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RESEARCH PAPER

Study of the Technological Parameters of Ultrasonic Nebulization

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ABSTRACT

The principle of an ultrasonic nebulizer is based on the vibrations of a piezoelectric crystal driven by an alternating electrical field. These periodic vibrations are characterized by their frequency, their amplitude, and their intensity, which corresponds to the energy transmitted per surface unit. When the vibration intensity is sufficient, cavitation occurs, and droplets are generated. Ventilation enables airflow to cross the nebulizer and to expel the aerosol droplets. For a given nebulizer, the vibration frequency of the piezoelectric crystal is fixed, often in the range 1–2.5 MHz. In most cases, an adjustment in vibration intensity is possible by modifying vibration amplitude. The ventilation level is adjustable. The vibrations may be transmitted through a coupling liquid—commonly water—to a nebulizer cup containing the solution to be aerosolized. In this work, we studied the influence of the technological parameters of ultrasonic nebulization on nebulization quality. Our study was carried out with a 9% sodium chloride solution and a 2% protein solution (α1 protease inhibitor). Three different ultrasonic nebulizers were used. An increase in vibration frequency decreased the size of droplets emitted. The coupling liquid absorbed the energy produced by the ultrasonic vibrations and canceled out any heating of the solution, which is particularly interesting for thermosensitive drugs. An increase in vibration intensity did not modify the size of droplets emitted, but decreased nebulization time and raised the quantity of protein nebulized, thus improving performance. On the other hand, an increase in ventilation increased the size of emitted droplets and decreased

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nebulization time and the quantity of protein nebulized because more drug was lost on the walls of the nebulizer. High intensity associated with low ventilation favors drug delivery deep into the lungs.

Key Words: *Frequency; Intensity; Nebulization quality; Ultrasonic nebulization; Ventilation*

INTRODUCTION

The principle of an ultrasonic nebulizer is based on the vibrations of a piezoelectric crystal (transducer) driven by an alternating electrical field. Ultrasounds are sound waves with a frequency higher than 20,000 Hz (1,2).

A sound wave is a periodic disturbance in a material medium in which the molecules in certain regions are momentarily displaced from their equilibrium positions and experience a compensating force because of the elasticity of the medium. This force is responsible for propagating the disturbance wave in the form of an oscillation of the molecules around their mean position, and its magnitude influences the velocity with which the wave is propagated.

The propagation of sound waves through the medium involves alternating positive and negative deviation from the mean values of density, pressure, temperature, particle velocity, and particle acceleration. If the pressure amplitude is sufficiently high and causes great changes in pressure, a very significant effect called *cavitation* takes place, which is the formation and collapse of small bubbles in the liquid. The formation is related to the negative pressure portion of the sound waves, which causes some of the vapor in the liquid to come out of the solution in the form of minute bubbles. These bubbles then act as weak spots for the further tearing apart of the liquid to form larger cavities.

Then, when the pressure becomes positive, in the other half of the sound wave cycle, the cavities collapse with a violent hammering action that generates high local instantaneous pressures and temperature. During the implosion of the bubbles, the instantaneous particle velocities reach supersonic speed, and a tiny shock wave is produced, resulting in a water geyser at the surface. Periodic hydraulic shocks set the surface of the liquid into vigorous oscillatory motion, with the formation of standing capillary waves of finite amplitude on its surface and the spontaneous excitation of the standing capillary wave.

If vibration intensity—the mean power that is transmitted per surface unit—is sufficiently high, the amplitude of the capillary waves will also grow, and their shape will increasingly deviate from that of a sine wave due to nonlinearities. Finally, at high amplitudes, droplets will be propelled from the crests of the wave as they are unstable, and this leads to atomization of the liquid (3–5).

During ultrasonic nebulization, waves formed on the surface of the solution have a wavelength λ (1):

$$\lambda = (8\pi\gamma/\rho f^2)^{1/2}$$

where f is the frequency of the ultrasonic vibrations, and γ and ρ are the surface tension and density of the liquid, respectively. The diameter of the droplets formed from the waves is

$$D = \alpha\lambda$$

where α is a proportionality coefficient.

For a given nebulizer, the vibration frequency of the transducer is fixed and is often in the range 1–2.5 MHz.

For a given vibration frequency, the intensity of the wave is proportional to the square of wave amplitude a and its frequency f:

$$I = kw^2a^2 \quad \text{with } w = 2\pi f$$

In most cases, an adjustment in vibration intensity is possible by modifying the vibration amplitude of the transducer.

Although air is not involved in the initial formation of droplets by ultrasonic vibrations, a flow of air is used to expel the aerosol droplets. Ventilation, generally adjustable, sends an airflow through the nebulizer and carries out the aerosol produced.

The vibrations may be transmitted through a coupling liquid—commonly water—to a nebulizer cup containing the solution to be aerosolized (1,2,6–8).

In a previous work, we studied the influence of technological parameters of jet nebulization, that is, the nebulizer and dynamic conditions (airflow and pressure), on the quality of nebulization. Our results

showed the importance not only of defining the formulation, but also of associating it with the proper nebulizer(s) and conditions of use (9). It seemed of interest, as a corollary to this study, to consider the influence of the technological parameters of ultrasonic nebulization on nebulization quality to improve the efficiency of ultrasonic nebulizers.

EXPERIMENTAL

Materials

Nebulization was carried out with a 9% sodium chloride solution and 2% aqueous solution of α1 protease inhibitor (α1 PI) (LFB, Lille, France). The α1 PI is a glycoprotein of human origin with a molecular weight of 52,000 Da.

The characteristics of the ultrasonic nebulizers used are presented in Table 1. The three ultrasonic nebulizers were used to study the influence of the following technological parameters: vibration intensity, ventilation level, vibration frequency of the transducer, and presence of a coupling liquid.

The coupling liquid was water. It was used to transmit the ultrasonic vibrations to the solution to be aerosolized. It prevents the direct contact of the drug solution with the transducer.

Environmental temperature and relative humidity were maintained constant at 20°C and 40% and 45%, respectively.

Method

As the three nebulizers studied had different vibration frequencies, we studied the influence of vibration frequency on droplet size for similar ventilation levels.

A study was made of the influence of a coupling liquid on the solution temperature. For the other parameters (vibration intensity and ventilation level), we studied their influence on the size of droplets emitted, the quantity nebulized, and the nebulization time. Each result is the mean of three replicate measurements.

Evaluation of Nebulization Quality

Size of Droplets Emitted

Aerosol size distribution emitted from the solution was determined with a Mastersizer X (Malvern, Orsay, Paris) laser size analyzer. The solution was directly nebulized in the laser beam. After repeated testing, the measurement variation was 2.4%. The results are expressed as the percentage of droplets below 5.79 µm and the median diameter. Indeed, particles must have a diameter below 5.79 µm to reach the lungs.

Percentage of Solution Nebulized

The amount of solution remaining in the nebulizer was subtracted from the mass initially placed in the system, making it possible to calculate the percentage of solution nebulized.

Nebulization Time

The nebulization time parameter is important for patient compliance and must be taken into consideration.

Table 1

Characteristics of Ultrasonic Nebulizers

Nebulizer	Vibration Frequency (MHz)	Vibration Intensity	Ventilation Level	Coupling Liquid
A	1.5	Does not vary	0–20 L/min	No
B	1.63	3 positions: • minimum • median • maximum	0–30 L/min	Yes
C	2.4	6 positions: 1 to 6	0–50 L/min	Yes

Temperature of the Solution

We measured the temperature of dead volume to show a possible increase in temperature due to ultrasonic nebulization.

RESULTS AND DISCUSSION

Table 2 presents the influence of vibration intensity and ventilation level on the size of emitted droplets. During previous assays, we noted that results relating to the 9% sodium chloride solution and the 2% aqueous solution of α1 PI were comparable. Indeed, the concentrations of the two solutions were low, so they were very fluid and had a Newtonian rheologic behavior. Their surface tensions were 53 mN/m for the 2% α1 PI solution and 50.6 mN/m for the 9% sodium chloride solution.

In a previous work (9), jet nebulization of 2% and 3.5% aqueous solutions of α1 PI was comparable because surface tension and viscosity were not different. Protein level will have no influence on nebulization parameters if surface tension and viscosity are not significantly different.

Whatever the nebulizer considered, for a given intensity, an increase in ventilation increased the size of emitted droplets. Droplet size was greater because higher turbulence in the airstream makes droplets aggregate.

For a given nebulizer and ventilation, the increase in intensity did not influence the size of emitted droplets.

Table 3 indicates the influence of vibration intensity and ventilation level on the quantity of solution nebulized and nebulization time. For a given intensity, an increase in ventilation did not influence the percentage of solution nebulized, but decreased nebulization time. The observations are the same when vibration intensity increased for a given ventilation. A decrease in the quantity of drug nebulized was associated with the increase in nebulization time for the same ventilation. This decrease is explained by the concentration of the solution due to water evaporation (10). On the other hand, an increase in ventilation decreased the quantity of α1 PI nebulized because of higher turbulence in the airstream, which increases the loss of drug to the wall of the nebulizer. It means that the antielastase activity of the protein, evaluated during the dosage of α1 PI, was maintained during ultrasonic nebulization in presence of a coupling liquid. These results are in concordance with those of Taylor et al. (11). They observed that operating the nebulizer at maximum setting decreased the time required to nebulize pentamidine isethionate solution, but also decreased delivery efficiency.

Table 2

Influence of Vibration Intensity and Ventilation Level on the Size of Emitted Droplets

Nebulizer	Vibration Intensity	Ventilation Level	% Droplets < 5.79 μm	Median Diameter (μm)
A		Mini: 10 L/min	87.57 (± 2.1)	3.37 (± 0.18)
		Maxi: 20 L/min	77.14 (± 1.12)	4.74 (± 0.29)
B	Minimum	Mini: 15 L/min	Not measurable	—
		Maxi: 30 L/min	52.32 (± 0.87)	5.52 (± 0.31)
	Median	Mini: 15 L/min	84.21 (± 2.48)	3.70 (± 0.17)
		Maxi: 30 L/min	56.75 (± 0.90)	5.34 (± 0.35)
	Maximum	Mini: 15 L/min	78.03 (± 2.1)	4.13 (± 0.39)
		Maxi: 30 L/min	54.83 (± 0.89)	5.43 (± 0.37)
C	4	$V_{1/2}$: 25 L/min	86.89 (± 2.51)	1.64 (± 0.65)
		V_1: 50 L/min	35.02 (± 2.5)	9.13 (± 0.7)
	5	$V_{1/2}$: 25 L/min	82.47 (± 1.72)	1.66 (± 0.12)
		V_1: 50 L/min	38.85 (± 2.88)	9.18 (± 0.74)
	6	$V_{1/2}$: 25 L/min	84.70 (± 1.53)	1.66 (± 0.05)
		V_1: 50 L/min	36.68 (± 0.89)	9.97 (± 0.31)

Each result is the mean (± SE) of three experiments.

Table 3

Influence of Vibration Intensity and Ventilation Level on the Percentage of the Solution Nebulized and Nebulization Time

Nebulizer	Vibration Intensity	Ventilation Level	% of Solution Nebulized	% α1 Protease Inhibitor Nebulized	Nebulization Time
A		Mini: 10 L/min	82.05 ($\pm$0.077)		11 min30 ($\pm$0.10)
		Maxi: 20 L/min	82.95 ($\pm$0.95)		10 min15 ($\pm$0.15)
C	4	$V_{1/2}$: 25 L/min	83.4 ($\pm$0.31)	55.22 ($\pm$2.08)	30 min ($\pm$0.10)
		V_1: 50 L/min	80.33 ($\pm$0.18)	43.00 ($\pm$1.6)	25 min ($\pm$0.80)
	5	$V_{1/2}$: 25 L/min	84.37 ($\pm$0.29)	62.99 ($\pm$1.1)	28 min ($\pm$1)
		V_1: 50 L/min	82.86 ($\pm$0.15)	46.93 ($\pm$1.23)	23 min ($\pm$0.25)
	6	$V_{1/2}$: 25 L/min	85.71 ($\pm$0.29)	72.85 ($\pm$2.7)	20 min ($\pm$0.10)
		V_1: 50 L/min	83.20 ($\pm$0.18)	58.70 ($\pm$2.64)	17 min ($\pm$1)

Each result is the mean ($\pm$SE) of three experiments.

Table 4

Influence of Vibration Frequency of the Transducer on the Size of Emitted Droplets

Nebulizer	Vibration Frequency of the Transducer (MHz)	Ventilation Level (L/min)	% Droplets $< 5.79\,\mu m$	Median Diameter (μm)
A	1.5	20	67.14 ($\pm$1.12)	4.74 ($\pm$0.29)
B	1.63	30	56.75 ($\pm$0.9)	5.34 ($\pm$0.35)
C	2.4	25	82.47 ($\pm$1.72)	1.66 ($\pm$0.12)

Each result is the mean ($\pm$SE) of three experiments.

Table 5

Influence of the Coupling Liquid on the Temperature of the Solution Nebulized

Nebulizer	Coupling Liquid	Initial Temperature of the Solution	Temperature of the Solution After 10 min of Ultrasonic Nebulization at the Minimum Ventilation
A	No	20°C ($\pm$0.1°C)	41°C ($\pm$0.1°C)
B	Yes	20°C ($\pm$0.1°C)	23°C ($\pm$0.1°C)
C	Yes	20°C ($\pm$0.1°C)	24°C ($\pm$0.1°C)

Each result is the mean ($\pm$SE) of three experiments.

Table 4 presents the influence of the vibration frequency of the transducer on the size of emitted droplets. To limit the influence of ventilation, we compared the nearest ventilation levels. An increase in ventilation increased the size of emitted droplets. Now, if we compare the 1.5- and 2.4-MHz frequencies, we can see that the percentage of the droplets below 5.79 μm was higher and the median diameter lower for the 2.4-MHz frequency, although ventilation was higher.

The increase in vibration frequency decreased the size of emitted droplets. This is difficult to observe with the 1.63-MHz frequency compared to 1.5 MHz because ventilation was at its highest.

Table 5 presents the influence of a coupling liquid on solution temperature after nebulization

for 10 min. With nebulizers B and C, the increase in temperature was moderate because of the presence of a coupling liquid that prevented contact between the solution and the transducer. With nebulizer A, the temperature of the solution after nebulization for 10 min was higher than 40°C. The coupling liquid absorbed the energy produced by ultrasonic vibrations and cancelled out any heating of the solution, which often occurs with ultrasonic nebulizers (11–13). The rise in temperature might be responsible for drug degradation. For example, after ultrasonic nebulization, Ip et al. (13) reported denaturing of a protein (recombinant methionyl interferon consensus) that could be avoided by not heating the solution. In the same way, Cipolla et al. (12) noted an aggregation of rH DNase because of heightened temperature.

The use of ultrasonic nebulizers at high vibration intensity and low ventilation gives satisfactory nebulization of solutions as regards the size of emitted droplets, the quantity of drug nebulized, and the nebulization time. A low ventilation level is preferable, on the one hand, for the emission of the smaller-size droplets required to administer the drug deep into the lungs and, on the other hand, for better compatibility with patient administration. High intensity is preferred because it increases the quantity of drug nebulized and therefore the quantity of drug likely to reach the lungs. The presence of a coupling liquid is interesting because it prevents the increase in temperature that could degrade some drugs. High vibration frequency is better because it makes it possible to obtain smaller-size droplets.

For a given ultrasonic nebulizer, the vibration frequency of the transducer is fixed. Only vibration intensity and ventilation level have to be defined to nebulize a given solution with an ultrasonic nebulizer. In contrast, with jet nebulization, a nebulizer with given geometric characteristics has to be chosen: liquid and air tube orifice diameters, size and shape of the reservoir, shape and position of the impaction system. All these have to be associated with defined airflow and pressure conditions.

CONCLUSION

An ultrasonic nebulizer is efficient, with high vibration frequency, for drug administration into the lungs. High vibration intensity associated with a low ventilation level is preferable for the delivery of drugs deep into the lungs. Using a coupling liquid that transmits ultrasonic vibrations to the solution and limits any increase in temperature is favorable. This is particularly interesting for thermosensitive substances that could be used with this type of nebulizer.

To maintain a constant quantity of drug for the patient at each administration, it is necessary to standardize operating conditions: vibration intensity and ventilation level therefore have to be defined.

It is indispensable that solutions for nebulization should be subjected to thorough pharmaceutical trials before use to define the best-adapted nebulizer(s) and the operating conditions for those retained. In the interest of public health, when a Marketing Authorization Application file is requested for a liquid preparation to be nebulized and its droplet size greatly influences drug therapeutic activity, it seems important to us not only to define the formulation, but also to associate with it the proper nebulizer(s) and administration conditions. This is the case for both specialties Pentacarinat* (Bellon, Neuilly/Seine, France) containing pentamidine and Pulmozyme* (Roche, Neuilly/Seine, France) containing dornase alpha, which obtained the Marketing Authorization Application file in 1989 and 1994.

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