Inhalation drug delivery devices: technology update

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Abstract: The pulmonary route of administration has proven to be effective in local and systemic delivery of miscellaneous drugs and biopharmaceuticals to treat pulmonary and non-pulmonary diseases. A successful pulmonary administration requires a harmonic interaction between the drug formulation, the inhaler device, and the patient. However, the biggest single problem that accounts for the lack of desired effect or adverse outcomes is the incorrect use of the device due to lack of training in how to use the device or how to coordinate actuation and aerosol inhalation. This review summarizes the structural and mechanical features of aerosol delivery devices with respect to mechanisms of aerosol generation, their use with different formulations, and their advantages and limitations. A technological update of the current state-of-the-art designs proposed to overcome current challenges of existing devices is also provided.

Keywords: pulmonary delivery, asthma, nebulizers, metered dose inhaler, dry powder inhaler

Introduction

Inhalation therapy has been used for thousands of years, albeit in a different form and use. Inhalation therapy was practiced by ancient civilizations in Egypt, Greece, India, and People’s Republic of China as evidenced by different artifacts displayed in museums, that may be considered the first used inhalation devices.¹,²

Currently, inhalation therapy is the best option for lung diseases like asthma, cystic fibrosis, and chronic obstructive pulmonary disease (COPD). These local therapies allow the use of smaller doses and reduce systemic side effects.³ In the last two decades, a remarkable scientific interest in the technology for pulmonary delivery was spiked by the fact that the lungs can be used as a portal for systemic drug delivery.⁴ Pulmonary delivery is attractive as a route for systemic administration due to fast absorption by the massive surface area of the alveolar region, the abundant vasculature and thin air–blood barrier, and the avoidance of first pass metabolism.⁵ The effectiveness of an aerosol therapy is largely dependent on how much of the medication will reach the intended site of deposition.⁶ The deposition pattern of the administered aerosol is determined mainly by the formulation and the delivery device. Devices used to deliver therapeutic agents as aerosols are based on one of the three platforms: nebulizers, pressurized metered-dose inhaler (pMDI), and dry powder inhalers (DPIs). This review provides a description of the conventional and the current state-of-the-art design for inhaler devices and how this has improved the performance of these devices.
Basic principles of particle deposition to the respiratory tract
In order to understand the reasons behind the design of each inhaler and to assess the performance of devices currently in use, one has to understand the basic principles of drug deposition in the lung, factors that can influence the deposition pattern, and how these affect the therapeutic outcome of the inhaled treatment. Table 1 provides the parameters that should be considered in designing aerosol delivery devices.7,8

The mass median aerodynamic diameter and geometric standard deviation (GSD) are what determine the site of deposition in the respiratory tract. Large particles or droplets deposit by impaction in the upper respiratory tree of the lung (oropharyngeal and tracheo-bronchial region), where air velocity is high and the air flow is turbulent.9,10 Particles in the size range of 0.5–5 μm deposit by sedimentation in the terminal bronchioles and alveolar regions. The larger the GSD, the more sites that the aerosol will be deposited in the respiratory tract. In general, aerosols with GSD <2 are desirable and ideally, aerosol particles should be as close as possible to monodispersity to increase deposition at the desired site of action and increase the efficacy of the treatment.11 Since a detailed discussion of these topics is beyond the scope of this review, readers are encouraged to revise these concepts elsewhere.12

Challenges that patients face with current inhaler devices
The major problems with the use of inhaler devices are the deposition of aerosolized particles in the oropharyngeal region and upper airways and the lack of coordination between the device activation and inhalation due to lack of patient training.13,14

In general, pMDIs generate aerosol faster than the patient can inhale. Coordination between device actuation and patient inhalation is especially difficult in children and the elderly. With some DPIs, it is required that the patient inhales at maximum force to disperse then inhale the powder, which unless properly trained, is rarely achieved.15 In these scenarios, most of the aerosol deposits in the upper airways. For pMDIs, this problem was addressed by providing a spacer or by designing breath-activated inhaler instead of breath-coordinated devices.16

The effectiveness of pulmonary delivery is also dependent upon the breathing pattern of the patient. Rapid inspiration is not recommended when using pMDIs and nebulizers, since it creates a turbulent air flow and fast velocity which increases the deposition by impaction in the upper airways.17 However, rapid inspiratory air flow is required to deagglomerate drug particles for inhalation in DPI devices.18 Medical personnel should train the patients when the device for their medication is changed. For a proper aerosol deposition, patients are advised to take a deep initial breath, and then hold it for 10 seconds to allow for the aerosol to settle down in small bronchioles and the alveolar region.

Nebulizers
There are two types of nebulizers, jet and ultrasonic, that differ in the force used to generate the aerosol from the respective liquid. Depending on the model and the manufacturer, nebulizers generate 1–5 μm droplets. Nebulizers do not require patient coordination between inhalation and actuation, thus they are useful for pediatric, elderly, ventilated, non-conscious patients, or those who are unable to use pMDIs or DPIs. Nebulizers have the capability of delivering larger doses compared to the other aerosol devices even though this will require longer administration times.19

Jet nebulizers are based on Venturi’s principle which states that fluid pressure decreases as its passes through a narrow sectional area. In these nebulizers, air stream moves through a small capillary tube at high velocity creating a low pressure that drives the liquid to be aerosolized up the capillary tube.20 The high velocity blast of air carrying the droplets will bump into baffles placed in different numbers and positions depending on the design of the jet nebulizer. The impaction of large droplets on these baffles either break them into smaller sized droplets that will leave the nebulizer or will retain them in the device to be re-nebulized until their size is small enough to leave the nebulizer. Baffles also reduce
the velocity of the aerosol cloud emitted from the nebulizer, which reduces impaction in the oropharyngeal region when inhaled by the patient. The main issues with jet nebulizers are to generate the aerosol, the noise that some of them generate and the temperature drop of the liquid in the nebulizer chamber due to liquid evaporation in the nebulized droplets.

In ultrasonic nebulizers, sound waves are created due to the vibration of piezoelectric crystals at high frequency, creating crests that break the liquid into small droplets. Ultrasonic nebulizers are not completely portable because they still need electric supply for charging. Compared to jet nebulizers, ultrasonic nebulizers are more expensive and tend to increase the temperature of the nebulized drug solution; thus they are considered inappropriate to nebulize thermolabile peptides or DNA. They are also less efficient in nebulizing viscous liquids and suspensions than jet nebulizers, probably because of the reduced force that is used to atomize the liquid.

From the device perspective, the variables that need to be optimized to emit an accurate and consistent dose with the nebulizer are: 1) the volume of the drug solution that is loaded in the device (taking into account its "dead volume"); 2) the viscosity of the drug solution; 3) the air flow and pressure in case of jet nebulizers; and 4) the tubing, mask, or mouthpiece used. In unoptimized therapies, a large proportion of the emitted dose from the nebulizers may be lost in the tubing, may remain as "the dead volume", or be lost in the surrounding area in case of unvented nebulizers, exposing others to the aerosol. The lack of optimization of these variables is the main source of dose variability that a patient may receive. A disadvantage for the users of nebulizers is that they have to be assembled and loaded with the medication before each use. Then they have to be de-assembled and cleaned if they are to be reused. All these steps may be hard to follow for an untrained-young/elderly patient.

From the formulation perspective, liquid formulations used in nebulizers are cheaper and easier to develop compared to formulations used in pMDIs and DPIs. Also, different compatible drug solutions can be mixed and nebulized concurrently. However, it is important to alert users that the droplet size and the dose emitted by a particular device can be altered by a change in the viscosity of the solution and that nebulizer settings should be optimized for each medication.

**Technological advances in nebulizers**

Table 2 lists some of the newest nebulizer models in the market. These include breath-enhanced, breath-actuated, and vibrating mesh nebulizers.

### Table 2 Examples of nebulizers with novel technologies

<table>
<thead>
<tr>
<th>Nebulizer</th>
<th>Type</th>
<th>Company</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>AeroEclipse II BAN</td>
<td>Breath-actuated jet nebulizer</td>
<td>Monaghan Medical Corporation</td>
<td>23,28</td>
</tr>
<tr>
<td>AKITA® APIXNEB</td>
<td>Vibrating mesh nebulizer</td>
<td>Activaero GmbH</td>
<td>16,29</td>
</tr>
<tr>
<td>PARI CompAIR™ NE-C801</td>
<td>Jet nebulizer with virtual valve technology</td>
<td>OMRON Healthcare Europe BV</td>
<td>30</td>
</tr>
<tr>
<td>I-neb AAD System</td>
<td>Vibrating mesh nebulizer with metering chambers and adaptive aerosol</td>
<td>Koninklijke Philips NV</td>
<td>22,31</td>
</tr>
<tr>
<td>Micro Air® NE-U22</td>
<td>Vibrating mesh nebulizer</td>
<td>OMRON Healthcare Europe BV</td>
<td>32</td>
</tr>
<tr>
<td>PARI LC® Plus rapid</td>
<td>Breath-enhanced jet nebulizer</td>
<td>PARI international</td>
<td>33,34</td>
</tr>
<tr>
<td>PARI eFlow® Plus</td>
<td>Perforated oscillating membrane</td>
<td>Koninklijke Philips NV</td>
<td>33</td>
</tr>
<tr>
<td>SideStream Plus</td>
<td>Breath-enhanced jet nebulizer</td>
<td>Koninklijke Philips NV</td>
<td>25</td>
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appropriately and only then, it releases the dose, with droplet size of mass median aerodynamic diameter <4 µm and minimum drug loss (~ 1%).26 I-neb is also another example of vibrating mesh nebulizer coupled with an adaptive aerosol delivery software that adjusts the aerosol emission based on the breathing pattern of the patient, which reduces drug loss and increases the inhaled mass.27 This smart device can adjust the dose delivery based on last three breaths and provides feedback after dose delivery.15

**Pressurized metered-dose inhalers**

pMDIs are the most popular inhalers to treat local respiratory diseases such as asthma and COPD. The structural components of the conventional pMDI are the canister, metering valve, actuator, and a mouth piece.35 Canisters are made of inert materials capable of enduring the high pressures required to keep the propellant gas in liquid state. Plastic, stainless steel, glass, and aluminum have been used to make canisters.36

The metering valve is designed to deliver a precise aerosol amount (20–100 µL) each time the device is actuated. When the inhaler is not used, an inner valve between the canister and the meter chamber is open allowing the chamber to be filled with the propellant–drug mixture in liquid form. At the same time, another outer valve between the meter chamber and the outside air is closed. As the patient presses the canister for dose actuation, the inner valve closes while the outer valve opens releasing the metered drug–propellant mixture retained in the chamber through the actuating orifice in an aerosol form.37,38

Internally, the actuator includes the spray nozzle (actuator orifice) and the expansion chamber in which the released propellant from the metering chamber expands and partially volatizes due to the decrease in pressure. The design of the actuator significantly influences the performance of pMDIs. Smyth has shown that the diameter of both the actuator orifice and the expansion chamber in addition to the orifice jet length affects the spray pattern and the emitted particle size. Newer actuators are equipped with a dose counter that indicates the number of doses remaining.39

**Formulation of pMDIs**

pMDIs drug formulations can be solutions or suspensions in a single propellant or propellant mixture and may include excipients such as ethanol or surfactants to solubilize the drug or stabilize a drug suspension.40 Recently, the use of pMDIs has extended beyond bronchodilators and corticosteroids to deliver proteins,41 plasmid DNA,42 and live attenuated virus vaccines or bacteriophages.43

Ideally, propellants should be nontoxic, non-flammable, and compatible with the formulation and provide consistent vapor pressure during the entire life of the product. Chlorofluorocarbons, were used as propellants in pMDIs for decades44 but had deleterious effects including ozone layer depletion. After their mandatory ban by the Montreal Protocol, chlorofluorocarbons were replaced by hydrofluoroalkane (HFA) propellants in all pMDIs except for those in People’s Republic of China.44 However, reformulating pMDIs with HFA propellants was challenging, often needing to use new excipients and metering valves.40

**Technological advances of pMDIs**

New pMDIs can be classified as breath-actuated or coordination devices. Breath-actuated pMDIs, such as the Easibreathe®, were designed to address the problem of poor coordination between inhaler actuation and patient’s breathe. These mechanical devices are activated when the device senses the patient’s breathe and emits the dose in response.45,46 Breathe coordinated pMDIs were developed to synchronize the inspiration with the discharge of the dose from inhaler. The inhalation flow rate is coordinated through the actuator and the patient gets time to actuate the pMDI reliably during inhalation.40

A clever approach was proposed by Kelkar and Dalby to reduce the droplet size emitted from pMDIs: the addition of dissolved CO₂ to HFA-134 and ethanol blend. After dose actuation, the bursting of the CO₂ bubbles or “the effervescent effect” that occurs within the emitted HFA/ethanol droplet will break up the generated droplets into smaller ones; this approach aims to increase the respirable fraction emitted from a conventional pMDI.47

**Inhalation aids**

Spacers and valved holding chambers (VHCs) are used with pMDIs to increase the efficiency of aerosol delivery. A spacer is a tube or extension device that is placed at the interface between the patient and the pMDI. VHCs such as AeroChamber Plus® Flow-Vu® have a one-way valve at the mouthpiece end to allow inhalation and prevent exhalation into the chamber. VHC enables the patient to breath from a “standing aerosol cloud” that does not require breath coordination.48,49 These inhalation aids reduce the speed of the emitted aerosol and allow for the evaporation of propellant from larger droplets reducing oropharyngeal deposition and increasing deep lung deposition. However, they can also reduce the doses delivered from pMDI due to electrostatic precipitation.50 Newer spacers and VHCs are made of...
anti-static polymers that minimize adherence of the emitted particles to the inner walls of the spacer.\textsuperscript{38} New generations of spacers can indicate whether the patient is inhaling correctly or not, such as those that whistle when the patient is inhaling too quickly.\textsuperscript{15}

**Multi-dose liquid inhalers (Respimat® Soft Mist™ inhaler)**

The Respimat\textsuperscript{®} inhaler combines the advantages of pMDIs and nebulizers. It is a small, portable, hand-held inhaler with no need for power supply (like pMDIs) that slowly aerosolizes propellant-free drug solutions as a soft mist (like nebulizers), thus decreasing the chance for oropharyngeal deposition. Administration of one-half of the cumulative dose of ipratropium bromide and fenoterol hydrobromide by Respimat\textsuperscript{®} achieved the same therapeutic outcome as that of the full dose administered by pMDI to asthmatic patients.\textsuperscript{31} Dalby et al also showed that the oropharyngeal deposition of fenoterol was significantly reduced when administered by Respimat\textsuperscript{®} than by pMDIs, whereas a pMDI with a spacer had the lowest oropharyngeal deposition. However, Respimat\textsuperscript{®} has achieved the highest concentration of fenoterol in both central and peripheral lung regions.\textsuperscript{52} Respimat\textsuperscript{®} is the least recommended inhaler for patients with good inspiratory flow rates (>30 L/min).\textsuperscript{53} Combivent\textsuperscript{®} Respimat\textsuperscript{®} was the first Respimat to be approved by Food and Drug Administration (FDA) as maintenance therapy for COPD.\textsuperscript{54}

The drug solution for Respimat\textsuperscript{®} is stored in a collapsible bag inside the cartridge which is loaded inside the device. The Respimat\textsuperscript{®} device has a tension spring that when twisted at 180°, forces a metered volume of drug solution through a capillary tube into a micropump. Once the patient presses the dose release button, the energy released from the spring forces the dose into the “uniblock”, the unique structural part of this device. The uniblock allows the drug solution to pass through very fine filter channels releasing two jet streams of drug solution, that converge creating a large fraction of respirable droplets with slow velocity.\textsuperscript{52}

**Dry powder inhalers**

DPIs are portable devices that require minimum patient coordination between breathing and actuation of the device to deliver powder medications. DPI drug formulations have greater chemical stability than liquid formulations, but manufacturing powders with the appropriate characteristics for easy aerosolization and alveolar delivery is more complicated.\textsuperscript{55} Performance of DPIs depends on the powder formulation and on the design of the inhaler device.

**Formulation design for DPIs**

Traditional powder blends consist of micronized drug particles (1–5 µm) blended with an inactive excipient (lactose, mannitol, trehalose, sucrose, sorbitol, glucose) of larger sizes (40 µm).\textsuperscript{56} Particle engineering approaches are also employed to produce particles using different core materials and more recently of only pure drug.\textsuperscript{57}

Unoptimized powder blends can exhibit interparticulate cohesive forces (van der Waals forces, mainly), which cause particle aggregates, making powder dispersion very difficult.\textsuperscript{5} Drug carrier excipients added in appropriate sizes can reduce such cohesive forces, thus achieving a better flow and more uniform doses.\textsuperscript{56}

**DPI designs**

The design of DPI heavily influences the performance of the device. To aerosolize the drug powder, individual particles are deagglomerated by external forces, which can be airflow shear or particle–particle, particle–device impaction. The Clickhaler, the Multihaler, and the Diskus are designed to feed the powder into a high speed airflow that splits particle agglomerates, thus achieving respirable particles. Other devices like the Turbuhaler and the Spinhaler depend on the impaction between particles and surfaces of the device to deagglomerate.\textsuperscript{58,59}

A major challenge in DPI design is to balance between inhaler resistance and flow rate. In early DPIs, a rapid airflow was required to increase particle deagglomeration by creating more frequent and stronger impactions to achieve a higher fine particle fraction. However, a rapid airflow increases the chances of oropharyngeal deposition and reduces the dose delivered to the lungs.\textsuperscript{59,60} Moreover, high resistances are not suitable for asthma or COPD patients who already struggle to breathe.

**DPI classification**

DPIs can be classified by the number of doses the device can carry, the patient contribution to aerosolize the powder, or by the mechanism of powder dispersion.

By the number of doses, DPIs can be classified as single-unit dose, multi-unit dose, and multi-dose reservoirs (Figure 1). In single-dose DPIs, the dose is supplied in individual capsules. Before each administration, the patient has to load the device with one capsule for a single dose delivery. Single-dose DPIs can further be classified as disposable or reusable.\textsuperscript{53} Multi-unit dose DPIs use factory-metered and sealed doses packaged so that the device can hold multiple doses at the same time without having to be reloaded.
Typically, the packaging consists of replaceable disks, cartridges, or strips of foil-polymer blister packaging.\textsuperscript{6,61,62} Multi-dose reservoir DPIs store the powder in bulk and have a built-in mechanism to meter individual doses upon actuation. Issues such as the dependence of the dose emission on the flow rate and the moisture uptake from patient exhalation or the environmental humidity into the reservoir, have yet to be addressed in these new devices.\textsuperscript{62,63}

Based on the mechanism for powder aerosolization, DPIs can be classified as passively- or actively-actuated devices. The original passive DPI was a breath-actuated device, relying solely on the patient’s inspiration to provide sufficient air flow for entrainment and de-aggregation of the formulation. Device actuation was intrinsically tied to the patient’s inhalation, thus avoiding coordination issues associated with pMDIs.\textsuperscript{64,65} The first passive DPIs in the market were the Rotahaler\textsuperscript{TM} and the Spinhaler\textsuperscript{TM}, which are single-dose devices. In the Rotahaler\textsuperscript{TM}, a capsule with the powder dose is loaded in the device. Upon actuation, the capsule gets pierced and an impeller rotates the powder released from the capsule by the inspiratory force of the patient. In the Spinhaler\textsuperscript{TM}, the capsule gets split into two halves and the dry powder is released and fluidized when the patient inhales.\textsuperscript{18}

The main issue with passive DPIs was the lack of uniformity between the inspiratory force among patients with different age and disease state, as well as variation in the inspiratory force of the same patient. These variations significantly affect dose uniformity, even when the same device is used. Some devices are designed to reach optimum flow rate at a high pressure drop in order to reduce variability in the delivered dose. However, pediatric patients, elderly patients, and those with advanced respiratory diseases are not able to generate enough pressure drop to achieve the optimum flow rate.\textsuperscript{46,66} To enhance their performance, newer versions of passive DPIs are being developed to solve these issues (Table 3).

Active (power assisted) DPI devices are designed with an internal energy source to aerosolize the powder bed in the DPI, so that dose administration is no longer dependent on the patient inspiratory flow rate. This energy source can be a battery, compressed gas, or a spring mechanism. In active devices, the powder is dispersed by vibration, gas discharge, or an impeller. The Spiros\textsuperscript{TM} device (Dura, San Diego, CA, USA) has a battery-powered motor that disperses the powder by impaction of a rotating impeller to generate aerosol from

![Figure 1 Dry powder inhaler devices classified by the number of doses.](image-url)
the powder bed. The motor is activated by a very low breathing rate, which is convenient for asthmatic patients. Another source of powder dispersion, a piezoelectric polymer, was introduced in the Oriel device, a multi-dose blister DPI. When the patient inhales, an electrical impulse is sent to the blister, stimulating the piezoelectric polymer which is incorporated in each sealed blister to vibrate ejecting the powder into a flow stream.97 Although active DPIs appear easier to use than passive DPIs, none of these advanced devices has been marketed yet.

**Thermal vaporization aerosol devices**

The STACCATO® is a novel breath-actuated inhalation delivery system, which uses heat to vaporize a thin film of the drug, which later condenses in the lungs into droplets or particles depending on the nature of the drug.78 In that case, the drug is dissolved in volatile solvent/solvent mixture which is sprayed over a metal substrate such as zinc halides. The best drug candidates for such systems are those which are thermally stable and with low-melting points. The STACCATO® system can deliver the condensed aerosol deeply into the lungs with a fast onset of action making it suitable for systemic delivery. Nicotine is one example for drugs to be delivered through this aerosol device as a treatment for smoking withdrawal symptoms.79 The STACCATO® system is available in the market as Adasuve®, a recently FDA-approved DPI for agitation associated with schizophrenia or bipolar disorder in adults.80

**Future approaches**

The number of inhaler devices available in the market for inhaled therapies has increased significantly in the past decade. However, they have made modest differences in the clinical outcomes. Most of these newer devices are targeting the general adult population, but little to no attention had been placed in special patient populations such as the pediatric and geriatric populations. It will be desirable that pharmaceutical companies develop inhalers specific for each of these three distinct patient populations, considering their age and health condition in order to achieve the concept of “individualized inhaler”.

Another issue to be considered is tailoring specific devices to the different therapeutic molecules being developed. Pulmonary drug delivery is an attractive route of administration for diverse entities including micro and macromolecules such as vaccines, DNA, cytokines, antibodies, and hormones.16 Therefore, it is essential that the hardware technology of inhalers meets the needs of the pulmonary delivery of such diverse molecules. Devices should be manufactured to ensure maximal stability for these highly sensitive molecules.

Meeting future inhaler demands requires more sophisticated device design, but the inhalers should still be simple enough to be adequately used by the patients. Finally, it would be desirable that novel devices have low costs so that they can be afforded by all sectors of the general population.

**Conclusion**

Figure 2 depicts factors related to the patient, formulation, and device that should be addressed to achieve optimum aerosol delivery. The structure and design of inhaler have a major impact on the aerosol deposition to the lungs. An ideal inhaler should deliver precise and consistent doses to a targeted region in the lungs and maintain the stability of the delivered drugs. It is also desirable that devices are small and simple enough to be easily used by patients. DPIs are becoming more popular because of their ease of use and the powder stability. pMDIs are still facing challenges from the formulation and the design point of view. Nebulizers are being remodeled to broaden their applicability. In reality, there is no device that fulfills the myriad of requirements to deliver drugs with different physicochemical properties. The medical personnel must fully understand the capabilities of each inhaler and relate that to the needs of the patient, according to his health condition, to achieve the best therapeutic outcome.

**Disclosure**

The authors report no conflicts of interest in this work.

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