An update on inhalation devices

Focus on spacers
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The pressurized metered dose inhaler (pMDI) is the most widely used inhaler device in the world, with more than 500 million produced annually. Spacers are extensions to a pMDI, with a port at one end to which the pMDI is attached and a mask or mouthpiece fitted at the other end. They help in holding the medication for a few seconds after it has been released from the pMDI. The first pMDI in 1956 had a spacer.

**History of spacers**

The original pMDI product, as described in 3M's 1956 sales brochure, had an elongated mouthpiece. The purpose of this design was to allow some time and space for the rapidly moving propellant droplets to evaporate. This reduced the impact of the drug at the back of the throat, possibly increasing lung deposition. In effect, this was the first pMDI spacer device. Some years later, a larger spacer device was used for the delivery of inhaled corticosteroids to children.

This was a chamber that had a volume capacity of about 1 litre. Subsequently, a range of such devices were developed and marketed. With greater understanding of the working of spacers, these have now been further modified to include non-static spacers.
Spacers extend the mouthpiece of the inhaler and direct the cloud of medication towards the mouth. When the pMDI is fired or actuated, the aerosol cloud produced from the spacer device is finer and slower moving than when released from a pMDI alone. This results in evaporation of the propellants and settling down of the larger particles in the spacer.

This increases the amount of drug reaching the lower airways and limits the amount of particles in the mouth and throat, which in turn reduces the amount of drug absorbed systemically. At least 20% of the dose released from a pMDI will be delivered to the lungs via the spacer.

Using a spacer prevents a sore throat, which can occur with inhaled steroid use. Generally, patients using pMDIs with a spacer have to be trained to inhale slowly (≤ 30 litres/minute) and to hold their breath after aerosol inhalation for at least 10 seconds.
Advantages of spacer devices

Making pMDIs easier to use

Nearly 80% of the patients fail to use the pMDI correctly, with the major problem being co-ordinating the actuation with inhalation. This is easily overcome by a spacer, which holds the medication for a short time till the patient inhales.

Reducing oro-pharyngeal deposition

Normally, with a pMDI, close to 70–80% of the drug is deposited in the oro-pharynx. This is due to the speed with which the drug is emitted. When a spacer is used along with a pMDI, oro-pharyngeal deposition drops by more than 50% since most of the larger particles settle on the walls of the spacer. This reduces the likelihood of local as well as systemic side effects. The British Thoracic Society recommends the use of spacers in patients who are on a high dose of steroids (more than 1,000 mcg/day).

Improving pulmonary deposition

The velocity of the aerosol spray is reduced as it passes through the spacer. Also, the propellant droplet size is reduced by evaporation. These result in increased lung deposition. For example, in a study conducted in Mumbai, the mean percentage of salbutamol deposited in the lungs was found to be 11% with the pMDI alone, but the deposition increased to almost 24% with the use of a Zerostat Spacer.

As an alternative to nebulizers in acute asthma attacks

A systematic review of studies of treatment in children with acute exacerbations of asthma has found a pMDI with a spacer to be as effective as a nebulizer. This was also demonstrated in a study from New Delhi by Kabra et al. Also, compared to nebulizers, pMDIs with spacers have the following benefits:

- Cause fewer side effects due to less drug dose used.
- Provide greater savings in cost.
- Require no electric power.
- In case of the patient being hospitalized, facilitates faster discharge from the emergency department.
Who should use spacers?

- Children and the elderly.
- Patients with co-ordination problems.
- Those who are prescribed high-dose inhaled steroids (more than 1,000 mcg/day).
- Patients who are prescribed anti-cholinergic drugs (to avoid the spray particles from reaching the eyes).
- Patients with acute asthma requiring high-dose bronchodilators, as a substitute to nebulizers.
- Infants and small children who need inhaled drugs, as spacers can be used with masks.

Types of spacers

As a class, spacers are also known by other names, including “add-on devices” and “extension devices”.

Spacers can be classified into the following categories:

- **Simple tube extensions**: These are open tube spacers with no valve that simply distance the inhaler mouthpiece from the patient's oro-pharynx. Example: Zerostat Spacer.

- **Holding chamber**: Holding chambers share the properties of extension devices, but, in addition, they reduce the need for co-ordination between pMDI actuation and inhalation, and are generally easier for children and older, frailer patients to use than a conventional pMDI alone.
These have a “one-way valve” in the mouthpiece intended to hold the aerosol within the device until the patient’s inhalation opens the valve. They provide additional space for the aerosol plume to develop. The presence of a valve in a spacer prevents the dilution of the drug dose in the spacer as the patient exhales into the device.

However, the pressure flow characteristics of the valve can play a significant role in modifying drug delivery. The valve that operates on inhalation and exhalation must function effectively over the entire pressure range likely to be encountered with use of the valved holding chambers. This requirement is unlikely to be a problem for adults, since the pressure required to operate the valves of most add-on devices is less than 100–300 Pa. Small infants may be unable to generate sufficient pressure to open the valve. Hence, the valve should have low resistance so that it functions even at low inspiratory flow rates. Further, the valve should be robust, durable, easy to clean and should be made of non-static material.

Spacers reduce the need for patients to co-ordinate inhalation with actuation of the pMDI, but to maximize the drug delivery period, inhalation should start as soon as possible after actuation of the inhaler. Delay between actuation and inhalation may reduce the amount of drug available to the patient.

Patients who are unable to hold their breath for 4 seconds should use a spacer with a one-way valve (holding chamber), allowing the patient to obtain a suitable dose of medication in three to four tidal breaths. Valved holding chambers allow the patient to breathe tidally from the reservoir of drug and are especially helpful for children. The availability of a face mask for use with holding chambers has markedly improved the opportunities for the treatment of very young children with asthma. Example: Zerostat VT.

**Factors affecting drug delivery through spacers**

A number of factors affect drug delivery through spacers:

**Spacer volume: Optimum is about 250–300 ml**
The amount of drug delivered to the airways is inversely related to the volume of a spacer device. Fewer inhalations are required to empty smaller devices, which is advantageous for infants and small children. Small spacers with volumes less than 100 ml can reduce the amount of respirable drug available to the patient, compared to use of the pMDI alone, and they offer no protection against hand breath asynchrony. Since they are more compact, there may be a benefit for all patients in terms of compliance. In children younger than 4 years of age, a spacer of
300 ml delivers nearly double the amount of the drug dispensed by a 750 ml spacer. The optimum size of a spacer for a young child is approximately 250–300 ml. Very small or large spacers appear to be less effective in delivering anti-asthma drugs.

The adults can use both small as well as large-volume spacers. However, the large-volume spacers are bulky and difficult to carry.

**Spacer shape: Cone, pear or cylindrical**
Spacers are generally of a cone, pear or tube (cylinder) shape. The closer the shape of the spacer to the shape of the aerosol plume discharged from the pMDI, the better it is. Therefore, the ideal shape for a spacer is a cone or a pear shape. A cylindrical spacer will cause more aerosol deposition onto the walls of the spacer, leading to reduced delivery of the drug dose to the patient.

**Electrostatic charge: Non-static spacer is the best**
Among all the factors that influence drug delivery through a spacer, the electrostatic charge has been reported to be the most important. Until recently, all spacers were made of polycarbonate (plastic) material, resulting in accumulation of static charge on the spacer walls. This attracts highly charged aerosol particles from a pMDI, causing their rapid deposition onto the walls of the spacer chamber and rendering them unavailable for inhalation. Also, any delay in inhaling the drug after actuation (as may happen in younger children with low tidal volumes) results in a faster fall-out of aerosol in polycarbonate spacers, compared to non-static spacers. This, too, leads to a significant reduction in the dose available for inhalation.

The electrostatic charge on the spacer device can be reduced temporarily by doing the following:

- “Priming” the spacer before use: This is done by releasing 10–20 puffs of the aerosol into the spacer before attempting inhalation. A surfactant is present in many formulations as an excipient. Priming the interior surface of the holding chamber with several actuations of medication before use coats the interior surface with a layer of surfactant. This has been associated with an increase in whole lung deposition of the drug, ranging between 41% and 45%. However, although apparently effective at increasing medication delivery, this practice is wasteful of medication. Furthermore, since some of the new hydrofluoroalkane (HFA)-based formulations do not contain a surfactant, priming may lead to inconsistent results and studies with these formulations are lacking.
Washing the spacer in a liquid detergent: This is an alternative approach, since the detergents are actually surfactants and have the ability to spread onto a surface as a monolayer. The washed spacer should then be rinsed in tap water and then should be allowed to air-dry.

However, these methods could result in inconsistent drug delivery to the patient, depending on the condition of the spacer. Re-use of the spacer will initially increase drug availability, but the situation is complicated when the patient is required to wash out the device about once a week.

A permanent solution to the problem of static charge is to develop a spacer made out of anti-static material like polyamide, e.g. Zerostat VT Spacer. An inhalation delay of 2–5 seconds with a non-static spacer does not result in substantial loss of drug onto the walls of the spacer. A number of studies, conducted to evaluate the role of static charge on drug delivery have reported significant improvement in lung deposition after removal of the static charge.

**Increased lung deposition**

In an *in vivo* study, the influence of static charge on drug deposition in the lungs was evaluated using a detergent-coated (non-static) and a non-coated plastic spacer (static). Lung deposition of radiolabelled salbutamol was assessed in healthy adults, using imaging techniques.

**There was a three-fold increase in lung deposition from non-static spacers compared to static spacers (45.6% vs. 11.5%). The mean amount of salbutamol remaining in the static spacers was 76.7% compared to 33.1% in the non-static spacers (p <0.001).**
The lung deposition of inhaled salbutamol was assessed using the Asthalin Inhaler (salbutamol) with the Zerostat Spacer, employing gamma scintigraphy. The test drug (salbutamol) was radiolabelled by using the radionucleide Technetium 99m. Immediately after inhaling the radiolabelled aerosol, the subject had the imaging performed, using a gamma camera.

The mean percentage of salbutamol deposited in the lungs was found to be 11% with the pMDI alone; this was increased to almost 24% with the use of the Zerostat Spacer. Also, the Zerostat Spacer reduced the oropharyngeal deposition of the drug, as can be seen from the figure.
Another study evaluated the plasma salbutamol levels in children before and 5, 10, 15 and 20 minutes after inhalation from a static (350 ml and 145 ml) and a non-static (350 ml) spacer coated with benzalkonium chloride. The non-static spacer was found to deliver a significantly (p < 0.05) higher lung dose in comparison to the other two spacers. Electrostatic charge in plastic spacers reduced the delivered lung dose in children by at least twofold.

A randomized, double-blind, placebo-controlled, crossover trial evaluated the effect of a static charge on bronchodilator response to salbutamol. Accordingly, 12 asthmatic children, aged 13 to 17 years, inhaled 200 mcg of salbutamol from a CFC-pMDI with a static spacer and from a HFA-pMDI with a non-static (detergent-coated) spacer. The mean bronchodilator response after inhalation of salbutamol from the static spacer was 7.1%. The response after using the non-static spacer was 17.5%.
Compared to actuating a single dose into the spacer and then inhaling, firing multiple doses and then inhaling these doses in a single breath has been reported to reduce drug delivery. Also, longer the interval between actuation and inhalation, lesser is the drug delivered. This is especially seen with static spacers. A 20-second delay causes a two-thirds reduction in drug delivery.

**Inhalation technique: Has less impact in non-static spacers**

Compared to actuating a single dose into the spacer and then inhaling, firing multiple doses and then inhaling these doses in a single breath has been reported to reduce drug delivery. Also, longer the interval between actuation and inhalation, lesser is the drug delivered. This is especially seen with static spacers. A 20-second delay causes a two-thirds reduction in drug delivery.
Non-static spacers can overcome the drawbacks inherent in static spacers. For example, the half-life for aerosol “fall-out” within the spacer chamber is greatly increased with non-static spacers.

The longer residence time of the actuated aerosol gives infants and children with impaired respiration (especially small tidal volumes and low inspiratory flows) a better opportunity to inhale the aerosol cloud. The British Thoracic Society's 2004 guidelines have also acknowledged the role of anti-static spacers.

**pMDI + spacer : as effective as a nebulizer**

Several clinical studies have shown that spacers are at least as effective as nebulizers in the treatment of severe acute asthma attacks. However, the advantages of spacers over nebulizers include improved delivery efficiency, greater convenience, low risk of pulmonary infection, greater speed of administration and cost-effectiveness.
A randomized, double-blind trial has reported pMDIs with spacers to be as effective as nebulizers for the delivery of bronchodilators for emergency department treatment of wheezing in children (n = 85) aged 2 to 24 months. Compared with the spacer group, the nebulizer group had a significantly higher mean initial pulmonary index score* (7.6 ± 2.5 vs. 6.6 ± 2.0; p = 0.002). After controlling for the baseline pulmonary index score, there were fewer hospital admissions in the spacer group (5% vs. 20%; p = 0.05). According to the study investigators, “the introduction of pMDIs with spacers has provided a more efficient, cost-effective and easier way of delivering salbutamol to infants and young children.”

*Pulmonary index score is a validated asthma severity score. In this study, mild asthma had a pulmonary index score of zero to 3, moderate asthma had a score of 4 to 7, and severe asthma had a score of 8 to 12.

**pMDI + spacer: as effective as a dry powder inhaler**

A randomized, double-blind, double-dummy, three-period, placebo-controlled, crossover, single-centre study was conducted in 19 patients with stable chronic obstructive pulmonary disease (COPD).
Tiotropium, administered through both a pMDI (with spacer) and a DPI, showed significantly better mean FEV₁ (p<0.01) and mean FVC (p<0.01) differences from baseline, as compared to placebo. There was no difference in the efficacy between the pMDI and the DPI. Thus, tiotropium administered through a pMDI and spacer can be used by those COPD patients who prefer to use the pMDI device, and especially in those who cannot generate sufficient inspiratory flows required for using DPIs.

**pMDI + spacer : as effective as breath-actuated devices**

In a randomized, double-blind, crossover, placebo-controlled study, 18 subjects with stable, moderate, asymptomatic asthma were subjected to a methacholine challenge test. Administration of salbutamol via a pMDI + spacer or by the Autohaler, a breath-actuated device, resulted in a similar bronchoprotective effect against methacholine, as seen by the increase in PD20

![Bar chart](image)

LogPD20 (LogPD20 FEV₁ Methacholine; mean ± SD) during methacholine challenge test protected by placebo and salbutamol inhaled by pMDI, pMDI + spacer, and Autohaler, in subjects with correct pMDI inhalation technique (n = 13; yellow bars) and in subjects with incorrect pMDI inhalation technique (n = 5; blue bars). * = p < 0.05 between placebo and other groups by Friedman test.
The Zerostat VT is a novel holding chamber, which is valved, non-static and transparent.

It is small, portable, child-friendly, easy to carry and easy to clean. The Zerostat VT Spacer has all the advantages of a spacer, including overcoming co-ordination problems, reducing the spray effect at the back of the throat, reducing oro-pharyngeal deposition and enhancing lung deposition of the drug.

It is made of a non-static polyamide material, which helps in delivering a greater amount of medicine into the lungs.

As it is transparent, it enables the aerosol plume to be clearly seen following inhaler actuation.

It is diamond-shaped; thus, its shape matches the shape of the aerosol plume discharged from the pMDI.
The half life* \( (t_{1/2}) \) of the Zerostat VT Spacer is approximately 60 seconds. Hence, it gives more lag time for inhalation as compared to static spacers.

*Half life \( (t_{1/2}) \) of the spacer is the time lag between actuation and inhalation at which the percentage of fine particle mass drops to half of its original value.

**Flowgate valve technology in the zerostat VT spacer**

- Normal Position
- Opens during Inhalation
- Closes during Exhalation

The one-way valve is so designed that it opens during inspiration and closes during expiration, i.e. the valve shuts when the patient exhales into the chamber. This prevents dilution of the drug in the chamber and ensures its retention in the spacer for subsequent inhalation.

- Functional even at low inspiratory or expiratory flow rates.
- Moreover, the valve is robust, durable and can be easily cleaned.
**Steps to use the zerostat VT spacer**

1. Remove the mouthpiece cap from the mouthpiece of the inhaler. Shake the inhaler well.

2. Insert the inhaler firmly into the opposite end of the zerostatVT spacer.

3. To assemble your zerostatVT spacer, firmly push the two halves of the spacer together and rotate with the mouthpiece cap in place. The zerostatVT spacer comes with two locks which ensure proper assembling of the two halves.

4. Holding the inhaler, press down on the canister to release a dose into the zerostatVT spacer. You will see the dose released in the spacer.

5. Remove the mouthpiece cap from the zerostatVT spacer, breathe out fully and close your lips firmly around the mouthpiece to create a good seal as shown in the picture, (do not bite it) breathe in deeply through your mouth, thus inhaling the medicine through the spacer. Remove the zerostatVT spacer from your mouth and hold your breath for about 10 seconds, or as long as is comfortable. Breathe out slowly. If a second dose is required, wait for a minute, repeat steps 2 to 5.

For Children
Children should use the zerostatVT spacer under parental guidance.

For children below 3 years a face mask (Baby Mask) attached to the zerostatVT spacer should be used to facilitate administration.
Not all spacers are experts in providing the **optimal dose**

**CTP**
Unique transparent static free material, which increases drug available for inhalation

**Flow gate valve**
Flow gate valve prevents the patient from exhaling into the spacer

**Notch**
Two improved notches provided for fitting the two halves of the Zerostat VT spacer firmly

**Attached dust cap**
New hinged dust cap makes it easier to protect mouthpiece from contamination

**Air vents**
Reduces resistance when patient exhales

**pMDI insertion port**
New improved design allows snug fit with pMDI

**Mouthpiece**
Designed to give a comfortable fit during inhalation

CTP* - Customized Thermoplastic Polymer
Further reading

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- Pulm Pharmacol & Ther 2001; 14: 351–366
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- Comprehensive Management of Chronic Obstructive Pulmonary Disease by Danielle Beaucage and Suzanne Nesbitt. Chapter 6: Using Inhalation Devices