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Pulmonary drug delivery system: A review

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Abstract

An important route for the management of various drugs is the lung drug delivery system (PDDS). In recent years, the lungs have become increasingly concerned about the scientific and environmental value of treating lung diseases. Lung delivery of drugs has evolved into one of the most widely used routes of the planned or local drug rescuer Due to its potential localized lung function; drug delivery systems for the treatment of lung diseases are being developed. In this article, it is pointed out that PDSDS provides improved compliance with appropriate patient outcomes. In the traditional form, this novel drug delivery system has several advantages. Because of its potential therapeutic properties in the field of pulmonary embolism, the use of drug delivery systems (DDS) in the treatment of lung diseases is growing. This route also facilitates the placement of drugs in high-intensity areas within the patient-specific lungs, thereby reducing the total amount of medication administered to patients (10-20% of the peroral volume), and increasing local drug activity while minimizing side effects and systemic side effects and bypass the first-pass metabolism.

Keywords: Pulmonary Drug Delivery System; Piezoelectric Effect; Side Effects; Nasal Drug Delivery; COPD

1. Introduction

Pulmonary disease or lung disease constitutes diseases or disorders that affect the lungs and its associated structures in breathing effectively. It may be caused due to bacterial, viral, or fungal infections or may be due to environmental factors. According to the WHO Report 2017, Lung disease deaths in India constitute about 10.9% and are ranked about 4 in deaths caused by respiratory diseases. The primary illness includes Chronic Obstructive Pulmonary Disease, Asthma, Bronchitis, Emphysema, Pneumonia, Acute respiratory Distress, Interstitial lung disease, and Lung cancer. Pulmonary drug delivery comprises devices, systems, or formulations by which drugs are delivered to the lungs either for the treatment of respiratory ailments or for systemic delivery for other diseases. Currently, pulmonary drug delivery is achieved by inhalation of drugs orally or nasally and can be used for local and systemic action. They have a profound advantage in that the drug reaches directly to the systemic circulation and hence achieves higher bioavailability. It provides an effective non-invasive method and can also bypass the first-pass metabolism. However, the efficiency and stability of the inhalation system still constitute a significant problem. [1] Owing to the unique physiological features of the lungs, the pulmonary administration serves as an alternative route for systemic drug delivery. These unique physiological features involve [2, 3]. The large and highly vascularized alveolar surface area for drug absorption

- Non-invasive systemic drug delivery
- Epithelial barrier of low thickness hence high solute permeability
- Less proteolytic activity
- Bypass first-pass hepatic metabolism

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- Rapid onset of action Through this route, drugs could be targeted to the airways of a specific size or infected with a particular injury or disease within the lungs as opposed to other normal organs.

For example, ultrafine therapeutic particles have been introduced recently which causes drug deposition in deeper airways [3].

1.1. Advantages

- It is needle-free pulmonary delivery.
- It requires a low fraction of oral dose.
- Pulmonary drug delivery has negligible side effects since the rest of the body is not exposed to the drug.
- The onset of action is very quick with pulmonary drug delivery.
- Degradation of the drug by the liver is avoided in pulmonary drug delivery.

1.2. Disadvantages

- Oropharyngeal deposition gives local side effects.
- Patients may have difficulty using the pulmonary drug devices correctly.
- Drug absorption may be limited by the physical barrier of the mucus layer.
- Various factors affect the reproducibility of drug delivery in the lungs, including Physiological and pharmaceutical barriers.
- The lungs are not only accessible surfaces for drug delivery complexes but also delivery devices are required to target drug delivery.
- Stability of drug in vivo.
- Targeting specificity.
- Drug irritation and toxicity.
- Immunogenicity of proteins.
- Drug absorption may be limited by the physical barrier of the mucus layer.
- Patients may have some problems using the pulmonary drug delivery devices correctly.
- Oropharyngeal deposition gives local side effects.
- The duration of activity is often short-lived due to the rapid removal of drug from the lungs or due to drug metabolism 4,5

1.3. Anatomy and Physiology of Pulmonary Drug Delivery

The respiratory system works with the circulatory system to deliver oxygen from the lungs to the cells remove carbon dioxide and return it to the lungs to be exhaled. The exchange of carbon dioxide and oxygen between the air, blood, and body tissues is known as respiration. Healthy lungs absorb about 1 pint of air about 12–15 times each minute. All of the blood in the body is passed through the lungs every minute.6. The human respiratory system consists of two regions, 1. Conducting airway 2. Respiratory region. The airways are further divided into various types, i.e. nasal cavity, associated sinuses, nasopharynx, oropharynx, larynx, trachea, bronchi, and bronchioles. The respiratory region consists of respiratory bronchioles, alveolar ducts, and alveolar sacs. The human tract may be a branching system of air channels. The major task of the lungs is the gas exchange, by adding oxygen to and removing carbon dioxide from the blood passing the pulmonary capillary bed. 1. Lungs: The respiratory tract starts at the nose and terminates deep in the lungs at an alveolar sac. 2. Nasopharyngeal region: it's an "upper airway", which involves the respiratory airways from the nose right down to the larynx.

1.4. Factors Influencing Pulmonary Drug Delivery

Various factors that affect pulmonary drug delivery include both drug-related factors as well as formulation-related factors.[7]

- Drug Related Factors
- Formulation Related Factors

These factors refer to the various physicochemical and dosage form characteristics of the drug candidate

- Physicochemical Properties of Formulation The physicochemical properties are concerned with the pH, tonicity, and viscosity that individually affect the physical and chemical behavior of the drug as given in Table 3

- Dosage Form Characteristics Different dosage forms have different characteristics that govern their action inside the body. The nature of the drug, its proposed indications, and overall its marketing preferences determine the selection of dosage form. The important features of some of these dosage forms are summarized below in Table 4

Technologies for Producing Pulmonary Drug Particles Currently various newer technologies have been developed that are potentially useful for generating drug particles within the respirable range (1-5μm). These include:

- Micronization
- Spray freeze drying
- Supercritical Fluid Crystallization 8

Table 1 Barriers to Pulmonary Drug Delivery System and their Characteristic Description

Barrier Parameters	**Description**	**Examples**	**Reference**
Less bioavailability	Less permeability of membrane lowers the bioavailability of large molecular weight compounds	Polar drugs such as proteins and peptides	[18]
Lung clearance mechanisms	Deposited particles in the conducting airways exhibit smaller lung residence time and hence get removed rapidly by mucociliary and alveolar clearances	Bacteria, macrophages	[3, 11, 19]
Enzymatic degradation	Various metabolic enzymes appear both extracellularly and intracellularly in secretions, bound to the membrane, released by specific cells such as macrophages, lymphocytes, neutrophils, and mast cells	Natural peptides having molecular weight less than 3,000 D such as somatostatin, VIP, and glucagon	[3]
Limitations of conventional devices	Only 10-40% of the drug gets deposited to the target sites by conventional devices which results in the wastage of the rest of the drug	Venturi nebulizers deposit more amount of salbutamol into the lungs than conventional disposable jet nebulizers	[19]

Table 2 Description of Drug-Related Factors Affecting Pulmonary Absorption

Factors	**Description**	**Examples**	**References**
Lipophilicity	More lipophilic nature of mucosa with some hydrophilic character supports the permeation of lipophilic compounds	Lipophilic drugs such as alprenolol, propranolol, naloxone, buprenorphine, testosterone, and 17a-ethinyloestradiol are almost completely absorbed as compared to the hydrophilic drugs such as metoprolol which do not show marked absorption rat	[9, 10-11]
Polymorphism	Both the dissolution rate and solubility of the drug are affected by polymorphism which in turn affects the absorption of the drug through the biological membrane	-form of steroid KSR-592 (needles) shows improved inhalation properties and in vitro respiration as compared to its -form (plates)	[9, 12]
Chemical nature	Structural modification such as the conversion of a drug into its salt or ester form affects the pulmonary absorption rate	In-situ carboxylic acid esters of L-Tyrosine show significantly greater absorption than that of L-Tyrosine	[13]

Molecular weight	Lipophilic compounds exhibit direct whereas hydrophilic compounds inverse relationship between molecular weight and drug permeation	Drugs with molecular weight less than 300 Da permeate through aqueous channels and the rate of permeation of compounds with molecular weight equal to and greater than 300 Da is highly sensitive to molecular size	[14]
pKa and partition coefficient	According to pH partition theory, unionized species show better absorption compared with ionized species, and the same holds in the case of pulmonary absorption	Aminopyrine shows an enhanced rate of absorption at increased pH; while on the other hand, salicylic acid shows substantial deviations in its absorption profile at different pH	[15]
Dissolution rate and solubility	Both parameters affect pulmonary absorption as particles need to be dissolved before absorption	Solution form absorbs more rapidly than a solid dosage form	[9]

1.5. Recent Trends in Applications of Pulmonary Drug Delivery

Apart from asthma and COPD pulmonary drug delivery is employed for the following indication

- Insulin by Aerosol
- Treatment of Migraine
- Nicotine Aerosol for Smoking Cessation
- Aerosols for Angina.
- Aerosol Vaccination.
- Alpha 1 Antitrypsin
- Aerosols in Transplantation
- Pulmonary arterial hypertension
- Acute Lung Injury
- Surfactant Aerosol
- Gene Therapy via Aerosol
- In Cancer chemotherapy
- Pentamidine Aerosol 7

1.6. Drug Delivery Devices

For the Pulmonary route, drug delivery devices play an important role equivalent to the formulation of that formulation. It is difficult to administer a formulation through a pulmonary route without suitable drug delivery devices[9, 10, 11, 12]. The drug delivery devices are given below:

- Metered dose inhaler
- Dry powder inhaler
- Nebulizer
  - Jet nebulizers
  - Ultrasonic nebulizers

1.6.1. Metered dose inhaler

The metered-dose inhaler called an MDI for brief, may be a pressurized inhaler that delivers medication by employing a propellant spray. It's composed of 4 essential components: the bottom formulation (drug, propellant, excipients, etc) the container, the metering valve, and the actuator (or mouthpiece). It's a drug delivery device that provides the fine droplets of a medicament having a particle size of fewer than 5 micrometers. It's used for the treatment of respiratory diseases like asthma and COPD. They will tend from suspension or solution. just in the case of suspension formulations, the substances that are insoluble within the propellant and solvent are dispersed within the suitable propellant vehicle. Particle size and the solubility of active ingredients and surfactants or dispersing agents are the important factors to be considered in formulating MDI suspension formulations. A solution formulation of MDI contains the active ingredient dissolved during a pure or mixture of propellants. Solution aerosol is relatively easy to formulate provided the ingredients are soluble in the propellant-solvent system. MDIs contain the propellant like chlorofluorocarbons and

hydrofluroalkanes. They contain a micronized sort of the drug during a propellant struggling with surfactants to stop the clumping of drug crystals. Lubricants for the valve mechanism and other solvents are the opposite constituents. When the device is actuated, the propellant gets exposed to atmospheric pressure, which leads to aerosolization of the drug. As it travels through the air, the aerosol warms up resulting in evaporation of the propellant that reduces the particle size to the desirable range. How to use the MDI, Currently, inhalation therapy is the best option for lung diseases like asthma, cystic fibrosis, and chronic obstructive pulmonary disease (COPD). These local therapies allow the use of smaller doses and reduce systemic side effects. In the last 20 years, an interesting scientific interest in the technology for pulmonary delivery was spiked by the very fact that the lungs are often used as a portal for systemic drug delivery. Pulmonary delivery is attractive as a route for systemic administration thanks to fast absorption by the huge area of the alveolar region, the abundant vasculature and thin air–blood barrier, and the avoidance of first-pass metabolism. The effectiveness of an aerosol therapy is largely dependent on how much of the medication will reach the intended site of deposition13, 14, 15.

How to use the MDI,

- Shake the inhaler well before use (3 to 4 shakes)
- Remove the cap
- Breathe out, away from your inhaler
- Bring the inhaler to your mouth. Place it in your mouth between your teeth and shut your mouth around it
- Start to breathe in slowly. Press the highest of your inhaler once and keep inhaling slowly until you've taken a full breath.
- Remove the inhaler from your mouth, and hold your breath for about 10 seconds, then breathe out. The major problem that arises from MDIs is patients must be educated to operate the device. Another problem in MDIs is that less quantity of drug can be delivered into the lungs. The key parts of the pressurized metered-dose inhaler are given below.

1.6.2. Dry powder inhaler

It's a flexible system that needs a point of dexterity. The name itself indicates that the formulation is in solid form. It's a bolus drug delivery device that contains the solid drug during a dry powder mix that is fluidized when the patient inhales. It contains the active drug alone or features a carrier powder mixed with the drug to extend the flow properties of a drug. Dry powder inhaler features greater stability, and simple handling, and are comparatively cheap in comparison to metered dose inhaler. There's no need for harmful propellent like CFC. They will be designed for one or multi-dose purposes.

Advantages of Dry Powder Inhalers (DPIs)

- A larger drug is available for payloads per puff.
- Blending is not required for it.
- Enables use of small, flow-rate independent inhalers.
- The particles readily disaggregate despite their small size.
- Enables improved lung deposition, dose decrease variability, and potential for condensed dose through enhanced dispersibility16, 17, 18

Unit-Dose Devices

Single-dose powder inhalers are devices in which a powder-containing capsule is placed in a holder. The capsule is opened within the device and powder is inhaled.

It consists of:

- Spinhaler:

It works similar to rotahaler, except that outer sleeves slide down to pierce the capsule and propellant disperse the drug.

- Rotahaler:

Insert a capsule into the rotahaler, the colored end first twists the rotahaler to break the capsule. Inhale deeply to get the powder into the airway. Several breaths may be required but do not require the coordination of the aerosol.[19, 20]

Multi-dose Devices

The multi-dose device uses a circular disk that contains either four or eight powder doses on a single disk. The doses are maintained in separate aluminum blister reservoirs until just before inspiration. It consists of,

Turbohaler: It is a dry powder inhaler available in an easy-to-use format. It can overcome the need for both a carrier and loading individual doses.[21, 22]

1.6.3. Nebulizer

The nebulizer is widely used as an aerosolizing drug solution or suspension for drug delivery to the respiratory tract and is particularly used for the treatment of a hospitalized patient. It is commonly used in treating cystic fibrosis, asthma, and other respiratory disease.

A nebulizer is formulated by,

- The pharmaceutical solution technology- parenteral products
- Formulated in water
- Co-solvents
- pH above 5

There are two types of the nebulizer, namely jet and ultrasonic,

- Jet nebulizer: In a jet nebulizer, the liquid is converted and sprayed into fine droplets by use of compressed gas, for the prevention of exits of a large droplet from the device the baffles are used in a jet nebulizer. Disadvantage: • Time consumption • Drug wastage
- Ultrasonic nebulizer: In ultrasonic type, aerosol droplets are produced through high-frequency vibrations of a piezoelectric crystal, for that the ultrasound waves are formed in it23, 25,26. Ultrasonic nebulizers have played an important role in pulmonary drug delivery. As the process in which aerosol droplets are generated is independent and does not require breath actuation, ultrasonic nebulizers, in principle, offer the potential for instantaneously finetuning the dose administered to the specific requirements of a patient, taking into account the patient's breathing pattern, physiological profile, and disease state. Nevertheless, owing to the difficulties and limitations associated with conventional designs and technologies.24

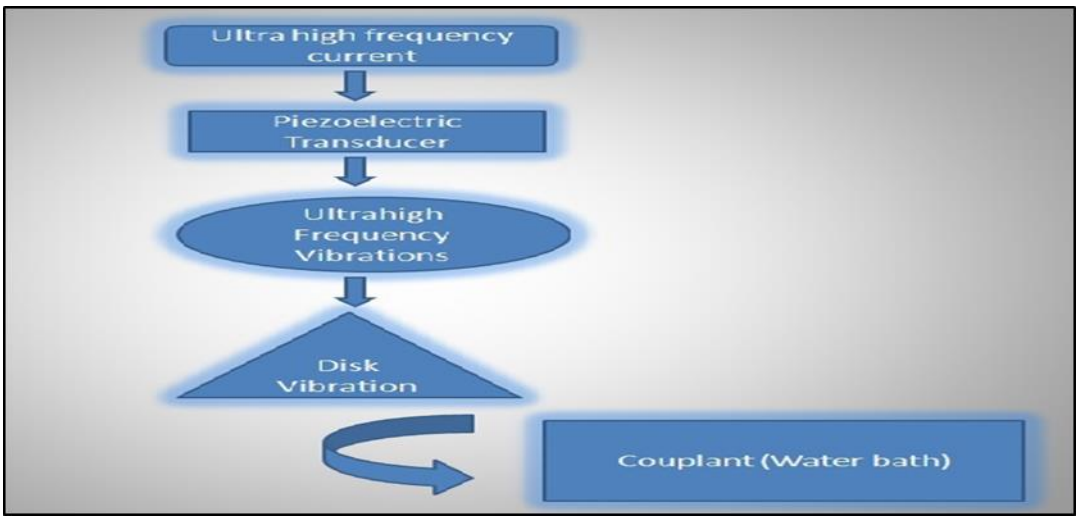

Figure 1 Working principle of piezoelectric crystal effect

1.7. Factors Affecting Absorption:

Pulmonary administration of drugs plays an important role in the treatment of various respiratory and systemic diseases and displays an attractive area for future drug development. The effects of an aerosol-based drug are dependent on a variety of factors: starting from the nature of the compounds, cellular aspects, characteristics of delivery systems, and aerosol administration to deposition in pulmonary clearance mechanisms multiple ways to manipulate drug delivery exist. An optimal delivery system would specifically deposit the drug at its pulmonary target region,

independent of ventilatory or pathophysiological parameters. To optimize current delivery systems, future studies addressing the unique molecular, biochemical, and physiological characteristics of various respiratory regions have to be carried out by applying modern techniques of molecular biology[25,] morphology [26, 27,] and physiology [28, 29.]

2. Recent Approaches for Pulmonary Drug Delivery System

2.1. 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 affect the oropharynx and larynx. [30]

2.2. Less Drug Mass per Puff

To get adequate effects by the pulmonary drug delivery system the delivery of many drugs requires 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).[31]

2.3. Poor Formulations Stability for Drugs

Most traditional small-molecule asthma drugs are crystalline, 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. [32]

2.4. Improper Dosing Reproducibility

The main reason for poor dosing reproducibility is the worsening of diseases, problems in the device, and instability of formulation. To get maximum dose reproducibility patient education plays an important role.

2.5. Evaluation Aspects

In recent years, there has been considerable advancement in the field of evaluation and characterization of pulmonary drug delivery systems. These methods can be classified as in vitro, in vivo, and ex vivo methods. Various in vitro methods like physicochemical characterization of particles, evaluation of aerosol performance, particle dissolution studies and cell cultures study have been evolved. Drug administration systems, drug deposition, and pharmacokinetic studies are the in vivo methods that are currently in research studies. Ex vivo methods are also developed to check the efficacy and safety parameters of drugs and their delivery mechanisms. The morphological studies of nanoparticles can be done with transmission electron microscopy (TEM), which uses different techniques for the analysis of particles cryogenic transmission methods, negative staining method, and freeze-fracture method[33,34]. The particle's shape, structure, and arrangement can be identified by interpretation of the morphological data of TEM analysis. Similarly, particle size can also be estimated. Scanning electron microscopy (SEM) is used to evaluate the particle size and surface morphology of the particles. It uses high magnification for visualizing the surface morphology of the particles. The distinctive surface characteristics can be studied using the varied resolutions. Measurement of interparticulate forces and surface energy and imaging surface nanotopography of particles can be done using atomic force microscopy (AFM) [33.] The surface roughness of the particles is evaluated by this method and the scanned image is quantified by image analysis software. The degree of surface corrugation can also be expressed by surface fractal dimension determined by a light scattering method[35],[36,37] A real-time aerodynamic measurement of particles ranging from 0.5 to 20 microns with high resolution was done using the Aerodynamic Particle Sizer® 3321. The light-scattering intensity in the equivalent optical size range of 0.37 to 20 microns can be measured using these particle sizes. The paired data for each particle have been provided by these particle sizers and it helps the researcher in studying the aerosol makeup.[38.]

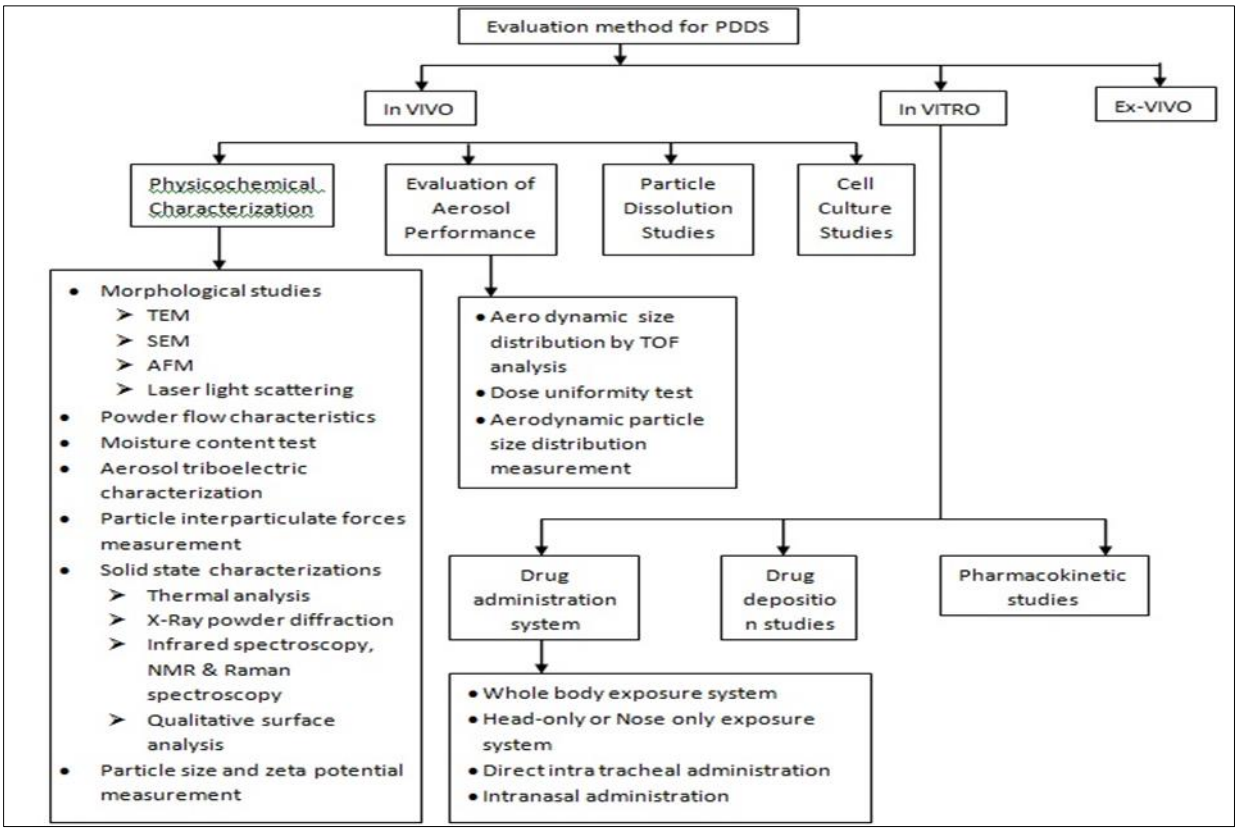

Figure 2 Evaluation Aspects of Pulmonary Drug Delivery

3. Conclusion

Pulmonary drug delivery is the oldest route of drug delivery. Which produces GI. Irritation is administered by this route. Particle size is the main hindrance To the targeted drug delivery to the lung. To achieve optimum particle size there are several methods Micronization, spray drying, double emulsion, and spray freeze drying. The large surface area of the human lung, with its rich blood supply, rapid onset of drug action with high bioavailability, and other physiological advantages, make it a potential route for treating asthma, COPD, and pulmonary disorders. Minimally invasive drug delivery through the lung can be achieved using environment-friendly propellants, non-aqueous inhalers, dry powder inhalers, and jet ultrasonic nebulizers.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest is to be disclosed.

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