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Nebulizer Therapy: A Platform for Pulmonary Drug Delivery

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ABSTRACT

Numerous technological advancements and developments have been carried out worldwide in the avenue of inhalation therapy. This therapy has become an indispensable part of the standard management plan for various pulmonary diseases such as asthma, chronic obstructive pulmonary disease etc. The commonly employed inhalers fall in three categories such as nebulizers, metered-dose inhaler and dry powder inhaler. Nebulization is a common method for generating medical aerosol and is utilized globally by adults and children; particularly both for emergency treatment of acute illness and for long term home treatment of pulmonary diseases. The present overview is an attempt to discuss various salient features of nebulizers along with its potential advantages and disadvantages. This manuscript also laid emphasis on various technical aspects of nebulised drug delivery systems.

Keywords: Pulmonary diseases, Drug delivery, Nebulizers, Inhalation therapy.

INTRODUCTION

Inhalation therapy has played a pivotal role in the vistas of pulmonary drug delivery since ancient times, as a way of relieving respiratory diseases. In this therapy, the active pharmaceutical ingredients are administered directly to the site of action. Several classes of drugs are available for inhalation, e.g. β_2-agonist, corticosteroids, anticholinergics drugs etc. Next to these antiasthamatic drugs, inhalation of antibiotics is frequently applied for patients with cystic fibrosis (CF) [1-4].

Drug delivery by the inhalation route is a rapidly developing and challenging aspect of pharmaceutical product development [5-7]. In general, there are three types of devices commonly employed for pulmonary drug administration such as metered dose inhalers (MDIs), dry powder inhalers (DPIs) and nebulizers [8, 9]. MDIs contain the drug in suspension, emulsion or solution form to which a propellant has been added. When the device is activated, a metered dose is released at high velocity which requires a simultaneous inhalation by the patient whereas DPIs are passively actuated, in which they utilize the respiratory intake of air by the patient to entrain and disintegrate the drug, which is in the form of dry powder particles [10, 11]. Among these, the nebulizers are preferred over the other aerosol generating devices because some patients cannot master the correct use of MDIs or DPIs, and some drugs for inhalation are only available in solution form [12-14].

Nebulization is a common method of medical aerosol generation and it is largely used by adults and children all over the world, particularly for asthma and chronic obstructive pulmonary disease (COPD) [15]. 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. As these devices aerosolize drug solution into a wet mist that floats deeply into the patient's airways as they inhale. In only a short duration, breathing the wet mist can relax patient's bronchial muscles and soothe raw air ways [16, 17]. 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 litres/minute is normally required to drive the nebulizer [18]. 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 [19].Various advantages of drug delivery directly to the airway include rapid onset of a therapeutic effect, reduced drug dose need and limitation of systemic side effects, far outweigh those of any enteral or parentral route of administration [20].

Finally successful therapy with any inhaled drug is the outcome of four events [21].
- Identification of a safe and effective active pharmaceutical ingredient.
- Assimilation of this drug into a formulation or carrier system.
- Design and manufacture of a device to administer the formulation.
- Admittance to and correct use of the device by a patient.

The objective of present manuscript is to highlight the types and development of nebulizers, their technical aspects along with various advantages and disadvantages.

Basic Components of Nebulizers

A nebulizer consists of various parts which are assembled together for its working such as medication reservoir, baffle, compressor, mouthpiece and facemask. Nebulizer solutions are dilute water based solutions of drug with excipients added to achieve several pharmaceutically desirable goals. All current nebulizer solutions are sterile and most are packaged as unit dose form-fill vials to avoid the invasion of anti-microbial agents and the need for dilution by the patient [18, 20, 22]. Given the delicate and sensitive nature of the tissue comprising the pulmonary tract, toxological effects of both the drug and excipients used are key limiting factors, not just nebulizers, but for any pulmonary drug formulation. The examples of common excipients included in nebulizer formulations are described in Table 1. Nebulizers are widely used for the inhalation of drug solution as they offer numerous significant advantages over other devices used in inhalation therapy. These are mentioned in the subsequent section of manuscript [18, 23, 24].

Advantages of Nebulizers
- 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.
- Delivery of inhaled steroids.
- Easy to administer in a very simple manner.

Nevertheless, these devices possess a number of additional drawbacks that tend to favour the use of alternate delivery devices. Drawbacks of inhalation therapy with nebulizers are summarized in this section [4, 23, 24]
- Low deposition efficiency of the drug in the target areas.
- Higher cost and size complications.
- Time consuming.
- 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.

Table 1: Commonly utilized excipients in nebulizer solutions

Excipients	Function
Sodium chloride	Isotonicity adjustment
Sodium hydroxide, hydrochloric acid sulphuric acid	pH adjustment to physiological conditions or maximize drug stability
Nitrogen	Headspace sparging to reduce oxidation
Benzalkonium chloride, EDTA, ethanol, propylene glycol	Antimicrobial preservative
Sodium citrate	Buffer component
Polysorbate 80	Surfactant
Disodium edentate	Cation chelating to enhance stability
Calcium chloride	Facilitate biological activity of DNAse

Types of Nebulizers

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

Jet Nebulizers

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' [15, 25-27]. 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. Owing to the large kinetic energy of the air jet, the liquid immediately breaks up into aerosol droplets as it emanates from feed tubes [11, 27]. 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 [28, 29]. The resultant large particles then impact upon one or more baffles, in order to generate small respirable particles. Only smaller droplets with less inertia can follow the streamlines of the air, pass the baffle [8, 30, 31]. More than 99% of the particles may be returned to the liquid reservoir. Before delivery into the patient's respiratory tract, the aerosol can be further conditioned by environmental factors such as relative humidity of the carrier gas [32-37]. Particle size of the droplets will depend not only on the kinetic energy used during nebulization, but also on the pore diameter of critical orifice and physical properties of the liquid formulation. Jet nebulizer is driven by air pressurized at 20-40 psi [1]. The schematic representation of a jet nebulizer is shown in figure 1. Jet nebulizers remain the inhalation device most commonly used in mechanical ventilated patients. They offer several advantages: large or continuous doses and drug mixtures may be aerosolized; oxygen may be used as a driving force, able to deliver aerosols over multiple breaths, low operational cost thereby, started to label it as portable device [38, 39]. Compared to all the competing inhalers and nebulizers, jet nebulizers are fairly inefficient; delivery of drug dose is dependent on the patient's inhalation profile, as with other inhalation devices. Also, the requirement for compressed air or oxygen confines jet nebulizers to home or hospital use. Moreover, drug wastage is high, being trapped in the baffles and residual nebulizer volume exhaled or deposited in the oropharynx and swallowed [11, 22, 40].

Factors Affecting the Deposition and Output of Jet Nebulizer

Various technical, patient related and physical factors have been considered which provide impact on the penetration and deposition of aerosols generated by jet nebulizers [41-49]. These factors are depicted in table 2.

Clinically important characteristics of Jet nebulizers

Clinically important characteristics of nebulizer performance is respirable dose provided for the patient, determined by mass output of nebulizer and size of the droplet that are produced. Other important characteristics of nebulizer performance include nebulization time, cost ease of use and requirement for cleaning and sterilization. A short nebulization time that delivers and effective dose is desirable. Many nebulizers are low cost, mass produced, single-patient-use devices [50-53]. For delivery of an expensive medication, a nebulizer bowl may be most desirable, even if the delivery rate in not maximal. Commercially available jet nebulizers, all with the same initial fill, and all driven by the same air compressor, varied greatly in total delivery of fluid, the time required to deliver this fluid, and percent of the delivered fluid in the respirable range. [54-57].

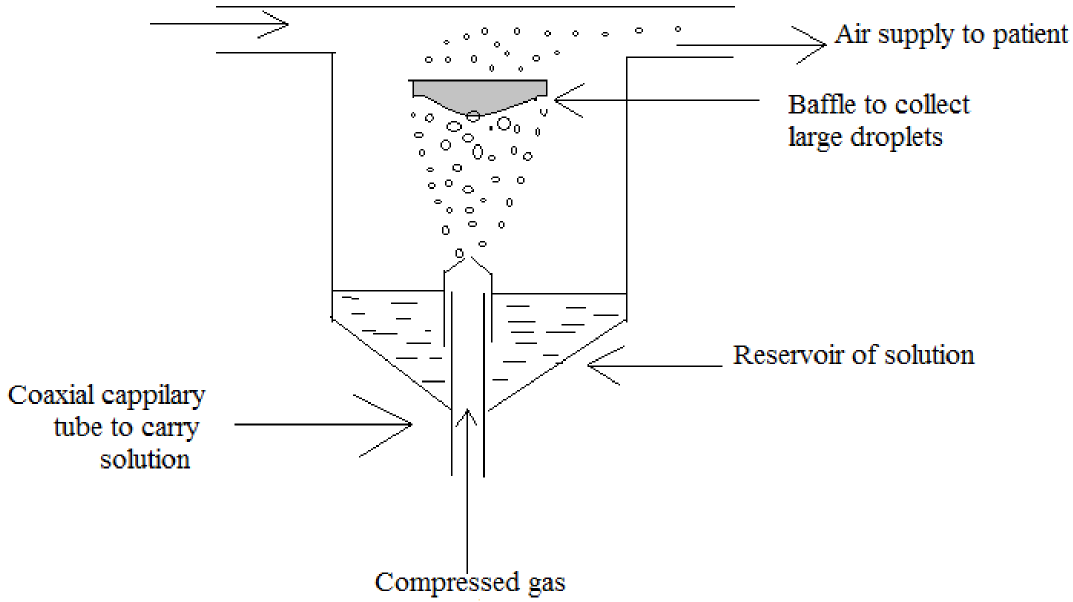

Figure 1: Schematic representation of an air jet nebulizer

Table 2: Factors affecting the performance of nebulizers

Technical factors	Patient factors	Physical factors
• Manufacturer of nebulizer • Flow utilized to power nebulizer • Fill volume of nebulizer • Solution characteristics • Composition of the driving gas • Designs to enhance nebulizer output • Continuous versus breath actuated • Performance difference of nebulizers	• Breathing pattern • Airway obstruction • Positive pressure delivery • Artificial airway and mechanical ventilation • Cleaning and disinfection to prevent contamination of nebulizer	• Droplet size distribution - Gas flow rate - diameter of the nozzle - Physical properties of the drug solution such as viscosity, surface tension • Drug output rate - Driving gas flow - Volume fill - Static charge - Solution temperature - Residual volume of drug - Solution viscosity and surface tension - Concentration of nebulizer solution - Nebulization time

Ultrasonic Nebulizers

Ultrasonic nebulizers work by applying an alternating electric field to a piezoelectric transducer, which converts the electrical signal into a periodic mechanical vibration, in contact with the liquid to be nebulized [15]. Ultrasonic vibrations from the crystal are transmitted to the surface of drug solution where standing waves are formed. Droplets break free from the crests of these waves and are released as aerosol. The size of droplets produced is inversely proportional to two thirds of the power of acoustic frequency. Like jet nebulizers, baffles within this nebulizer remove large droplets and much of the aerosol produced impacts on these, falling back into the drug reservoir [58]. An ultrasonic nebulizer has three components: the power unit, the transducer and a fan. The power unit converts electrical energy to high-frequency ultrasonic waves at a frequency of 1.3-2.3 megahertz. The power unit also controls the amplitude of the ultrasonic waves. The transducer vibrates at the frequency of the ultrasonic waves applied to it (piezoelectric effect). The conversion of ultrasonic energy to mechanical energy by the transducer produces heat, which is absorbed by the solution over the transducer. A fan is used to deliver the aerosol produced by ultrasonic nebulizer to the patient, or the aerosol is evacuated from the nebulization chamber by inspiratory flow of the patient. Small-volume ultrasonic nebulizers are commercially available for delivery of inhaled bronchodilators and large-volume ultrasonic nebulizers are used to deliver inhaled antibiotics in patients with CF (e.g. tobramycin) [59-69]. The need for cleaning, inhalation of doses over multiple breaths, and variability in aerosol generation performance is common to ultrasonic and jet nebulizers [21]. The working mechanism of an ultrasonic nebulizer is shown in figure 2.

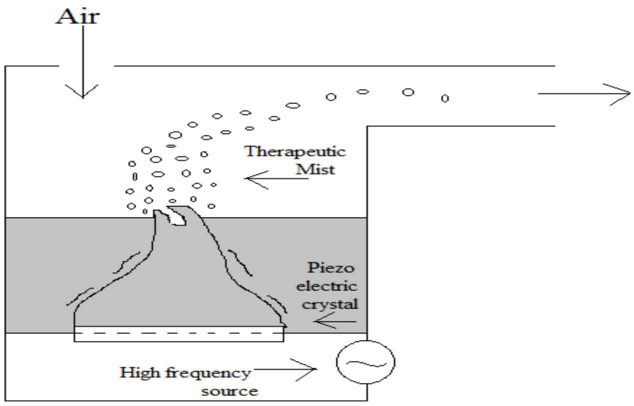

Figure 2: Ultrasonic nebulizer representing vibration of fluid with release of particles

Depending on the method used to produce aerosol droplets, ultrasonic class of nebulizers can be sub-classified into:
Passive vibrating devices: Passive vibrating mesh ultrasonic devices are small battery-operated nebulizers which utilize a piezoelectric crystal in an ultrasonic horn to force drug solutions through a mesh of hundreds (or thousands) of micron-sized holes for creating an aerosol [70].

Active vibrating devices: Active vibrating mesh ultrasonic nebulizers ensure the mesh in contact with the reservoir fluid is vibrated directly by a piezoelectric crystal to generate the aerosol cloud. These devices use a perforate membrane and a micro-pumping action to draw jets of fluid through the holes in the membrane, dispersing the jets into a drug cloud. The size of aerosol droplets is controlled by the shape/size of the holes and the surface chemistry and composition of the drug solution [71]. Ultrasonic nebulizer possesses a number of advantages and disadvantages which are described in the subsequent section [1, 21].

Advantages
- Little patient management required.
- Aerosol accumulates during exhalation.
- Small dead volume.
- High dose output and fast drug delivery.
- No propellants requirement.
- Operate for several days on a single recharge.
- Silent during operation.
- Compact.

Disadvantages
- Large particle size and less efficient.
- Microbial contamination risk.
- Poor portability and expensive.
- Prerequisite of electric power supplier.
- Drug preparation required.
- Prone to electrical and mechanical breakdown.

Various technical and physical factors which affect the performance of ultrasonic nebulizer includes fluid characteristics such as density, viscosity, surface tension, vapour pressure. Other factors which affect the performance are residual volume, flow from fan, solution characteristics, coupling of medication chamber to transducer, piezoelectric transducer etc [62, 72].

CONCLUSION

Phenomenal diversity in the newer technologies and products utilized for inhalation therapy has been observed globally. 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. This technology also offers tremendous possibilities for the development of miniature inhalation therapy devices with the ability to tune the administered dose as per patient specific requirements. Nevertheless, there remain a considerable challenge that need to be addressed before such personalized delivery system can be realized. This manuscript is valuable to provide clinicians and patients with accessible information on the scientific basis of nebulizer treatment and factors to be considered while using as well as choosing the particular equipment. The prospect of these devices is very evident in many of the versatile nebulizers that have yet to be commercialized.

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