ELSEVIER

International Journal of Pharmaceutics 178 (1999) 101–109

international journal of pharmaceutics

Influence of formulation on jet nebulisation quality of α_1 protease inhibitor

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Received 30 March 1998; received in revised form 8 October 1998; accepted 23 October 1998

Abstract

As foam appears during solution constitution and nebulisation of α_1 protease inhibitor (α_1 PI), we selected in a previous work, antifoams likely to be associated with an α_1 PI solution to be nebulised: span 65 at a 0.025% concentration and cetyl alcohol at a 0.05% concentration associated with tyloxapol at 0.025% concentration. The purpose of this study was, on the one hand to study the influence of the formulation on nebulisation quality by relating physicochemical properties and nebulisation capacity, and on the other hand, to define the α_1 PI that will be retained for a clinical study. The properties of the different α_1 PI formulations are compared: surface tension, viscosity, time required to constitute the protein solution and pH. Nebulisation quality is evaluated under different operating conditions by measuring the droplet size, the quantity of α_1 PI nebulised, nebulisation time and the quantity of α_1 PI likely to reach the lungs which was subjected to statistical analysis. The statistical analysis of results indicates that the addition of the cetyl alcohol/tyloxapol mixture improves nebulisation effectiveness by significantly increasing the quantity of drug nebulised and therefore the quantity of α_1 PI likely to reach the lungs. It is this formulation that will be retained for clinical trials. We check that the nebuliser and operating conditions influence all the parameters, that is to say the respirable fraction, the quantity nebulised and the nebulisation time. Although there is no interaction between the nebuliser and the formulation, nebulisation quality is the combined result of the formulation, the nebuliser and the operating conditions.

Keywords: α_1 Protease inhibitor; Formulation; Antifoam; Surface tension; Nebulisation quality

1. Introduction

α_1 Protease inhibitor (α_1 PI) is a protein used in the treatment of pulmonary emphysema and is being considered for cystic fibrosis. As foam ap-

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0378-5173/99/$ - see front matter
PII: S0378-5173(98)00354-8

pears during solution constitution and nebulisation of α_1 PI, we already selected in a previous work antifoams likely to be associated with an α_1 PI to be nebulised and also described the interactions between α_1 PI and the antifoams tested (Flament et al., 1997a). Span 65 at a 0.025% concentration and cetyl alcohol at a 0.05% concentration associated with tyloxapol at a 0.025% concentration have an antifoaming capacity compatible with pulmonary administration of α_1 PI.

The aim of this work is 2-fold:

- to study the influence of the formulation on nebulisation quality by relating physicochemical properties and nebulisation capacity.
- to define the α_1 PI solution. The freeze drying conditions of this solution will be studied in a future work and the latter will be retained for a clinical study.

Variables such as surface tension and viscosity may influence the fragmentation into droplets (Moren, 1987) and therefore affect output and particle size (Davis, 1978; Davis et al., 1978; Clay et al., 1983a; Newman et al., 1985, 1986; Moren, 1987; Newman et al., 1987; Taylor et al., 1992; O' Doherty et al., 1993; Mc Callion et al., 1995, 1996a,b).

For Newman et al. (1986), an increase in surface tension by adding carbenicillin results in nebulisation times which are longer than those for saline solutions at an equivalent flow rate. Davis used co-solvents like ethanol and propylene glycol to modify the surface tension of the aqueous solution of drugs (Davis, 1978; Davis et al., 1978). Aerosol output depends on the concentration of the co-solvent. When the co-solvent is ethanol, an increasing proportion of ethanol results in decreasing surface tension and in greater total output from the nebuliser—both solution output and vapour output. The increase in output is greater for solvent vapour because of the higher volatility of ethanol.

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 (Davis, 1978; Davis et al., 1978).

Surface tension effect on the size of emitted droplets is much debated.

Mc Callion et al. (1996a) also reported that a lower surface tension increases the output but also the mass median diameter. Mercer (1973) reported that the primary droplets produced by atomization have a mass median diameter related to the liquid surface tension. However, this 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. (1983a) noted that increases in surface tension reduce the rate of aerosol released from the nebulisers but the effect on aerosol size distribution is small.

An increase in viscosity results in longer nebulisation times than those for saline solutions at equivalent flow rates and increases droplet size distribution (Davis, 1978; Newman et al., 1986). This can occur with antibiotic solutions which often have higher viscosity than saline solutions (0.83 mPa/s) (Newman et al., 1985), for example 2.13 and 2.75 mPa/s (Newman et al., 1986). For instance, Newman et al. (1985) reported that nebulisation times for gentamicin solutions (viscosity $\sim$50% higher than that of normal saline) were higher and droplet sizes larger than those observed for normal saline nebulised by Inspiron (Inspiron Minineb, Bard.) and Upmist (Medic. Aid, Hook Lane, Pagham, Sussex, UK P 021) nebulisers at 6 and 8 l/min. That is why higher flows may be necessary to nebulise effectively some viscous antibiotic solutions for respirable aerosol.

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 (Davis, 1978). This concords with Davis's findings in that an increased percentage of propylene glycol, decreases particle size by increasing viscosity (Davis, 1978). 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.

Mc Callion et al. (1996b) found that droplet size was inversely related to solution viscosity (over 1–6 cp). The surface tension largely re-

mained consistent. Beyond this critical value droplet size increased as viscosity increased.

Mallol (1993) 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.

We have previously studied the influence of technological parameters, that is to say the nebuliser and the dynamic conditions (airflow and pressure) on the nebulisation quality of an α_1 PI solution (Flament et al., 1997b). Upstream pressure in the nebuliser greatly influences nebulisation quality: the size of droplets emitted and the nebulisation time decrease with pressure but the quantity nebulised is not affected. Higher pressure increases the impaction speed on the impaction system which favours the disintegration of primary droplets, whereas variations with the airflow compressor are very low. However, this high pressure has to be compatible with administration to patients. Using a lower pressure, according to the clinical condition of the patient, can make it possible to obtain satisfactory granulometry if the characteristics of the formulation and the constituent nebuliser elements are favourable. The shape and size of the reservoir have an effect on dead volume and so on the quantity of drug nebulised. The diameter of the air tube orifice influences upstream pressure in the nebuliser and airflow at the outlet of the nebuliser: a narrower orifice increases upstream pressure in the nebuliser but decreases outlet airflow. The diameter of the orifice of the liquid tube is also important. A large diameter results in the aspiration of a considerable quantity of liquid which reduces the disintegration of primary aerosol and droplets are more likely to aggregate. The quantity drawn up will also depend on the airflow through the nebuliser, itself dependent on the diameter of the air tube orifice. The ratio of air tube orifice and liquid tube orifice is essential. When the impaction system is near the buzzard, its role is double: a retention effect of large particles, associated with a disintegration of primary aerosol. This influences the quantity nebulised per unit of time.

For this work related to formulation, the influence of nebulisation conditions (pressure, nebuliser) was taken into consideration.

2. Materials and method

2.1. Materials

A total of 5 ml of water for injection or 5 ml of aqueous antifoam dispersion was added to 100 mg of freeze dried α_1 PI (LFB, Lille, France).The antifoam dispersions studied were obtained by adding to water for injection:

either span 65 (ICI Speciality chemicals, Essen, Germany) at a 0.025% concentration;

or cetyl alcohol (Henkel, Boulogne Billancourt, France) at a 0.05% concentration associated with tyloxapol (SIGMA chimie, Saint-Quentin Fallavier, France) at a 0.025% concentration.

Four nebulisers representative of those on the market were used (Table 1). They differ as regards impaction system, the position and dimensions of air and liquid tubes and size and shape of the reservoir.

2.2. Method

2.2.1. Properties of the solution

The α_1 PI solutions were defined by their physicochemical properties in relation to nebulisation capacity: surface tension, viscosity. Time required to constitute the protein solution and the pH were also measured. Measurements of surface tension and viscosity were made at ambient temperature (20°C). The results are the mean of three replicate measurements.

2.2.1.1. Surface tension. The surface tension measurement method consists in measuring the force that has to be exerted on a platine/irridium stirrup piece, which is in contact with the solution surface, to stretch the interfacial liquid film. Surface tension measurements were made as soon as the solution was obtained, with a Lauda TD1 ten-

Table 1
Characteristics of the constituent nebuliser elements

	Air and liquid tubes	Reservoir shape	Reservoir diameter (mm)	Reservoir height (mm)	Diameter of the air tube orifice (mm)	Diameter of the liquid tube orifice (mm)	Liquid tube height (mm)	Impaction system
Up Draft HU 1705[a]	Concentric	Rounded	33	25	0.5	1	19	Sphere
Microneb NA 400[b]	Concentric	Slightly rounded	29	15	0.625	1.125	19	Sphere
NL 5[c]	Concentric	Rounded	38	17	0.75	1.25	16	Convex surface far away from the buzzard
Peters minineb[d]	Separate	Conical	38	46	0.75	2.5* 1.125**	36	Plan face

[a] Hudson Respiratory Care Inc., Temecula, CA, USA.
[b] Europe Medical UK Ltd, Fleet, UK.
[c] Diffusion Technique Française, St. Etienne, France.
[d] Hospitak, 10 Daniel Street, Farmingdale, NY 11735, USA.
* Aspiration orifice.
** Output orifice.

siometer (Prolabo, Paris, France), the measuring range of which is 0–100 mN/m, precision 0.1 mN/m and sensitivity 0.001 mN/m.

2.2.1.2. Viscosity. Viscosity of the solutions, the behaviour of which is Newtonian, was measured with a capillary viscosimeter following the method that is described in the European Pharmacopeia.

2.2.1.3. pH. pH of the α_1 PI solutions was measured with a CG 818 pH meter (Schott, Geräte, Hofheim, Germany).

2.2.1.4. Protein solution constitution. A comparison of solution constitution duration was made between a 100 mg α_1 P1 dose with 5 ml of water for injection and the same dose with 5 ml of antifoam dispersion. The temperature of protein reconstitution was ambient temperature (20°C). No agitation was employed to avoid foam formation. The end of solution constitution was considered to be reached when no freeze dried particles were visible to the naked eye.

2.2.2. Study of nebulisation quality

Trials had to be performed with two pressures. Indeed the influence of viscosity and surface tension depends on the pressure used. The pressures chosen were the extremes found: 0.5 and 2.5 bars. The airflow of the compressor when no nebuliser is connected was 16 l/min. Temperature and relative humidity were maintained constant, that is to say, at 20°C and 40–45%. The results are the mean of three replicate measurements.

Although droplet size is a commonly used parameter, it is not sufficient to forecast efficiency. It must be associated with the quantity of drug nebulised and, to a lesser extent, nebulisation time.

2.2.2.1. Percentage of droplets below 6.4 μm. Aerosol size distribution emitted from α_1 PI solution was determined with a laser size analyser Mastersizer (Malvern, Orsay, France). The solution was directly nebulised in the laser beam. After repeated testing, the measurement variation was 2.4%.

2.2.2.2. Quantity of α_1 PI nebulised. The amount of α_1 PI released as aerosol was obtained by dosing the amount remaining in the nebuliser by immunonephelometry with a 'Behring Nephelometer Analyser', precision being within 3%.

2.2.2.3. Quantity of α_1 PI likely to reach the lungs. The quantity of drug likely to reach the lungs can be calculated by associating the respirable fraction and the quantity of drug nebulised. The respirable fraction is the portion of the inhaler output that may be expected to penetrate the lungs during inhalation (USP XXIII, 1994).

When it is determined in aerodynamic conditions with the twin impinger as impactor, it is defined as the fraction below 6.4 μm, collected in the lower part.

In a previous study, we compared the granulometric fraction below 6.4 μm obtained with laser size analyser and twin impinger for the three α_1 PI solutions with and without antifoam (Flament et al., 1997b). Similar results were obtained with the two methods.

In the case of the α_1 PI solution, the laser size analyser commonly used will make it possible to define the fraction below 6.4 μm and to calculate the quantity of drug likely to reach the lungs.

2.2.2.4. Nebulisation time. This parameter is important for patient compliance and must be taken into consideration when evaluating the performance of nebulisers (Aiache, 1973). The end of nebulisation was considered when total aerosol production ceased. This aerosol was not tapped to assist aerosol production.

2.2.3. Analysis of data

The main parameter being the quantity of α_1 PI likely to reach the lungs, this was subjected to a statistical analysis using a variance analysis with three factors on independent series (ANOVA with three factors).

The effect of formulation and also of the nebuliser and the pressure on the parameter 'α_1 PI quantity likely to reach the lungs' was studied.

Comparisons of the means of individual groups were performed using Newman–Keul's test. For all analyses, $P < 0.05$ denoted significance.

Table 2
Solution constitution durations of 100 mg α_1 PI in 5 ml of diluent and pH of the obtained solutions

Diluent	Water for injection	Water for injection + 0.025% span 65	Water for injection + 0.05% cetyl alcohol and 0.025% tyloxapol
Solution constitution duration (min)	11 ± 1.2	8 ± 0.35	6 ± 0.25
pH	6.92 ± 0.02	6.95 ± 0.011	6.94 ± 0.006

Nebuliser 2 (Microneb NA 400) was eliminated because the α_1 PI quantity cannot be calculated under certain conditions.

3. Results

3.1. Physicochemical characteristics of the solution

Surface tension results of the α_1 PI solution with and without antifoam are the following:

- α_1 PI solution: 53 ± 0.13 mN/m.
- α_1 PI solution + 0.025% span 65: 49 ± 0.19 mN/m.
- α_1 PI solution + 0.05% cetyl alcohol and 0.025% tyloxapol: 47.5 ± 0.15 mN/m.

The presence of antifoam decreases surface tension, particularly in the case of a cetyl alcohol/tyloxapol mixture.

α_1 PI solution viscosity is the same for the three formulations. It is 1.25 mPa/s and is close to that with water.

Solution constitution durations of freeze dried α_1 PI and pH are presented in Table 2.

The decrease in surface tension improves solution constitution duration by making freeze-dried wetting easier and is expressed by the absence of foam during the α_1 PI freeze dried solution constitution.

3.2. Influence of formulation on nebulisation quality

3.2.1. Influence of formulation on the percentage of droplets below 6.4 μm

Table 3 presents the percentage of droplets below 6.4 μm obtained for the three α_1 PI formulations in different operating conditions. The trials showed that the presence of 'cetyl alcohol/tyloxapol' antifoam avoided foam projections that sometimes appeared during the nebulisation of the other two solutions.

3.2.2. Influence of formulation on the quantity of α_1 PI nebulised and nebulisation time

Table 4 presents the percentage of α_1 PI nebulised and the nebulisation time obtained for the three formulations nebulised in different operating conditions.

Microneb NA 400 is a particular case because when upstream pressure in the nebuliser is low, there are foam projections during the nebulisation of the α_1 PI solution without antifoam and that containing span 65. For the 2.5 bar pressure, some projections also appear with the α_1 PI solution without antifoam leading to a nebulised percentage lower than with the solution containing span 65.

3.2.3. Influence of formulation on the α_1 PI quantity likely to reach deep into the lungs

The results are presented in Table 5. A statistical analysis was envisaged to determine if the differences we observed are significant.

The results of the variance analysis show that there is no significant statistical interaction between formulation and nebuliser ($P > 0.0500$), between formulation and pressure ($P > 0.0500$), and between nebuliser and pressure ($P > 0.0500$), and that means of each factor significantly differ.

Means of each factor were analysed using the method of multiple comparison of means (Newman–Keuls test).

As regards the factor 'formulation', at the threshold of 0.05, there is a statistically significant

Table 3
Influence of formulation and operating conditions on the percentage of droplets below 6.4 μm and on the mean diameter

Formulation	α_1 PI solution		α_1 PI solution + 0.025% span 65		α_1 PI solution + 0.05% cetyl alcohol and 0.025% tyloxapol	
Nebuliser and pressure	% < 6.4 μm	Mean diameter	% < 6.4 μm	Mean diameter	% < 6.4 μm	Mean diameter
Up Draft						
0.5 bar	64.9 ± 2.1%	4.9 ± 0.37 μm	57.7 ± 2.3%	5.2 ± 0.38 μm	65.1 ± 1.25%	5.05 ± 0.11 μm
2.5 bars	75.8 ± 1.6%	4.4 ± 0.25 μm	72.9 ± 1.1%	4.45 ± 0.25 μm	72.5 ± 1.3%	4.70 ± 0.2 μm
Microned NA 400						
0.5 bar	66.5 ± 1.55%	4.85 ± 0.2 μm	65.2 ± 1.41%	4.83 ± 0.12 μm	67.4 ± 2.6%	4.85 ± 0.4 μm
2.5 bars	91.3 ± 2.1%	2.4 ± 0.14 μm	92.1 ± 2.05%	2.7 ± 0.2 μm	91 ± 2.4%	2.4 ± 0.3 μm
NL 5						
0.5 bar	80.6 ± 1.5%	4.3 ± 0.21 μm	77 ± 1.58%	4 ± 0.3 μm	83.9 ± 2.5%	3.4 ± 0.3 μm
2.5 bars	100 ± 0.01%	2.43 ± 0.3 μm	100 ± 0.01%	2.2 ± 0.17 μm	96.8 ± 1.6%	1.8 ± 0.01 μm
Peters minineb						
0.5 bar	50 ± 0.4%	7.8 ± 0.2 μm	52.05 ± 0.25%	7.3 ± 0.1 μm	50.66 ± 1.06%	7.8 ± 0.28 μm
2.5 bar	61.11 ± 1.2%	6.5 ± 0.2 μm	54.76 ± 2.2%	6.7 ± 0.1 μm	62.35 ± 1.3%	6.4 ± 0.15 μm

difference between the groups cetyl alcohol/tyloxapol mixture and span 65 and between the groups cetyl alcohol/tyloxapol mixture and water for injection.

As regards the factor 'nebuliser', at the threshold of 0.05, there is a statistically significant difference between the groups NL 5 and Up Draft and between the groups Peters and Up Draft.

As regards the factor 'pressure', at the threshold of 0.05, there is a statistically significant difference between the groups 0.5 and 2.5 bars Table 5.

4. Discussion

The statistical study indicates that the addition of cetyl alcohol and tyloxapol significantly improves the quantity of α_1 PI likely to reach the lungs.

Antifoam addition does not increase the respirable fraction. On the other hand, the quantity of α_1 PI nebulised is increased when the solution contains cetyl alcohol and tyloxapol, whatever the nebuliser and the pressure used.

The results concerning the particle size emitted show that for our study, it is the impaction system that determines the respirable fraction by selectively retaining large-sized primary droplets. The decrease in foam quantity and in the formation of primary droplets that are recycled in the nebuliser after contact with the impaction system are reflected by a decrease in the dead mass and an increase in the quantity of α_1 PI nebulised. This confirms the influence of the nebuliser design on aerosol size previously described by different authors (Mercer, 1973; Newman et al., 1985, 1986).

For the formulation tested, nebulisation time was not modified. On the other hand, we checked that the increase in pressure decreases nebulisation time, increases the respirable fraction but does not influence the quantity of drug nebulised. This has been reported previously by some authors (Clay et al., 1983b; Newman et al., 1986).

Even though the respirable fraction does not vary for the nebulisers tested with the formulation, the nebulisers significantly differ from one to another. The differences focus on the droplet size emitted, the nebulisation time, the quantity of α_1 PI nebulised and are related to differences in the characteristics of the constituent nebuliser elements.

Peters minineb nebuliser, the air and liquid tubes of which are separated, presents a higher

Table 4
Influence of formulation on the percentage of α_1 PI nebulised and nebulisation time when a 100 mg α_1 PI dose is nebulised with different nebuliser and pressure.

	α_1 PI solution		α_1 PI solution + 0.025% span 65		α_1 PI solution + 0.05% cetyl alcohol and 0.025% tyloxapol	
	0.5 bar	2.5 bars	0.5 bar	2.5 bars	0.5 bar	2.5 bars
% of α_1 PI solution						
Up Draft HU 1705	73.43 ± 4.6	79.65 ± 2.6	75.18 ± 1.25	77.25 ± 1.8	85.13 ± 1.9	86.2 ± 2.5
Microneb NA 400	–	58.27 ± 9.3	–	64.72 ± 0.9	50.02 ± 6.0	69.29 ± 1.85
NL 5	32.46 ± 3.7	36.17 ± 5.0	34.28 ± 5.0	36.50 ± 4.4	46.29 ± 5.0	47.6 ± 1.35
Peters minineb	65.22 ± 8.4	67.43 ± 5.6	66.87 ± 1.3	67.83 ± 3.4	73.56 ± 2.0	75.38 ± 1.43
Nebulisation time (min)						
Up Draft HU 1705	42.5 ± 2.3	16.5 ± 1.0	42 ± 4.5	15 ± 0.55	39 ± 4.5	15.5 ± 0.55
Microneb NA 400	–	28 ± 4.3	–	25 ± 1.80	85 ± 6.0	28 ± 1.9
NL 5	32 ± 3.6	18 ± 2.0	29 ± 2.8	14 ± 0.50	35 ± 1.25	16 ± 0.3
Peters minineb	17.5 ± 1.0	10 ± 0.86	16 ± 3.5	11 ± 0.7	17 ± 1.30	10 ± 0.85

orifice on the liquid tube which leads to the emission of bigger droplets. The NL 5 nebuliser differs as regards its impaction system placed far away from the buzzard which decreases the quantity nebulised per unit of time, increases the loss on the walls and leads to a lower quantity nebulised. The Microneb NA 400 nebuliser, unlike the Up Draft HU 1705 nebuliser, possesses a less rounded reservoir and does not have rectangular parts vertically arranged around the liquid tube, which explains the lower quantity nebulised.

For this solution, formulation only influences the quantity of drug nebulised. As the viscosities of the solutions are the same, this influence is mainly related to the surface tension. Our results are in agreement with those of Mc Callion et al. (1996a,b). The formation of small droplets that results in the increase in surface is facilitated by the decrease in surface tension. The path of droplets is not modified by the baffles. The reduction in surface tension results in an increased drug output.

Table 5
Influence of formulation on the calculated α_1 PI quantity (mg) likely to reach deep into the lungs for a 100 mg dose nebulised with different nebulisers and pressures

	α_1 PI solution	α_1 PI solution + 0.025% span 65	α_1 PI solution + 0.05% cetyl alcohol and 0.025% tyloxapol
Up Draft HU 1705			
2.5 bars	60.37 ± 0.05	56.31 ± 0.02	62.50 ± 0.03
0.5 bar	47.65 ± 0.1	43.67 ± 0.03	55.42 ± 0.025
NA 40			
2.5 bars	53.20 ± 0.19	59.60 ± 0.02	63.00 ± 0.045
0.5 bar	–	–	33.37 ± 0.15
NL 5			
2.5 bars	36.17 ± 0.005	36.50 ± 0.005	46.07 ± 0.02
0.5 bar	26.16 ± 0.05	26.39 ± 0.08	38.38 ± 0.125
Peters minieb			
2.5 bars	41.20 ± 0.06	37.14 ± 0.075	46.99 ± 0.02
0.5 bar	32.61 ± 0.035	34.88 ± 0.003	37.26 ± 0.02

On the other hand, the nebuliser and operating conditions influence all the parameters, that is to say the respirable fraction, the quantity nebulised and the nebulisation time.

Although there is no interaction between the nebuliser and the formulation, nebulisation quality is the result of the formulation, the nebuliser and the operating conditions.

5. Conclusion

Nebulisation effectiveness is improved when the antifoam mixture cetyl alcohol associated with tyloxapol is added to the α_1 PI solution. The surface tension decrease increases the quantity of α_1 PI nebulised. It is this formulation that will be retained for clinical trials. A study of the freeze drying conditions of this formulation is being considered.

The choice of the surfactants added to the drug solution is limited because of the administration route. Those retained here produced only a slight decrease in the surface tension.

For the most important drugs, it seems indispensable for a liquid preparation to be nebulised to define the formulation for which the appropriate nebulisers and conditions of use are associated to obtain adapted and reproducible activity.

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