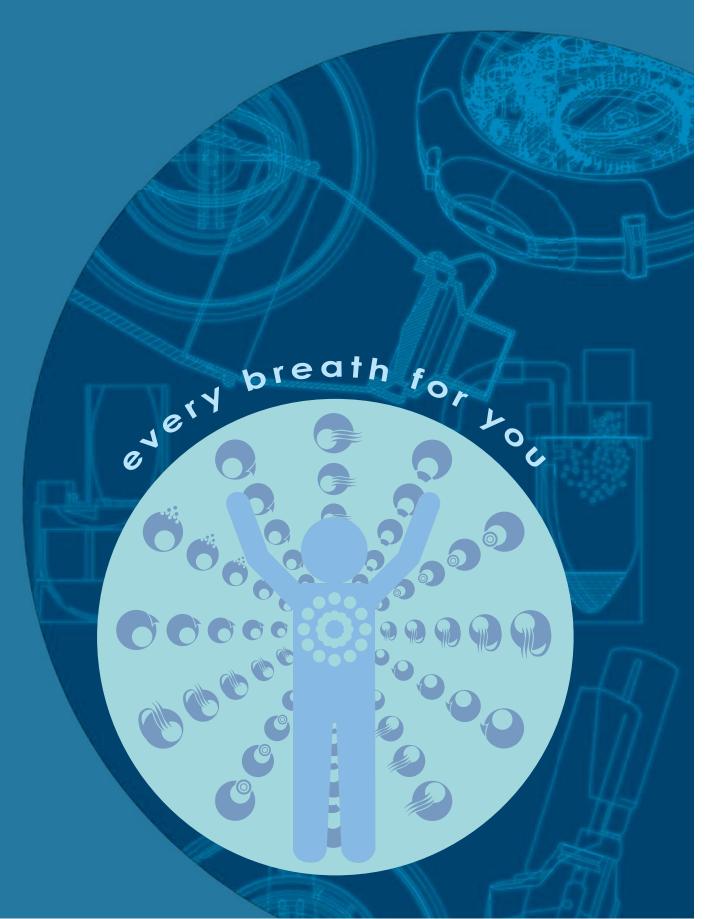
Cipla Inhaled Drug Delivery Systems



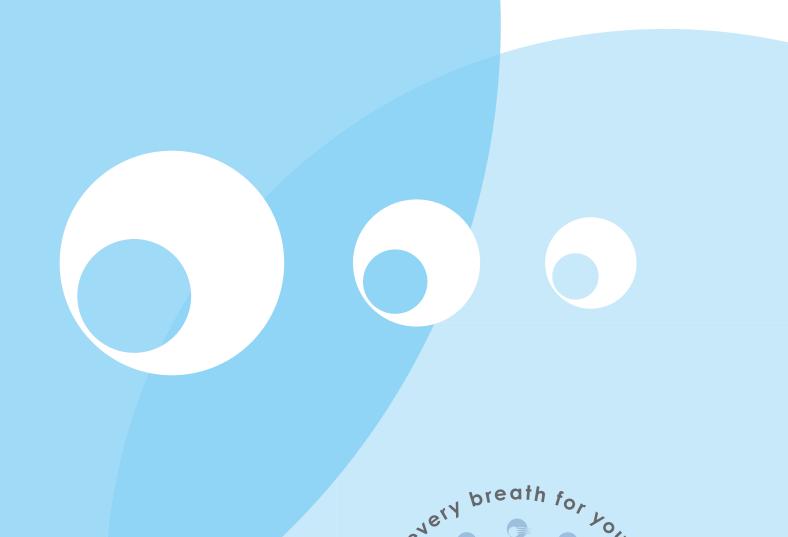
Millions of people suffer every day
from chronic respiratory diseases and these
constitute a large part of a physician's practice.
According to the recent WHO estimates (2007), currently
300 million people have asthma; 210 million people have
chronic obstructive pulmonary disease (COPD) while millions have
allergic rhinitis and other often-underdiagnosed chronic respiratory
diseases.

Inhalation therapy has now become an indispensable part of the standard management plan for respiratory diseases such as asthma and COPD. By prescribing the right drug and inhalation device, a physician can successfully manage these conditions at any age and stage.

Recent years have seen a phenomenal diversity in the products and the technologies applied in this field. The spectrum of inhaler devices and drug/device combinations available today has made inhalation therapy more convenient and accessible. However, choosing the optimal device is essential to ensure the effectiveness of the therapy and the best control for the individual patient.

The intent of this booklet is to serve as a guide to help physicians appreciate the benefits of inhalation therapy and the various delivery systems available.

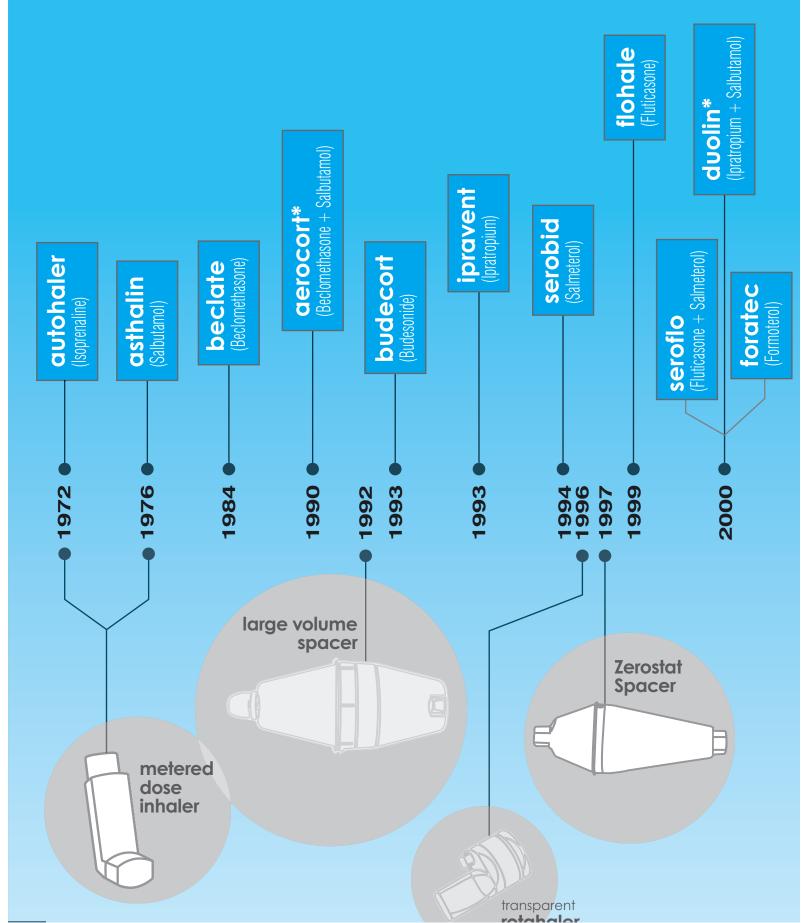
This is yet another expression of Cipla's continuining commitment to respiratory care.

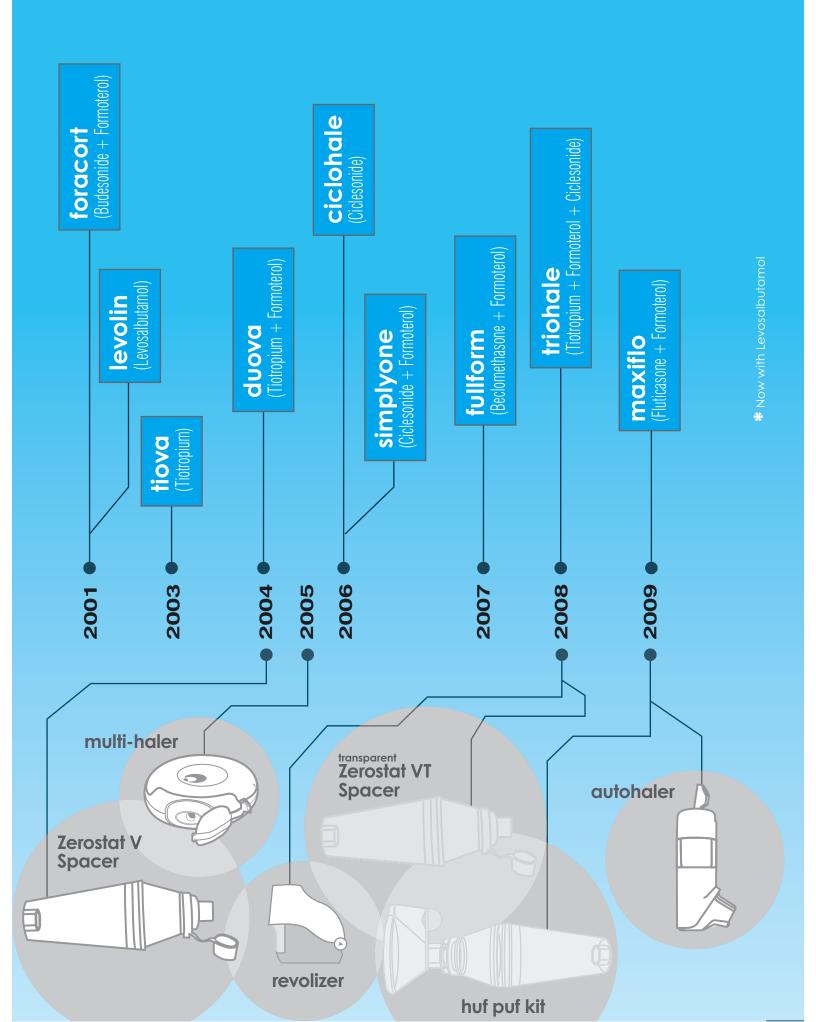


Cipla

Inhaled Drug Delivery Systems

ciple in inhalation therapy





over 30 years of dedication to respiratory care

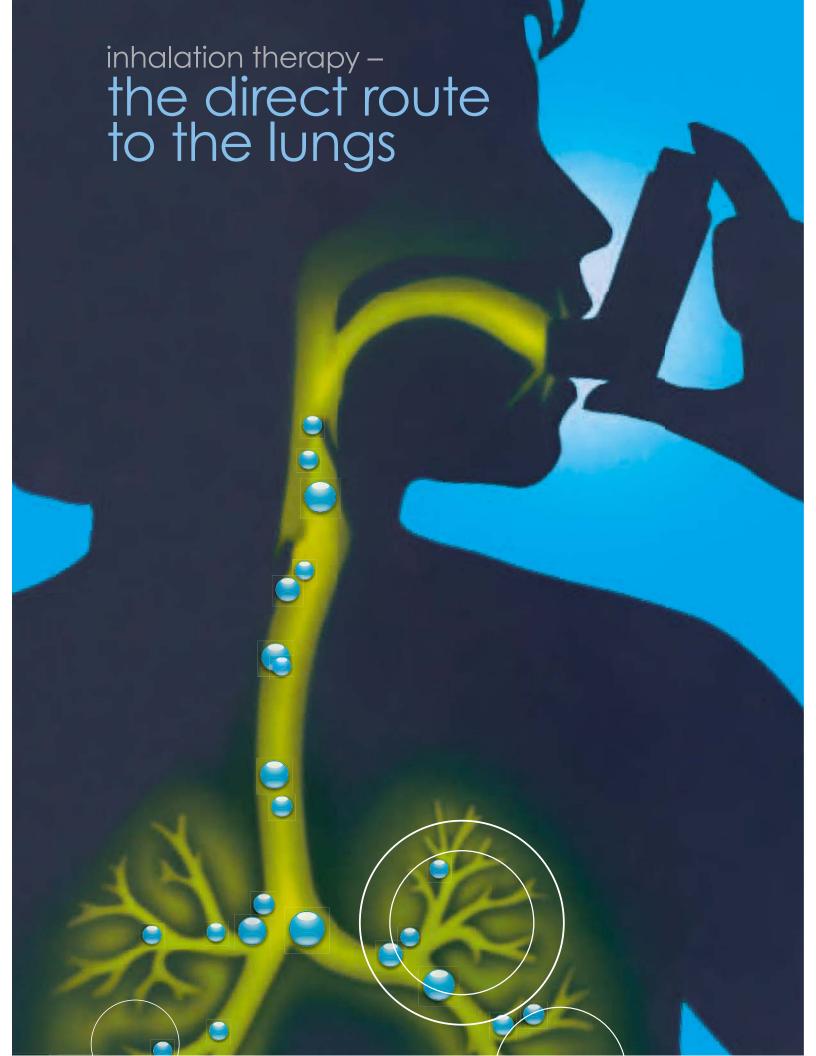


Cipla Inhaled Drug Delivery Systems



- The world's largest range of aerosol medications and devices.
- World class manufacturing facilities approved by international regulatory authorities.
- A trusted name in aerosol therapy in over 170 countries.
- The world's first transparent dry powder inhaler the **Rotahaler** and a novel single-dose dry powder inhaler the **Revolizer**.
- A unique single-action, multi-dose dry powder inhaler the **Multi-haler**.
- An exclusive range of non-static spacers Zerostat and Zerostat VT.
- First breath-actuated metered dose inhaler in India the Autohaler.

and the commitment continues



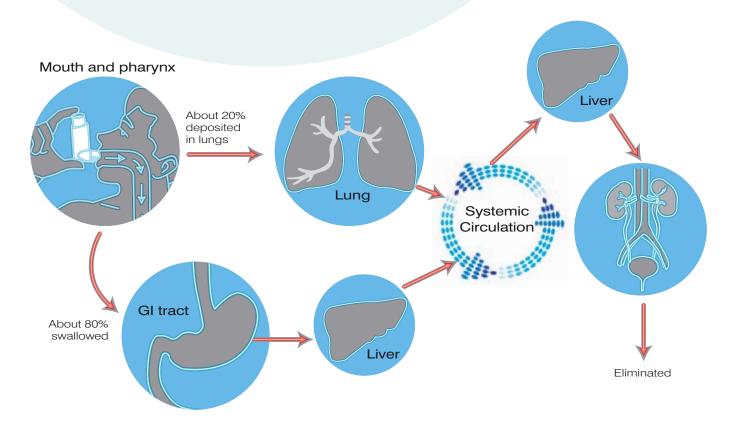
The world over, most patients with asthma and COPD are now treated with inhaled drugs. Inhaled drug delivery puts the drug where it is needed, whereas oral tablets and syrups must be absorbed in the gastrointestinal tract and need to travel through the bloodstream to various parts of the body before they reach the lungs.

- The inhaled route is the most effective method to get the medicine where it is supposed to go – directly to the airways.
- The therapeutic effect is rapidly achieved especially symptom relief with inhaled bronchodilators.
- The dose intake is low and a fraction of the oral dose the drug content of one tablet of 4 mg salbutamol is equivalent to 40 doses from a metered dose inhaler (MDI).
- Side effects are minimal since the rest of the body is not exposed to the drug. This is very important, especially when steroid therapy is required.
- Some drugs are therapeutically active only when inhaled (e.g., most inhaled corticosteroids, sodium cromoglycate, salmeterol).
- Exclusive steroids have been developed for inhalation therapy.
 They have high, localized activity in the lungs and remarkable safety since the swallowed portion is inactivated by its very first passage through the liver.
- Since chronic respiratory diseases require long-term treatment, the exceptional safety of inhaled therapy is especially valuable.

In the last few decades, a variety of inhalers have been developed to treat chronic respiratory diseases. They have helped millions of people breathe better and have transformed their lives.

Respiratory care in India has also undergone a dramatic transformation. Cipla is proud to have facilitated this change by supporting physicians with the latest medications and highly effective inhalation devices.

dynamics of inhaled drugs



The efficacy of both bronchodilators and anti-inflammatory agents in asthma and COPD results from their local effects in the airways. Thus, achieving a high local concentration of these agents in the lung should maximize their intended effects and minimize their systemic absorption and potential adverse actions.

About 15-40% of drug released from an inhaler device is deposited in the lungs. This is more than sufficient to achieve a clinical effect. 60-80% is deposited in the throat and the remaining in the inhaler device. The amount deposited in the throat can be considerably reduced by using a spacer device.

- The portion of the drug that is deposited in the lungs has its pharmacological effect and is then absorbed from the lungs into the systemic circulation.
- Drug deposited in the throat is swallowed and subsequently absorbed from the gastrointestinal tract into the systemic circulation via the liver where it undergoes metabolism and subsequent elimination.

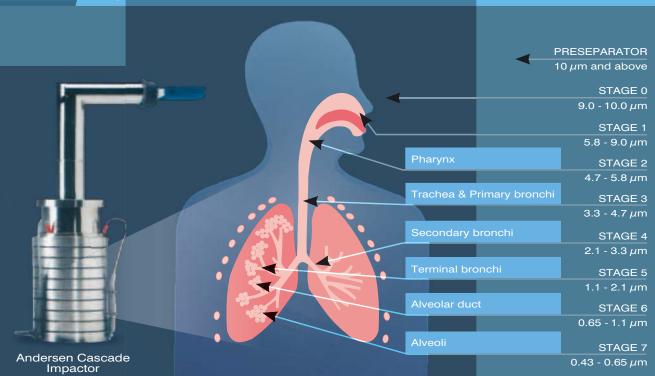
Fine particle dose (FPD)

- FPD is the proportion of the delivered dose reaching the lungs.
- The in vitro FPD simulates the amount of drug that is expected to reach the lungs.

The FPD is measured by an instrument called the Andersen Cascade Impactor

- 1–5 μ m: most efficiently deposited in the lower respiratory tract
- $< 0.5 \,\mu\mathrm{m}$: unlikely to deposit in the lungs
- >5 μ m: unlikely to deposit in the lungs

FPD is the sum of the amount of drug deposited from stage 2 to stage 7 as shown in the figure below

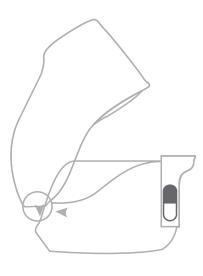


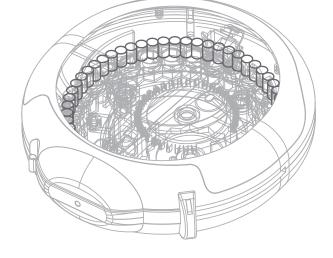
dry powder inhalers (DPIs)

DPIs, as their name implies, dispense medication as a dry powder formulation without the use of propellants as in MDIs. The drug in a DPI is provided as a micronized powder (particle size $2.5-5\,\mu\text{m}$) with an inert carrier such as lactose. DPIs are breath-activated devices and, unlike the MDIs, do not require coordination between actuation and inhalation. The patient exhales out a full breath, places his/her lips around the mouthpiece, and then quickly breathes in the powder. The technique is different from that of the MDIs. DPIs are easy to use and as effective as MDIs. Hence, DPI therapy has become increasingly popular in the last few years.

DPIs are of two types: unit-dose and multi-dose. While the Rotahaler and Revolizer are unit-dose DPIs, the Multi-haler contains pre-filled multiple doses of the medication.

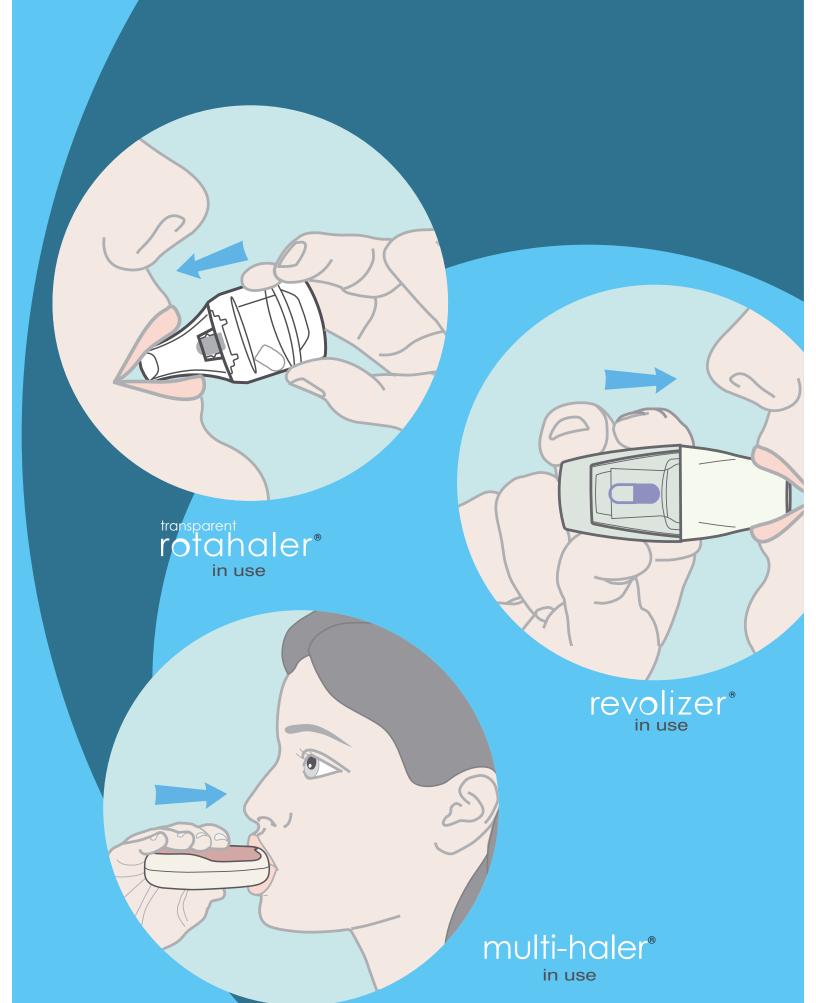
Cipla DPIs have been exclusively developed to ensure consistent dose delivery through patient-friendly devices and the right dry powder formulations - Rotacaps and Multihalers - comprising the actives and a high grade excipient.





unit-dose

multi-dose







The Revolizer is a new generation patient-friendly dry powder inhaler exclusively developed by Cipla. It is probably the easiest device to use. The patient simply opens the Revolizer, inserts the rotacap, shuts the device and inhales.



Sleek Design

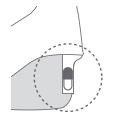
Ergonomically created to ensure high lung deposition with ease of use.



High Efficacy

Higher drug deposition in the lung compared to earlier DPI devices.

Functional even at low inspiratory flow rates.



Transparent Medication Chamber

Enables the patient to see that the dose has been inhaled.

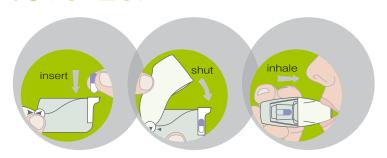


Ease of Use

Can be used by all age groups including patients with severe airway limitation.

The Revolizer incorporates all the features of an ideal inhaler device.

revolizer® in action











Transparent Design

Enables the patient to see that the dose has been inhaled.



High efficacy

Ease of use ensures high lung deposition.



Simplicity

Can be used by patients of all age groups.



Versatility

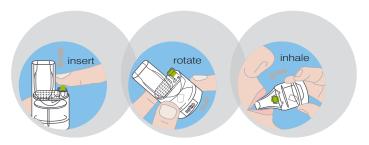
Single inhalation device for multiple medications.



Convenience
Easy to carry.

The Rotahaler heralded the era of patient-friendly inhalation therapy and has led to wider acceptance of the benefits of inhalation therapy. Since its introduction in 1996, millions of asthmatics have used the Rotahaler with dramatic results.

transparent rotahaler® in action







Multi-dose DPIs fall into two main categories:

- · Those which disperse the dose directly from a powder reservoir
- · Those which disperse individual, pre-metered doses from a blister

The Multi-haler is an example of the second type and it needs just a single step for use. A simple action of sliding the mouthpiece cover punctures a blister to release the drug powder, which is then inhaled through the mouthpiece. The reproducibility of the pre-measured dose is assured during the formulation, dose filling and device assembly process.



Ready to use
Avoids loading of
doses unlike unit dose
devices.



Dose Counter Confirms dose taken and also indicates number of doses left.

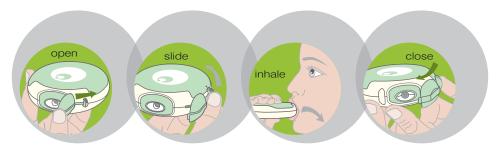


Compact and Convenient
Easy to carry.



High lung deposition
High lung deposition due to precision formulation and ease of use.

multi-haler[™] in action









The MDI is a device that delivers a specific and pre-metered amount of medication to the lungs, in the form of an aerosol spray that is inhaled by the patient. It consists of a canister of pressurized medication that fits into a plastic actuator sleeve and connects to a mouthpiece. The formulation in an MDI is made up of the drug and a liquified gas propellant.

Cipla MDIs are designed to deliver accurate dosing by employing the right formulation technology and using the most sophisticated metered dose valves, canisters and actuators.

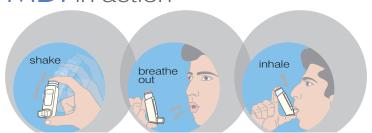
Advantages of MDIs

- Most widely used inhalation device.
- Compact and portable.
- Quick dose delivery requires no preparation except shaking.
- Suitable for all age groups.

Proper use of the MDI requires some practice. Unless the MDI is used correctly, the patient will not get the full dose of the drug and, hence, will not derive the full benefits. Many patients, including children, find it difficult to co-ordinate the actuation and inhalation of the drug released from the MDI. Such patients can benefit immensely by using a spacer attached to the mouthpiece. An MDI + spacer is generally as effective as a nebulizer.

In accordance with the Montreal Protocol (1987), the chlorofluorocarbon (CFC) propellants currently used in aerosol inhalers are being phased out and being replaced with hydrofluoroalkane (HFA).

MDI in action



Cipla Inhaled Drug Delivery Systems







The Autohaler is a new advance in MDI therapy. It is a unique breath actuated inhaler (BAI) and overcomes the key problem of the MDI which is coordination of actuation with inhalation. It is activated at low inspiratory flow rates of 22–30 l/sec.



Breath Actuated
Overcomes the
coordination problem of
MDIs.



Easy for All
Can be used by all
including children, older
patients, patients with
severe airflow
obstruction and those
with arthritis.

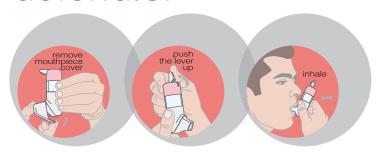


Single Step Usage
Easy to teach.
Easy to use.



High Efficacy
High lung deposition
even in patients with low
inspiratory flow rates.

autohaler[™] in action





spacers and related devices

Spacers (sometimes also called holding chambers) are devices that hold the medication for a few seconds after it has been released from the MDI. They serve two main purposes:

- They overcome the "co-ordination" problem the need for synchronization between firing the aerosol and inhalation. This allows the user to obtain the full benefit of the MDI.
- They slow down the aerosol spray before it reaches the mouth, thus allowing the propellants to evaporate and larger particles to settle in the spacer. This leads to less deposition in the oropharynx and greater deposition in the lungs. Decreased oropharyngeal deposition is particularly important for inhaled steroids since this reduces the incidence of oral thrush and also the amount of drug that is swallowed, thereby reducing any systemic side effects that may occur.

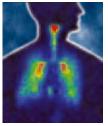
Plastic spacers have an inherent electrostatic charge. This causes the aerosol to stick to the inside of the spacer and, therefore, reduces the amount of medication that is inhaled into the lungs. Highly charged spacers have been shown *in vitro* and *in vivo* to reduce the output of medications released from the MDIs, thereby compromising the quantity of drug available for inhalation. Static-free spacers resolve this problem and result in a much higher drug deposition and enhance the effectiveness of MDI therapy.



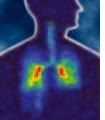
non-transparent spacer without a valve mechanism

Pulmonary delivery through the Zerostat Spacer

Aerosol deposition in the lungs assessed by gamma scintigraphy







Asthalin Inhaler + Zerostat Spacer







The Zerostat VT spacer is a unique transparent, static-free spacer with a valve mechanism. Because the Zerostat VT is non-static, hardly any drug sticks to its walls. Thus, more quantity of the drug reaches the lungs following inhalation. There is an increasing preference worldwide for spacers that are of small volume and made of non-static material.

FlowGate Valve Technology in the Zerostat VT spacer

- The valve shuts when the patient exhales into the chamber. This ensures that the residual dose is retained in the spacer for subsequent inhalation.
- Functional even at low inspiratory or expiratory flow rates.
- · Robust and durable.
- Easy to clean.

The Zerostat VT spacer ensures that patients receive a high and consistent quantity of medication, dose after dose.



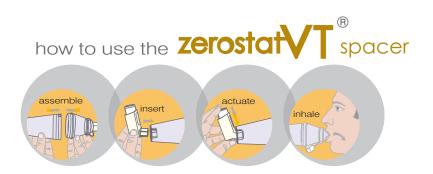
Normal position



Opens during inhalation



Closes during exhalation





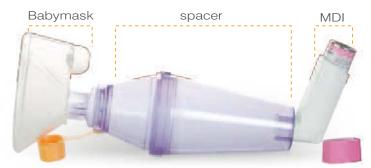






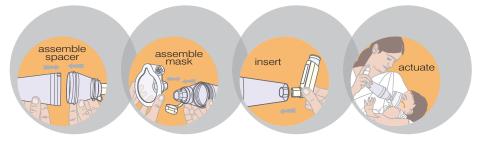
The Babymask makes it easy to deliver inhaled medicines to young children using an inhaler and a spacer device. It is made of comfortable, soft, clear silicon and is reusable. It fits snugly and is also equipped with an exhalation vent for easy breathing.

The Babymask is particularly helpful for young children up to 3 years of age. It is also useful for those who have difficulty in maintaining a good lip seal on the mouthpiece of the MDI.



Assembled unit

how to use the babymask®





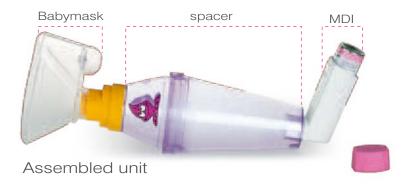




The Huf Puf Kit consists of a Zerostat VT Spacer attached to a Babymask and can be used with any Cipla MDI.

Features of the Huf Puf Kit

- Easy to use no need to dismantle and re-assemble the kit every time.
- Attractive and child friendly pack.
- Convenient to carry.





nebulizers

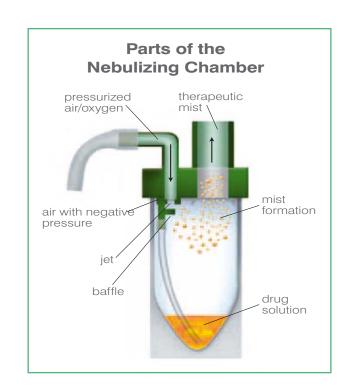


The nebulizer converts the drug solution into a continuous fine aerosol mist, which can be inhaled directly into the lungs via a face mask or mouthpiece. Nebulizing chambers are small plastic devices into which the drug solution is placed. These devices are driven by a compressor (electric/battery operated) or oxygen. A gas flow of about 6-8 litres/minute is normally required to drive the nebulizer.

Drug inhalation is accomplished by normal tidal breathing over a 5-10 minute period.

Advantages of nebulizers

- No effort required; needs only tidal breathing.
- A large dose of the drug can be administered simply and effectively.
- Home treatment for patients who are too ill, short of breath, or otherwise unable to use hand-held inhalers.
- A very effective method for treating asthma in children below 3 years of age, who cannot use other inhalation devices.



Main Clinical Indications for Nebulizer Therapy

- Emergency treatment of acute asthma and COPD.
- Long-term treatment of airway diseases in patients unable to use other devices.
- Bronchodilator treatment under intensive care.
- Delivery of antibiotics in diseases like cystic fibrosis.

Types of Nebulizers

- Jet nebulizers are used with air compressor-driven machines called nebulizer compressors and are approved for use with all available nebulizer medications. These are the most widely used type of nebulizers.
- Ultrasonic nebulizers use sound waves to burst liquid molecules into mist.



selection of inhalation devices

1st choice	2nd choice
MDI + Spacer + Babymask	Nebulizer
MDI + Spacer + Babymask (4 years and above) MDI + Spacer or DPI or BAI	Nebulizer
MDI +	
or DPI or or BAI	
	MDI + Spacer + Babymask MDI + Spacer + Babymask (4 years and above) MDI + Spacer or DPI or BAI MDI + Spacer or DPI or

RAI: Breath Actuated Inhaler DPI: Dry Powder Inhaler MDI: Metered Dose Inhaler

Select Inhaled Medications

Bronchodilators

AsthalinSalbutamol

Levolin

Ipravent Ipratropium

Tiova

Combination Bronchodilators

Duolin

Ipratropium + Levosalbutamol

Duova

Tiotropium + Formoterol

Inhaled Corticosteroids (ICS)

BudecortBudesonide

Ciclohale

ICS / Bronchodilator Combinations

Aerocort

Triohale Tiotropium + Formoterol + Ciclesonide Foracort

Beclomethasone + Formoterol

Fluticasone + Formoterol

Nebulized Formulations

Levolin Levosalbutamol

Budesal Budesonide + Salbutamol

Ipratropium + Levosalbutamol

Ipravent

Budecort

Flohale

Inhalex



Devices

Babvmask

For use with Cipla spacers/inhalers only

Huf Puf Kit

(Zerostat VT Spacer + Babymask) For use with Cipla inhalers only

Revolizer

For use with Cipla rotacaps only

Rotahaler

For use with Cipla rotacaps only

Zerostat Spacer

For use with Cipla inhalers only

Zerostat VT Spacer

For use with Cipla inhalers only

Inhaled Drugs for Airway Diseases

Aerocort Rotacaps
Beclomethasone 100 mcg +
Levosalbutamol 100 mcg

Aerocort Inhaler Beclomethasone 50 mcg +

Levosalbutamol 50 mcg

Aerocort Forte Rotacaps Beclomethasone 200 mcg + Levosalbutamol 200 mcg

Asthalin Rotacaps Salbutamol 200 mcg

Asthalin Inhaler Salbutamol 100 mcg

Asthalin Eco Pack Inhaler Salbutamol 100 mcg

Asthalin Respiratory Solution Salbutamol 5 mg/ml

Asthalin Respule Salbutamol 2.5 mg/2.5 ml

Beclate 100 Rotacaps Beclomethasone 100 mcg

Beclate 200 Rotacaps Beclomethasone 200 mcg

Beclate 400 Rotacaps Beclomethasone 400 mcg

Beclate 100 Inhaler Beclomethasone 100 mcg

Beclate 200 Inhaler Beclomethasone 200 mcg

Budecort 100 Rotacaps Budesonide 100 mcg

Budecort 200 Rotacaps Budesonide 200 mcg

Budecort 400 Rotacaps Budesonide 400 mcg

Budecort 100 Inhaler Budesonide 100 mcg

Budecort 200 Inhaler Budesonide 200 mcg

Budecort 0.5 mg Respule Budesonide 0.5 mg/2 ml **Budecort 1 mg** Respule Budesonide 1 mg/2 ml

Budesal 0.5 Respule Budesonide 0.5 mg + Salbutamol

Budesonide 0.5 mg + Salbutamo 2.5 mg/2.5 ml

Budesal 1 Respule

Budesonide 1 mg + Salbutamol 2.5 mg/2.5 ml

Ciclohale 200 Rotacaps

Ciclesonide 200 mcg

Ciclohale 80 Inhaler Ciclesonide 80 mcg

Duolin Rotacaps Levosalbutamol 100 mcg + Ipratropium 40 mcg

Duolin Inhaler

Levosalbutamol 50 mcg + Ipratropium 20 mcg

Duolin Respule

Levosalbutamol 1.25 mg + Ipratropium 500 mcg/2.5 ml

Duoset Rotacaps

Salbutamol 200 mcg + Ipratropium 40 mcg

Duova Rotacaps

Tiotropium 18 mcg + Formoterol 12 mcg

Duova Inhaler

Tiotropium 9 mcg + Formoterol 6 mcg

Flohale 50 Rotacaps

Fluticasone 50 mcg

Flohale 100 Rotacaps Fluticasone 100 mcg

Flohale 250 Rotacaps Fluticasone 250 mcg

Flohale 50 Inhaler Fluticasone 50 mcg

Flohale 125 Inhaler Fluticasone 125 mcg

Flohale 0.5 mg Respule Fluticasone 0.5 mg/2 ml

Flohale 2 mg Respule Fluticasone 2 mg/2 ml

Foracort 100 Rotacaps Budesonide 100 mcg + Formoterol 6 mcg

Foracort 200 Rotacaps

Budesonide 200 mcg + Formoterol 6 mcg

Foracort 400 Rotacaps Budesonide 400 mcg + Formoterol 6 mcg

Foracort 200 Multihaler Budesonide 200 mcg + Formoterol 6 mcg

Foracort 400 Multihaler Budesonide 400 mcg + Formoterol 6 mcg

Foracort 100 Inhaler Budesonide 100 mcg + Formoterol 6 mcg

Foracort 200 Inhaler Budesonide 200 mcg + Formoterol 6 mcg

Foracort 400 Inhaler Budesonide 400 mcg + Formoterol 6 mcg

Foracort Forte Rotacaps

Budesonide 400 mcg + Formoterol 12 mcg

Foracort Forte Inhaler

Budesonide 400 mcg + Formoterol 12 mcg

Foratec Rotacaps Formoterol 12 mcg

Fullform 200 Rotacaps
Beclomethasone 200 mcg +
Formoterol 6 mcg

Fullform 400 Rotacaps Beclomethasone 400 mcg + Formoterol 6 mcg

Fullform 100 Inhaler Beclomethasone 100 mcg + Formoterol 6 mcg

Fullform 200 Inhaler Beclomethasone 200 mcg + Formoterol 6 mcg

Inhalex Respule Ambroxol 15 mg/2 ml

Ipravent Rotacaps Ipratropium 40 mcg

Ipravent Inhaler Ipratropium 20 mcg

Ipravent Respiratory Solution Ipratropium 250 mcg/ml

Ipravent Respule Ipratropium 500 mcg/2 ml

Levolin Rotacaps Levosalbutamol 100 mcg

Levolin Inhaler Levosalbutamol 50 mcg

Levolin 0.31 Respule Levosalbutamol 0.31 mg/2.5 ml

Levolin 0.63 Respule Levosalbutamol 0.63 mg/2.5 ml

Levolin 1.25 Respule Levosalbutamol 1.25 mg/2.5 ml

Maxiflo 100 Rotacaps Fluticasone 100 mcg + Formoterol 6 mcg

Maxiflo 250 Rotacaps Fluticasone 250 mcg + Formoterol 6 mcg

Maxiflo 125 Inhaler Fluticasone 125 mcg + Formoterol 6 mcg

Maxiflo 250 Inhaler Fluticasone 250 mcg + Formoterol 6 mcg

Maxiflo Forte Rotacaps
Fluticasone 500 mcg +
Formoterol 12 mcg

Mucinac Respules Acetylcysteine 200 mg/ml

Serobid Rotacaps Salmeterol 50 mcg

Serobid Inhaler Salmeterol 25 mcg

Seroflo 100 Rotacaps Fluticasone 100 mcg + Salmeterol 50 mcg

Seroflo 250 Rotacaps

Fluticasone 250 mcg + Salmeterol 50 mcg

Seroflo 500 Rotacaps

Fluticasone 500 mcg + Salmeterol 50 mcg

Seroflo 250 Multihaler Fluticasone 250 mcg +

Salmeterol 50 mcg

Seroflo 500 Multihaler

Fluticasone 500 mcg + Salmeterol 50 mcg

Seroflo 50 Inhaler Fluticasone 50 mcg + Salmeterol 25 mcg

Seroflo 125 Inhaler Fluticasone 125 mcg + Salmeterol 25 mcg

Seroflo 250 Inhaler

Fluticasone 250 mcg + Salmeterol 25 mcg

Seroflo 125 Autohaler Fluticasone 125 mcg +

Fluticasone 125 mcg + Salmeterol 25 mcg

Seroflo 250 Autohaler Fluticasone 250 mcg +

Salmeterol 25 mcg

Simplyone 100 Rotacaps Ciclesonide 100 mcg +

Formoterol 6 mcg

Simplyone 200 Rotacaps Ciclesonide 200 mcg +

Formoterol 6 mcg

Simplyone 160 Inhaler

Ciclesonide 160 mcg + Formoterol 4.5 mcg

Tiova Rotacaps Tiotropium 18 mcg

Tiova Inhaler Tiotropium 9 mcg

Tiova Multihaler Tiotropium 18 mcg

Triohale Inhaler

Tiotropium 9 mcg+ Formoterol 6 mcg + Ciclesonide 200 mcg

Triohale Multihaler

Tiotropium 18 mcg+ Formoterol 12 mcg + Ciclesonide 400 mcg

Inhaled Antibiotics

Tobamist Respules Tobramycin 300 mg/5 ml

Xylistin Injection, Infusion or Inhalation
Colistimethate sodium 1 MIU

"The use of inhaled aerosols allows selective treatment of the lungs by achieving high drug concentration in the airways and reducing systemic adverse effects.

The effectiveness of inhaled drugs depends not only on the formulation but perhaps even more on the delivery device and the patient's ability to use the device correctly."

Respir Care 2005; 50:1376-83



helping the world breathe better Cipla

For more details, log on to: www.cipladoc.com
The Cipla website for the medical profession has an entire section devoted to information on asthma and COPD, and contains downloadable material for doctors and patients. Links to related sites are also provided.