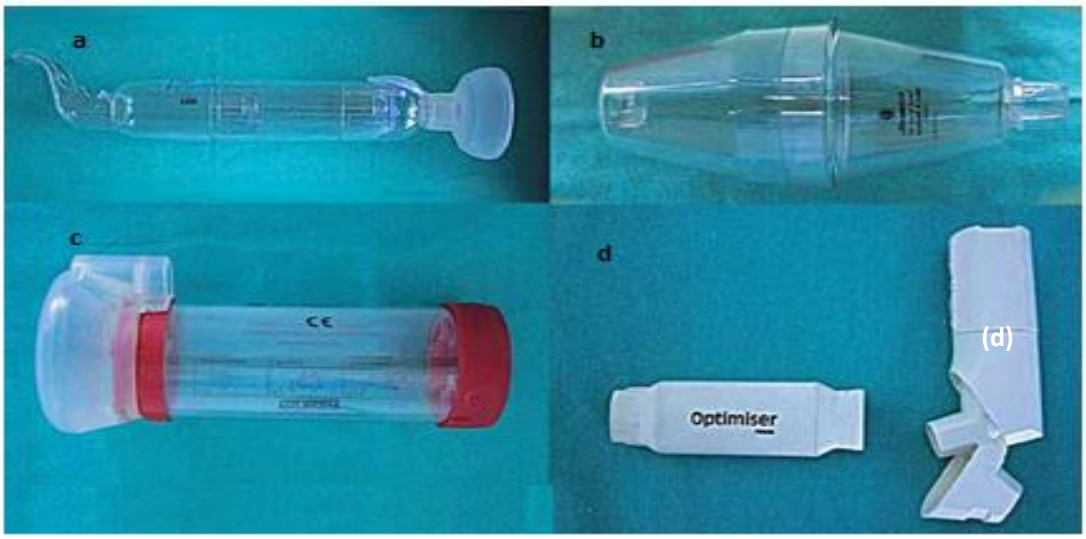

Figure 8. Spacer devices; **(a)** Babyhaler spacer; **(b)** Volumatic spacer; **(c)** Aerochamber + mask spacer; **(d)** Optimiser connected to breath-actuated inhaler

A study compared the use of pMDI solely with pMDI combined with a large-sized spacer in an in vitro volumetric study. The particles of fluticasone propionate, flunisolide, and beclomethasone dipropionate were assessed when using pMDI alone and when pMDI is connected to the Volumatic spacer at an inspiration flow rate of 30 L/min) (GlaxoSmithKline, Ware, UK). For all three medications, the pMDI with Volumatic spacer resulted in a considerable decrease in MMAD and an elevation in the dose of small particles [43].

Furthermore, spacers have the function of size selectivity, trapping non-inspirable particles, and lowering the effect of cold sensation as well as drug accumulation in the oropharynx region. Furthermore, medication loss caused by improper hand-breath coordination is minimized by using valved holding chambers [29].

Updated guidelines have relvealed that using pMDI with spacer is the best recommended approach for administrating β_2-agonists and aerosolized corticosteroids in children whose age is less than five [44].

Most spacer gadgets are made from plastic materials, which can collect static charge if not properly cleaned, particularly when it is touched. The transportation of drugs from spacers can be improved by applying a static-resistant coating on the device's internal barriers [45]. It has been discovered that cleaning spacers that are manufactured from plastic in liquid soap before use instead of cleaning them in water and leaving them to air-dry [29] or utilizing metal spacers (**Figure 10**) [46] can lessen the amount of electrostatic charges on their surface. The aerosol half-life in a metal spacer is around thirty seconds compared to ten seconds in a modern spacer manufactured from plastic [47]. It is worth mentioning that the shortened half-life raises the necessity for the successful coordination between dose discharge and inhalation. For spacers to develop non-electrostatic properties, introduce a much larger dose for spacers manufactured from plastic. On the other hand, using large spacers increase the dose that reaches the lungs by nearly 50% [47].

Figure 9. Nebuchamber spacer made from metal (AstraZeneca, Sweden) with a capacity of 250 ml

There are different types of spacers and holding chambers. Delivering of drug dose differs based on the design. There are spacers that transport aerosolized medication from pMDIs to intubated patients and those who are tracheotomised [48] or on mechanical ventilation [49,50].

Inhalation from spacers needs to be done in slow manner. The practise of repeatedly pressing the actuation button should be avoided since it reduces the amount of drug delivered through the spacer [51].

Some spacers are manufactured to accommodate only one kind of pMDI, while other types can be utilized with any type of pMDI (AeroChamber). The correct type of spacer must be utilized, with the most appropriate type being selected after trying a variety of devices on the patient. Spacers have the drawback of being heavy, and it is difficult to be carried around; also, the valves may clog or otherwise, malfunction. During an acute exacerbation, the inhalation of SABA via pMDI and a large spacer has been found to be more suitable than a nebulizer [29].

There are many different types of spacers. The three main types of spacers are as follows: simple-tube spacers, holding-chamber spacers, and reverse-flow spacers. A simple-tube spacer is a mouthpiece extended for the inhaler. The mouthpiece of most holding-chamber spacers has a single direction valve. A reverse-flow spacer is one that sprays into a sack or container from which the patient inhales.

The Nebuhaler is spacer that is large in size with a capacity of 750 ml [52]. However, the Volumatic is a spacer with a valve, having a total capacity of 750 ml. It promotes in vitro transportation of small particles [53] and increases the accumulation of medication in the lungs when compared to using pMDI alone [54]. It also reduces oropharyngeal deposition when compared to pMDI alone. The Fisonair is different type of large-sized spacer that has the same efficacy of sodium cromoglycate pMDI that is used to prevent exercise-induced asthma in paediatric patients [55].

Taking several periodic breaths from a large-sized spacer has been shown to be more feasible than applying individual cavernous breaths, particularly in paediatric patients, as it produces more enhanced bronchodilation effect [56,57].

The Aerochamber has gone through a number of design and configuration modifications since its invention. The Aerochamer has three different sizes: adult size (alone or with a mask), child size (usually with a mask), and infant size (with a mask). Its capacity is 149 ml, and its mouthpiece and mask size vary according to patients' age group. The Babyhaler is a device designed exclusively for treating babies and infants [58]. It is a 350 mL polycarbonate tube that makes it easier for a child to empty it [54]. A facemask added to the spacer also aids in the treatment of newborns and infants [59]. In the paediatric population (newborns and children), the facemask is a good alternative to nebulizers [44,60].

2.3. Dry powder inhalation devices (DPIs)

The four key components of a DPI are the powder receptacle, the system of dose metering, the disintegration concept, and the DPI mouthpiece. DPIs are classified into two different classes based on these functional elements: single dose inhaler and multiple-dose inhalers.

Reservoir systems in addition to multiple-dose inhalers are the two different forms of multi-dose inhaler designs. Turbuhaler, Pulvinal, and Clickhaler are examples of reservoir systems. The powder formulation is held in a reservoir in this sort of inhaler, from which single doses are volumetrically metered and delivered with a specific dose metering device. For this sort of inhaler, precise dose metering demands careful handling of the device. Individual doses are placed into appropriate dose chambers (such as blisters) by the production company. All previously manufactured DPIs were under unit dose systems as in Spinhaler (**Figure 11**) [61], followed by Rotahaler. They both use metered doses distributed into capsules made from hard gelatine and have a distinct powder delivery mechanism as single dose inhalers. The cap and body of the capsule must be detached before inhalation, or the capsule must be perforated at both ends. Single dosages are stored within a blister on a disc in the Diskhaler (**Figure 11**). Before inhaling, the dose is delivered by splitting both superior and inferior surfaces of the blister.

In 1994, GlaxoSmithKline introduced the Diskus/Accuhaler. It has 60 discretely administered dosages placed on a coiled strip inside the inhaler. The multiple dosing reservoir device contains approximately 100 to 200 pre-metered doses. Turbuhaler (**Figure 11**) was introduced to transport 500μg per dose of terbutaline sulphate without any carrier. It is considered the most frequently used DPI that leads to sufficient accumulation of medication in lungs in case of adequate inhalation flow [2]. Patients with decreased inspiratory capacity would not acquire full benefit from using Turbuhaler [52].

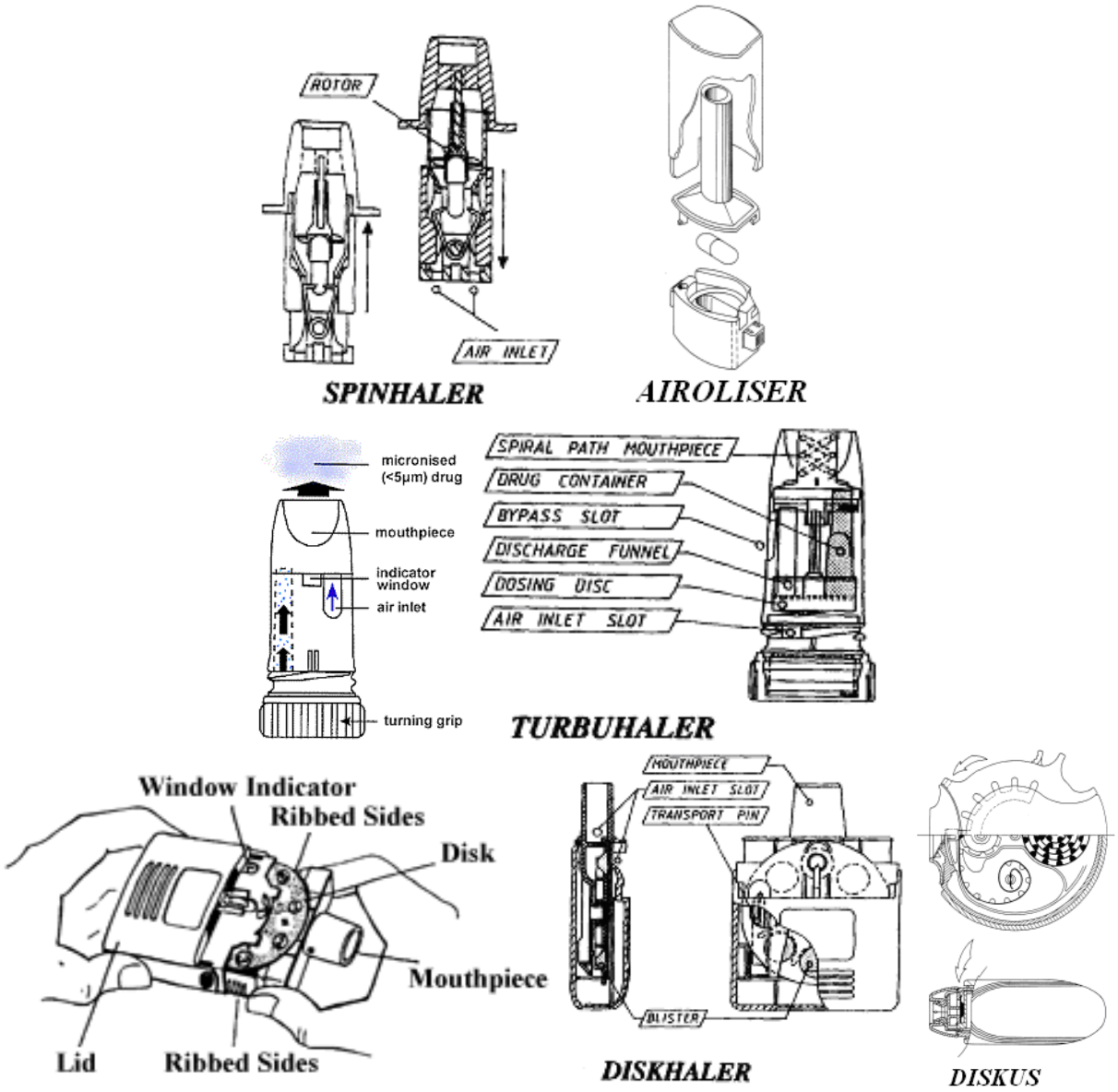

Figure 10. Commercial inhalers in the market

At present, many DPIs that have reservoir for multiple doses have been manufactured, such as Clickhaler, Pulvinal, and Easyhaler. These DPIs produce a reasonably uniform dose regardless of the inhalation technique used by patients in different age groups [62]. The Novolizer was introduced in 2001 [32]. It has a refillable cartridge system with numerous dosing reservoirs. To discharge a dose, it must be inhaled at a rate higher than 35 L/min) [63,64]. When the patient's inspiration flow is below 35 L/min, no dose will be discharged. From a study conducted by researchers to determine if asthmatic children can create enough peak inspiratory flow with the Novolizer, they discovered that the Novolizer's medium to low intrinsic resistance allows for a higher PIF throughout the apparatus.

Two types of powder formulations are used in commercialised dry powder inhalers: spherical pellets and adhesive mixture. In the Turbuhaler, spherical pellets are used. Without the use of a binding agent, the drug microparticles accumulate into larger spherical units, resulting in free-flowing powder. At the smallest dose, certain micronized solvents such as lactose or glucose may be added to the active ingredient. During inhalation, spherical pellets must be broken down nearly completely into much smaller aggregations or even primary particles within the required size range for deep penetration into the

pulmonary tract. All of the other DPIs have adhesive mixtures in them. The micronized drug particles are dispersed over the surface of rather large carrier crystals, principally α-lactose monohydrate. Throughout inhalation, the drug particles should be liberated from the carrier to produce an aerosolized cloud that contains the drug molecules of a desired size, so as to penetrate the lungs. The drug deposited in the mouth may cause localized side effects, which include candidiasis (oral thrush) in case of inhaled corticosteroids and sore throat.

A DPI's operating idea depends on utilizing the patient's own inhalation flow to release the medication dose and deliver fine medication particles for deposition in the lungs. The adhesive mixtures or spherical pellets are large; thus, they cannot be deposited in the lungs. As a result, the pellet or mixture must be fragmented to produce aerosolized mist with a high percentage of particles within the required size of less than 5 μm. There are numerous disintegration principles; they might be as simple as a screen (Rotahaler, Diskhaler) or as complex as the twisting powder method (Turbuhaler). Inhalers with no discernible disintegration principle (**Figure 12**) primarily achieve a reduced resistance to air flow. Therefore, lower resistance to airflow results in a larger differential in PIF.

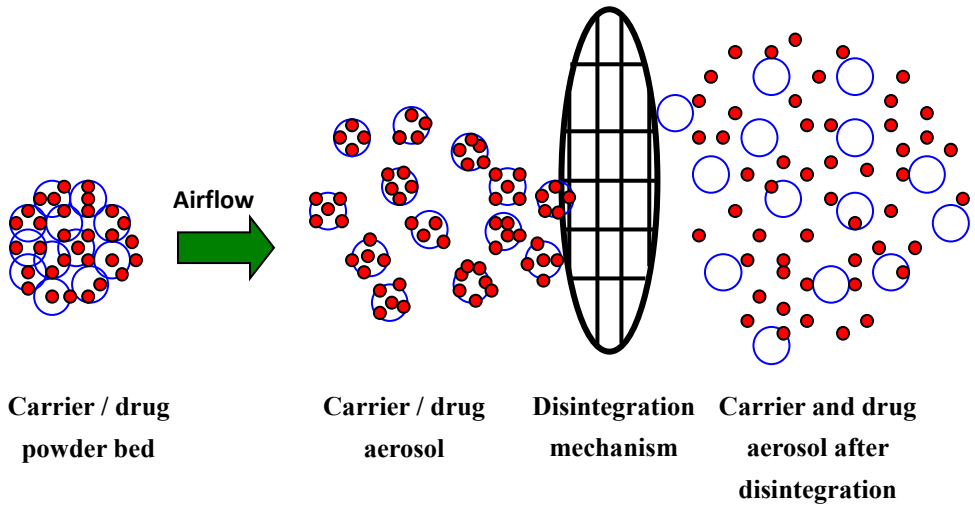

Figure 11. Disintegration of micro-sized drug particles from carrier crystals by passing through a non-specific model for disintegration

More specialized systems of disintegration (Turbuhaler) make better usage of inspiratory flow (**Figure 13**). Fine particle production mainly depends on the patient's inhalation capacity based on the inhaler design. Hence, small particle output is influenced by the flow. The accurate maximum dispersion of aerosol for Turbuhaler, which has high internal resistance, occurs at a PIF value of not less than 60 L/min. If patients fail to attain the desired PIF value, then they may be unable to attain the highest possible efficacy from the inhaled drug [65,66]. Air flow resistance is considered an important aspect in consideration of the DPIs that are used to optimize the efficiency of inhalation flow and improve the accumulation of aerosolized molecules inside the airways [67].

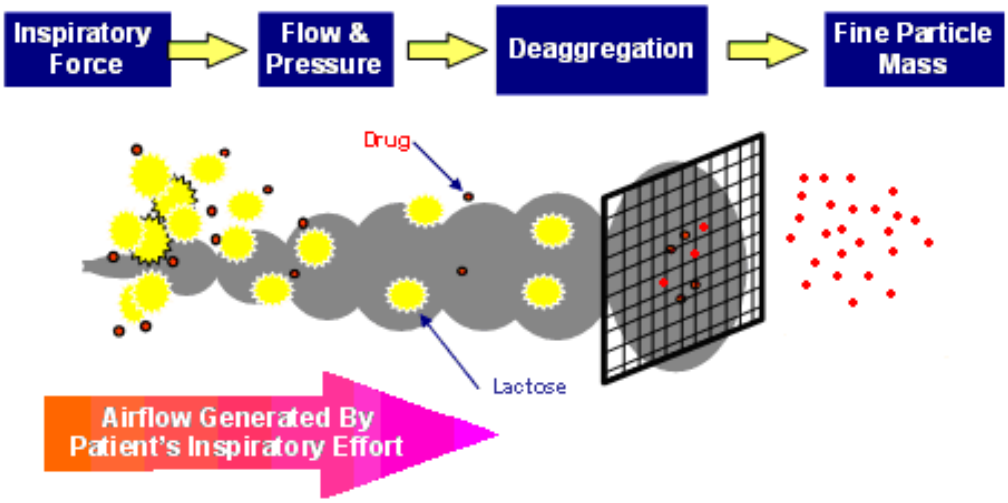

Figure 12. Disintegration of spherical pellets [68]

The PIF produced by DPIs will determine the device's performance. The following equation illustrates the relationship between the rate of inhalation and inhaler resistance.

$F = \sqrt{\Delta P} / R$ [67]
F = flow that takes place throughout the inhaler (litre per minute)
ΔP = variance in pressure constructed through the device (cmH_2O)
R = resistance obtained by inhaler, measured in $(cm\ H_2O)^{0.5}$ / litre per minute

The increase of resistance in inhalers will lead to a reduction in inspiratory flow. The strong defiance to flow of air restricts the range of inspiratory flow that can be used. However, as compared to non-specific degradation systems, the small particle production is larger because of higher disintegration efficiency [29]. In order to limit drug accumulation in the oral cavity and pharynx, the mouthpiece can be utilised to adjust the inhaler's defiance to airflow and the orientation of the aerosolized medication cloud in the patient's throat and mouth [69]. The PIF, inspiration time, device's resistance to flow, speeding rate, and the nature of the drug contained in the inhaler are the critical parameters that will affect the dose administered [61]. The overall released dosage and the amount of small particles emitted from DPIs markedly differ in view of the differences in inspiratory flow [5]. Both, drug delivery and particle size distribution may be influenced by the inhalation profile used [70]. A study was done to compare the dose produced and the fine particle fraction of salbutamol from each of the following devices: Easyhaler, Diskus, and Turbuhaler [71]. The study revealed that the released dosage and fine particle proportion with both Easyhaler and Diskus were less flow dependent than with Turbuhaler. As a result, patients may not be able to use all DPIs in the same way [72]. The requirement of energy varies among different DPI devices. Patients who use the Turbuhaler need to must use much more inspiratory strength in comparison with other types of DPIs for the purpose of achieving an equivalent inhalation flow rate [65,66]. As a result, patients who use DPIs to relieve symptoms during acute asthma attacks may experience complications [2]. Changing the delivery mechanism can also leave a negative impact on the inhaled drug's safety and efficacy. Hence, DPIs should not be used interchangeably [73,74]. **Table 2** summarizes some advantages and disadvantages of dry powder inhalers [75].

Table 2. Advantages and disadvantages of DPIs

Advantages of DPIs	Disadvantages of DPIs
Free from propellants	Performance of device mainly relies on the rate of inhalation flow
Demands lower degree of coordination	Resistance to airflow of the device
Low susceptibility towards issues concerning formulation	Difficulty in achieving dose consistency
Less issues in terms of drug stability	More liable to be affected by environmental factors and patient misuse
Less extractable development from the device's constituents	More costly

When using dry powder inhalers (DPI), chronic obstructive pulmonary disease (COPD) patients exhibit lesser inspiratory flow rate compared with patients with asthma [76]. Moreover, the increase in the severity of airway obstruction will decrease the inhalation flow from various dry powder inhalers [76]. Another research inferred that it is inappropriate to use Turbuhaler in pre-school children owing to their low inspiratory flow [77].

3. Conclusion

Aerosolized medications can precipitate in pulmonary airways through three mechanisms: Brownian diffusion, inertial impaction, and sedimentation. However, inhaled therapy can be delivered via different types of devices: nebulizers, pMDIs, and DPIs. Nebulizers are mainly used for delivering large-sized particulated medications in high doses. There are different types of nebulizers based on their mechanism of action, such as vibrating mesh nebulizer, air-jet nebulizer, and ultrasonic nebulizer. MDIs are frequently used for medicating pulmonary obstructive disorders; however, they need to be combined with proper inhalation techniques to achieve full benefit from the inhaled medication. Breath-actuated metered dose inhalers or Autohalers are designed to decrease the demand for harmonization between dose ejection and the start of inhalation in asthmatics. pMDI can be used alone or connected to spacer devices. Using pMDIs with spacers can improve the inhalation technique, especially among children, as well as decrease undesired side effects, such as oral thrush, by reducing drug accumulation in the oropharynx region. The three main types of spacers are simple tube spacers, holding-chamber spacers, and reverse-flow spacers. For dry powdered inhalers (DPIs), its mechanism of use mainly depends on the patient's inspiratory flow rate to release the medication dose and deliver small drug particles into the lungs. Most of the available DPIs devices are breath-actuated devices.

Disclosure statement

The authors declare no conflict of interest.

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