

RESPULES

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INTRODUCTION

Respules may be defined as a type of sterile suspension for administering through inhalation. These are prepared in nebulizing suspensions forms, administered from jet nebulizers at adequate flow rates, via face masks or mouthpieces. They are also referred as Respirator Suspension Formulation for respiratory diseases, used in the management of asthma and chronic obstructive pulmonary disease (COPD). It contains active ingredients delivered via a single inhaler. Most drugs are sterile suspension for inhalation via jet nebulizer and contains micronized active ingredient, and the inactive ingredients. It prevents the release of substances in the body that cause inflammation to prevent asthma attacks.

Respules are manufactured using Blow-Fill-Seal (BFS) technology, it is a manufacturing technique used to produce small (0.1mL) volume liquid-filled containers. Originally developed in Europe in the 1930s, it was introduced in the United States in the 1960s, but over the last 20 years it has become more prevalent within the pharmaceutical industry and is now widely considered to be the superior form of aseptic processing by various medicine regulatory agencies including the U.S. Food and Drug Administration (FDA) in the packaging of pharmaceutical and healthcare products.

The basic concept of BFS is that a container is formed, filled, and sealed in a continuous process without human intervention, in a sterile enclosed area inside a machine. Thus this technology can be used to aseptically manufacture sterile pharmaceutical liquid dosage forms. So respules may also be defined as sterile dosages for respiratory diseases.

Overview of Asthma

Asthma (AZ-ma) is a chronic (long-term) lung disease that inflames and narrows the airways. Asthma causes recurring periods of wheezing (a whistling sound when you breathe), chest tightness, shortness of breath, and coughing. The coughing often occurs at night or early in the morning.

To understand asthma, it helps to know how the airways work. The airways are tubes that carry air into and out of your lungs. People who have asthma have inflamed airways. The inflammation makes the airways swollen and very sensitive. The airways tend to react strongly to certain inhaled substances.

When the airways react, the muscles around them tighten. This narrows the airways, causing less air to flow into the lungs. The swelling also can worsen, making the airways even narrower. Cells in the airways might make more mucus than usual. Mucus is a sticky, thick liquid that can further narrow the airways.

This chain reaction can result in asthma symptoms. Symptoms can happen each time the airways are inflamed.

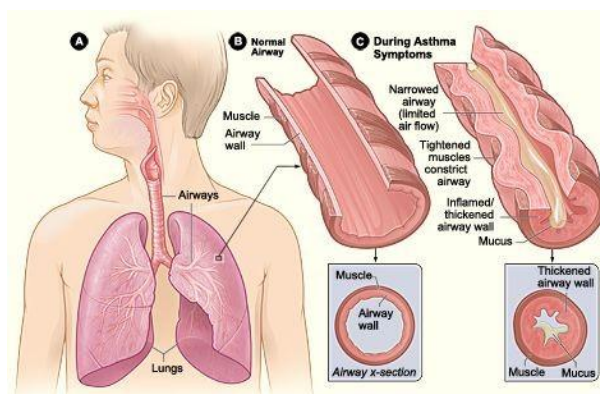


Fig. A. shows the location of the lungs and airways in the body. Fig B. shows a cross-section of a normal airway. Fig C. shows a cross-section of an airway during asthma symptoms.

Sometimes asthma symptoms are mild and go away on their own or after minimal treatment with asthma medicine. Other times, symptoms continue to get worse.

When symptoms get more intense and/or more

symptoms occur, you're having an asthma attack. Asthma attacks also are called flareups or exacerbations.

Treating symptoms when you first notice them is important. This will help prevent the symptoms from worsening and causing a severe asthma attack. Severe asthma attacks may require emergency care, and they can be fatal.

Asthma has no cure. Even when you feel fine, you still have the disease and it can flare up at any time.

Asthma Treatment & Management

There is no cure for asthma, but symptoms can be controlled with effective asthma treatment and management.

Controller medications are taken daily and include inhaled corticosteroids (fluticasone, budesonide, ciclesonide, flunisolide, beclomethasone and others).

Combination inhalers contain an inhaled corticosteroid plus a long-acting beta-agonist (LABA). LABAs are symptom-controllers that are helpful in opening your airways. However, in certain people they may carry some risks.

LABAs should never be prescribed as the sole therapy for asthma. Current recommendations are for them to be used only along with inhaled corticosteroids. Combination medications include fluticasone and salmeterol, budesonide and formoterol (Symbicort), and mometasone and formoterol.

Leukotriene modifiers are oral medications that include montelukast, zafirlukast and zileuton.

Quick-relief or rescue medications are used to quickly relax and open the airways and relieve symptoms during an asthma flare-up, or are taken before exercising if prescribed. These include: short-acting beta-agonists. These inhaled bronchodilator medications include albuterol, levalbuterol and pirbuterol. Quick-relief medications do not take the place of controller medications.

Overview of COPD

COPD, or chronic obstructive pulmonary disease, is a progressive disease that makes it hard to breathe. "Progressive" means the disease gets worse over time. COPD can cause coughing that produces large amounts of mucus, wheezing, shortness of breath, chest tightness, and other symptoms. Cigarette smoking is the leading cause of COPD. Most people who have COPD smoke or used to smoke. Long-term exposure to other lung irritants, such as air pollution, chemical fumes, or dust, also may contribute to COPD.

To understand COPD, it helps to understand how the lungs work. The air that you breathe goes down your windpipe into tubes in your lungs called bronchial tubes or

airways.

Within the lungs, your bronchial tubes branch into thousands of smaller, thinner tubes called bronchioles. These tubes end in bunches of tiny round air sacs called alveoli.

Small blood vessels called capillaries run through the walls of the air sacs. When air reaches the air sacs, oxygen passes through the air sac walls into the blood in the capillaries. At the same time, carbon dioxide (a waste gas) moves from the capillaries into the air sacs. This process is called gas exchange.

The airways and air sacs are elastic (stretchy). When you breathe in, each air sac fills up with air like a small balloon. When you breathe out, the air sacs deflate and the air goes out.

In COPD, less air flows in and out of the airways because of one or more of the following:

- The airways and air sacs lose their elastic quality.
- The walls between many of the air sacs are destroyed.
- The walls of the airways become thick and inflamed.
- The airways make more mucus than usual, which can clog them.

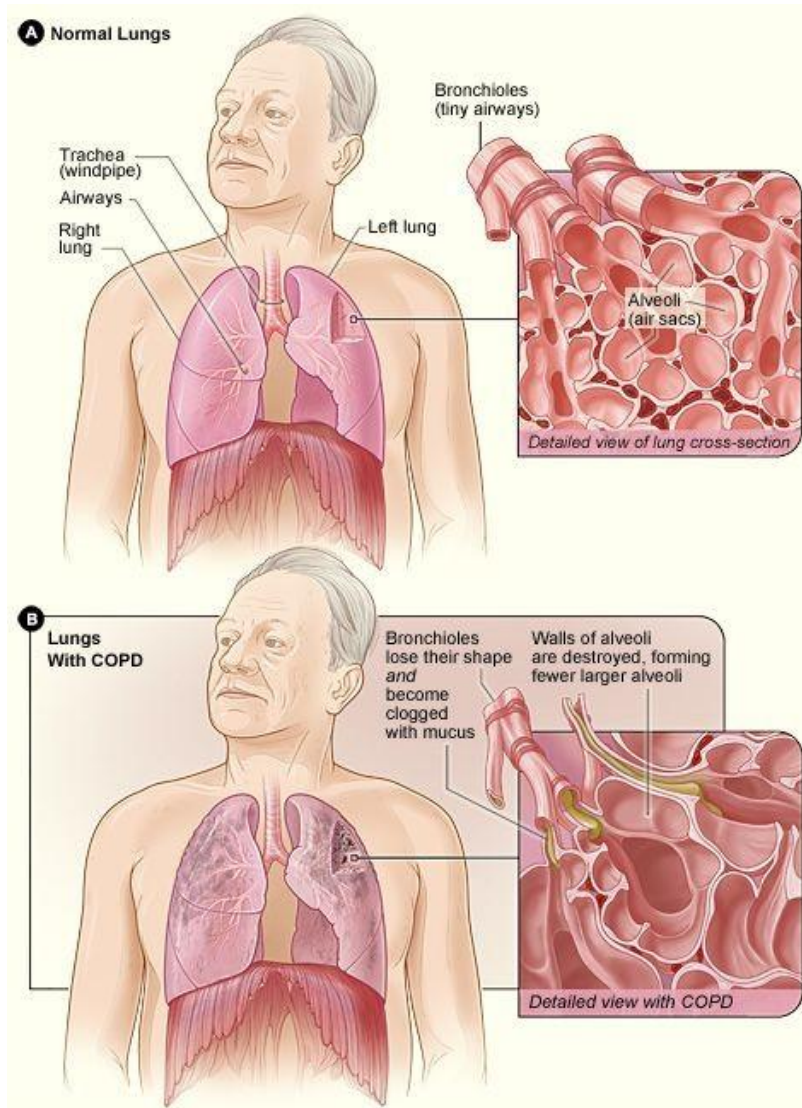


Fig. A shows the location of the lungs and airways in the body. The inset image shows a detailed cross-section of the bronchioles and alveoli.

Fig. B shows lungs damaged by COPD. The inset image shows a detailed cross-section of the damaged bronchioles and alveolar walls.

In emphysema, the walls between many of the air sacs are damaged. As a result, the air sacs lose their shape and become floppy. This damage also can destroy the walls of the air sacs, leading to fewer and larger air sacs instead of many tiny ones. If this happens, the amount of gas exchange in the lungs is reduced.

In chronic bronchitis, the lining of the airways is constantly irritated and inflamed. This causes the lining to thicken. Lots of thick mucus forms in the airways, making it hard to breathe.

Most people who have COPD have both emphysema and chronic bronchitis. Thus, the general term "COPD" is more accurate.

Treatment

Short-acting bronchodilator inhalers

Short-acting bronchodilator inhalers deliver a small dose

of medicine directly to your lungs, causing the muscles in your airways to relax and open up.

There are two types of short-acting bronchodilator inhaler:

- Beta-2 agonist inhalers, such as salbutamol and terbutaline
- Antimuscarinic inhalers, such as ipratropium

The inhaler should be used when you feel breathless and this should relieve the symptoms.

Long-acting bronchodilator inhalers

If a short-acting bronchodilator inhaler does not help relieve your symptoms, you may be recommend for a long-acting bronchodilator inhaler. This works in a similar way to a short-acting bronchodilator, but each dose lasts for at least 12 hours.

There are two types of long-acting bronchodilator inhalers:

- Beta-2 agonist inhalers, such as salmeterol, formoterol and indacaterol
- Antimuscarinic inhalers, such as tiotropium, glycopyrronium and aclidinium

Steroid inhalers

Steroid inhalers, also called corticosteroid inhalers, work by reducing the inflammation in your airways.

If you are still getting breathless or having flare-ups even when taking long-acting bronchodilator inhalers, your GP may suggest including a steroid inhaler as part of your treatment. Most people with COPD will be prescribed a steroid inhaler as part of a combination inhaler.

Instruments used in administrating Respules

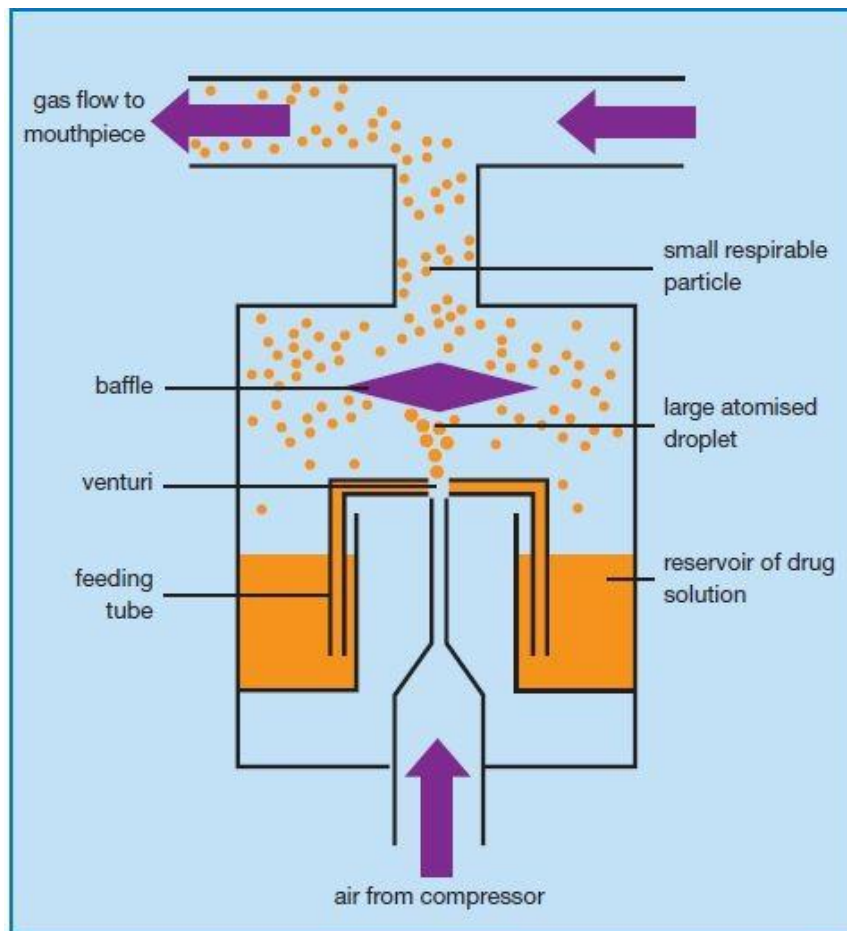
Respules are administered through inhalation. They are manufactured as nebulizing suspensions forms and

administered by jet nebulizers and pressurized Metered Dose Inhalers.

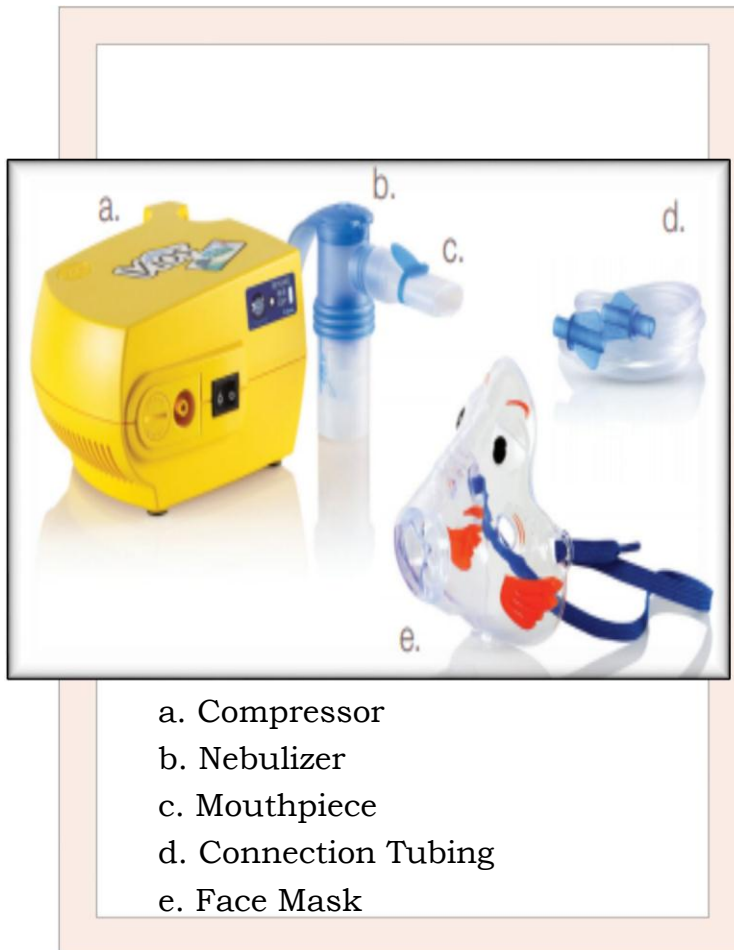
Jet nebulizers

A jet nebulizer is an instrument that turns sterile liquid medicines into a fine mist that we can simply inhale through a face mask or mouthpiece. And it delivers the medicine straight to the lungs, where it is required. Jet nebulizers are also called as "atomizers".

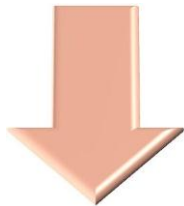
Jet nebulizers are connected by tubing to a compressor which causes compressed air or oxygen to flow at high velocity through a liquid medicine to turn it into an aerosol, which is then inhaled by the patient. However Jet nebulizers are commonly used for patients in hospitals who have difficulty using inhalers, such as in serious cases of respiratory disease, or severe asthma attacks.



Jet nebuliser design. Compressed air or pressurised gas is forced through a narrow hole (venturi). Negative pressure adjacent to this fast-flowing jet sucks liquid up from a reservoir into the jet via feeding tubes. The liquid is atomised into large particles that impact on a baffle to generate smaller respirable particles.

How to use the jet nebulizer

Open the sealed foil envelope along the dotted line. Record the date that the envelope was first opened. Any unused ampules should be discarded after two weeks.



Remove 1 ampule from the strip. Place the remaining ampules in the foil envelope, store at room temperature, and protect from light.



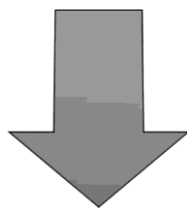
After the PULMICORT RESPULES ampule is opened, it should be used right away.



Keep in mind, any remaining ampules should be used within two weeks.



Gently swirl the ampule using a circular motion, making sure to not squeeze the ampule and keeping it in an upright position.



Twist off the top of the ampule and squeeze all the liquid into the nebulizer. If the patient is using a face mask, make sure it fits snugly



Turn the compressor on and continue treatment until the mist stops, generally in 5 to 10 minutes.

Pressurized Metered Dose Inhaler (pMDI)

A pressurized metered-dose inhaler (pMDI) is a device that delivers a specific amount of medication to the lungs, in the form of a short burst of aerosolized medicine that is usually self-administered by the patient via inhalation. It is the most commonly used delivery system for treating asthma, chronic obstructive pulmonary disease (COPD) and other respiratory diseases. The medication in a metered dose inhaler is most commonly a bronchodilator, corticosteroid or a combination of both for the treatment of asthma and COPD. Other medications less commonly used but also administered by MDI are mast cell stabilizers, such as cromoglicic acid or nedocromil.

A metered-dose inhaler consists of three major components; the canister which is produced in aluminium or stainless steel by means of deep drawing, where the formulation resides; the metering valve, which allows a metered quantity of the formulation to be dispensed with each actuation; and an actuator (mouthpiece) which allows the patient to operate the device and directs the aerosol into the patient's lungs. The formulation itself is made up of the drug, a liquefied gas propellant and, in many cases, stabilising excipients. The actuator contains the mating discharge nozzle and generally includes a dust cap to prevent contamination.

To use the inhaler the patient presses down on the top of the canister, with their thumb supporting the lower portion of the actuator. Actuation of the device releases a single metered dose of the formulation which contains the medication either dissolved or suspended in the propellant. Breakup of the volatile propellant into droplets, followed by rapid evaporation of these droplets, results in the generation of an aerosol consisting of micrometer-sized medication particles that are then inhaled.

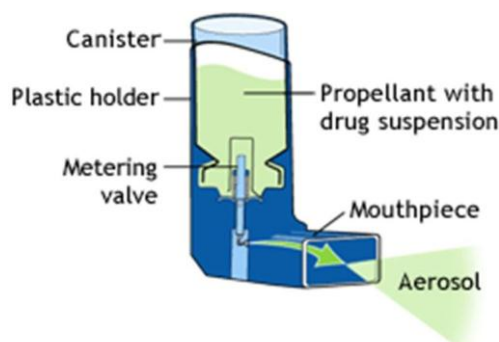


Fig: Pressurized Metered Dose Inhaler (pMDI).

How to use a pressurized Metered-Dose Inhaler

Using a pressurized Metered Dose Inhaler (pMDI) seems simple; many patients do not know how to use it in the right way. If the inhaler is used in wrong way, less amount of medicine can reach the lungs. Following steps can help to use inhaler effectively.



Step 1: At first remove the cap from mouthpiece.



Step 2: Shake the inhaler well before each use.



Step – 3: If the inhaler is new or if it has not been used for a week or month, release one puff into the air to make sure that it works.



Step – 4: Hold the pressurized Metered Dose Inhaler (pMDI) with the mouthpiece down. Breathe out fully through the mouth, expelling air from your lungs as much as possible.



Step 5: Place the mouthpiece into the mouth and close the lips around the mouthpiece.



Step – 6: Press down firmly and fully on the metallic canister to release medicine while breathe in deeply and slowly through the mouth. Take the finger off the canister after the spray comes out.



Step – 7: Remove the inhaler from the mouth and then close the mouth after breathed in all the way. Hold the breath as much as possible, up to 10 seconds, and then breathe normally.



Step – 8: If a patient need more inhalations, wait one minute and shake the salbutamol inhaler again then repeat above steps.



Step – 9: Cleanse the inhaler at least once a week. Remove the metallic canister and rinse the plastic case and cap in warm water but do not put the metallic canister in the water. Dry the plastic case and cap thoroughly and gently replace the metallic canister into the plastic case with a twisting motion. Put the cap back onto the mouthpiece. It is very important to keep the plastic case clean so the drugs will not build-up and block the spray. If it is not cleaned correctly, the inhaler may stop spraying.

Step – 10: The metallic canister should be discarded when the labeled numbers of inhalations have been used.

Currently there seems to be a demand among physicians to prefer prescription of a pressurized Metered Dose Inhaler (pMDI) for their patients, instead of a Jet nebulizer that generates a lot more noise (often 60 dB during use) and is less portable due to a heavier weight.

The main advantage of the Jet nebulizer is related to its low operational cost. If the patient needs to inhale medicine on a daily basis the use of a pMDI can be rather expensive.

Today several manufacturers have also managed to lower the weight of the Jet nebulizer down to 635 grams (22.4 oz), and thereby started to label it as a portable device. Compared to all the competing inhalers and nebulizers, the noise and heavy weight is however still the biggest drawback of the Jet nebulizer.

Uses of Jet nebulizers

Nebulisers are used for emergency and domiciliary treatment of many respiratory diseases. Indications for nebuliser use include the management of exacerbations and long-term treatment of chronic obstructive pulmonary disease (COPD), management of cystic fibrosis, bronchiectasis, HIV/AIDS and symptomatic relief in palliative care. The British Guideline produced jointly by the British Thoracic Society (BTS) and Scottish Intercollegiate Guidelines Network (SIGN) on the management of asthma identifies a limited use for nebulisers in this condition.

Uses of pressurized Metered Dose Inhaler (pMDI)

Metered-dose inhalers are only one type of inhaler, but they are the most commonly used type. There uses are as follows,

- Asthma inhalers contain a medication that treats the symptoms of asthma.
- Portability
- Multidose delivery capability
- Lower risk of bacterial contamination

Drugs used in respules

Mostly anti-inflammatory drugs are manufactured in respule dosage form.

Commercial names of Respules: Levolin, budecort, Asthalin, Bricanyl, Symbicort, etc.

Levolin and Asthalin

Levolin and Asthalin are the commercial names of respules. They contains salbutamol as its active pharmaceutical ingredient. It is manufactured by Cipla.

Salbutamol is a short-acting β_2 -adrenergic receptor agonist used for the relief of bronchospasm in conditions such as asthma and chronic obstructive pulmonary disease.

Mechanism of action

Salbutamol stimulates β_2 adrenergic receptors which are predominant receptors in bronchial smooth muscle of the

lung. Stimulation of β_2 receptors leads to the activation of enzyme adenyl cyclase that form cyclic AMP (adenosine-mono-phosphate) from ATP (adenosine-tri-phosphate). This high level of cyclic AMP relaxes bronchial smooth muscle and decreases airway resistance by lowering intracellular ionic calcium concentrations. Salbutamol relaxes the smooth muscles of airways, from trachea to terminal bronchioles.

High level of cyclic AMP are also inhibits the release of bronchoconstrictor mediators such as histamine, leukotriene from the mast cells in the airway.

- Inhaler preparations – Two types of inhaler present; one is salbutamol metered dose inhaler (MDI) and another is salbutamol dry powder inhaler (DPI). MDI contains salbutamol in a pressurized aerosol form. It is used by oral inhalation only. Each inhalation contains 100 microgram salbutamol in HFA (hydrofluoroalkane) propellant. HFA is an ozone benign, environment friendly, CFC free propellant. DPI presents in capsule form. Each capsule contains 200 microgram salbutamol in a dry powder form. This DPI capsule is used only by oral inhalation via an inhalation device. Learn more.
- Nebulizer solution – Each ml nebulizer solution contains 5 mg salbutamol.

Dosage

Sabutamol may be given as following dosage

- Inhaler formulation – One to two puffs (100 to 200 microgram) of salbutamol metered dose inhaler is inhaled as need basis, and one to two capsules (200 to 400 microgram) of salbutamol dry powder inhaler is inhaled as need basis.
- Nebulizer solution – 1 to 2 ml of salbutamol nebulizer solution should be diluted with normal saline to final volume of 2-4 ml is inhaled from a nebulizer until aerosol generation ceases. It may be required repeated in severe acute attack.

Mechanism of action of salbutamol inhaler

Salbutamol inhaler directly reaches the lungs where it stimulates adenyl cyclase enzyme. This enzyme increases the level of cyclic adenosine-mono-phosphate (AMP) in the cells. Next, the cyclic AMP inhibits the entry of calcium ions into the cells, thus relaxing bronchial smooth muscle and decreasing airway resistance. High level of cyclic AMP in the mast cells of the airway also inhibits the release of bronchoconstrictor mediators such as histamine, leukotriene.

Pharmacokinetics of salbutamol inhaler

After inhalation, only 10 – 20% of salbutamol reaches in the lungs. The remainder is retained in the delivery system or deposited in the mouth from where it is swallowed. It acts within 3-5 minutes after inhalation with a peak at 15-20 minutes. Overall duration of action is 4-6 hours. Mainly metabolized in the liver and is excreted via the urine.

Uses of salbutamol inhaler

Salbutamol inhaler is indicated for adults, adolescents and children over 4 years of age. Pediatric clinical studies show that this inhaler is not safe for children below 4 years of age. It is inhaled in the following conditions:

- Bronchial asthma
- Chronic obstructive pulmonary disease (COPD)

Dosage of salbutamol inhaler

Dosage of salbutamol metered dose inhaler for adults, adolescents and children over four years of age:

1. Acute episodes of bronchial asthma or other conditions associated with acute bronchospasm: Usual dose is 1 to 2 puffs (100 to 200 microgram) repeated every 4 to 6 hours.
2. For chronic maintenance therapy in bronchial asthma: Usual dose is 1 to 2 puffs (100 to 200 microgram) 3 or 4 times daily.
3. For the prophylaxis of bronchospasm caused by exercise: Two puffs (200 microgram) 15 minutes before exercise.

Side effects of salbutamol inhaler

At standard inhaled doses, the amount of salbutamol reach in the body is very small compared with tablet, injection or liquid drug. Therefore, side effects of salbutamol inhaler are much less than with tablet, injection or liquid drug. However, some side effects may occur in some patients.

Common side effects

1. Palpitation
2. Tremor
3. Tachycardia
4. Nervousness
5. Headache

Uncommon side effects

1. Irritation of mouth or throat
2. Muscle cramps
3. Hypersensitivity reactions
4. Hypokalemia – It may occur after several doses. Salbutamol causes excess entry of potassium into the cells, as a result blood potassium level fall.
5. Paradoxical bronchospasm – It is a condition in which narrowing of the airway occurs after inhalation of a salbutamol inhaler causing breathing difficulty and coughing. It may due to other compounds that used for salbutamol inhaler preparations but the true mechanism remains unknown. If it develops, inhaler should be discontinued immediately and alternative therapy should be instituted.

Budecort

Budecort is the commercial name of Budecort Respules manufactured by Cipla. It contains Budesonide as its active pharmaceutical ingredient.

Budesonide is nebulized for maintenance and prophylactic treatment of asthma including patients who require oral corticosteroids and those who may benefit from systemic dose reduction.

Budesonide – Mechanism of action

Budesonide is a glucocorticosteroid, which, when inhaled, has a dose-dependent anti-inflammatory action in the airways. Inhaled budesonide has fewer severe adverse effects than systemic corticosteroids. Budesonide has been shown to be very effective against the characteristic inflammation of asthma, although the exact mechanism responsible for the anti-inflammatory effect of budesonide is unknown. COPD has a distinctly different pattern of chronic on-going airway inflammation to asthma and there are conflicting results regarding the benefits of inhaled corticosteroid (ICS) therapy when used alone. However, budesonide is reported to reduce the risk of COPD exacerbations and slow the rate of decline of health-related quality of life in symptomatic COPD patients.

Bricanyl

Bricanyl is the commercial name of Bricanyl Respules manufactured by AstraZeneca UK Limited. It contains Terbutaline sulphate as its active pharmaceutical ingredient.

Indication

Bricanyl (terbutaline) belongs to a class of fast-acting beta 2 antagonist which work to dilate airways and relieve airway obstruction. It is mainly used as a reliever medication for asthmatic symptoms and acute asthmatic exacerbations. It is also used in other conditions where acute bronchospasm is a possible complication such as chronic bronchitis (chronic cough and sputum production), emphysema (destruction of the air spaces) and chronic obstructive pulmonary disease (COPD). In particular, bricanyl is used for prevention against acute exercise induced asthma attacks where it can be taken before exercise to open up the airways in patients who experience wheezing from exerting themselves. There are different bricanyl formulations discussed below. Bricanyl Turbuhaler is intended for short-term management of bronchospasm as well as maintenance therapy, whilst Bricanyl injection solution is recommended for acute use only.

Mechanism of Action

Bricanyl acts by activating specific receptors in the airways known as beta 2 adrenoceptors. This leads to reduced airway constriction (bronchoconstriction) and an increased airway diameter making breathing much easier. It has a rapid onset of action (particularly the injection form) which means it can be used to relieve acute and life-threatening asthma attacks and other conditions where the airways are suddenly narrowed. The effects of the drug last for 4-5 hours.

Symbicort

Symbicort is the commercial name of Bricanyl Respules manufactured by AstraZeneca UK Limited. It contains budesonide and formoterol in combination as its active pharmaceutical ingredients.

Symbicort (budesonide/formoterol delivered via the inhaler device) is indicated in the regular treatment of asthma where use of a combination (inhaled corticosteroid [ICS] and long-acting β_2 adrenoceptor agonist [LABA]) is appropriate as patients not adequately controlled with ICS and “as needed” inhaled short-acting β_2 adrenoceptor agonists (SABAs) or patients already adequately controlled on both ICS and LABA.

Formoterol – Mechanism of action

Inhaled formoterol, a selective LABA, results in rapid and long-acting relaxation of bronchial smooth muscle in patients with airways obstruction. The bronchodilating and bronchoprotective (prevention of bronchospasm by asthma triggers) effect is dose-dependent, with an onset of effect within 1–3 minutes. Studies performed in both stable and acute severe asthma confirm that formoterol works as fast as salbutamol or terbutaline and faster than salmeterol. The duration of effect is at least 12 hours after a single dose.

Excipients Used In Respules

Sodium chloride, disodium edetate, water for injections.

Sodium chloride

Sodium chloride nebulizer solution is used for Diluting other medicines for use in a nebulizer. It may also be used for other conditions as determined by your doctor. Sodium chloride nebulizer solution is a saline solution.

How to use sodium chloride nebulizer solution

Sodium chloride nebulizer solution is for inhalation in a nebulizer only. Do not take sodium chloride nebulizer solution by mouth or inject it.

Sodium chloride nebulizer solution is used to dilute other medicines. Follow the instructions provided by your doctor.

Sodium chloride nebulizer solution may come in a single-dose vial or in a container with multiple doses. Be sure to use the proper amount of sodium chloride nebulizer solution. If you are using sodium chloride nebulizer solution from a multiple-dose container, use a measuring device marked for medicine dosing. Ask your pharmacist for help if you are unsure of how to measure your dose.

If you are using a vial, use your dose immediately after opening the vial and throw away any unused medicine. Do not save the contents of an opened vial for later use.

Do not use sodium chloride nebulizer solution if it contains particles, is cloudy or discolored, or if the vial is cracked or damaged.

This product is intended to dilute other medicines for use in a nebulizer. If you miss a dose of your medicine, follow the missed dose instructions for the medicine that you are mixing with this product.

Edetate disodium

Edetate disodium (EDTA) and benzalkonium chloride (BAC) are often present as preservative or stabilizing agents in nebulizer solutions used to treat asthma and chronic obstructive pulmonary disease. Benzalkonium chloride is a potent bronchoconstrictor when inhaled in concentrations similar to those in which it is present in these solutions.

Water for Injection is water of extra high quality, which is used for production of sterile substances.

CONCLUSION

Respules are sterile suspension for inhalation via jet nebulizer and pressurized metered-dose inhaler (pMDI) is a device that delivers a specific amount of medication to the lungs, in the form of a short burst of aerosolized medicine that is usually self-administered by the patient via inhalation they consist of the active ingredient (micronized), and the inactive ingredients disodium edetate, sodium chloride, sodium citrate, citric acid, polysorbate 80, and Water for Injection. Three dose strengths are available in single-dose ampules (Respules ampules): 0.25 mg, 0.5 mg, and 1 mg per 2 mL RESPULES ampule. For respules, like all other nebulized treatments, the amount delivered to the lungs will depend on patient factors, the jet nebulizer utilized, and compressor performance. Mostly corticosteroids are used in the management of bronchial asthma and Chronic obstructive pulmonary disease (COPD).

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