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Original Article

RECENT ADVANCES IN NEBULISER TECHNOLOGY, A REVIEW

Pawan Jalwal*[1], Anju Jangra[1], Lalita Dahiya[1], Kusum Tomar[1], Rajiv Saroha[2], Yashpal Sangwan[2]

Affiliated to:
[1]Faculty of Pharmaceutical Sciences, Shri baba Mastnath Institute of Pharmaceutical Sciences & Research, Asthal Bohr, Rohtak
[2]P.D.M. College of Pharmacy, Safidon, Deptt. of Pharmacy, Kurushestra University, Kurushestra

ABSTRACT

A 'nebuliser' is actually the small plastic container that is filled with a medicine solution. A compressor (usually electric) is used to blow air or oxygen through this solution to make a fine mist of medicine. This mist is breathed into the lungs through a mouthpiece or mask. A nebuliser is a device that converts a liquid into aerosol droplets and must be loaded with the medication before each treatment.

Keywords: Nebulizer, Aerosol, Reliever Drug, Controller Drug

*Corresponding author:
Email: pawan_jalwal@rediffmail.com

1.0 INTRODUCTION

The lungs/ airways represent a unique organ system in the human body, their structure allowing air to come into contact with blood, this being one of the principle adaptations permitting existence of terrestrial life. This adaptation also makers airways a useful route of drugs administration in inhaled or aerosol form. Numerous techniques have been developed to aerosolize liquids, re-suspend particles, or to generate aerosol particles. Inhalation drug delivery has been used for many years for the delivery of pharmacologically active agents to treat respiratory tract diseases. Inhalation route is used because of its inherent advantages of low dose requirement, instant effectiveness and its non-invasiveness. Inhalation is gaining increasing acceptance as a convenient, reproducible and non-invasive method of drug delivery to the lung tissue and the systemic circulation. In fact inhalation of aerosolized drugs has become a well-established means of treating localized disease states within the lung including asthma. Pulmonary delivery of drug also avoids first pass effect and is generally more acceptable by patients than an injection. There are three methods of targeted drug delivery systems are used to lungs, i.e., dry powder inhalers, metered dose inhalers and the most recent drug delivery system that is nebulizers.

A 'nebuliser' is actually the small plastic container that is filled with a medicine solution. A compressor (usually electric) is used to blow air or oxygen through this solution to make a fine mist of medicine. This mist is breathed into the lungs through a mouthpiece or mask. A nebuliser is a device that converts a liquid into aerosol droplets and must be loaded with the medication before each treatment. There are three types of nebulisers: **jet nebulizers**, which can nebulise all drugs and can be disposable; **ultrasonic nebulizers**, which are silent but can only nebulise aqueous solutions and may heat the drug; and **mesh nebulizers**, which can be used to nebulise aqueous solutions, but can be less efficient in nebulising suspensions. The latter are silent, portable and small. They can reduce the nebulisation time without reducing drug efficiency, but disinfecting and cleaning can be difficult.

1.1 Three parts of Nebulisers

1. Face mask or mouthpiece.
2. Nebulisers chamber – This a part which actually changes the liquid solution of the drug into a mist.
3. Power source – A compressor that supplies the nebulizer with the gas to change the solution into a mist.

1.2 Advantages of Nebulisers

- Some drugs for inhalation are available only in solution form.
- Some patients cannot master the correct use of metered-dose inhalers or dry powder inhalers.
- Some patients prefer the nebuliser over the other aerosol generating devices.
- There are two types of medical nebulisers: the **Jet nebuliser**, which is powered by compressed air and the **Ultrasonic nebuliser** which derives the energy required to aerosolize drugs from high-frequency sound waves.
- Co-ordination is unimportant so they can be used by patients of all ages, including young babies;
- Nebulised therapy is effective in severe asthma, so is often used to treat acute exacerbations.
- No cooperation required from the child.
- Even very young and very sick children can be nebulised with a face- mask.
- Almost immediate effect of reliever medication by direct delivery to the lungs.

Disadvantages of nebulisers

- That they are cumbersome, expensive (both the machine and the drugs),
- Treatment takes a long time - often around ten minutes.
- Noisy and scary for a small child.
- Expensive, compared to a spacer and metered dose inhaler.
- Bulky, difficult to carry about.
- Needs electricity, though manually operated ones are available sometimes.
- Needs several minutes for a single dose.
- May harbour infection, especially if one machine is used for many patients.

2.0 Types of nebulisers

- **Jet nebulisers**
- Ultrasonic nebulisers
- Mesh nebulisers

2.1 Jet nebulisers

Principle: Jet nebulisers are driven either by a portable compressor or from a central air supply. Essentially, a high-speed airflow through a narrow nozzle orifice entrains and disperses the liquid into droplets (primary generation) via a viscosity-induced instability [(1)]. Droplet dispersion is improved by impaction on a baffle structure adjacent to the nozzle orifice transferring kinetic energy further into increased droplet surface area (secondary generation).

The resulting droplet size distribution still contains only a small fraction of respirable aerosol (droplets below 5µm to 6µm in size) and

the large droplets are recirculated with in the nebuliser by means of secondary impaction structures. This process is associated with evaporation effects that cause the gas phase to be nearly saturated with vapour, as well as a temperature decrease within the nebuliser. A considerable part of the vapour arises from the larger recirculating droplets, thus increasing drug concentration in the remaining liquid. Therefore, assessment of nebuliser systems cannot be conducted with a simple gravimetric measurement alone, but also requires chemical assays. It requires a pressurized gas supply as the driving force for liquid atomization. Compressed gas is delivered through a jet, causing a region of negative pressure. The solution to be aerosolized is entrained into the gas stream and is sheared into a liquid film [(2)].

For nebulisation of suspensions, preferential containment of suspension particles in larger droplets can occur if the suspended particles are of similar size as the nebulised droplets,[(3)] so that chemical assay may be necessary for proper particle sizing of some nebulised suspensions. For liposomal formulations, disruption of liposomes can occur due to mechanical stresses during nebulisation, possibly during primary generation [(4)] and/or secondary generation, although such disruption is device-specific and is most pronounced for large liposomes [(5)].

With jet nebulisers, all commercially available inhalation solutions and suspensions can be administered. Mechanical damage, which may cause denaturation of sensitive drug compounds (i.e. proteins and peptides), is minimized. Further advantages of nebulisers are their ability to deliver high doses of drug to the lungs and the minimal co-ordination and effort required for inhalation in comparison to pMDIs or DPIs. Nebulisers fill a niche in the treatment of young children and the elderly, especially in exacerbations and emergency situations.

2.2 Ultrasonic nebulisers [(6)]

Ultrasonic nebulisers use the vibration (1.2–2.4 MHz) of a piezo-electric crystal to generate the aerosol. Vibrations are transmitted to a liquid drug, generating a liquid-drug fountain comprising large and small droplets. Large droplets drop into the liquid-drug reservoir or are thrown onto the side of the nebuliser and recycled. Small droplets are stored in the nebulisation chamber to be inhaled by the patient or leave the nebuliser with the airflow produced by a ventilator. Like the jet nebuliser, some residual mass is trapped in the nebuliser, but there is little leakage since there is no gas source to transport the aerosol out of the nebuliser during exhalation. There are two types of ultrasonic nebulisers.

- Standard nebulisers are those where the drug is directly in contact with the piezo-electric transducer. This contact causes the drug temperature to increase due to heating of the transducer. In addition the piezo-electric transducer is difficult to disinfect.

- Ultrasonic nebulisers with a water interface use a volume of water between the piezo-electric transducer and a separate reservoir for the drug. Water reduces drug heating and the drug is not in contact with the transducer. Ultrasonic nebulisers do not nebulise suspensions or liquids with high viscosity or a high surface tension, the residual mass is often >50% of the drug mass loaded in the nebuliser and the aerosol is heated. Ultrasonic nebulisers are silent, but often bulky.

2.3 Mesh Nebulisers

New nebulisers based on mesh technology have recently been introduced into the market. They can operate with batteries and are small enough to be carried. They are efficient, silent and comply with active drug compounds. Mesh nebulisers can be classified into two types: **static mesh and vibrating mesh nebulisers**.

2.3.1. Static mesh nebulisers

Static mesh nebulisers apply a force on the liquid drug to push it through a static mesh. The first mesh nebuliser had a limited introduction in the 1980s by Omron Healthcare (Bannockburn, IL, USA). The Micro air® NE-U22V nebuliser uses an ultrasonic transducer to generate vibration (180 kHz) of the liquid drug and push the droplets through the static mesh [(7)], which can then be inhaled directly by the patient. Unlike jet and ultrasonic nebulisers, the aerosol is not recycled in the mesh nebuliser.

Droplets generated through the mesh have a ~3 m, which are produced by electroplating. The Micro air® NE-U22V can nebulise aqueous solutions and suspensions [(8)]. The residual volume in the nebuliser reservoir is ~0.3 mL. The mesh cannot be disinfected by an autoclave process, and, instead, should be submerged in a 0.1% solution of benzalkonium for 10–15 min. Other cleaning agents such as bleach must not be used due to a risk of corrosion. The Omron mesh must be cleaned by generating a distilled water aerosol. It can be loaded with a maximum volume of 7 mL.

2.3.2. Vibrating mesh nebulisers

Vibrating mesh nebulisers use mesh deformation or vibration to push the liquid drug through the mesh. An annular piezo element, which is in

contact with the mesh, is used to produce vibration around the mesh, and the liquid drug is in direct contact with the mesh. Holes in the mesh have a conical structure, with the largest cross-section of the cone in contact with the liquid drug [9]. The mesh deforms into the liquid side, thus pumping and loading the holes with liquid. This deformation on the other side of the liquid-drug reservoir ejects droplets through the holes, which can be inhaled by the patient. The Aeroneb® Go is a vibrating mesh nebuliser (Nektar Therapeutics, San Carlos, CA, USA), which utilizes a horizontal mesh containing 1,000 holes obtained by electrolysis, and vibrates at 100 kHz. It consists of a nebuliser and a separate battery pack or AC power adapter. There is a reservoir above the mesh, and the aerosol is produced towards the bottom of the nebuliser. Droplets ejected from holes at a moderate velocity are selected by impaction on the nebuliser base. Residual drug mass is negligible in the reservoir, but can be appreciable in the nebuliser. The aerosol leaves the nebuliser in standing cloud at low velocity.

3.0 Basically two types of drugs can be nebulized:

- **Reliever drugs**
- **Controller drugs**

3.1 Reliever drugs

Reliever drugs are those drugs that relieve the symptoms of asthma. They are the drugs used when a child has an acute attack of asthma, with wheezing, severe cough, inability to participate in physical activity, and difficulty in breathing. Over the past few years, better and better drugs have become available, along with devices to deliver the drugs directly to the lungs. This has made reliever therapy very effective and safe. For example, Salbutamol and terbutaline are airway dilators that are commonly used and give quick relief. Ipratropium is another drug that can be mixed with one of the dilator drugs to give additional effect in relieving airway obstruction of asthma.

3.2 Short acting beta agonists

These are the mainstay of the acute asthma therapy today. Two drugs are available in India - **salbutamol and terbutaline**. The two drugs are fairly similar; they have quick onset of action, and the action lasts 4-6 hours. They are available as oral forms (syrups, tablets, capsules, and slow release forms), injections, and inhaled forms (metered dose inhalers, dry powder inhalers, and solutions for nebulisation). The best therapeutic effect is seen with the inhaled forms. The drug is used in very low doses, it goes straight to the lungs, and the rest of the body has minimal

exposure to the drug. Quick, potent action, and low incidence of side effects. Oral forms are also much used, though these drugs have unreliable absorption and action. The incidences of side effects like a fats heart rate, tremor, and vomiting is also much greater. The slow release forms offer the advantage of prolonged duration of action, but must be swallowed whole, a task possible only for older children.

3.3 Anticholinergics

These drugs act by inhibition of the cholinergic nerves, and so reverse some airway narrowing. Not effective enough to be used alone, but useful when added to inhaled short acting beta agonists for the management of acute, severe asthma. The only drug of this class in use today is **Ipratropium bromide**, which is available as metered dose inhalers and as a solution for use with nebulisers.

3.4 Controller drugs:

These are the drugs that control a child's asthma. Children with mild, intermittent asthma do not need any controller therapy; all children with more severe forms of asthma should be on controller therapy. This therapy is aimed at keeping the asthma under control, thus protecting the lungs from irreversible damage and allowing the child a normal life. For example, budesonide has recently become available in India for nebulisation. It has no role in the treatment of an acute attack, and nebulisers are too tedious for the long- term daily therapy of asthma.

3.5 Sodium cromoglycate

This drug is believed to reduce the inflammation in the airways and so reduce the acute attacks of asthma. It is the safest of all anti asthma drugs. It is often taken by children for years, and side effects are rare. The onset of action takes some weeks, and many patients do not benefit at all. Cromoglycate is the drug of choice for initiating treatment in mild asthma. It is also useful as pretreatment in children who suffer from exercise-induced asthma. A puff of this drug, taken before participating in games, will protect the child. Problems with the drug include dosing four times a day, and cost significantly higher than corticosteroids.

3.6 Inhaled steroids

The steroids used for inhalation have some properties in common - they act on the surface of the airways, and the liver rapidly inactivates them. This latter property prevents side effects. The three drugs available in India are **beclomethasone, budesonide, and fluticasone**. The most recent used inhaled steroid is ciclesonide in the form of metered-dose inhalers and dry powder inhalers. These drugs are reliably effective in asthma. They reduce airway

inflammation and bronchial hyper responsiveness, and prevent the deterioration in lung function that is an accompaniment of asthma. Used regularly, they can allow the child to have a normal life. At low doses, and used with precautions to reduce side effects, they have been found to be very safe at low doses. At high doses, too, they are far safer than the doses of oral steroids that would be required to maintain equivalent control of asthma.

Advantages of this class drugs is that they need to be taken only twice a day. They are less expensive than cromoglycate, and more effective Side effects include fungal infection of the mouth, hoarseness, and cough. At high doses, they may also cause growth reduction, and suppression of the pituitary and adrenal glands, though these effects are controversial. They may sometimes cause cataracts, and thinning of the bones.

Table : In-vitro characterization of nebulizers

Factors	Tests
The important tests being conducted for the pharmaceutical development studies of nebulisers	Minimum fill justification. Extractables / Leachables. Individual stage particle size distribution. Droplet size distribution and drug output (excluding metered dose nebulisers). Shaking requirements. Compatibility (excluding metered dose nebulisers). Preservative efficacy (excluding single dose nebulisers). Physical characterization. Device development.
Including these tests, some tests are conducted for metered dose nebulisers only.	Dose uniformity and fine particle mass through container life. Single dose fine particle mass. Actuator deposition. Initial and re-priming requirements. Cleaning requirements. Performance after temperature cycling. Robustness
Various tests included in the drug product specification for nebulisers products.	Description. Assay. Delivered dose uniformity (excluding single dose nebulisation). Fine particle mass. Weight. Microbial limits (excluding single dose nebulisation). Leachables. Preservative content. Number of actuations per container (for metered dose nebulisation).
On the basis of physicochemical properties of the drug product, the tests for nebulisers solution are	Description. Osmolality (or osmolarity). Surface tension. Viscosity & pH Buffering capacity & Specific gravity.

4.0 Minimum fill justification

A study should be conducted to demonstrate that the individual container minimum fill, as defined by the drug product manufacturing process, is sufficient to provide the labeled number of actuations. The final doses should meet the drug product specification limits for delivered dose uniformity and fine particle mass.

4.1 Extractable / Leachables

Detail and justification of the study design (solvent used, temperature, and storage time) and the result should be provided. Identification of the compounds should be attempted and safety assessment should be conducted. A study should be conducted to determine the extractables profile from the container closure components that are in contact with the formulation during storage and / or use.

4.2 Individual stage particle size distribution

Using a multistage impactor or impinger, the drug mass on each stage and the cumulative mass undersize a given stage should be determined rather than the percentage of emitted dose as these can hide variations in delivered dose. A plot of cumulative percentage less than a stated cut-off diameter versus cut-off diameter should usually be provided. From this, the Mass Median Aerodynamic Diameter (MMAD) and Geometric Standard Deviation (GSD) may be determined, if appropriate (in the case of log-normal distribution).

4.3 Shaking requirements

For products requiring shaking before use, a study should be conducted to demonstrate that the shaking instructions provided to the consumer are adequate. The possibility of excessive shaking leading to foaming and inaccurate dosing should be examined by testing the delivered dose uniformity.

4.4 Compatibility

Compatibility should be demonstrated with all diluents over the range of dilution proposed in the labeling and with respect to the principal drug as well as the co-administrated drug. Parameter such as precipitation, pH, and droplet size distribution, output rate and total drug output should be tested, and differences from the original product should be assessed for their significance.

4.5 Preservative efficacy

For products containing a preservative, a study should be conducted to demonstrate the effectiveness of the preservative at the lower specification limit for the preservative concentration.

4.6 Physical characterization

Physical characterization such as solubility, size, shape, density, rugosity, charge, and crystallinity of the drug substances and / or excipients may influence the homogeneity and reproducibility of the finished product. Development studies should include physical characterization of drug substance and excipients, relevant to their effect on the functionality of the product.

4.7 Device development

The development of the device should be described. Any changes implemented in the design (e.g. change of component materials) and /or manufacturing process of the device (e.g. scale up from single cavity to multiple cavity tooling) during the development of the product should be discussed in terms of the impact on the product performance characteristics (e.g. delivered dose, fine particle mass, etc.).

4.8 Delivered dose uniformity and fine particle mass through container life

A study should be conducted to demonstrate the consistency of the minimum delivered dose and the fine particle mass through the life of the container from the first (post-priming) dose until the last labeled dose. At least ten doses from the combination of the beginning, middle, and end of the container should be tested. A sufficient number of containers of containers should be tested in order to evaluate intra-batch variability. The dose obtained should meet the drug product specification limits for delivered dose uniformity and fine particle mass.

The doses between the last labeled dose and the last container exhaustion dose should also be tested for delivered dose uniformity and fine particle mass, and information on the tail-off profile should be provided. At least three containers from two different batches should be investigated.

4.9 Delivered dose uniformity and fine particle mass over patient flow rate range

A study should be conducted to demonstrate the consistency of the minimum delivered dose and the fine particle mass over the range of flow rates achievable by the intended patient population at constant volume. For each flow rate (minimally the minimum, median, and maximum achievable rate), the results obtained should be compared against the drug product specification limits for delivered dose uniformity and fine particle mass.

4.10 Actuator deposition

The amount of drug deposited on the actuator should be determined and, where applicable, demonstrated to be consistent with any correction factor used to support ex-valve label claims.

4.11 Initial priming of the container

A study should be conducted to determine the number of actuations that should be fired to waste (priming actuations) prior to the consumer using the product for the first time. The number of priming actuations required until the subsequent doses meet the drug product specification limits for delivered dose uniformity should be determined.

4.12 Re-priming of the container

A study should be conducted to determine the length of time that the product may be stored without use (after initial priming) before re-priming, as well as the number of re-priming actuations required.

4.13 Cleaning requirements

The study should be conducted under conditions of normal patient usage, in accordance with recommendations for priming, dosing intervals, and typical dosing regimen. Since most products demonstrate acceptable performance with a weekly cleaning regimen, any requirement for more frequent cleaning may adversely affect patient compliance and should therefore be fully warranted and justified.

4.14 Performance after temperature cycling

Containers should be stored in various orientations and cycled between recommended storage conditions and a temperature below freezing (0ºC). For suspension products cycling between the recommended storage conditions and a high temperature should be considered. Storage time should be at least 24 hours under each condition, and containers should be stored under each condition at least five times.

4.15 Robustness

The product performance should be investigated under conditions to simulate use by patients. This includes activating the device at the frequency indicated in the instructions for use. Carrying the inhaler between use and simulation of dropping the device, etc. should be considered.

4.16 Description

A description of both the formulation and the full device should be given where applicable.

4.17 Assay

The amount of drug substance in one actuation should also be determined by calculating the mean of the content uniformity or delivered dose uniformity test results, with corrections as necessary to convert from “per dose” amounts to

"per actuation" amounts. Limit of ± 15% of the label claim apply.

4.18 Delivered dose uniformity and fine particle mass over patient flow rate range

A study should be conducted to demonstrate the consistency of the minimum delivered dose and the fine particle mass over the range of flow rates achievable by the intended patient population at constant volume. For each flow rate (minimally the minimum, median, and maximum achievable rate), the results obtained should be compared against the drug product specification limits for delivered dose uniformity and fine particle mass.

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