Drug Development and Industrial Pharmacy

The effectiveness of aerosol therapy depends on the proportion of inhaled drug deposited at the site of action , and for certain drugs , on the proportion that is retained in the lungs (2) . The deposition site of inhaled aerosols depends on the physical characteristics of the aerosol but also on factors related to the patient (mode of inhalation , degree of abnormality of the airways) (3) .

There are essentially three types of inhaling devices :
- *metered dose pressurised inhalers (MDI)* containing drugs in suspension or in solution in a liquefied gas propellant . Manual activation delivers a measured dose through a valve .
- *dry powder inhalers (DPI)* containing micronized drug which is dispersed by the inspiratory airflow .
- *nebulisers* in which liquid preparations are pulverized by compressed gas or by the vibration of a quartz .

In recent years , use of this last one has been greatly extended, in particular because of the presumed adverse effects of chlorofluorocarbon propellants on the environment and also because of the advantages it offers :
- a higher dose can be administered
- some drugs cannot be formulated as MDI because the drug is incompatible with propellants
- the problem of coordination between inhalation and activation which appeared with DPI can be avoided

In most cases , the nebulisation of a solution does not include operating conditions - the doctor only states the posology , as the therapeutic indication of the AMM file is generally not associated with conditions of administration . This lack may explain insufficient efficiency in some cases or even the ineffectiveness of some treatment by nebulisation .
To envisage a more effective use of nebulisation , it seems interesting to define factors that can modify aerosol . Aerosol can be characterized by certain measurements we shall explain as well as methods of evaluating them .

A. NEBULISERS

Liquid preparations for inhalation must be fragmented into small droplets in order to reach the respiratory tract . To this end , two types of nebulisers are commonly used , each based on a different principle :
- jet nebulisers
- ultrasonic nebulisers

1. Jet nebulisers

The principle of these nebulisers follows Bernoulli's theorem : when a fluid circulates at high velocity its pressure is low , whereas at low velocity , pressure is high (4) . When air passes through the shrinkage of a tube , its velocity increases but the pressure falls . When this tube is plunged into a liquid the pressure of which is atmospheric , the fall in pressure produces aspiration of the liquid which blends with air . This is the Venturi effect .
In jet nebulisers , gas (compressed air or oxygen) passes rapidly through the narrow orifice of the air inlet tube , and the pressure falls . This causes suction of the liquid contained in the reservoir which emerges from the orifice of the liquid

inlet tube (5) (6) (7) (8) (9) (10) (11) (12) . This liquid emerges as a primary spray which contains a wide range of droplet sizes . Large droplets strike on baffles placed in the path of the droplets and drain back into the reservoir for re-nebulisation . This impaction causes disintegration of primary spray into smaller droplets .Only the smaller particles are carried out of the nebuliser on the airstream. The nebuliser continues to generate droplets as long as there is a flow of liquid through the inlet tube .

II. Ultrasonic nebulisers

Ultrasonic nebulisers operate differently from air jet nebulisers . Although a flow of air is used to carry out the aerosol droplets , air is not involved in the initial formation of these droplets by ultrasonic vibrations (5) .
Vibrations of a piezo-electric crystal (transducer) driven by an alternating electrical field are transmitted through a coupling liquid to a nebuliser cup containing the solution to be aerosolised (6) (8) (9) (13) (14) .
This ultrasonic vibration creates a fountain of liquid from which droplets are emitted.The droplets are generated by the formation and collapse of cavities within the liquid : the cavitation phenomenon is characterized by periodic hydraulic shocks producing waves at the surface of the liquid . At sufficiently high amplitudes of vibration , the wave crests break up to form droplets (8) .
Ultrasonic nebulisers produce highly concentrated aerosols (5) (13) .
In general , ultrasonic nebulisers have a higher output than jet nebulisers but produce larger particles (6) (7) (9) (15) (16) (17) (18) .
However results from previous studies must be interpreted with precaution because there are many factors influencing aerosol properties . These factors can be related to formulation , technology and even ambiant conditions .We shall define parameters required to evaluate the efficiency of nebulisers as well as elements of formulation and technology that influence this efficiency . This should result in a better understanding of nebulisation and a more effective use of nebulisers .

B. TESTING THE EFFICIENCY OF NEBULISERS

Different parameters can be evaluated to judge nebulisation efficiency .

1. Evaluation of particle size

The deposition of inhaled aerosol particles in the lung depends notably on aerosol particle size . It is assumed that for optimal deposition in the lower respiratory tract , the size of droplets must be in the range 1 - 5 µm (respirable fraction) and some researchers limit it to 1 - 3 µm .
The aerodynamic diameter of a particle is the diameter of a spherical particle with an apparent density of 1g/ml which settles at the same rate as the particle described (6). This aerodynamic diameter is determined to take into consideration physical properties such as mass , diameter , shape , and surface characteristics , that affect aerodynamic behaviour (54) (55) .
Two principal methods are commonly used for aerosol particle sizing (56) :
- one using the technique of inertial impaction to separate the particles of droplets into different size ranges . This consists of multistage liquid impactors , twin impingers , multistage cascade impactors (Andersen , Marple ....) . The aerosol passes through a device simulating the respiratory tract .

- one using laser : the laser diffraction method makes it possible to measure particle size distribution in the aerosol cloud .

1.1. Inertial separation methods

These methods are based on the principle that the aerodynamic diameter of a droplet affects the impaction site when the droplet is carried on an airstream with changing direction and velocity (5) .
Air is drawn through the devices by a pump which simulates a patient's inspiration. In the airstream , small spherical particles will have lower inertia than larger spherical particles of the same density (57) . An obstacle placed in the path of this flowing stream of air will suddenly change its direction . If the inertia of the droplet is sufficient to overcome the drag force that tends to keep it in the airstream , the droplet will impact on the surface placed in its path (58) (59) . The separation of particles into various size ranges is obtained by successively increasing the velocity of the airstream , through successively decreasing the jet sizes at each stage of the impactor (or the impinger) (58) . Consequently , small particles eventually acquire enough inertia to impact on obstacles and particle sizing of the aerosol is achieved (59) . The relation between aerodynamic diameter (also called Effective Cut-off Diameter or ECD) and the obstacle serving as a separator depends on particle size : particles larger than the aerodynamic diameter of the separator are impacted , whereas smaller particles are not (57) . The systems of impaction are calibrated for a specific air flow throughout the device (8) (60) (61) . Different devices use this inertial separation principle . They differ as to the number of stages and the presence or absence of liquid in the receiving stages .

1.1.1. Multistage cascade impactors

Different cascade impactors are commercially available and differ as to the number of stages , the airflow rate through the device , the use of multiple or single jets at each stage , slit or circular jets and removable or stationry collection surfaces (58) . Particles can bounce and blow-off at any stage .
The evaluation of the mass of material impacted at each stage is determined :
- by weighing the collection surfaces before and after sampling , but in this case we cannot differentiate drug from excipient (58)
- by washing the collection surfaces with an appropriate solvent and analysing the drug by a specific method (58) (59)(62) (63) .
The amount of drug impacted on each collection disc is quantified and a cumulative distribution percentage of the drug is determined . The mass median aerodynamic diameter (MMAD) is then calculated .
The impactors that are most commonly found are :
- an 8 - stage Andersen Sampler (1) (58) (62) (63) (64) (65) (66) , calibrated for an airflow of 28.3 l / min. The different ECD of the stages are : 9.0 μm , 5.8 μm , 4.7 μm , 3.3 μm , 2.1 μm , 1.1 μm , 0.7 μm and 0.4 μm (63) (67) .
This impactor is described in the project for the monograph " Inhalanda - Preparations for inhalation " for the European Pharmacopeia , published in Pharmeuropa. Apparatus D is used for the aerodynamic evaluation of fine particles (1) . Its cut-off diameter used to define respirable fraction is 5.8 μm (62) (65).
The 8 - stage impactor is also described in the USP XXIII (68) .
- a 6 - stage Delcron DCI-6 (58)(59)(64) , calibrated for an airflow of 12.5 l / min. The ECD are 16 , 8 , 4 , 2 , 1 and 0.5 μm (59) .
- a 10 - stage cascade impactor (Andersen ; California instruments)

- a 5 - stage Marple-Miller impactor (64) , with a model calibrated for an airflow ot 60 l / min (Model 160) and a model calibrated for an airflow of 30 l / min. (Model 150). The cut-size diameters are 10 μm , 5 μm , 2.5 μm , 1.25 μm and 0.625 μm (69).
It is important to draw air through the device at the airflow specified by the manufacturer , because Effective cut-off diameters of the stages are established for this specific airflow .
A cascade impactor is not marketed as a " complete " system , it generally lacks the "throat" . But the "throat" or inlet chamber adapted on the impactor can influence its collection efficiency (67) (70) , that is why it is important to retain the device described in the analytical method .

1.1.2. Multistage liquid impactor (MLI)

This is a round jet cascade impactor with wet sintered glass impaction plates and a final impinger stage containing solvent (70) (71) (72) . The moisture of the plates reproduces the humid conditions of the human lung and prevents the bounce and blow-off of particles (72).
The MLI was originally described by May and contains 4 stages . ECD obtained by Hallworth and al. (70) are 12.6 μm , 7.4 μm , 3.8 μm and 1 μm for an airflow of 60 l / min. Bell and al. (71) used a model consisting of a slightly modified version of May's original design obtaining ECD of 10.2 μm , 5.5 μm , 3 μm and 0.8 μm for an airflow of 60 l / min.
The monograph project " Inhalanda-Preparations for inhalation " for the European Pharmacopoeia describes an MLI with apparatus C used for the aerodynamic evaluation of fine particles (6) . It consists of 3 stages and an after-filter . The cut-off diameters are 13 μm , 6.8 μm and 3.1 μm respectively for each stage (66) . The flow rate for aspiration is 60 l / min .

1.1.3. Simple cascade impactors

Multistage devices provide mass data for a variety of particle-size ranges . They are other devices which have a single cut-off diameter used to define respirable fraction . These devices divide the dose into that part of the dose that is thought to be respirable , and that which is likely to be non - respirable (73) . This is a simpler but reproducible method for routine use (56) .
Two devices are described , both by the British Pharmacopoeia (BP) , and in the monograph project "Inhalanda-Preparation for inhalation " for the European Pharmacopoeia (1) and the USP XXIII .

a) Twin- stage liquid impinger (Twin impinger)

This is Apparatus A of the BP and of the monograph project "Inhalanda.." and apparatus 2 of USP XXIII which has a cut-off diameter of 6.4 μm at an airflow rate of 60 l / min. (56) (65) (66) (67) (73) . The apparatus , made of glass , consists of an upper impingement chamber , a lower impingement chamber and a so-called "throat" (66) . It requires solvent in both chambers to collect the aerosol cloud . The throat and the upper impinger are defined as stage 1 , and the lower impinger is defined as stage 2 (which represents the respirable fraction) (73) .
Good correlation has been established between respirable dose and clinical effect for bronchodilatator drugs (67)(73).

b) Single - stage liquid impinger

This is apparatus B of the BP and of the monograph project "Inhalanda" and apparatus 3 of USP XXIII which has a cut-off diameter of 9.4 μm at an airflow of 60 l / min. (65) (73) . The apparatus, made of metal , consists of an impingement chamber with a sintered glass disc and a so-called "throat" consisting of a right-angled , metal tube . Particles passing the impingement stage are captured on a filter (66) . Its design was essentially taken from the top of an original multistage liquid impinger (73) . For nebulisers , the impingement chamber is used without solvent (1) .

All the devices previously described use the same principle of inertial impaction , but they differ in their conception and in the airflow used , and thus in their cut-off diameters .
Size - measurement results are expressed differently :
- multistage cascade impactors , liquid or not , produce particle size distribution of the aerosol . Plotting the cumulative percentage data versus the aerodynamic diameter of each stage on log-probability paper makes it possible to obtain the MMAD (57) .
- simple cascade impactors divide the aerosol into two parts , one inferior and the other superior to the ECD of the device . The MMAD cannot be obtained .

1.2. Laser diffraction

This method is based on the theories of Fraunhofer and Mie (6) (74) (75) . When a beam of light is projected onto a particle , as long as particle size is much greater than the wavelength of the light , there is a deviation of the light beams (76). The diffraction angles are inversely related to particle diameter (6) (74) (75) (76) (77) (78).
Fraunhofer's theory compares the particle to an opaque disc that the light does not go through . The diameter is calculated from the projected surface of the particle .
Mie's theory compares a particle to a transparent sphere . Light passes through this particle and is diffracted . The light flux measured is proportional to the volume of the particle .
To quantify the diffracted light , a Fourier optical system is used to focus the light :
- the undiffracted light is focused into a single point in the centre of the array of sensing detectors . The undiffracted light is generally used to monitor the beam strength .
- all light that is diffracted from any of the particles in the beam into a given scattering angle , is focused by the Fourier lens into a thin annulus , centered around the point where the undiffracted light is focused . Light diffracted into small angles produces annuli of smaller radii and that diffracted into larger angles results in annuli of larger radii .
The picture of the diffraction of a light beam consists of concentric rings , the intensity of which decreases with the distance to the centre (78) . The angular distribution of diffracted intensity can lead to particle size distribution (78) . The signal from each detector element proportional to the intensity of light falling on it is amplified and digitised and transferred to the controlling computer where it is analysed (6) (77) .
Analysis by the computer of the detectors' output yields size distribution by volume (75).

Knowledge of particle size alone is insufficient and must be associated with the percentage of nebulised drug .

2 . Mass of drug released as aerosol

The amount of drug released as aerosol is obtained by subtracting the amount remaining in the nebuliser from the mass initially placed in the system . The mass of drug M (mg) released as aerosol can be calculated as (21) :

$$M = (M_0 C_0 / \rho_0) - (M_f C_f / \rho_f)$$

where M_0 and M_f are respectively the mass of drug solution (g) initially placed in the nebuliser and the mass of drug solution (g) remaining after nebulisation ; C_0 and C_f are the initial and final drug concentrations (mg/ml) ; and ρ_0 and ρ_f the initial and final solution densities (g / ml) .
Determination of the mass released as aerosol makes it possible to estimate the amount of drug retained within the nebuliser at the end of nebulisation , that is to say the "dead" mass which is lost for the patient .

3. Nebulisation time

This parameter is important for the compliance of patients and must be taken into consideration when evaluating the performance of nebulisers . Aerosolisation can last from 15 to 30 minutes (53) ; 15 min. being better tolerated by patients. If the duration of nebulisation is too long , patients may stop the treatment too soon , with an adverse effect on clinical efficiency .
A specific nebuliser must be accompanied with operating conditions allowing for acceptable nebulisation times . If the other efficiency parameters are identical , this element can be decisive in the choice of the system .

The choice of one particular method for aerosol particle sizing is difficult because of the numerous methods that exist . The measured diameter differed according to the method :
- inertial impaction methods lead to the aerodynamic diameter .
- laser diffraction leads to a diameter of the sphere the volume of whichs would be the same as that of the measured particle . It is obtained by an optical method of light diffraction .
Aerodynamic diameter takes into consideration the fall of the particle and is in relation to the behaviour of droplets in the respiratory tract . When the density of the solution to be nebulised is close to 1, aerodynamic diameter and diameter measured by laser are very similar .

Using the aerodynamic diameter and the quantity of nebulised drug , it is interesting to calculate the quantity of drug that is assumed to reach the lower part of the respiratory tract .

C . FACTORS INFLUENCING NEBULISATION EFFICIENCY

In jet nebulisers , droplets are formed by the disintegration of the liquid in an airstream . The characteristics of solution , air and nebuliser influence the fragmentation into droplets .

In ultrasonic nebulisers , droplets are obtained by fragmentation of the liquid by ultrasonic vibrations . This division depends on the characteristics of the solution and the conditions under which the nebuliser is used .

I. JET NEBULISERS

1. Formulation

** Nature of the nebulised form*

Both solutions and suspensions may be aerosolised with nebulisers(5). The formulation of the drug in a solution rather than in a suspension is often preferred to satisfy the reproducibility of the dose delivered to the patient (10, 12) , because suspension may cause problems with sedimentation . For example , in studies concerning the inhalation toxicity of insoluble particles , it was found that the atomizing of suspensions does not yield high air concentrations , making it impossible to use suspensions . Particles have to be aerosolised from the dry powder state (8) . That is why most formulations are aqueous solutions . The solvent is an aqueous medium the pH of which varies between 3 to 8.5 (1) . Sometimes , it requires a co-solvent like ethanol , polyethylene glycol or propylene glycol to make the drug soluble. This can change the viscosity and surface tension of the liquid and consequently aerosol characteristics (7)(10)(12).

** Surface tension*

Variables such as surface tension may influence the fragmentation into droplets (10) (12) . Many researchers agree that surface tension affects output and particle size (6)(7)(19)(20)(21)(22)(23) (24).
An increase in surface tension results in nebulisation times which are longer than those for saline solutions at an equivalent flow rate and may alter the droplet size distribution (22) .This was studied by Davis who used co-solvents like ethanol and propylene glycol to modify the surface tension of the aqueous solution of drugs (19) (25) . Aerosol output depends on the concentration of the co-solvent . When the co-solvent is ethanol , an increasing proportion of ethanol results in greater total output from the nebuliser - both solution output and vapour output (19) . The increase in output is greater for solvent vapour because of the higher volatility of ethanol . The addition of ethanol decreases surface tension .
For a 50% (v/v) water and 50% ethanol-propylene glycol mixture , an output of aerosol solution droplets of 5 μm and below increases with ethanol content , attributable to the effect of ethanol on surface tension (19) (25) .

Jet nebulisation can be dissociated in two steps :
. formation of primary droplets
. drain back of larger droplets into the reservoir to be recirculated

Mercer (8) reported that the primary droplets produced by atomization have a mass median diameter (D_m) calculated by :

$$D_m = D_l \ (2\gamma / \rho_a V^2 D_l)^{45}$$

where

D_l is the diameter of the liquid flow tube (m)

V is the relative velocity between air and liquid (m/s)

γ is the liquid surface tension (mN / m)

and ρ_a is the volumic mass of air (g / cm^3)

Surface tension appears in the equation which defines D_m . However , the influence of surface tension does not always have repercussions on the size of the droplets emitted : indeed , baffles retain larger primary droplets . This retention is not affected by surface tension .

Likewise , Clay et al. (20) noted that increases in surface tension reduce the rate of aerosol released from the nebulisers but the effect on aerosol size distribution is small .

However , the surface tension of the solution may affect the proportion of a dose which is nebulised (26)

When formulating , there is a compromise to be found between nebulisation time , output and particle size .

* *Viscosity*

Viscosity may also influence the fragmentation into droplets (10) (12) . An increase in viscosity results in longer nebulisation times than those for saline solutions at equivalent flow rates and increases droplet size distribution (22)(25) . This can occur with antibiotic solutions which often have higher viscosity than saline solutions (0.83 mPa.s) (21) , for example 2.13 and 2.75 mPas (22) .

For instance , Newman and al. (21) reported that nebulisation times for gentamicin solutions (viscosity about 50% higher than that of normal saline) were higher and droplet sizes larger than those observed for normal saline nebulised by Inspiron[1] and Upmist[2] nebulisers at 6 and 8 l / min. (21) .

That is why higher flows may be necessary to nebulise effectively some viscous antibiotic solutions for respirable aerosol (9) .

Mallol (27) compared the Mass Median Aerodynamic Diameter (MMAD) obtained with two jet nebulisers for isotonic saline solution and gentamicin solution . Under the same nebulising conditions , the MMAD was the same with one nebuliser for the two solutions whereas with the second the MMAD was higher for gentamicin solution (which has greater viscosity) . The design of the nebuliser is also very important and will interact with the formulation .

Searls and Snyder agree with previous researchers that increased viscosity extends nebulisation time but on the contrary , they note the mean droplet size falls markedly (25). This concords with Davis's findings in that an increased percentage of propylene glycol decreases particle size by increasing viscosity (25) . In this case however both viscosity and surface tension are modified : as the % of propylene glycol rises , viscosity increases while surface tension decreases . This competitive effect influences particle size .Viscosity may also affect the proportion of a dose which is nebulised (26) .

In fact, researchers agree that aerosol output is correlated to surface tension and viscosity : an increase in these two parameters leads to decreased output (and vice versa)

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[1] Inspiron Minineb , Bard

[2] Upmist ,Medic-Aid Limited , Hook Lane , Pagham , Sussex , U.K. PO21

As regards particle size , it is the association between surface tension , viscosity , nebuliser design and operating conditions which are important . Formulation and nebuliser are dependent .

* *Isotonicity of the solution*

In the respiratory tract , fluids are approximately isotonic to plasma at 37°C . Aerosol particles will tend to lose (for hypotonic particles) or absorb (for hypertonic particles) water until they are isotonic with the airway fluid (6) . The size of droplets from an isotonic solution will not be modified (10) in the airway .

* *Concentration of the solution*

The concentration of the drug is another factor which modifies output characteristics and particle size .
Any modification in concentration can change the surface tension and viscosity of the solution . The effect of concentration on aerosol size distribution can be small for some drugs (like terbuline) but much greater for some highly viscous antibiotic solutions (20). During nebulisation , solvent output is considerable , leading to an increase in drug concentration in the liquid remaining in the chamber of the nebuliser . When the solution is more concentrated , output decreases (25) : when the concentration of a solution increases , its vapour pressure decreases and the output of solvent vapour decreases .
Mercer notes an increase in particle size with concentration (8) .
Generally , in experimentation , the same quantity of drug is added to different diluent volumes , which modifies the concentration and also the final volume of solution . These two parameters are related and the effect of volume on aerosol characteristics is studied in preference to that of concentration .

* Volume

At the end of nebulisation , there is always some volume of solution which is not nebulised and is lost for the patient . This is the " dead volume" which is more concentrated than the initial solution (owing to preferential evaporation of solvent (28)) and represents 0.5 to 1 ml and sometimes more (15) . If the initial volume is low, according to the type of nebuliser , the dead volume will represent a high proportion of the dose .
Increasing the initial volume fill can raise the quantity of aerosol released from the nebuliser and minimize the effect of concentration (26)(28)(29) (30) .
However , the time required for each treatment will be increased (6) (26)(31).
There is a compromise to be found between volume fill , efficiency and nebulisation time to make it acceptable to patients .
This improvement in nebuliser efficiency has not been observed for all models of nebuliser studied (6)(22)(31)(32) . For each nebuliser , there is a volume making it possible to optimise the nebulised percentage and nebulisation time (31)(33) .

2. Ambiant conditions

* *Temperature*

Temperature may influence the output of a nebuliser and the particle size (6)(15)(32)(34).

Changes in the temperature of the solution are likely to modify viscosity , surface tension and also drug solubility (20)(24) (34) .
During nebulisation with jet nebulisers , solution temperature drops to about 10°C below ambient temperature because of evaporation (7) (10)(34) . In the case of a pentamidine solution (6% w/v) nebulised with Respirgard II[3] , the temperature falls from 20°C to 10°C in 6 minutes (34) .
When drugs present aqueous solubility dependent on temperature , this can cause problems in particular recrystallisation.This is the case for pentamidine isethionate(24) .
Afterwards , when ambient temperatures rise , particle size decreases because of the increasing evaporation of the droplet diluent (15) . When particle size is evaluated, temperature must be constant .

* *Relative humidity*

Changes in the size of aerosol droplets may occur after nebulisation because of the evaporation of water or the attraction of water to the particles , to attain equilibrium with the environment (room or lungs) (25)(36) (37) (13) (20) (35).
The change in aerosol particle size depends on the physico-chemical characteristics of droplets and on the nature of the environment .
In lungs , the relative humidity of 99-99.8% will cause an increase in particle size, differing according to the hygroscopicity of particles (12) (37) (38) .
Particles can change their size by a factor of 2.2 to 4.4 (38) .
Particles need time to reach their equilibrium size , which depends on the initial size (35) (38) . Small particles (less than 1 µm) reach their equilibrium size within a breathing cycle , while particles larger than 6 µm reach only 40% of their possible maximal increase.
The growth of particles influences their deposition in the respiratory tract (39) . So , Ferron et al. compare the deposition of particles whose size varies from 0.5 to 2 µm , in the bronchial and pulmonary regions (38) . The deposition doubles for hygroscopic particles whose size increases . For particle sizes between 2-4 µm , deposition is increased by up to 20% .
In views of these results , it seems that the growth of particles can improve deposition for this particle size range. This could be related to the deposition mechanism of particles in the lower part of the airway which is mainly sedimentation : particles are deposited under the influence of their weight which is greater when particles have grown .

3. Design of the nebuliser

All jet nebuliser systems use the same principle (Venturi effect) . However, when operating under the same nebulising conditions , nebuliser output and particle size vary . This shows the importance of the intrinsic design of the nebuliser on drug delivery .
Commercially available nebulisers differ on several points :

* *the size of the reservoir*
If the reservoir is wide , the dead volume will be higher . This implies a greater volume fill and is not suited to small nebulised doses .

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[3] Respirgard , Marquest , USA

Furthermore , a small reservoir reduces the evaporated liquid (5) . This is related to the width of the reservoir which determines the contact surface between air and solution .

* *Shape of the reservoir*
The lower part of the reservoir can be flat , rounded , or conical .
The rounded or conical shapes allow for better recuperation of the droplets which drip back into the reservoir , and decrease the dead volume .

* *Baffles*
The presence of baffles in the nebulisers reduces the emission of large droplets which impinge on the baffles and return into the reservoir . The capacity of baffles to "retain" large particles will depend on their shape , dimensions and also their position in the nebuliser . Indeed , Raabe (5) reported that if the jet baffle is too close to the point of disintegration of the liquid stream , it will interrupt the formation of small droplets and if too far away ,the disintegration of primary spray into small droplets will be less because of the lower speed of the air passing the baffle .

* *Characteristics of air and liquid tubes*
Two patterns of liquid and air tubes exist : either they are concentric , or they are separate .On the one hand , air can be introduced through the lower part of the reservoir , by a system of 2 concentric perforated tubes .The diameter of the air jet hole influences the size of the droplets . A smaller jet orifice produces smaller particles but it requires greater air pressures (8)(13)(23) .
The diameter ratios of the two orifices also influence the size of droplets .For instance , in the Releex 70/N nebuliser the jet orifice has an interior diameter of 0.5 mm and the secondary orifice (liquid tube) is 0.75 mm . By reducing the secondary orifice , the airflow speed as it passes the jet baffle increases so that the disintegration of the primary spray is enhanced (5) .
On the other hand , air tube and liquid tube can be separated . There is an air jet quite separate from the capillary through which the liquid to be aerosolised is drawn into the air stream .
Characteristics of the air and liquid tubes are presented on figure 1 .

**Presence of an auxiliary air flow*
Some nebulisers possess a second vent which allows auxiliary air to be drawn through the nebuliser , thus increasing the output of aerosol but decreasing the concentration of droplets in the aerosol (8) (40) .

4. Air flow

The solution output from the nebuliser and the particle size of the aerosol are dependent on the airflow imposed on the nebuliser . It is generally admitted that an increasing compressed air flow rate decreases droplet size and simultaneously nebulisation time (9)(12)(15)(21)(26)(40)(41)(42) .
But if the flow rate is too high , it may result in higher oro-pharyngeal deposition by impaction and cause coughing and / or vomiting because it is beyond the inhalation capacity of the patient (24) .
Some researchers recommend a compressed gas flow rate superior or equal to 6 l / min in order to ensure an aerodynamic particle diameter inferior or equal to 5 μm , with most types of jet nebulisers (29)(43) . With some jet nebulisers , this result

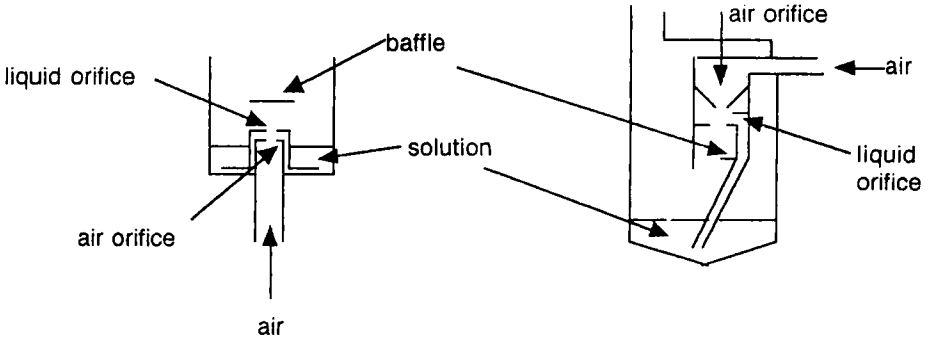

Figure 1 : Characteristics of the air and liquid tubes

can be obtained with lower air flow (4 l / min) (20) . In fact there is an interactive effect between nebuliser model and flow rate (31) , which is why operating conditions must be determined individually for each nebuliser system .
Depending on the nebuliser used , the airflow necessary is in the range 4 - 12 l / min with a most frequently used flow of 6 - 8 l / min (6) .
We have noted that the flow rate can be one of three things (figure 2) :

- the flow rate of air coming from the compressor (free air-flow) *(1)*
- the flow rate with the nebuliser connected to the compressor *(2)*
- the flow rate leaving the nebuliser , which can be different from the previous when there is an auxiliary vent *(3)*

Researchers do not always specify which flow rate they mean , which can cause misunderstandings and difficulties in reproducibility .
Indeed , different compressors with the same free air flow can lead to different flow rates when the same nebuliser is connected (44) , according to the power of the compressor .This can lead then to ineffectiveness of treatment by using an inadequate compressor .
In our opinion it is more appropriate to talk of flow rate when the nebuliser is connected to the compressor because this reflects the real flow rate received by the patient .In any case , it is important to state precisely which flow rate is being used .

5. Air pressure

Reduction in droplet size and in delivery time can also be obtained by increasing the driving pressure (15) (25) (28) .
In operating conditions , air flow is more often specified than pressure which is nevertheless an important factor : the outlet pressure of air affects the flow rate of aerosol, which increases as the pressure becomes higher (44) (45) .
In fact , these two parameters are related . It is the combination of one air flow and one pressure driving the nebuliser which determines aerosol characteristics .
As regards the compressor , the air flow is at its maximum when no resistance is applied (free air flow of the compressor) . The connection of the nebuliser

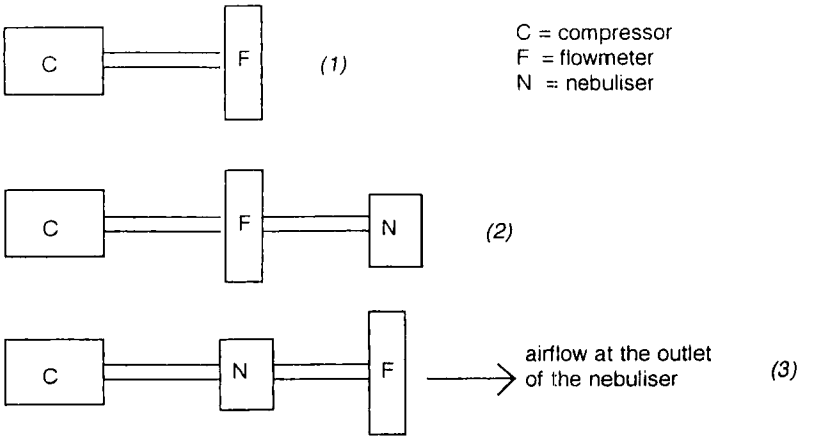

Figure 2 : Different flow rate considered by researchers

represents a resistance which raises the outlet pressure but decreases the air flow (46) .
For a nebuliser , when the upstream pressure increases , the air flow rate through the nebuliser increases but in a non-linear way (figure 3) (46) .
For nebuliser 2 , higher pressures are necessary to obtain a given flow rate , compared to nebuliser 1 , reflecting a higher resistance .
When associating the same compressor to different nebulisers or the same nebuliser to different compressors , the air flow at the outlet of the nebuliser and the upstream pressure in the nebuliser will be different . There are close links between technological parameters , namely air flow , pressure and nebuliser .
Operating conditions have a major influence on efficiency , so according to the power of the compressor and also the type of nebuliser , drug delivery varies .
That is why certain manufacturers recommend their compressor to be used with a specific type of nebuliser (46) .
In fact , each nebuliser should be tested individually with different compressors ,in order to optimise nebulising conditions for a certain drug and determine the optimal combination for this drug .

In the case of jet nebulisers , the type of nebuliser is of great importance but most of all the association of compressor and nebuliser . Optimal nebulising conditions should be determined individually for each formulation , because the quantity of drug available in the alveolar region will depend on all the previously-mentioned parameters .

Our experimentation shows it is essential to specify operating conditions and nebulisers that must be used with one medicinal solution . 5 ml of an aqueous solution containing 100 mg of drug is nebulised with four types of nebulisers : A , B , C and D and with a free air flow of 16 l / min and two different upstream pressures in the nebuliser : 0.5 and 2.5 bars . We determined :
- the percentage of droplets of less than 6.4 µm

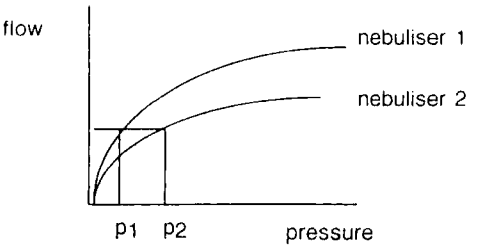

Figure 3 : Flow - pressure relation for nebuliser

- the percentage of nebulised drug
- nebulisation time

The results are presented in table 1 .

These results confirm the importance of the nebuliser and the operating conditions on the effectiveness of nebulisation .
The effectiveness of jet nebulisation is influenced by factors related to formulation and technology . The table 2 summarizes this .

II. ULTRASONIC NEBULISERS

1. Formulation

The influence of different formulation parameters , namely the nature of the nebulised form , surface tension , viscosity , concentration and isotonicity has been studied for jet nebulisers .For ultrasonic nebulisation , the influence of formulation is the same (12)(7) .

2. Volume

In the case of jet nebulisers , using larger volume fill increases aerosol delivery , as well as increasing nebulisation time (47)(48) . Drug concentration in the nebuliser solution is also to be observed (7) (10). Dead volume is in the range of 1 ml (49) .
Ultrasonic nebulisers often have larger capacity than jet nebulisers , so increased volumes of solution can be nebulised (6) (47) (48) .

3. Outside conditions

Aerosol droplets will be emitted into an environment at a certain temperature and relative humidity level . The effect of these parameters will be the same as for jet nebulisers .But in contrast to jet nebulisers , the temperature of the liquid in ultrasonic nebulisers is higher than the ambient temperature (between 10 and 20 °C according to the nebuliser) because part of the energy from the piezoelectric crystal is converted into heat (7)(10) (49). This increase in temperature may change the

TABLE 1
Influence of Nebuliser and Pressure on Nebulisation Efficiency

		Nebuliser A	Nebuliser B	Nebuliser C	Nebuliser D
%< 6.4 μm	2.5 bars	75.8 %	61.11%	91.3 %	100 %
	0.5 bar	64.9 %	50 %	65.5 %	80.60 %
% nebulised drug:	2.5 bars	79.65 %	67.43 %	58.27 %	36.17 %
	0.5 bar	73.43 %	65.22 %	50.02 %	32.46 %
Nebulisation time:	2.5 bars	16.5 min	10 min	28 min	18 min
	0.5 bar	42.5 min	17.5 min	85 min	32 min

TABLE 2
Relation between Formulation , Technological Parameters and Efficiency of Jet Nebulisation

	Size of droplets	Percentage nebulised	Nebulisation time
Formulation	+	+	+
Air flow	+	+	+
Pressure	+	+	+
Nebuliser	+	+	+
Ambiant conditions	+	+	–

+ : influence , – : no influence

surface tension and the viscosity of the liquid and thus affect the aerosol characteristics (49) .

4. Frequency of the vibrations of the quartz

The frequency of ultrasonic vibrations determines the size of aerosol droplets : an increase in operating frequency reduces particle size (6) (7) (9) (15) (28) (42). When the device operates in the kilocycle range (800 kHz) , a Mass Median Aerodynamic Diameter (MMAD) of up to 11μm can be obtained , but in the megacycle range (1-2 MHz) MMAD of between 4 and 7 μm are obtained (50) . According to Mercer (8) , waves are formed on the surface of the solution , with wavelength λ :

$$\lambda = (8 \pi \gamma / \rho f^2)^{1/3}$$

where f is the frequency of the ultrasonic vibrations and γ and ρ are the surface tension and density of the liquid .
When vibration amplitude is sufficiently high , wave crests break up to generate droplets with an average diameter of :

$$D = \alpha \lambda$$

where α is a proportionality coefficient .
High vibration frequency is necessary to obtain small droplet size but this may be incorrect for certain drugs which undergo chemical breakdown at such high frequency (13). This has been observed in particular for polypeptides (51).

5. Presence of a fan

Ultrasonic nebulisers possess a fan to blow aerosol out of the nebulisation chamber (48) . This fan makes it possible to regulate ventilation which can affect aerosol characteristics (47) . Ventilation will affect aerosol output , concentration of droplets in the aerosol , nebulisation time and particle size .

6. Intensity of setting

In most cases , an adjustment in ultrasonic intensity by modification of the amplitude of ultrasonic vibrations is possible . Intensity variations do not modify the size of aerosol droplets but act effectively on its concentration (14) . With maximum setting , mist will be dense and output high . But delivery can be less efficient with higher settings because more drug is lost to the walls of the nebuliser (49) (52) and particles are more likely to aggregate after formation in a dense mist (52) .

Ultrasonic nebulisation is influenced by factors related to formulation and technology . The table 3 summarizes this .

TABLE 3
Relation between Formulation , Technological Parameters and Efficiency of Ultrasonic Nebulisation

	Size of droplets	Percentage nebulised	Nebulisation time
Formulation	+	+	+
Frequency of the vibration of the quartz	+	–	–
Intensity of setting	–	+	+
Ventilation	+	+	+
Ambiant conditions	+	+	–

+ : influence , – : no influence

CONCLUSION

For aerosol generators such as nebulisers , the aerosol characteristics that influence location and the amount of deposition in the lungs are dependent upon :

. formulation
. type of nebuliser
. air flow and air pressure for jet nebulisers
. frequency of the vibrations of the quartz and intensity of setting for ultrasonic nebulisers
. ambiant conditions

Most of the time , the using of nebulisers is badly defined : neither nebulisation parameters , nor the type of nebuliser are specified for a given solution . However, it is of prime necessity to specify these parameters as they influence the particle size, the percentage of solution nebulised and the nebulisation time , that is to say the efficiency of nebulisation .
This suggests that each solution should be tested with different combinations of nebulisers and operating conditions , in order to determine optimal conditions . Thus , the efficiency of nebulisation could be guaranteed .
Particle size , percentage of nebulised solution and nebulisation time can be studied "in vitro" . When evaluating particle size , the equipment , the method and the operating conditions must be specified .

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