Nebulizers: Past to present platforms and future possibilities

Brief insights into nebulizer history and technologies in use or in development, including conventional and novel approaches

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A brief history of nebulizers

The use of inhalation therapy for medicinal purposes was first noted in Ayurvedic medicine in India about 2,000 BC, thereby being more than 4,000 years old. At that time, a paste of Datura species and herbs were smoked through a pipe to relive lung disorders.[1] Over the following years, there are a number of examples using smoke and/or vapors to treat various respiratory disorders. [2-5]

The concept of breaking up liquid into airborne droplets was first mentioned in the mid-1800s when atomizers were developed, initially in France by Dr. Auphon Euget-Les Bain in 1849.[6] This was probably a further development of the concept of splashing water onto walls that was used by Auphan in the early 1800s.[4]At that time and during most of the 19th century, the words “atomizer” and “nebulizer” were used simultaneously to describe nebulizers.

Almost ten years later, in 1858, Jean Sales-Girons presented a portable nebulizer that could be operated manually by using a pump to feed liquid to a nozzle, where it was ejected onto a plate and disintegrated into an aerosol (Figure 1).[7]. In the years to come, improvements were made and the first mention of a nebulizer based on the Venturi principle of 1738 was made by Bergson in 1862 in his “Hydrokonium” device.[8] The device was later enhanced by the introduction of a baffle system. One of the first examples was described by Evans in 1891.[9] Additional descriptions of nebulizers with baffles have been described in the literature by authors such as Waldenburg (1862), Solis-Cohen (1867) and Moeller (1882).[4, 10, 11]

The use of the Venturi principle was, from there on, the predominant design pathway for jet nebulizers. Major milestones in development were introduction of the Wright nebulizer and the DeVilbiss no. 40 nebulizer. The DeVilbiss nebulizer was often operated by squeezing a rubber bulb. However, the introduction of electricity in the early 1900s made it possible to connect a nebulizer to a compressor, which made use easier for the patient. An example of a compressor nebulizer is the Pneumostat, which was manufactured in Germany in the early 1930s (Figure 2).[7]

Figure 1

Sales-Girons portable device (Image from The Inhalatorium)[7]

Current conventional technologies

When we refer to nebulizers, we often think of the stationary, table-top devices that are used in hospitals and domestic settings. While there are many nebulizer types, in this author’s view, they can be divided into two general categories: jet nebulizers and ultrasonic nebulizers.

A jet nebulizer typically consists of a compressor and a plastic nebulizer unit. Occasionally, these are combined into an integrated unit to make them more portable. In a jet nebulizer, the aerosol is generated by compressed air.

In ultrasonic nebulizers, the aerosol is generated by vibration of a piezoelectric unit in an aqueous media (i.e., formulation). Ultrasonic nebulizers first appeared in the United States in 1949. Initially, they were used as

Figure 2

Pneumostat with electrical compressor (Image from The Inhalatorium)[7]

humidifiers but doctors rapidly recognized their potential and began adding medications to them, thereby producing therapeutic aerosols.

Both conventional and miniaturized nebulizers vary in critical characteristics such as airflow rate, fill volumes and droplet size distribution.[12] The variability is a direct consequence of differences in physical design and the interaction between device and formulation.[13] For instance, in some cases, mesh nebulizers may show clogging over time, which could affect the consistency of their performance and therefore increase variability.[14] In general, conventional nebulization technologies are capable of delivering high doses of a drug since they can typically be filled with 2 ml up to more than 5 ml of aqueous formulation.[14]

Types of jet nebulizers

Conventional jet nebulizers

Conventional jet nebulizers, or pneumatic nebulizers, are operated by a supply of pressurized gas that acts as a driving force for the atomization of the liquid in the nebulizer cup (Figure 3). The pressurized gas is fed through a tube to an orifice (nozzle) where the compressed air rapidly expands and increases in velocity, causing a local negative pressure. The negative pressure is used to suck liquid into a tube, to the point of air expansion, where it is sheared into a liquid film. The film stretches and becomes unstable, thereby breaking up and forming droplets due to surface tension forces.[15, 16] The droplets are conveyed towards a baffle situated just above the aerosol production area. The baffle "sieves off" the larger droplets by impaction and returns the liquid from the droplets back into the reservoir while the smaller droplets are transported to the nebulizer outlet (and the patient). More than 99% of the aerosol produced is returned to the reservoir; only about 1% reaches the nebulizer outlet.[17, 18] The nebulizer nozzles have two designs; one where the air and liquid are internally mixed then ejected through a secondary orifice and the other that uses an external mixing design where the secondary nozzle is omitted (Figure 4). Both types are frequently seen in various nebulizer brands.

Figure 3

Jet nebulizer operating principle

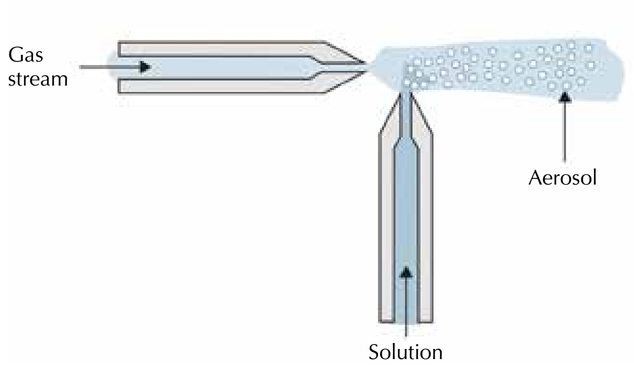
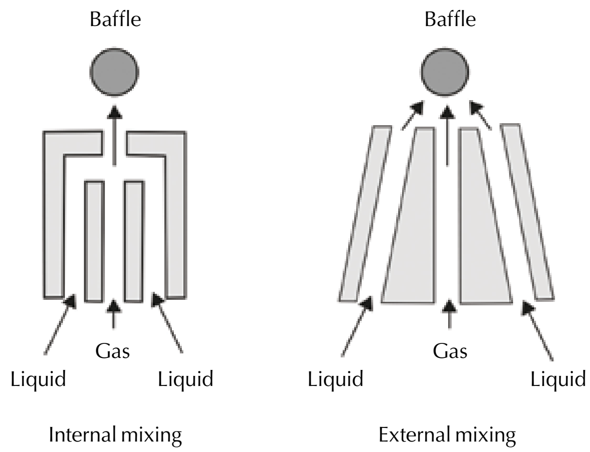


Figure 4

Typical nebulizer designs



Breath-enhanced jet nebulizers

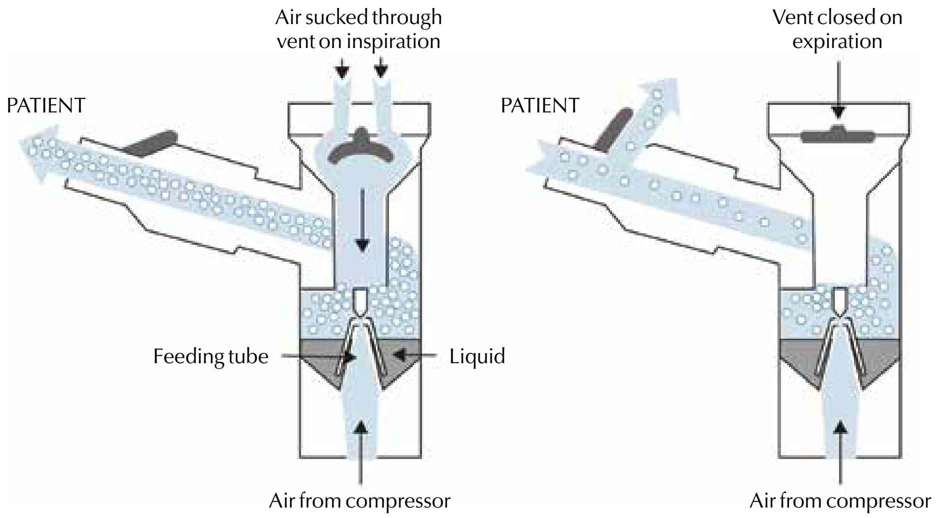
Although conventional jet nebulizer technologies have reached maturity, they are still being continuously honed. Over the last several years, jet nebulizers have been improved by the introduction of breath-enhanced delivery. In these devices, the nebulizer operates as a conventional jet nebulizer during exhalation, but increased output is achieved when the nebulizer is used during inhalation (Figure 5). Using these nebulizers, both drug delivery per unit time and total drug delivery are increased and treatment time is shortened.[19]

Breath-actuated jet nebulizers

Further improvements to nebulizers have been made by the introduction of breath-actuated nebulizers. They have the same working principle as breath-enhanced nebulizers yet they deliver aerosol only when a patient

Figure 5

Breath-enhanced nebulizer



inhales but not when a patient exhales (Figure 6). They are intended to enable more efficient use of the liquid to be aerosolized and can shorten overall treatment time.

There is an additional difference between breath-actuated and breath-enhanced technologies that is recognized[20] and should be noted. If a nebulizer of each type were loaded with the same dose and volume of medication and a patient were to use the breath-actuated nebulizer to the point of dryness, they would likely receive a larger dose of medication than with the breath-enhanced nebulizer run to dryness (because a breath-enhanced nebulizer delivers medication during the exhalation phase when a patient is not inhaling). In some circumstances, with a breath-actuated nebulizer, this may result in both longer nebulization times and overdosing. However, this difference in the two technologies can be managed by prescribing physicians and clinicians and explained to patients and caregivers before usage of a breath-actuated nebulizer.

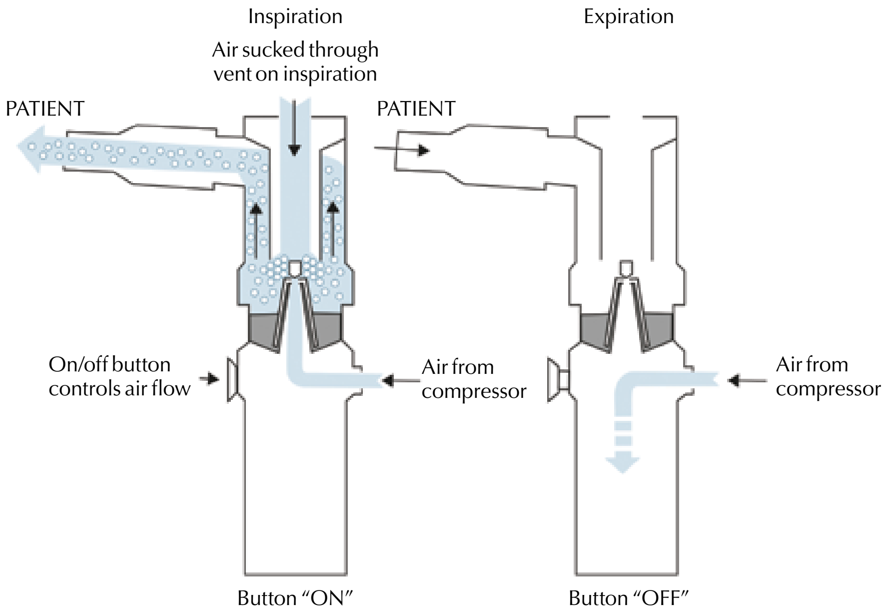
Categories of ultrasonic nebulizers

Conventional ultrasonic nebulizers

Ultrasonic devices, on the other hand, typically comprise a piezo member mounted in a chamber that is liquid-filled (often with water) where a medicinal cup filled with the formulation to be nebulized is immersed (Figure 7). The water is used a coupling media to transfer the ultrasonic vibration of the piezo member to the medicinal cup and thereby induce aerosolization by a capillary wave, causing cavitation of the liquid at the liquid/air interface.[21] The droplet size distribution is affected by factors such as the energy input/frequency, viscosity and surface tension.[22]

Figure 6

Breath-actuated nebulizer



Enhanced ultrasonic nebulizers

Over the last two decades, conventional ultrasonic nebulizers have also been refined. Incorporation of mesh technology, in particular, has made these devices smaller and more convenient to use. This, together with the introduction of ultrasonic horn technology, has enabled ultrasonic nebulizer manufacturers to miniaturize concepts and designs (Figure 8). Liquid is fed in between the mesh and the horn, either by gravity or by capillary forces, and the horn is made to vibrate in the kilohertz frequency range thereby expelling liquid through the holes in the mesh.[21, 22] Recently, sonic acoustic wave (SAW) technology (Figure 9) has been introduced for smaller and enhanced ultrasonic nebulizers.[23] This technology is more energy efficient than conventional ultrasonic nebulizers and can be seen as a complement to horn technology. A number of companies are developing or have developed products using these technologies, which are available today in a number of designs worldwide. Like conventional nebulizers, enhanced nebulizers such as mesh types (vibrating plate) are affected by viscosity and surface tension of the liquid to be nebulized.[23]

Figure 7

Ultrasonic nebulizer

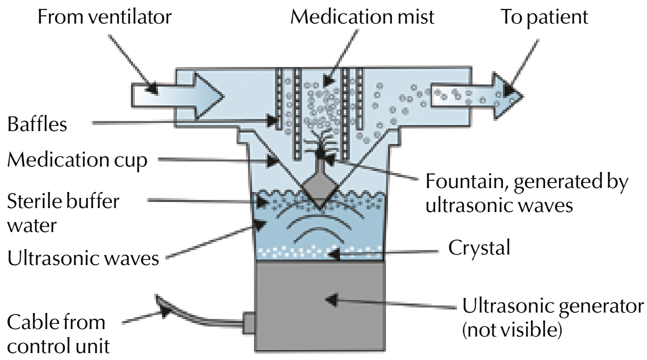


Figure 8

Horn transducer nebulizer

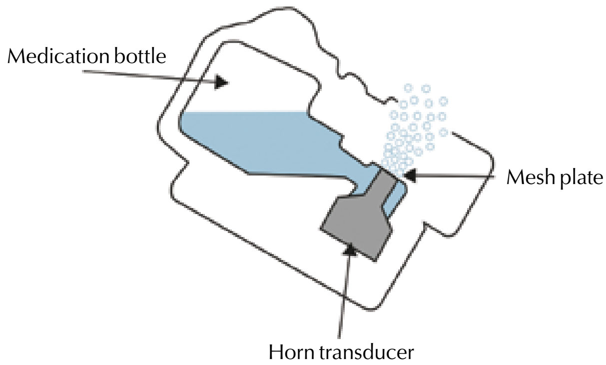
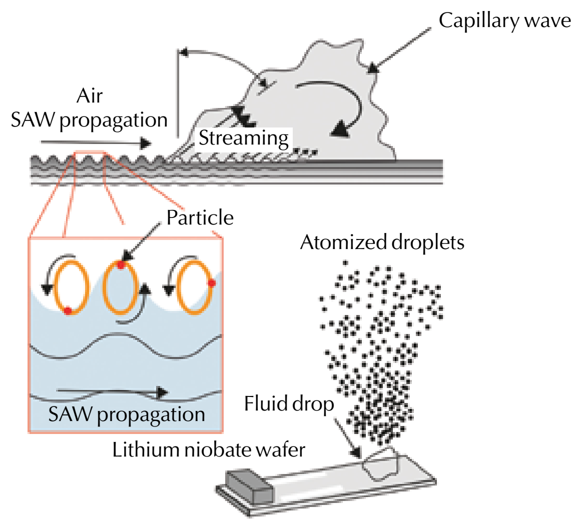


Figure 9

Sonic acoustic wave (SAW) technology



Handheld nebulization technology

The following sections discuss miniaturized or handheld nebulization devices. Several technology platforms that have potential for development or are in use in portable handheld devices are presented.[25-29] This discussion does not claim to be complete but will give a flavor of some options.

Some of these nebulizer technologies may enable a product developer or manufacturer to design small, handheld, portable devices that deliver a dose in only one or several inhalations. In that regard, they would be similar to dry powder inhalers (DPIs) and metered dose inhalers (MDIs). They also share characteristics with the nebulizer systems described earlier. Even though these devices are small, they contain multiple parts, often more than seen in simple capsule-based DPIs and simple MDIs. Some also incorporate electronics and batteries, which is likely to impact their pricing.

Colliding jet technology

In colliding jet nebulization, two liquid jets are angled towards each other and when they collide, droplets for distribution are formed.[24, 25] The jets are produced by pressing liquid through angled nozzles (Figure 10). Droplet size is governed by the liquid jet diameter, angle and jet impact velocity. Typically, this type of technology can deliver microliters of formulation per second, depending on the nebulizer configuration.

High-pressure spray technology

High-pressure spray nebulization uses a micron mesh and pushes liquid through it to produce liquid jet filaments that will break into droplets.[26, 27] The process of droplet breakup is influenced by shear forces as the jet filaments are ejected into the air and is also dominated by Rayleigh[15] and Weber[16] liquid breakup theory. Commonly, these devices use silicon chip technology in the manufacture of their nozzle arrays. The hole size and spacing in the nozzle arrays can be varied to obtain the desired droplet size (Figure 11). Using this technology, a metered dose in the microliter range can be aerosolized and administered during a single inhalation.

Vibrating plate technology

With respect to hole mesh, vibrating plate technology is similar to high pressure spray technology.[27, 28] The mesh holes can be manufactured as tapered electro-

Figure 10

Colliding jet technology

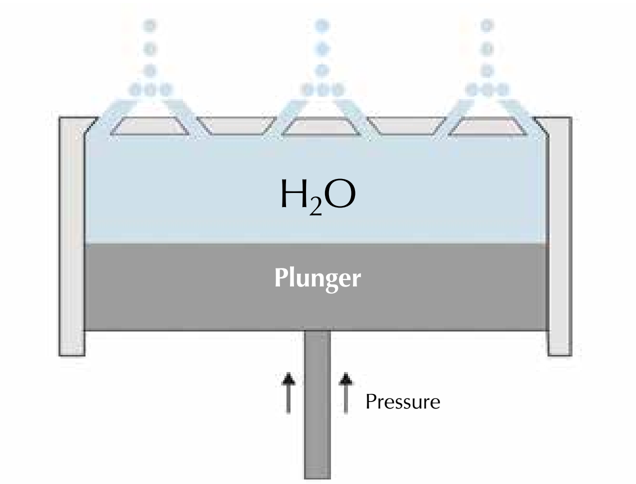
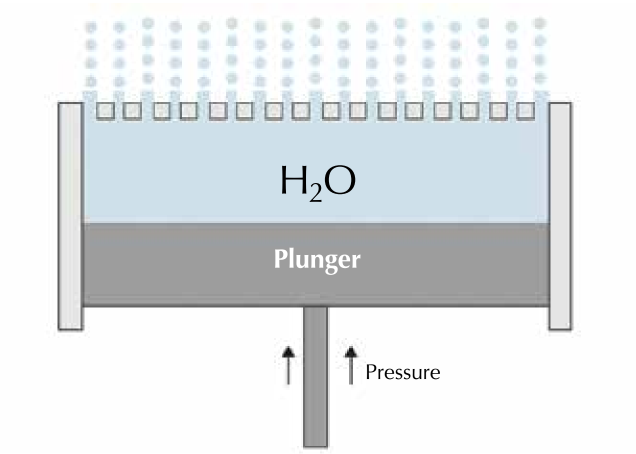


Figure 11

High pressure spray technology



formed nozzles in a metal plate or as holes drilled by a laser through a metal plate. Hole size can be adjusted, as can distance, to form an array that can produce the desired droplet size distribution. However, the principle of generation differs from that of high pressure jet technology. In vibrating plate technology, jet filament production and break up into droplets is performed by a vibrating piezo member bonded to the metal mesh. The preferable configuration is circular and vibration is often in the kilohertz frequency range (Figure 12). A number of versions have been envisioned, and to some extent developed, where the piezo element has been bonded to a silica substrate with etched holes.[28] The technology is affected by viscosity and surface tension, as mentioned previously for conventional and enhanced ultrasonic nebulizers.[29]

Piezo horn technology

Piezo horn nebulization technology uses the same mesh types as seen in vibrating plate technology: electroformed nozzles or laser-drilled holes in a metal plate. Liquid is placed on the back of the mesh plate and an acoustic horn made of piezo material is placed in contact with the liquid. The horn is vibrated in the kilohertz frequency range, ejecting liquid from the upper side of

Figure 12

Vibrating plate technology

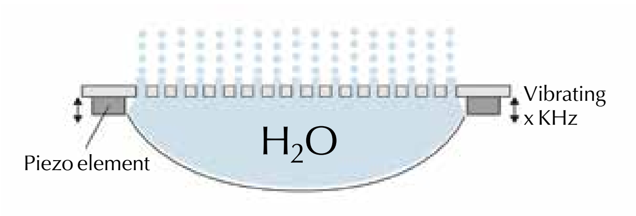
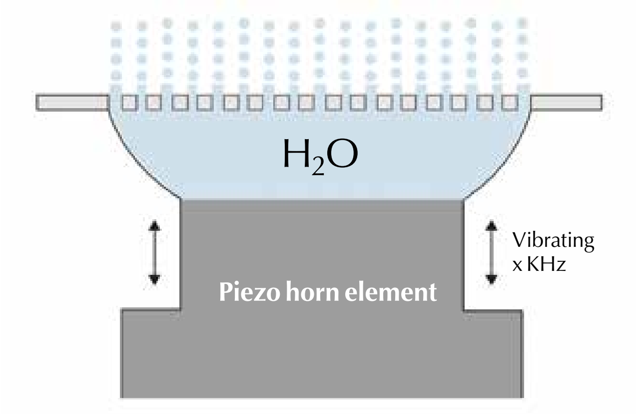


Figure 13

Piezo horn technology



the mesh (Figure 13). The configuration is also preferably circular. This technology has been implemented in conventional and small handheld nebulizers.[30]

Additional technology candidates

Other technologies have been explored or developed but have not quite become viable concepts for inhalation therapy, either due to limitations in technology or lack of suitable formulations for use with such technologies. Some of these include electro-hydrodynamic spray technology, condensation liquid aerosol technology and ink jet technology.

Looking back, looking ahead

This article has discussed the basics of conventional nebulization technologies that are available for the inhalation therapy.[13,14] It has also presented a number of novel approaches that have been implemented or may have the best likelihood for future use in miniaturization of conventional nebulizers and development of handheld, single or multiple dose nebulization systems.

Looking back to the early 1850s when the first nebulizer system was invented and at the numerous design improvements and new nebulized medications introduced since, it can certainly be said that nebulizer development is still ongoing[9] and holds promise for the future.

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