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AEROSOLS IN THE MANAGEMENT OF ASTHMA AND COPD

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ABSTRACT
Pharmaceutical aerosol is a pressurized system that depends on the power of a compressed or liquefied gas to expel the contents from the container. Therapeutic performance of pharmaceutical aerosols is affected by various factors such as actuator tube design, orifice diameter, concentration of surfactant in the system, moisture content. A pharmaceutical aerosol must satisfy certain standards to claim it to be a quality drug. The main standard for the quality of any drug is the intrinsic and extrinsic elements which contribute directly or indirectly to the safety, potency, efficacy, stability, patient acceptability and regulatory compliance of the products. Historically pharmaceutical aerosols have been employed for the treatment of obstructive airway diseases, such as asthma and chronic obstructive pulmonary disease. Chronic obstructive pulmonary disease (COPD) represents a socio-economic burden and requires regular and ongoing treatment. Inhalation therapy is recommended at all stages of the disease and allows the delivery of active molecules directly to the target site of action, whilst minimizing adverse side-effects. Inhalers therefore play a crucial role in the effective management of patients with COPD and Asthma and their choice is as important as that of the drug. Poor inhalation technique is associated with decreased treatment effectiveness. Choosing the optimal device, together with proper education, improves inhalation technique, adherence and outcomes or effectiveness but has to be performed regularly and rigorously, including visual checking of the patient's ability to use the inhaler.

KEYWORDS: Tuberculosis, aerosols, inhaled vaccines, treatment, chronic obstructive pulmonary disease, inhaler, asthma, effectiveness, devices, health care providers, education.

INTRODUCTION
The aerosol container is referred to as a pressurized package in which the therapeutically active drug is dissolved or suspended in compressed or liquefied gas. The delivery of therapeutically active drug in the form of spray or foam or solid stream is dependent on the ability of the liquefied or compressed gas. The delivery of contents of aerosol depends on its valve assembly, containers, actuators as well as on the propellant. The two components of aerosols are product concentrate and propellant. The product concentrate contains the therapeutically active ingredients. Propellant can also act as the solvent or vehicle for the product concentrate.[1]

COMPONENTS OF AEROSOLS[2]

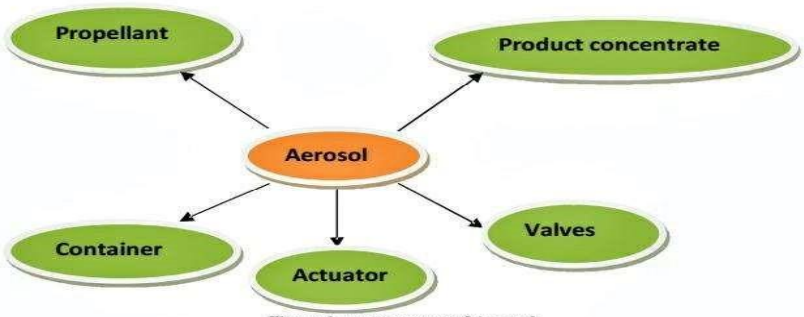


Figure 1: components of Aerosol

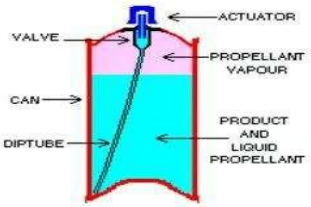


Figure 2: components of Aerosols[9]

TYPES OF AEROSOL SYSTEMS

Solution system or two-phase system

It is also called two-phase system as it contains both the vapour and the liquid. Based on the desired spray, the propellant can be used single or a mixture of propellants can be used. Propellant 12 is added alone or in mixture. If propellants having vapour pressure lower than propellant 12 is added to propellant 12, a reduction of vapour pressure is achieved but bigger sized aerosol particles are obtained. Also, bigger sized aerosol particles are obtained on addition of cosolvents like ethyl acetate, propylene glycol, ethyl alcohol, glycerine and acetone. No other solvent is required if the drug is soluble in the propellant. The solution system is administered in topical application. Some of the commonly used propellant combinations in solution systems are propellant 12/11 (30:70), propellant 12/114 (45:55), propellant (12/114) (55:45).[3]

Water based system or three phase system

In the water based or three phase system, large quantity of water is present to solubilise the contents. The water is immiscible with the propellant. Generally, water-based system is a three-phase system consisting of a water phase, vapour phase and the propellant. So, the solubility of propellant in water can be increased by adding a cosolvent such as ethanol and also by adding surfactants at a range of composition 0.5% to 2.0%. The propellant composition ranges from 25 to 60%. The nonpolar surfactants such as esters of Oleic acid, palmitic acid, stearic acids are more preferred than the polar surfactants. The surfactants act by reducing the interfacial tension existing between the water phase and the propellant, and thus produce a uniform dispersion by increasing the solubility of the propellant in the water. The drawback associated with water-based system is that the addition of ethanol, not only increases the solubility of propellant in water, but also increases its flammability. The presence of large quantities of water delivers content in liquefied form. The recent advancement is the vapour tap valve and the aquasol valve. In aquasol system, water or the mixture of water and alcohol are used to dissolve the drug. The addition of alcohol increases the solubility of propellant in water. Aquasol system is advantageous than water-based system as a vapourised propellant is delivered rather than the liquefied propellant. The vapourised propellant delivers small sized, fine particles and dried contents in the form of fine mist or spray to the site of action. Moreover, the vapourised propellant is non-flammable in nature.[4]

Suspension or dispersion system

Suspension system is the dispersion of the active ingredients in the propellant or the mixture of propellant by adding surfactants or the suspending agents.

Foam system: The liquefied propellant is emulsified. Aqueous or nonaqueous vehicles, propellant and the surfactants are its ingredients. Foam system is further classified as aqueous stable, nonaqueous stable and the quick breaking foam.

Aqueous stable foams: The aqueous stable foam consists of propellant in the range of 3.0 to 4.0%. A dry spray is produced by the propellant. It finds its application in steroid antibiotics.

Non-aqueous stable foams: The nonaqueous stable foam contains glycol as the emulsion base and is used as the emulsifying agent.

Quick breaking foams: Here the external phase is propellant. The product will come out as foam which soon merges to form liquid. This type of system can be applied to small area or larger surface. These are used for

topical application. Cationic or anionic or non-ionic surfactants are used in the formulation.

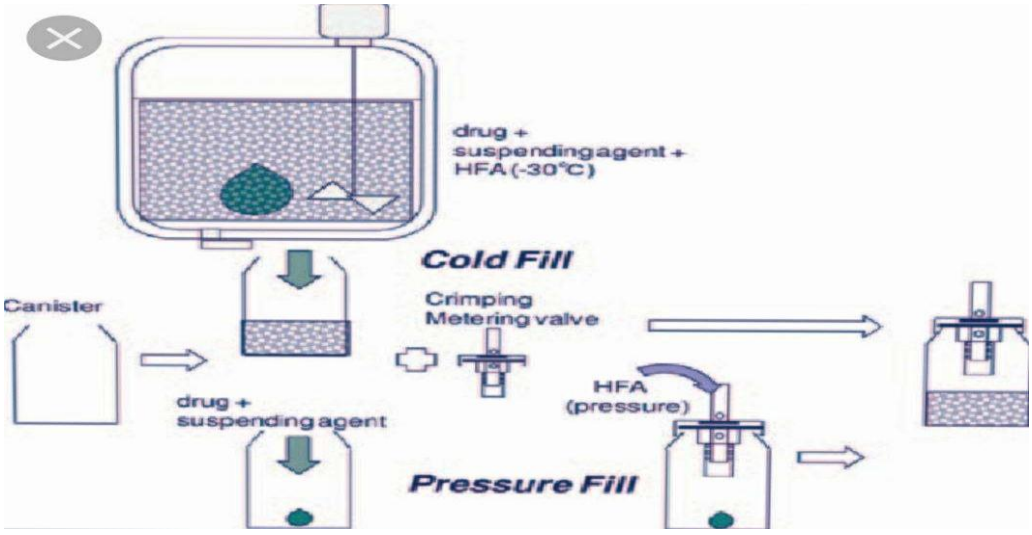
Thermal foams: The aerosol which is delivered in the form of foam upon the application of heat is called thermal foam. They are used in shaving creams.[5]

MANUFACTURING OF PHARMACEUTICAL AEROSOLS

Cold filling method: It consists of an insulated box fitted with copper tubings. The insulated tubings are filled with dry ice or acetone. The copper tubings increase the surface area and cause faster cooling. The hydrocarbon propellant is not to be stored in the copper tubings as it might cause explosion Two methods are involved:

- In the first method, the product concentrates are chilled to a temperature of – 30 to – 400 F. The chilled product concentrates are added to the chilled aerosol container. The chilled propellant is added through an inlet valve present under side of the valve of the aerosol container.
- In the second method, both the product concentrate and the propellant are chilled to – 30 to – 400 F. Then the mixture is added to the chilled container.
- In both the above methods, after the aerosol containers are filled, the valves are set in its place and the filled aerosol containers are passed through a water bath 0in which the contents of the containers are heated to 130 F to test for leaks and strength. Then the containers are air dried, capped and labelled. Cold filling method is advantageous for the filling of metering valve containing aerosol container. The pressure filling method is more prominant than cold filling method as most of the formulations cannot be cooled to very low temperatures.

Pressure filling method: Pressure filling apparatus consists of a metering burette capable of measuring the amount of propellant to be filled to the aerosol container. The propellant is added through the inlet valve present to the bottom of the valve under its own vapour pressure. A cylinder of nitrogen or compressed gas is attached to the top of the valve and the pressure of nitrogen causes the propellant to flow to the container through the metering burette. The propellant flows to the container stops when the pressure of the flowing propellant becomes equal to the pressure of the container. The product concentrate is filled to the aerosol container through the metering pressure filling burette at room temperature. The propellant is added through the inlet valve located at the base of the valve or under the valve after the crimping of valve. The flow of propellant to the aerosol container continues till the pressure of the filling propellant becomes equal to the pressure within the container. The aerosol container are capped and labelled.[6]



Compressed gas filling method: A compressed gas propellant is used. As the compressed gas is under high pressure, so the pressure is reduced by pressure reducing valve. A pressure of 150 pounds per square inch gauge is required to fill the compressed gas propellant in the aerosol container. The product concentrate is placed in the pressure gauge and the valve is crimped in its place. The air is evacuated. Thrilling head is inserted in to the valve opening upon the depression of the valve, the compressed gas propellant is allowed to flow into the container. The compressed gas stops flowing when the pressure of the compressed gas flowing to the container from the burette becomes equal to the pressure within the container. In case of increasing the solubility of the gas in the product concentrate and also when an increased amount of compressed gas is required, carbon dioxide and Nitrous dioxide is used. The container is needed to be shaken during and after the filling operation to enhance the solubility of the gas in the product concentrate.[7]

EVALUATION TESTS OF PHARMACEUTICAL AEROSOLS

Evaluation tests of pharmaceutical aerosol includes the testing of propellant, valves, actuator and dip tubes, containers, weight checking, leak testing and spray testing.

PROPELLANT

All quality control testings of propellents are accompanied by specification sheets. A sample is taken out and vapour pressure is determined which then is compared to specifications. The density is also checked when necessary. Other tests include – Identification of two or more blends of propellant by Gas chromatography. Purity of the propellant is checked by moisture, halogen, and non-volatile residue determinations.

VALVES, ACTUATORS, AND DIP TUBES

Both physical and chemical examinations are done. They are sampled according to the standard procedures as found in "Military Standard Mil – STD-105D". A test method was developed for metered dose pharmaceutical aerosol by Aerosol specifications committee, Industrial Pharmaceutical Technology section, Academy of Pharmaceutical Sciences with an objective of determining the magnitude of valve delivery and degree of uniformity between individual valves.[8]

Testing procedure

· Take 25 valves and placed on suitable containers.
· The containers are filled with specific test solutions.
· A button actuator with 0.02 inch orifice is attached to the valves.
· The filled containers are placed in a suitable atmosphere at a temperature of 25 ± 10 C.
· When the products have attained the temperature of 25 ±10 C, the filled containers are actuated to fullest extent for 2 seconds.
· This procedure is repeated for a total of 2 delivered from each 25 test units.
. The valve delivery per actuation in µl = Individual delivery weight in mg. Specific gravity of test solution out of 50 deliveries:
· If 4 or more deliveries are outside limits, then valves are rejected.
· If 3 or more deliveries are outside limits, another 25 valves are tested.
. 0 Lot is rejected if more than 1 delivery is outside specification.
· If 2 deliveries from 1 valve are beyond limits: another 25 valves are tested.
. Lot is rejected if more than 1 delivery is outside specification.

CONTAINERS: Containers are examined for defects in linings. Quality control aspects include degree of conductivity of electric current as measure of exposed metals. Glass containers examined for flaws.

LEAK TEST: It is done by measuring the crimp's valve dimension and comparing. Final testing of valve enclosure is done by passing filled containers through the water bath.[9,10]

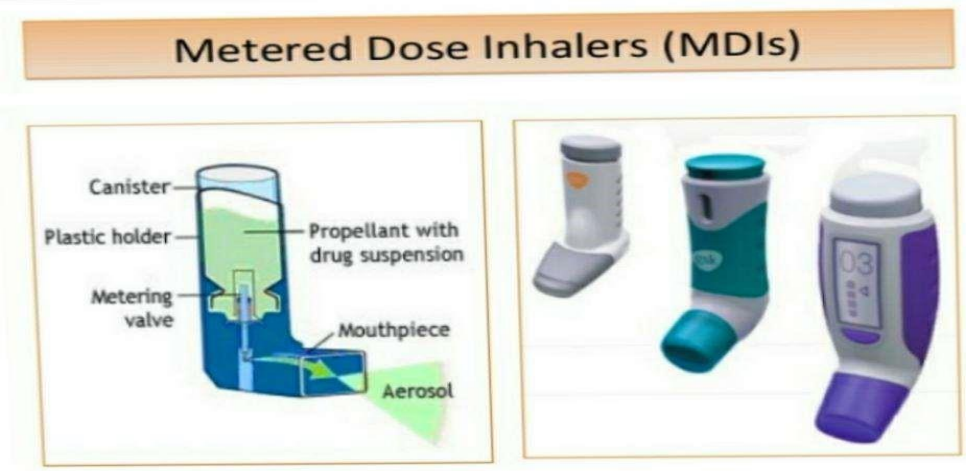
CONTROL OF ASTHMA BY AEROSOLS

Asthma is characterized by chronic, variably severe, airway inflammation that is associated with mucosal edema, hyper secretion, and bronchospasm and that results in variable airflow obstruction. During the past 15 years, the most important advances in the control of asthma have been the establishment of the concept of prophylaxis and the development of steroid aerosols that are very active typically but have low systemic bioavailability. Our approach is in essential agreement with that of others. The therapeutic goals of freedom from symptoms and from drug side effects can usually be achieved with aerosolized medications in various drug combinations. Mild asthma is readily managed with sympathomimetic aerosols that are taken only as necessary; treatment with oral adrenoceptor agonists or theophylline is rarely needed. Among patients with moderate asthma, in whom the next level of therapy traditionally consisted of regular administration of sympathomimetic aerosols three or four times daily, together with sustained release theophylline, there is evidence that cromolyn can be substituted for theophylline, thus avoiding theophylline's often unpleasant and occasionally life- threatening side effects. Inhalation of adrenoceptor agonists five minutes before going out into cold weather or before exercise will often prevent attacks of asthma. In the relatively few patients with most severe chronic asthma, treatment with oral theophylline and daily or alternative day administration of a systemic steroid may be needed, in addition to aerosol, for maintenance therapy.

TYPES OF INHALERS

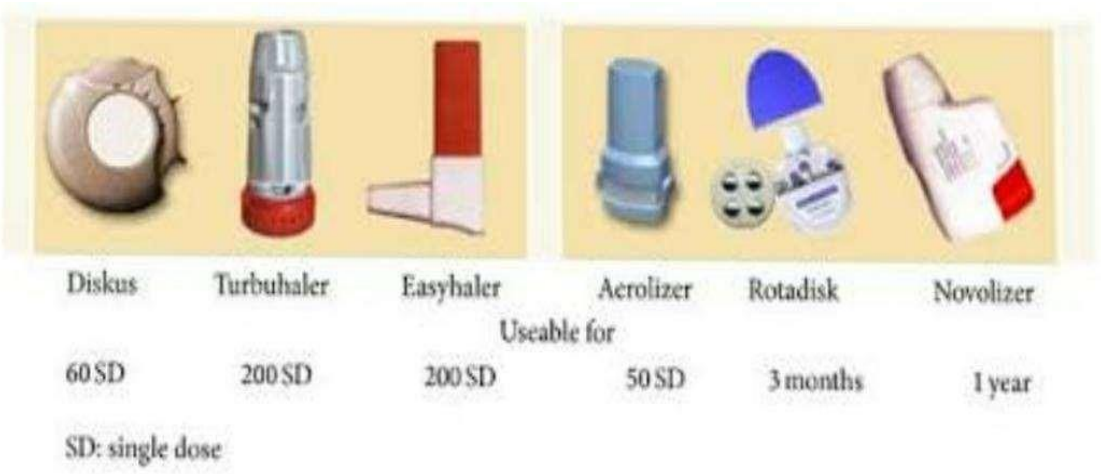
1. Pressurized metered dose inhalers (pMDIs)
2. Dry powder inhalers (DPIs)
3. Nebulizers.

Metered dose inhaler (pMDIs) The pressurized metered dose inhalers (pMDIs) are composed of a canister, and actuator, and sometimes a spacer. The canister is composed of a metering dose valve with an actuating stem. The formulation (containing the active ingredient i.e. drug, a liquefied gas propellant, and a stabilizer) is present in the canister. The drug may be suspended or dissolved in the liquefied gas propellant. Upon actuation, the metering dose valve is opened which releases a single metered dose of medication along with the liquified gas propellant to spray out of a canister. This process is called cavitation. The liquefied gas propellant is volatile in nature; breaks down into liquid droplets which evaporates rapidly, and the dried micronized drug are inhaled to the lung.



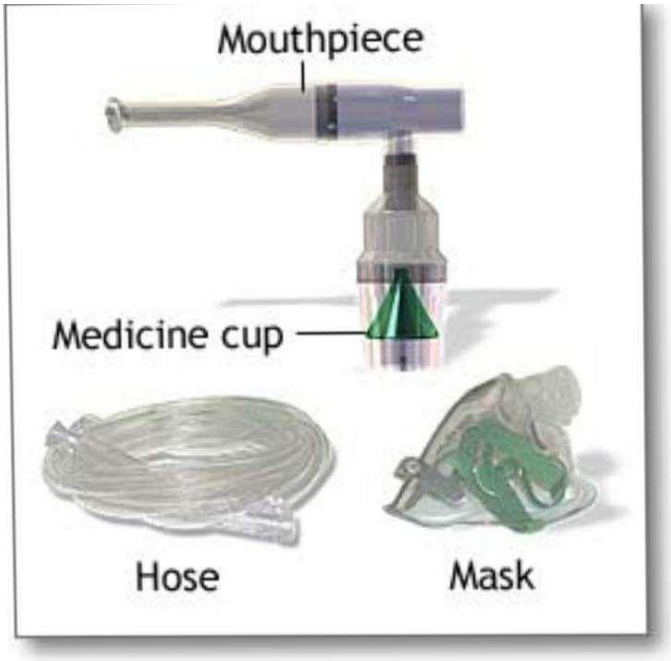
Dry powder inhalers (DPIs)

DPIs are composed of micronized powdered drug particles. The micronized powdered drug particles (of sizes < 5µm) are mixed with much larger sugar particles (of size < 30 µm) eg. Lactose monohydrate. The smaller drug particles forms loose aggregate with lactose monohydrate. The micronized powdered drug particles have high cohesive force, so they have a tendency of adhering to each other. The addition of large particle sized lactose monohydrate reduces the cohesive force of the micronized drug particles and form loose agglomerate with the micronized drug particles. It helps in an easy deaggregation of the agglomerates, upon inhalation, the agglomerates get broken down into its constituent particles, with the help of mechanical devices such as screens, on which the particles agglomerates impact. It releases the smaller sized powdered drug particles into the air to be inhaled to the lung. The larger sized lactose monohydrates particles are left behind in the device and in the mouse throat.



Nebulizers

Nebulizer is a device used to administer aerosolised medication in the form of a mist inhaled into the lungs. Nebulizers use oxygen, compressed air or ultrasonic power to break up medical solutions and suspensions into small aerosol droplets called mists that can be directly inhaled from the mouthpiece of the device. Nebuliser produce a mist of drug containing water droplets for inhalation. The drug is present either in solution form or suspension form in the nebulizer. It is usually of two types:Electronic nebulizer and Jet or ultrasonic nebulizer. Jet or ultrasonic nebulizer uses a source of pressurised air to blast a stream of ait through a drug containing water reservoir, producing water droplets. In contrast, electronic nebulizers develop mechanical vibration to produce water droplets. The nebulisers are generally used for the treatment of acute conditions (e.g. acute asthma, respiratory infection) or in those patients who have difficulties using other respiratory dosage forms.



Inhaler devices for treating COPD patients

Aerosols are either solutions containing the medication or, solid drug particles suspended in a gas or in a dry powder. Aerosols can be delivered from different pMDIs, DPIs and nebulisers. In recent years, several technological innovations in device engineering and formulation science have significantly improved the performance of all existing categories of inhalation devices, and some highly effective delivery systems have been developed. The new 'generation' of inhalers have pulmonary deposition fractions of 40–50% of the nominal dose, which are considerably higher compared with the 10–15% that inhalers currently used in clinical practice achieve.[11]

Mechanism and Ways of Pulmonary Drug Administration

In the course of the most recent decade, the systemic absorption of a board scope of therapeutic agents after pulmonary application has been shown in animals and also in people. Through pulmonary course, the medication can be controlled by two essential modes; to start with, intranasal organization, which has anatomical impediment, for example, narrows airway lumen, second, oral inhalative organization. By oral inhalative organization obviously better outcomes can be normal as it permits controlling small particles with a concentration loss of just 20% in correlation with 85% by nasal route. Oral inhalative organization can again be delegated intratracheal instillation and intratracheal inhalation. The most well-known technique utilized as a part of research facility is the intratracheal inhalation. In the intratracheal instillation, a little measure of medication arrangement or scattering is conveyed into the lungs. The most well-known strategy utilized as a part of labs is the intratracheal instillation. In the intratracheal instillation, a little measure of drug solution or dispersion is conveyed into the lungs by an exceptional syringe. This gives a quick and quantifiable technique for drug conveyance to the lungs. The localized drug deposition is accomplished with a relatively small absorptive range. In this way, the instillation procedure is much basic, non-costly, and has non uniform drug distribution. In preclinical creature (animals) studies intratracheal instillation has as often as possible been utilized to evaluate the pulmonary absorption and systemic bioavailability, particularly as to the exact dosing and viability related with this technique.[12,13]

Recent Approaches For Pulmonary Drug Delivery System

Low Efficiency of Inhalation System The major challenge in pulmonary drug delivery is the low efficiency of presently available inhalation systems. Ideal aerosol particle size is very important for deep lung delivery (pulmonary drug delivery). Since if the particles are too small, the optimum particle size for deep lung deposition is 1-5 mm, they will be easily exhaled, and if the particle size is too large, they effects on the oropharynx and larynx.[14]

Less Drug Mass Per Puff To get adequate effects by the pulmonary drug delivery system the delivery of many drugs which require milligram doses but with most existing systems, the total amount of drug per puff transferred to the lower respiratory tract is too low (less than 1000mcg).

Poor Formulations Stability for Drugs Most traditional small molecule asthma drugs are crystalline in nature, comparatively moisture resistant in the dry molecules. Whereas in the case of corticosteroids, which are unstable in liquid state, amorphous, and highly moisture sensitive in the dry state.

Improper Dosing Reproducibility The main reason for poor dosing reproducibility is worsening of diseases, problem in device, and instability of formulation. To get maximum dose reproducibility patient education play important role.[15,16]

Current Applications of Pulmonary Drug Delivery Systems

Applications of pulmonary drug delivery in Asthma and COPD Asthma is a chronic lung disease that is categorized under inflammation and narrowing of airways. Asthma causes periods of wheezing, breath shortness, and coughing. Asthma affects people of all ages, but it most often starts in childhood. COPD means chronic obstructive pulmonary diseases, which is correlated to smoking, chronic bronchitis and emphysema. All these three classes of drugs are only given by pulmonary route. Levosalbutamol inhalers are present in the market to treat asthma. Titropium inhalers are present in market to teat COPD.[17,18,19]

Recent role in Pulmonary Delivery in Patients on Ventilators Nowadays to improve inhalation coordination of patient devices are mostly used like Baby mask. This mask is attached to spacer for small tidal volumes and low inspiratory flow rates infant and young Childers. We can easily give medication to child up to 2 years by using baby masks this is recent advancements in applications of pulmonary drug delivery.[20]

New use of Pulmonary Delivery in Diabetes Diabetes is a syndrome of disordered metabolism and hyperglycaemia resulting from an insufficiency of insulin secretion or resistance which cause the blindness, kidney disorder, nerve damage, heart attack and other health problems. The most common form of this therapy is twice-daily Application of Pulmonary Delivery in Migraine Drug Ergotamine is choice for migraine. This drug used successfully to treat migraine headache via metered dose inhaler (MDI).[21]

Application of Pulmonary Delivery in Angina Pectoris Angina pectoris is not a disease itself it is symptoms of myocardial ischemia and it is arises as a result of imbalance between oxygen supply and demand of myocardium. Nitroglycerine is a drug of choice for angina pectoris, and is given through sublingual route.

Isosorbide aerosol has also been reported useful in hypertensive emergency.[22,23]

Application of Pulmonary Drug Delivery in Cancer Chemotherapy Lung cancer is the leading cause of cancer death and inhaled chemotherapy is approach for the treatment of lung cancer. A multicentre phase I clinical trial is evaluating doxorubicin HCl inhalation solution in lung cancer patients. As many as 4lakh lung cancer patients a study is going on aerosolized paclitaxel solution to mice with lung tumours. The treatment significantly reduced lung tumours and prolonged survival. Aerosol drug delivery of the anticancer agents like difluoromethylornithine and 5- fluorouracil reduced lung tumours in mice 50% and 60%, respectively. Interleukin-2 stimulates immune function in cancer patients, but injections cause fever, malaise, and locals welling.[24]

CONCLUSION

Pharmaceutical aerosols is a noninvasive pulmonary drug delivery system which is considered to be one of the best methods as compared to other routes of administration. Its advantages over the other route of administration enhance its wide range of application in the treatment of illness including asthma, COPD etc. The inhaled route remains crucial for the treatment of bronchial diseases. However, drug deposition and subsequent treatment effectiveness are highly dependent on inhalation technique, which is incorrect in many patients with asthma and COPD. Many inhalation devices are available and others are currently being developed with the aim of simplifying required handling, and thus improving treatment safety. Nonetheless, at present, proper training and regular checking of inhalation technique remain critical to optimize treatment effectiveness. Involved healthcare professionals have to be adequately trained before providing this service The inhaled route remains crucial for the treatment of bronchial diseases. However, drug deposition and subsequent treatment effectiveness are highly dependent on inhalation technique, which is incorrect in many patients with asthma and COPD. Many inhalation devices are available and others are currently being developed with the aim of simplifying required handling, and thus improving treatment safety.

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