Dry Powder Inhalers: Particle Size and Patient-Satisfaction

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Abstract

Inhalational route is the cornerstone for drug delivery in asthma. Dry powder inhalers efficiently deliver drug particles to lungs depending on patients' breath actuation and without using propellants. Drug delivery in lungs is dependent primarily on particle size distribution of the formulation. Several studies have proved that drug particles 1–3 μm in size provide optimum efficacy with minimum adverse events. Particles $>3 \mu\text{m}$ are deposited in the oropharynx and those $<1 \mu\text{m}$ are exhaled. However, these fine particles might not be felt in the mouth due to which patients may feel that appropriate amount of drug was not dispensed. This perception may negatively influence patient satisfaction and confidence on the device. The patient education on the absence of mouthfeel is thus essential. Treating physicians should provide optimum patient counseling and education addressing the importance of particle size for desired clinical effects.

Keywords: Asthma, chronic obstructive pulmonary disease, dry powder inhaler, inhalational devices, mouthfeel, particle size, patient education

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) and asthma are leading causes of mortality and morbidity; in 2015, COPD and asthma caused 3.2 million and 0.4 million deaths, respectively. In 2002, COPD ranked 8th and asthma ranked 23rd as causes of disease burden.^[1] COPD now ranks as the second leading individual cause of disease burden in India.^[2] Pulmonary drug delivery by the inhaled route is the mainstay of treatment for asthma and COPD.^[3] The major advantages include lower dose requirement for intended clinical efficacy, faster onset of action (because of topical application), and circumvention of first-pass metabolism. The devices routinely used for delivering inhalation drugs are classified into pressured metered dose inhalers (pMDIs), dry powder inhalers (DPIs), and nebulizers.^[4]

nebulizers are some types of nebulizers available in the market. Nebulizers can be used by patients who are unable to coordinate breathing, such as geriatric and pediatric patients, and where large drug doses are required.^[5,6]

pMDIs contain the drug in a suspension or solution formulation, which is released as aerosol upon combination with high pressure liquefied propellants, usually chlorofluorocarbons or hydrofluoroalkanes (HFA-134a and HFA 227). Several pMDIs are available, such as Proventil®, Ventolin®, Qvar®, Flovent®, and Advair®.^[3] pMDIs are easy to use, portable, inexpensive, low maintenance devices and can deliver the drug into deep regions of the respiratory tract; however, coordination between actuation and inhalation is required.

DPIs are generally single-dose devices containing the drug in a capsule form or multi-dose devices storing the drug in

TYPES OF DRUG DELIVERY

Inhalation devices

Nebulizers are the oldest available inhalational devices, where the drug, in a solution or suspension, is packed usually into single-use containers and is nebulized into fine droplets. Jet nebulizers, ultrasonic nebulizers, and vibrating mesh

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a bulk reservoir with a metering valve. Another type of DPI is a multi-dose device with individual doses inside. DPIs are easier to use than pMDIs as they are breath-actuated and use the energy from a person's inhalation to de-aggregate the particles into smaller particles.

The four main DPI systems are a capsule-based single-dose device, where patients load a capsule containing the powered formulation into the device before each use; disposable devices containing a premeasured single dose; multiple-dose inhalers that have a built-in mechanism to meter a single dose from a reservoir with each actuation; and multiple-dose inhalers with individual doses packed in the device.^[7-12] Figure 1 shows several subtypes of DPIs. Table 1 shows the advantages and disadvantages of nebulizers, DPIs, and pMDIs.

Dry powder inhalers

Development and current scenario

The idea of DPIs was patented by Vincent Alfred Newton in

the mid-eighteenth century, but the first DPI (Aerohaler[®]) was launched in 1948, approximately 100 years after the patent. DPIs are formulated to carry the drug alone or in combination with an inactive excipient such as lactose. Before 2010, all DPIs used the breath-actuated technique for delivering fine drug particles in the respiratory system. However, the breath-actuated technique does not generate enough flow rate for extracting the dose and good powder dispersion and does not achieve the desired therapeutic effect.

Battery-operated DPIs are advantageous as they have a battery-operated propellant or use pressured air from a hand piston for drug dispersion. They deliver flow rate-independent fine particle aerosol.^[9] Currently, the mainstream developments that distinguish earlier and present DPIs comprise overcoming the weaknesses in the earlier design concepts, particle engineering, understanding pulmonary drug deposition and distribution from DPIs.^[9]

EFFECTIVENESS OF DRY POWDER INHALERS

The effectiveness of DPIs is dependent on the device design. Drug delivery into lungs is determined by several factors such as aerodynamic particle size distribution, inspiratory flow rate, airway geometry, and patient education and training. DPIs require a higher inhalation flow rate, usually higher than 60 L/min, which helps in de-aggregating and dispersing the drug powder. In case of airway geometry, the usual distribution of drug particles from DPIs occur in a 1:1:1 ratio among conducting (upper) airways, intermediate (transitional) airways, and peripheral (lower) airways.

Usmani *et al.* observed similar distribution, with a flow rate of 30–67 L/min.^[13] However, as the airway surface area increases toward the alveoli, and approximately 95% of the lung surface area is within the peripheral airways, the actual drug concentration in the peripheral airways decreases by a factor of 100. This factor

Figure 1: Types of dry powder inhalers^[10]

Table 1: Advantages and disadvantages of nebulizers, pressurized metered dose inhalers, and dry powder inhalers^[10]

Inhaler	Formulation	Advantages	Disadvantages
Pressurized metered dose inhaler (pMDI)	Drug suspended or dissolved in propellant (with surfactant and co-solvent)	Portable and compact Multi-dose device Relatively inexpensive Cannot contaminate contents Available for most inhaled medications	Contains propellants Not breath-actuated Many patients cannot use it correctly High oropharyngeal deposition
Dry powder inhaler (DPI)	Drug blend in lactose, drug alone, drug/excipient particles	Portable and compact Breath-actuated (no coordination needed) Does not contain propellants	Requires a minimum inspiratory flow May not be appropriate for emergency situations Many patients cannot use it correctly Most types are moisture sensitive
Nebulizer	Aqueous solution or suspension	May be used at any age No specific inhalation technique required Vibrating mesh is portable and does not require an outside energy source May dispense drugs not available with pMDIs or DPIs	Jet and ultrasonic nebulizers require an outside energy source Treatment times can be long Performance varies between nebulizers Jet nebulizers cannot aerosolize a certain volume of solution Risk of bacterial contamination Newer nebulizers are expensive

is clinically relevant for drugs such as corticosteroids that target smaller airways, but not for beta-blockers or anticholinergics that target the larger airways.^[14-16]

Aerodynamic particle size determines the site and extent of particle deposition. Particle size is an important criterion for the success of DPIs. For an optimum pharmacodynamic effect, a particle size between 1 and 3 μm is most suitable, as particles $<1 \mu\text{m}$ are inevitably exhaled and those $>5 \mu\text{m}$ are deposited in the oropharynx.^[11,17] Drugs that reach the alveoli have higher chances of getting absorbed into systemic circulation and have increased potential for adverse events. Therefore, optimum topical effect requires a balance between inspiration and particle size. Engineering Drug Particles for Optimal Lung Deposition Pulmonary drug delivery is more complex than oral drug delivery. It requires a delivery system that can generate an appropriate particle size at the intended flow rate so that drug particles can reach the lower respiratory tract and lungs and create an optimal effect.

Aerodynamic diameter is a prime factor responsible for this process. Particle size measurements for inhaled DPI and pMDI steroids along with reported lung deposition values from literature reveal a median mass aerodynamic diameter of $>2.6 \mu\text{m}$. Lung deposition values with larger drug particles appeared to be not $>20\%$, with an oropharyngeal deposition of 80% to 90%.^[18-20] Optimal size of the particles in the aerosols depends mainly of the physical properties of carrier particles such as their shape, roughness of their surface, density, and geometric diameter. The effect of these variables on aerosol performance has been studied using three model polystyrene spheres as carriers. The results showed that aerosol performance increased as particle size decreased.^[21] A dose-comparison calculation study showed that compared with an ultrafine-particle inhaled steroid, a large-particle inhaled steroid would take 2.6 times the dose to achieve the same improvement in forced expiratory volume.^[22]

EFFECT OF PARTICLE SIZE ON DRUG PENETRATION

Aerodynamic particle size determines drug penetration in the bronchial tree and thus determines the actual dose delivered. Three basic principles are the main determinants of the site and extent of deposition: inertial impaction, sedimentation, and (to a lesser extent) diffusion.^[14] During inertial impaction, larger particles are deposited in the proximal airways as the turbulence and velocity are extremely high. Sedimentation allows the particles to deposit on the basis of their weight and gravity and prevents particle exhalation. Diffusion through Brownian motion allows the particles to traverse through the bronchial tree; particles $<1 \mu\text{m}$ are exhaled.^[2,13,14] Figure 2 shows the effect of particle size on drug deposition.

Several trials have determined the effect of particle size on drug deposition.^[3,12,23] de Boer *et al.* studied several DPIs and observed that the respirable dose ranges from 1 to 3 μm .^[2] Laube *et al.* studied the effect of particle size distribution on lung deposition. Smaller particles achieve greater lung

Figure 2: Effect of particle size on drug deposition in the respiratory tract $<1 \mu\text{m}$ Exhaled $>5 \mu\text{m}$ oropharynx deposition 2–6 μm tracheal deposition 0.5–3 μm alveolar deposition recreated from: Demoly *et al.*^[14]

deposition with highest being at 1.5 μm (56% lung deposition, distal penetration index 0.79, and peripheral lung deposition at 25%). As the particle size increases, these factors decrease with 46% lung deposition, 0.36 distal penetration index, and 10% peripheral lung deposition at 6 μm .

Increased oropharyngeal losses can be compensated by increasing delivered fine particle dose with increasing flow rate. This helps in more constant lung deposition and more uniform distribution.^[24] In patients with asthma, better lung deposition and penetration in distal airways was observed with 1.5- μm particles compared with 3- and 6- μm particles.^[13,24] Figure 3 shows the percentage drug deposition in lungs per the Usmani *et al.* (2005) study. However, smaller particles are not felt in the mouth and have no taste, possibly leading to lesser patient satisfaction as there is no mouthfeel of drug.

EFFECT OF PARTICLE SIZE ON SAFETY AND TOLERABILITY

The oropharyngeal-laryngeal deposition of drug particles is an important concern for all inhaled formulations. Particle size plays an important role in the incidence of adverse events with inhaled corticosteroids. With DPIs, approximately 50% of the inhaled drug is deposited in the oropharyngeal region. This deposited drug causes several topical adverse events such as caries, oral thrush, and dysphonia. Sometimes, the drug particles are swallowed and enter systemic absorption from the gastrointestinal tract and might cause systemic adverse events.^[25]

A meta-analysis of 23 studies observed a three-fold increase in the incidence of oral thrush in patients using DPIs.^[26] Dekhuijzen *et al.* conducted a real-life study on the effects of inhaled corticosteroids, drug, dose, and device on the incidence of oral thrush. Overall, the incidence increased with inhaled corticosteroids and was dose dependent for fluticasone propionate/salmeterol therapy.^[27] Price *et al.* observed that direct spraying of the medication into the oral cavity leaves a substantial portion of the dosage on the patient's tongue, which might promote fungal growth on the tongue.^[28] Although there is no clear evidence of dental caries caused by antiasthmatic drugs, the lactose content of DPIs might indirectly cause

Figure 3: Effect of particle size on percent drug deposition in lungs^[12] recreated from: Usmani *et al.*^[13]

dental caries.^[29] Dysphonia is another local adverse event due to oropharyngeal deposition.^[30]

The reduced rate of oropharyngeal and laryngeal adverse effects, such as oropharyngeal candidiasis and dysphonia, found with inhaled corticosteroid treatment is probably a consequence of low oropharyngeal deposition seen with DPIs with a lower aerodynamic particle size.^[31] Thus, a smaller particle size reduces the risk of oral candidiasis, hoarseness of voice, aftertaste, an effect on the throat (such as cold, dry, or sore), and cough, which are common with bigger particle size.

DRUG NOT FELT: OPTIMUM CLINICAL OUTCOME

The goal of managing patients with COPD and asthma is gaining control on the symptoms, preventing disease exacerbation, and improving the quality of life. This goal can be achieved by delivering the optimum dose of prescribed drugs to the target site in the respiratory system and preventing drug losses midway. Thus, studies have stressed on the importance of drug availability and administration time; patient age and ability to use the device correctly; convenience; costs; and physician and patient preference while selecting drugs and devices for inhaled formulations.^[16,23] Consistency in dose delivery to the lungs is required for efficient therapy and drug safety and tolerability also depend on consistent dose delivery. Consistent dose delivery shows codependency with device characteristics and drug formulation.

Particle size distribution from DPIs plays a significant role in drug deposition in the target areas. The drug dose from DPIs may be substantially lower than expected because of losses in the inhaler, oropharyngeal deposition, and exhalation of very fine particles. The amount of drug deposited in the upper respiratory tract (up to the larynx) and mouth does not contribute to the pharmacological activity of drug. Only the drug available in the lower part of the bronchial tree and alveoli is effective in treating the symptoms of asthma and COPD.^[2] Several studies have observed that particle sizes ranging from

1 to 3 µm are best suited for lung deposition. Particles <1 µm are exhaled through the lungs, and particles >5 µm are deposited in the oropharynx and thus lost to activity.^[2,13]

Clinical studies have shown that the mouthfeel of particles is dependent on particle size. A study analyzed the effect of particle size on the feel or grittiness of aqueous suspension and found that <50% of patients could perceive grittiness when the average particle size was <10 µm.^[32] Engelen *et al.* observed that a particle size of 2 µm was responsible for rough to slippery lip-tooth feel that was perceived only when a thin compressed layer was applied on the lips and tongue.^[33] Users are able to detect particle size as less as 5.2 µm only when the particles are rough or angular in shape.^[34] Hence, if the drug particle size in the DPI formulation is <5 µm (1–3 µm), the formulation characteristics makes it likely that more drug will be deposited at the target site and there will be less losses due to oropharyngeal deposition. Consequently, there will be less adverse events due to the local action of drugs in the oropharynx.

The patient adherence to treatment is an important factor for the success of inhalational therapy. Adherence is dependent on the ease of use, patient education for application of correct technique, patient satisfaction, and tolerability of drug formulation.^[16] In case of a smaller particle size, although tolerability is likely to be higher because of lesser oral adverse events, patient satisfaction might be hampered as the drug is not felt in the mouth. This may also lead to misuse or overuse of the inhaler as the patient may feel that an adequate amount of drug was not dispensed from the device. This ultimately may lead to therapy noncompliance, lack of patient satisfaction, less confidence about the device, and may cause relevant economic losses to the patient and health care industry in general.

Patient awareness and education will be critical in limiting these problems. Patients should be made aware that the optimum drug particle size may not have any taste or mouthfeel. The current guidance also recommends that practitioners should first understand devices that are available to patients, key device characteristics, and how these characteristics might affect patient preference and practice. Health-care practitioners and patient advisors must initiate proper training and counseling for patients at therapy initiation and during therapy.

CONCLUSION

Consistent drug dose to the lungs is mandatory for an adequate and efficient inhalational therapy. The efficiency and safety of pulmonary drug administration through DPIs depend on the aerodynamic size of desired drug particle for optimum drug deposition in the target area. What is “lost” in the mouth–throat region does not contribute to the therapeutic effect and can cause adverse local or systemic side effects. However, fine particle size may not cause sensation or aftertaste, which may lead to patient dissatisfaction or concern. Thus, treating physicians should provide optimum patient counseling and education addressing the importance of particle size for desired clinical effects.

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