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Formulation and Product Development of Nebuliser Inhaler: An Overview

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Abstract
The inhaler therapy using nebulizer is commonly used for local and systemic drug delivery of drug, through lung is promising now days. Inhalation therapy using nebulizer having several advantages large dose can be administered, quick action, easy and convenient to patient to administer the drug. Nebulizer formulations are known as inhalation suspension or solution, which consists of drug dispersed or solublised in aqueous based formulation containing other excipients. Nebulizer instrument are of three types jet nebulizer, ultrasonic nebulizer and mesh nebulizer. Nebulizer characterization includes delivered dose, aerodynamic particle size distribution, and droplet size distribution, degradation product which determines in-vitro and in-vivo performance. The present overview discusses various features of nebulizers along with its potential advantages, disadvantages and formulation aspects of nebulised drug delivery systems.

Keywords: Nebuliser, jet nebuliser, ultrasonic nebuliser, mesh nebuliser, formulation, and characterisation

1. Introduction
Inhalation therapy has played a vital role in the relieving respiratory diseases asthma, chronic obstructive pulmonary disease & respiratory infection etc. Such pulmonary drug delivery compositions are designed to be delivered by inhalation by the patient so that the active drug within the dispersion can reach the lung. It has been found that certain drugs given by pulmonary route are readily absorbed through the alveolar region directly into blood circulation. Pulmonary route possesses many advantages over other routes of administration for the treatment of specific disease states, particularly lung associated large protein molecules which degrade in the gastrointestinal conditions and are eliminated by the first pass metabolism in the liver can be delivered via the pulmonary route if deposited in the respiratory zone of the lungs. There are three main methods of delivering respiratory drugs for most of the asthma patients metered dose inhaler (MDI), dry powder inhaler (DPI) and nebulizers. The dry powder inhalers (DPI) active pharmaceutical ingredient (API) powder with or without carrier fine micronized particles are inhaled. The aggregates are converted into an aerosol by inspiratory airflow. In the metered dose inhaler (MDI) the API dispersed or solubilised in a high vapour pressure propellant and metered accurately in tens to hundreds of micrograms and administered directly to the lungs. Nebulizer is a devices used to administer aerosolized medication in the form of a mist inhaled into the lungs. Nebulizer uses oxygen, compressed air or ultrasonic powder to break up medical solutions and suspensions into small aerosol droplet called mists that can be directly inhaled from the mouthpiece of the device [1, 2].

The method of nebulization is maily used by adults and children all over the world, particularly for asthma and chronic obstructive pulmonary disease (COPD). The word "nebulizer" (from the Latin "nebula", mist) was first used in 1872 and was defined in 1874 as "an instrument for converting liquid drugs into a wet mist". These devices aerosolize drug solution into a wet mist that floats deeply into the patient's airways as they inhale. These are small plastic devices into which the drug solution is placed and are driven by a compressor (electric/battery operated) or a supply of compressed air or oxygen. A gas flow of about 6-8 liters/minute is normally required to drive the nebulizer. Nebulizers use oxygen, compressed air or ultrasonic power to break up medical solutions/suspensions into small aerosol droplets that can be directly inhaled from mouth piece of the device. The aim of nebulizer therapy is to deliver a therapeutic dose of desired drug in the form of an aerosol of respirable particles with in a fairly short period of time usually 5-15 min. There are various advantages of drug delivery directly to the airway which includes rapid onset of a therapeutic effect; reduced drug dose need and limitation of systemic side effects, far outweigh those of any enteral or parental route of administration. This review illustrates the advantages, disadvantages, types and formulation development of nebulizers, their technical aspects [3, 4].

2. Basic Components of Nebulizers
Nebulizer formulation consists of solutions or suspension type liquid formulation in which drug with excipients added to achieve several pharmaceutically desirable goals. Currently all nebulizer solutions or suspension are sterile and most are packaged as unit dose form-fill vials to avoid the invasion of anti-microbial agents [5]. A nebulizer consists of various parts which are assembled together for its working such as medication reservoir, baffle, compressor, mouthpiece and facemask (fig. 1).

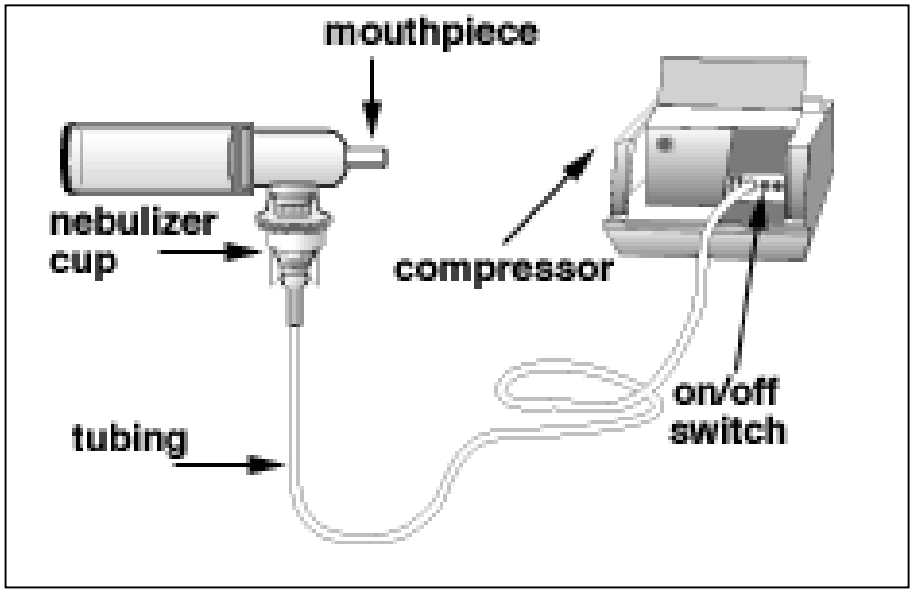

Fig 1: Components of nebulizer

There are several advantages of using nebulizers over other devices used in inhalation therapy which are as follows:

3. Advantages

- Large dose of drug can be administered over multiple breaths.
- Can be used at any age group.
- Require no propellants that can damage the atmosphere.
- Ensures more efficient intrabronchial drug deposition.
- In emergency medicine used to treat acute bronchial asthma and acute exacerbations of COPD, frequently in combination with positive pressure ventilation.
- Easy to administer in a very simple manner [5, 6].

4. Disadvantages

- Higher cost and size complications.
- Time consuming compared to MDI & DPI.
- Noisy.
- High maintenance requirements i.e. the equipment must be cleaned and sterilized on regular basis and the air filtered.
- Dependent on outside power sources, electricity.

5. Formulation of nebulizer

Nebuliser formulation commonly called inhalation solution and suspension drug products, which are typically aqueous-based sterile formulations that contain therapeutically active ingredients and can also contain additional excipients. Inhalation solutions and suspensions are intended for delivery to the lungs by oral inhalation for local or systemic effects and are to be used with a specified nebulizer [5]. Various excipients are used in the nebuliser formulation includes, buffer, preservative, co-solvent, suspending agent, surfactant, tonicity adjusting agent, humectants etc. The examples of common excipients included in nebulizer formulations are described in Table 1.

Table 1: Commonly used excipients in nebulizer formulations

S. No.	Category	Role	Example
1	Isotonicity adjustment	Used to adjust the tonicity of the formulation	Sodium chloride, Dextrose
2	pH adjustment	Used to adjust pH same to physiological conditions and maximize drug stability	Sodium hydroxide, hydrochloric acid sulphuric acid
3	Purging	Purging used to reduce oxidation	Nitrogen
4	Antimicrobial preservative	To avoid the microbial growth in the formulation	Benzalkonium chloride, ethanol, propylene glycol, Beczoyl Alcohol, chlorobutanol, Methyl paraben
5	Buffer component	It gives the buffer capacity to formulation at desire Ph	Sodium citrate, Sodium Phosphate, citric acid
6	Surfactant	Increases suspendability and stability of suspension	Polysorbate 80,20
7	Cation chelating agent	Forms chelate with ions present in the formulation and increases the stability	Disodium EDTA
8	Suspending Agents	Increases viscosity and suspendability of suspension	CMC, Na CMC
9	Co-Solvent	Helps to improve solubility	Alcohol, PEG 400, Propylene Glycol
10	Humactant	Used to maintain humidification in the formulation	Glycerin

6. Types of Nebulizers

Traditional nebulizers can be broadly classified into three categories depending on their operating principle such as jet, ultrasonic and mesh nebulizers (Table 2). The jet nebulizer uses compressed air to aerosolize the drug solutions, whereas the ultrasonic nebulizer uses energy from high frequency sound waves.

Table 2: Types of nebulizers

S. No.	Nebulizers	Advantages	Disadvantages
1a)	Jet nebulizers with corrugated tubing	• Cheap • Easy to use • Effective in delivering drugs that cannot be delivered with pMDIs and DPIs	• Inefficient • Difficult to clean • Need compressed and additional tubing
1b)	Breath-actuated & Breath-enhanced jet nebulizers	• Drug delivery only during inhalation • Easy to use • Less medication wasted • More efficient than JNs with 3tubing	• Need sufficient flow to trigger drug delivery • Takes longer to deliver drug • Not ventilator-enabled • More expensive
2)	Ultrasonic nebulizers	• E4asy to use • More efficient than jet nebulizers	• Large residual volume • Inability to aerosolize viscous solutions • Degradation of heat-sensitive materials
3)	Mesh nebulizers	• Fast, quiet, portable • Self-contained power source • Optimize particle size for specific drugs • More efficient than other nebulizers • Easy to use	• More expensive • Cleaning can be difficult • Medication dosage must be adjusted • Not compatible with viscous liquids or those that crystallize on drying

6.1. Jet Nebulizers [6, 8]

Jet nebulizers are widely used in paediatric and adult medical practice, for acute and domiciliary treatment of a variety of respiratory diseases. They are also known as ‘atomizers’ or ‘pneumatic nebulizers’. These nebulizers require 2 to 10 L/min of pressurized gas to draw medication up through a capillary tube from the nebulizer reservoir in order to generate a wide range of particle sizes that are blasted into one or more baffles, which take larger particles out of suspension and return them to the reservoir.

Jet nebulizers operate on the Bernoulli principle, use high velocity air flow through nozzle to draw liquid containing the drug side feed tubes into the nozzle region as a consequence of suction arising from the expansion of the jet at the nozzle orifice. The liquid immediately breaks up into aerosol droplets as it emanates from feed tubes due to the large kinetic energy of the air jet. Baffle is a standard component of a jet nebulizer which provides a surface for aerosolized droplets to impact and subsequently coalescence, thus draining back into the reservoir (fig 2).

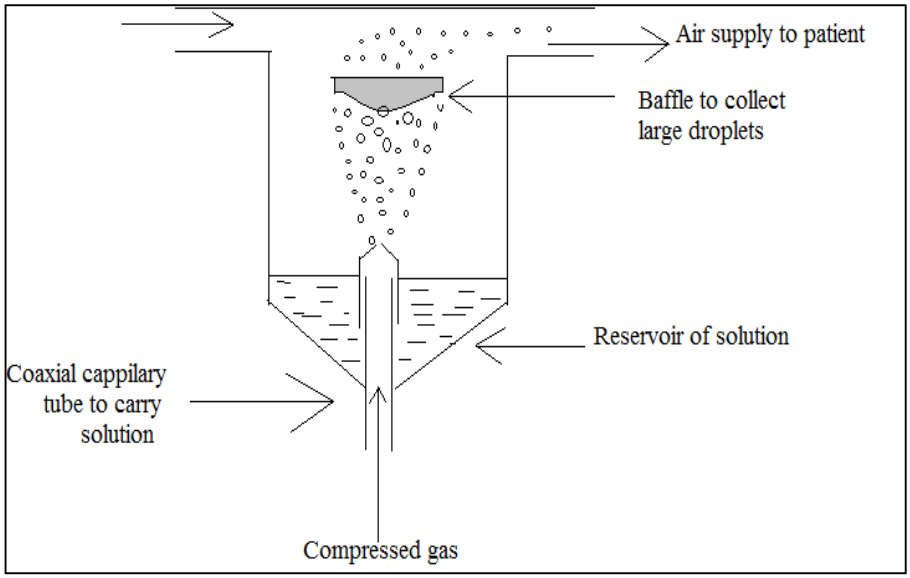

Fig 2: Schematic representation of an air jet nebulizer

Jet nebulizers are divided into four categories: (1) jet nebulizers with a corrugated tube, (2) jet nebulizers with a collection bag, (3) breath-enhanced jet nebulizers, and (4) breath-actuated jet nebulizers.

a) Jet Nebulizers with a Corrugated Tube

Jet nebulizers with a corrugated tube are conventional constant-output nebulizers that generate continuous aerosol during inspiration, expiration, and breath-hold. Although the corrugated tube attached to the jet nebulizer acts as a reservoir, there is still significant drug loss during expiration with this type of nebulizer. While jet nebulizers with a corrugated tube have several disadvantages, they are easy to use and have a good profile on patient compliance with treatment.

b) Jet Nebulizers with a Collection Bag

A jet nebulizer with a collection bag is considered a dosimetric nebulizer that releases aerosol only during inhalation. Aerosols generated during expiration are stored in the collection bag and given to the patient with the next inspiration through a one-way valve that is located between the mouthpiece and the collection bag. The Circulaire (Westmed INC, Tucson, AZ) is an example of this type of nebulizer. The Circulaire decreases the amount of drug loss.

c) Breath-Enhanced Jet Nebulizers

Breath-enhanced jet nebulizers release more aerosols during inhalation through one-way valves in the mouthpiece. They generate aerosols using a negative pressure created by a patient's inspiratory effort. PARI LC Plus, (PARI, Midlothian, VA) PARI LCD (PARI, Midlothian, VA), and Nebu Tech, (Salter Labs, Arvin, CA) are examples of breath-enhanced jet nebulizers. The efficiency of breath-enhanced nebulizers is better than jet nebulizers with corrugated tubing.

d) Breath-Actuated Jet Nebulizers

Breath-actuated jet nebulizers (BANs), like the Aero Eclipse (Monoghan/Trudell Medical International, London, Ontario, Canada), sense the patient's inspiratory flow and deliver aerosol only on nspiration. Therefore, these nebulizers decrease drug wastage during aerosol therapy but can increase treatment time. Since it generates aerosol in response to the patient's inspiratory maneuver, it has a low level of drug loss to the environment. The Aero Eclipse is easy to use and is associated with a lower occurrence of adverse events. Also, patients and respiratory therapists had greater satisfaction with the BAN in adult patient populations, compared to the jet nebulizer with a corrugated tube.

6.2. Ultrasonic Nebulizers

Ultrasonic nebulizers incorporate a piezoelectric crystal vibrating at high frequencies (1-3 MHz) in order to produce aerosol (fig. 3). Ultrasonic nebulizers have many limitations compared to jet nebulizers. For instance, they have large residual volumes, an inability to aerosolize viscous solutions, and degradation of heat-sensitive materials. Therefore, they should not be used with suspensions and proteins. An ultrasonic nebulizer converts electrical energy to high-frequency ultrasonic waves. Small-volume ultrasonic nebulizers are commercially available for delivery of inhalable bronchodilators [9].

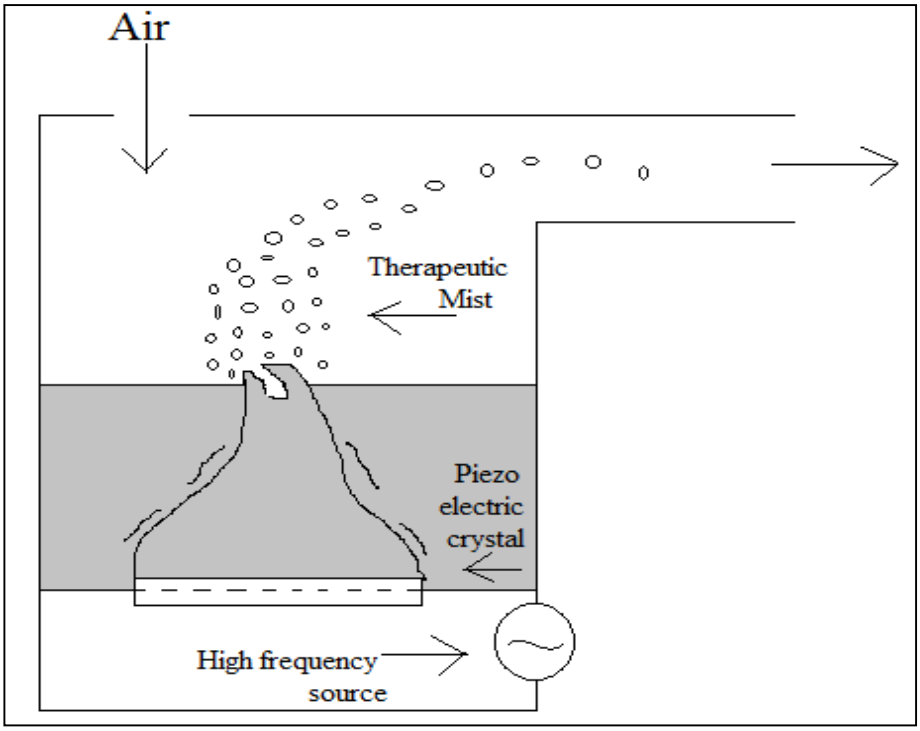

Fig 3: Ultrasonic nebulizer representing vibration of fluid with release of particles

6.3. Mesh nebulizers

The mesh nebulizer consists of a mesh or plate that has multiple apertures to produce an aerosol. These devices use a vibrating mesh or a vibrating horn. In the case of the vibrating mesh (eg, Aerogen Aeroneb, Nektar, San Carlos, California; eFlow, Pari, Richmond, Virginia), contraction and expansion of a vibrational element produces an upward and downward movement of a domed aperture plate. The aperture plate contains up to 1,000 tapered holes. The holes have a tapered shape with a larger cross-section on the liquid side and a smaller cross-section on the side the droplets emerge. The medication is placed in a reservoir above the domed aperture plate. Sound pressure is built up in the vicinity of the membrane, creating a pumping action that extrudes solution through the holes in the plate to produce an aerosol (fig. 4). The aerosol particle size and flow are determined by the exit diameter of the aperture holes. The size of the holes in the plate can be modified for specific clinical applications.

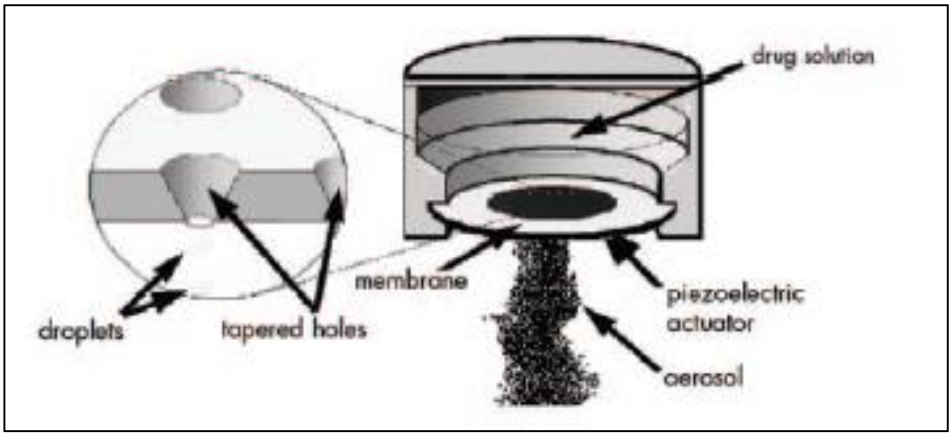

Fig 4: Schematic representation of mesh nebulizer

7. Characterization of Nebulizer [10, 12]

7.1. pH

For both inhalation solution and suspension, the pH of the Formulation should be tested and an appropriate acceptance criterion established. Thus the stability can achieve by proper selection of pH of formulation. However, the pH of formulation should be (4.5-6.5) to prevent the sneezing.

7.2. Osmolality

For formulations containing an agent to control the tonicity or for products having a label claim regarding tonicity, the osmolality of the formulation should be tested and controlled at release. Some existing marketed products have reported osmolality in the range of 300-700 mOsmol/Kg.

7.3. Impurities and Degradation Products

The levels of impurities and degradation products should be determined by a validated analytical procedure or procedures. Acceptance criteria should be set for individual and total impurities and degradation products**.** All related impurities appearing at levels of 0.1 percent or greater should be specified according to ICH guideline for impurities.

7.4. Preservatives and Stabilizing Excipients Assay

If preservatives, antioxidants, chelating agents, or other stabilizing excipients (e.g., benzalkonium chloride, phenylethyl alcohol, edetate) are used in the formulation, there should be a specific assay for these components with associated acceptance criteria. Acceptance criteria for the chemical content of preservatives at the time of product release and through the product shelf life should be included in the drug product specification.

7.5. Delivered Dose

Delivered dose testing is carried out to determine the total amount of drug that the patient might be expected to receive during a treatment period. Two discrete metrics are defined and measured: the active substance delivery rate and the total active substance delivered. Reflecting the mode of operation of nebulisers, delivered dose testing is carried out using well-defined breathing profiles for specific patient types. The defined profiles for child, infant and neonate patients are based on significantly smaller volumes, higher breathing frequencies and different inhalation/exhalation ratios.

To measure active substance delivery rate the output from the nebulizer is captured on a filter, under appropriate test conditions, over a specified time (typically 60 seconds). Longer test times are applied to provide sufficient mass (greater than the limit of quantification) for reliable analysis, where delivery rates are low. Replacing the filter and continuing the test until nebulisation stops, because the reservoir is empty, enables calculation of the second metric – total active substance delivered. This is the total mass collected during steps 1 and 2 of the test.

Mean Nebulisation Time (MNT) and Mean Delivered Dose (MDD) determined at the labelled flow rate of 5.5 L/min through such time that mist is no longer coming out of the mouthpiece.

7.6. Aerodynamic particle size distribution (APSD)

Generally speaking a particle size range of < 5 microns is taken as being optimal for pulmonary deposition. Cascade impaction is the preferred method for APSD measurement because of its ability to provide well-resolved, drug specific particle size data in the size range of interest.

Next generation impactor (NGI) instruments that operate under constant constant flow rate of 15 L/min used to determine

APSD. Cooling of the NGI prior to testing is specified to decrease the evaporation of droplet. The aerodynamic size distribution may be characterised by the fine particle dose (FPD), mass median aerodynamic diameter (MMAD) and the geometric standard deviation (GSD). The MMAD is the most important parameter defining particle size, i.e. drug deposition. Theoretically, a monodisperse aerosol will exhibit a GSD of 1.0, in practice however, a GSD of ≤1.22 is considered as monodisperse.

7.7. Droplet size distribution

The DSD of a nebuliser is a critical parameter, since it significantly influences the *in vivo* deposition of the drug in the lung. The droplet size is hereby mainly influenced by the formulation and the nebuliser device. If a laser diffraction method is used, droplet size distribution can be controlled in terms of ranges for the D10, D50, D90, span [(D90-D10)/D50], and percentage of droplets less than 10 µm.

8. Marketed formulations

Some of the marketed formulations for nebulisers are given below

Table 3: Marketed formulations of nebuliser

S. No.	Brand	Drug	Manufacturer
1	Accuneb®	Albuterol Sulfate	Dey Pharma
2	Xopenex®	Levoalbuterol HCL	Sunovion Pharma
3	DuoNeb®	Ipratropium Bromide, Albuterol Sulfate	Dey Pharma
4	Perforomist®	Formoterol Fumarate	Dey Pharma
5	SteriNeb®	Budesonide	Teva Pharmaceutical
6	Pulmozyme®	Doranase Alpha	Genentech Inc.
7	Caysten®	Aztreonam	Gilead Sci.

9. Conclusion

Nebulizers have been used clinically for many years. Despite the increasing use of metered-dose inhalers and dry powder inhalers, it is likely that nebulizers will continue to be used in selected patients. Nebulizers provide a more consistent means for delivering drug mist with a very specific diameter and at controlled flow rates. The future of nebulization technology is very promising and fascinating. Recent advances in the development of nebulizers have made drug delivery more precise, less wasteful, and potentially much easier to use during inhalation therapy. Also, new types of nebulizers have yielded a number of improvements, such as compact design, portability, shorter treatment duration, and quick operation that are expected to improve patient adherence to therapy. However, despite developments in aerosol technologies, there is still a need to reduce the costs of these new nebulizers.

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