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Jet nebulisation: influence of dynamic conditions and nebuliser on nebulisation quality. Application to the α1 protease inhibitor

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Abstract

The use of nebulisers lacks standardisation, which may account for certain inefficiency. As part of a study of α1 protease inhibitor (α1 PI) nebulisation for pulmonary administration, we studied the influence of technological parameters that is to say the nebuliser and the dynamic conditions (airflow and pressure) on nebulisation quality. The quality of nebulisation is evaluated by measurement of the percentage of droplets below 5.79 μm, the quantity of α1 PI nebulised, the quantity of α1 PI likely to reach the lungs and nebulisation time. The use of different dynamic conditions results in variable nebulisation quality. Depending upon the power of the compressor and the type of nebuliser, drug delivery varies. The association of high airflow and high pressure improves the respirable fraction and compliance by decreasing nebulisation time. 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. The nebuliser is also to be taken into consideration. The characteristics of the constituent nebuliser elements, that is to say liquid and air tube orifices, size and shape of the reservoir, shape and position of the impartion system, are preponderant on nebulisation quality. © 1997 Elsevier Science B.V.

Keywords: α1 Protease inhibitor; Nebuliser; Dynamic conditions; Droplet size; Quantity of drug nebulised; Nebulisation time

1. Introduction

In most cases, the nebulisation of a solution does not take into account administering conditions that may explain a lack of efficiency in some cases or even the ineffectiveness of some treat-

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ment by nebulisation. Nebulisation quality is generally evaluated by a size-limit test to which it seems important to us to associate other parameters. Typically,a nebuliser is associated with a compressor whose pressure and airflow are fixed, whatever the model. It seems interesting to us to study the influence of dynamic factors, that is to say airflow and pressure, on nebulisation quality. We have compared nebulisation obtained from nebulisers in which the characteristics of the constituent nebuliser elements are different. This study is carried out with an $\alpha 1$ protease inhibitor solution. This is usually applied by the intravenous route for the treatment of pulmonary emphysema and is under consideration for cystic fibrosis. Administration by inhalation could make it possible to improve the quantity available in the lungs and to decrease side-effects. From our results, we shall define the nebulising conditions and the characteristics of the constituent nebuliser elements in relation to nebulisation quality.

Table 1
Nebulisers tested

Nebuliser	Manufacturer
Up Draft HU 1705	Hudson Respiratory Care Inc., Temecula, CA, USA
Misty Neb	Baxter Healthcare Corporation, Pharmseal Division, Valencia, USA
Peters Minineb	Hospitak, 10 Daniel Street, Farmingdale, NY 11735, USA
System 22	Medic Aid, Pagham, UK
Microcirrus	Intersurgical, Twickenham, UK
Pari LC	Pari, Starnberg, Germany
Pari Baby	Pari, Starnberg, Germany
Euroneb RN 300	Europe Medical UK Ltd, Fleet, UK
Microneb NA 400	Europe Medical UK Ltd, Fleet, UK
Rotaneb NA 10	Europe Medical UK Ltd, Fleet, UK
Optineb 1200 A Sidestream Nebuliser	Medic Aid, Pagham, Sussex, UK
NL 9	Diffusion Technique Française, St. Etienne, France
NL 7	Diffusion Technique Française, St. Etienne, France
NL 5	Diffusion Technique Française, St. Etienne, France

2. Materials and methods

2.1. Materials

A solution containing 100 mg of $\alpha 1$ protease inhibitor ($\alpha 1$ PI) (CRTS, Lille, France) and 5 ml of sterile water for injection is nebulised.

Fourteen nebulisers are compared using the same $\alpha 1$ PI solution (Table 1). Nebulisers differ, in particular in the characteristics of air and liquid tubes. Two patterns of liquid and air tubes exist: either air is introduced through the lower part of the reservoir by a system of two concentric perforated tubes, or there is an air jet quite separate from the capillary through which the liquid to be aerosolised is drawn into the air stream (Fig. 1). We have therefore measured the characteristics of the constituent nebuliser elements that may differ:

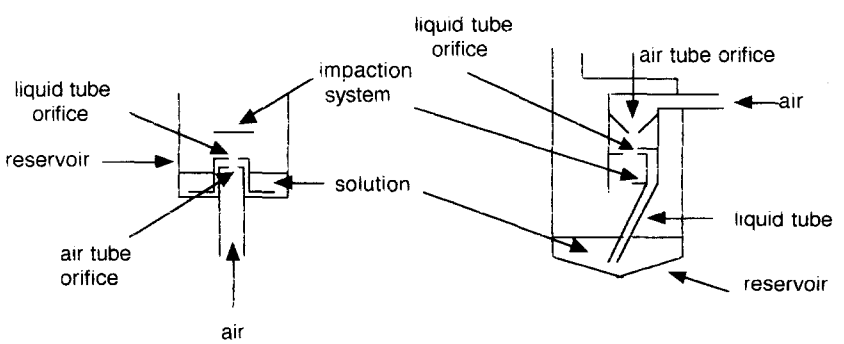

Fig. 1. Characteristics of the air and liquid tubes.

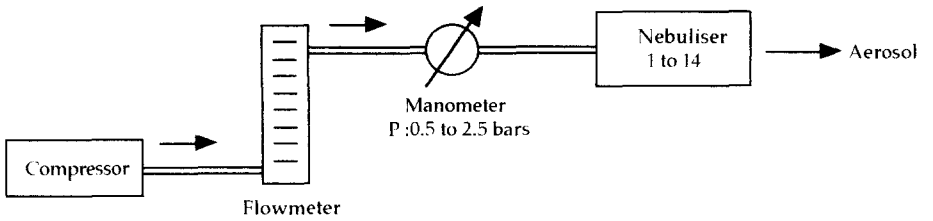

Fig. 2. Apparatus used to measure airflow and pressure.

the size and shape of the reservoir, the characteristics of air and liquid tubes, the shape dimensions and position of the impaction system (Table 2). When air and liquid tubes are separate, nebulisation involves the two liquid tube orifices we shall measure: the one that makes liquid aspiration possible, the one that makes liquid output possible. A compressor for which airflow and pressure are adjustable supplies the air needed by the nebuliser. The compressor capacities are 30 l/min and 10 bars. Pre-determined conditions of airflow and pressure are applied to the nebulisers containing the α1 PI solution. Temperature and relative humidity are maintained constant, that is to say, at 20°C and 40–45%.

2.2. Method

We have studied, on the one hand, the influence of airflow and pressure for each nebuliser and on the other hand the influence of the nebuliser on nebulisation quality. For the first part, free airflow from the compressor—that is to say airflow when no nebuliser is connected to the compressor—varies between 6 and 16 l/min and upstream pressure in the nebuliser from 0.5 to 2.5 bars. Airflow between compressor and nebuliser is also measured (Fig. 2). To study the influence of the characteristics of the constituent nebuliser elements, identical conditions of airflow and pressure, that is to say 16 l/min–2.5 bars, are applied to the nebulisers. For Rotaneb NA 10, the conditions used are 16 l/min–1.5 bars which are the maximum conditions for this nebuliser. Optineb comes equipped with an oxygen cylinder permitting an airflow of 18 l/min and an upstream pressure in the nebuliser of 3.5 bars.

2.3. Evaluation of nebulisation quality

The quality of nebulisation is evaluated by:

2.3.1. Percentage of droplets below 5.79 μm

Aerosol size distribution emitted from α1 PI solution is determined with a laser size analyser Mastersizer[1]. The solution is directly nebulised in the laser beam. After repeated testing, the measurement variation is 2.4%.

2.3.2. Quantity of α1 PI nebulised

The amount of α1 PI released as aerosol is obtained by dosing the amount remaining in the nebuliser by immunonephelometry with a 'Behring Nephelometer Analyser' whose precision is within 3%.

2.3.3. Quantity of α1 PI likely to reach the lungs

The quantity of drug likely to reach the lungs can be evaluated 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).

2.3.4. Nebulisation time

This parameter is important for patient compliance and must be taken into consideration when evaluating the performance of nebulisers (Aiache, 1973).

[1] Malvern, Orsay, France.

Table 2
Characterisitics 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	Concentric	Rounded	33	25	0.5	1	19	Sphere
Misty Neb	Concentric	Conical	30	20	0.625	1.25	12	Sphere
System 22	Concentric	Slightly pyramidal	32	23	0.75	1	18.5	Sphere
Microcirrus	Concentric	Pyramidal	39	28	0.625	1	20	Sphere
Pari LC	Concentric	Conical	33	30	0.5	1.375 × 3.5 (oval)	22 (conical)	Bar
Pari baby	Concentric	Conical	42	30	0.5	1.25 (two orifices)	20 (conical)	Bar
NL5	Concentric	Rounded	38	17	0.75	1.25	16	Convex surface far away from the buzzard
NL7	Concentric	Rounded	50	19	0.75	1.375	20	Convex surface far away from the buzzard
NL9	Concentric	Rounded	45	17	0.75	1.25	19	Bar
Optineb	Concentric	Rounded	34	30	0.70	0.95 (two orifices)	27	Bar
Microneb NA 400	Concentric	Slightly rounded	29	15	0.625	1.125	19	Sphere
Rotaneb NA 10	Concentric	Rounded	39	55	1	1.25	42	Bar + sphere
Euroneb RN 300	Separate	Conical	44	55	0.625	1.75[a], 0.875[b]	53	Plan surface
Peters Minineb	Separate	Conical	38	46	0.75	2.5[a], 1.125[b]	36	Plan surface

[a] Aspiration orifice.
[b] Output orifice.

Table 3
Comparison of the percentage of droplets (% vol) below 6.4 μm obtained with an Up Draft nebuliser by Twin Impinger and laser for α1 PI solution

	Solution 1		Solution 2		Solution 3	
	Twin impinger	Laser	Twin impinger	Laser	Twin impinger	Laser
Operating condition 1	77.2%	75.8%	77.4%	72.9%	73.2%	72.6%
Operating condition 2	65%	64.9%	58.8%	57.7%	Irregular emission of aerosol	

Repeatability: Twin Impinger, 5.5%; Laser, 2.4%.

3. Results and discussion

To compare the influence of nebulising conditions, the quantity of droplets below a defined size can be determined with a laser size analyser. But, to evaluate the respirable fraction, droplet size is determined in aerodynamic conditions with an impactor. We used a simple cascade impactor, the Twin Impinger, described in the British Pharmacopeia (1993), the USP XXIII (1994) and the European Pharmacopeia (1995). It is a glass collector which makes it possible to separate the emitted dose into particle sizes inferior and superior to 6.4 μm; the fraction below 6.4 μm being the respirable fraction (Hallworth and Westmoreland, 1987; Aiache et al., 1993; Atkins, 1993). Because the Twin Impinger presents a cut-off of 6.4 μm, we compared for the α1 PI solution, the granulometric fraction below 6.4 μm obtained with laser size analyser and Twin Impinger for three α1 PI solutions differing in the presence of a superficially active agent. Results obtained with a given nebuliser, the Up Draft nebuliser, for two types of dynamic conditions are presented in Table 3. Similar results are obtained with the two methods. With the Twin Impinger, separation depends on the kinetic energy of the droplet which is itself a function of the mass. With laser size analyser, distribution is made according to particle volume (Newman et al., 1986; Ranucci, 1992; O'Doherty and Miller, 1993). The α1 PI solution density of 1 g/cm^3 and the spherical shape of the droplets measured account for the percentage of droplets below 6.4 μm being the same with laser size analyser and Twin Impinger.In the case of the α1 PI solution, the laser size analyser commonly used will make it possible to define the fraction below 5.79 μm and from this fraction to calculate the quantity of drug likely to reach the lungs.

3.1. Influence of airflow and pressure on nebulisation quality

All the nebulisers studied (Table 1) present the same behaviour when airflow and pressure vary except NL7 and NL9 that give projections of liquid and foam during nebulisation because of their too small and wide reservoirs. Consequently they have been excluded from all the experiments. Table 4 presents, for different combinations of airflow and pressure, the percentage of droplets below 5.79 μm obtained with a Pari LC nebuliser which is representative of the behaviour of the other nebulisers. An increase in the free airflow of the compressor for any given pressure has no influence on the airflow measured between compressor and nebuliser because the orifice of the air tube acts as an 'obstacle', a throttle that does not make it possible to increase the airflow at the outlet of the nebuliser even if the free airflow of the compressor increases. However, there is a relation between the free airflow of the compressor and upstream pressure in the nebuliser. If this airflow is too low, high pressure upstream in the nebuliser cannot be obtained. Airflow and pressure are characteristic for a given nebuliser. In general, results show that the percentage of droplets below 5.79 μm increases with pressure. Higher pressure increases the impaction speed on the impaction system which favors the disintegration of primary droplets. Because of the small variations to be noted for differing free airflow rates, we shall retain only the influence of upstream pressure in the nebuliser on the percentage of α1 PI nebulised and nebulisation time.

Table 4
Influence of airflow and pressure on percentage of aerosol droplets below 5.79 μm produced by Pari LC for α1 PI solution

Free airflow (l/min)	Pressure				
	0.5 bar	1 bar	1.5 bars	2 bars	2.5 bars
6	31.55%	49.86%	Not feasible	Not feasible	Not feasible
8	30.08%	50.92%	55.19%	59.96%	Not feasible
10	31.95%	51.04%	54.77%	63.09%	Not feasible
12	39.76%	51.08%	55.27%	64.94%	65.57%
14	36.63%	49.93%	54.89%	62.64%	67.43%
16	36.99%	49.79%	59.40%	63.38%	71.82%
Airflow measured between compressor and nebuliser (l/min)	2.5	3.5	4	5	6

These two parameters are determined for extreme nebulising pressures, i.e. 0.5 bar and 2.5 bars. To obtain this high pressure whatever the nebuliser, we have used a compressor free airflow of 16 l/min. Table 5 presents the percentage of α1 PI nebulised and the nebulisation time obtained with three nebulisers.The variation in the quantity nebulised for extreme conditions of airflow and pressure is small. On the other hand, nebulisation time decreases with an increase in pressure.

Our study demonstrates the importance of pressure on size and nebulisation time, but it has no influence on the quantity nebulised. The association of high airflow and high pressure favours nebulisation efficiency. That is why we have retained compressor free airflow as fixed airflow at a rate of 16 l/min, and upstream pressure in the nebuliser at a value of 2.5 bars.

3.2. Nebuliser influence

For each nebuliser tested in the defined dynamic conditions, we evaluated nebulisation quality (Table 6). The results indicate that in addition to airflow and pressure conditions, the influence of the nebuliser on the nebulising efficiency of α1 PI solution is considerable. Some nebulisers like Microcirrus have a very high percentage of droplets below 5.79 μm but this does not make it possible to nebulise a large quantity of α1 PI, despite a prolonged nebulisation time. On the other hand, other nebulisers like Misty Neb have a lower percentage of droplets below 5.79 μm but the quantity of α1 PI nebulised is high and nebulisation time very acceptable.

The association of the percentage of droplets below 5.79 μm and the quantity of α1 PI nebulised for a 100-mg administered dose enabled us to calculate the quantity of α1 PI that is assumed to reach the lower part of the respiratory tract (Table 7). It can be noted that nebulisers for which the percentage of droplets below 5.79 μm is lower like NL5 for example, are not those which make it possible to deliver a higher quantity of α1 PI into the lower part of the respiratory tract. The high losses observed with the NL5 nebuliser lead to a decrease in the quantity of drug available for the patient. For some nebulisers, the α1 PI quantity likely to reach deep into the lungs is similar but the nebulisation time is very different. In this case, the nebuliser with lower nebulisation time is to be preferred. This is observed with Microcirrus and Up Draft HU 1705 where the quantity of α1 PI likely to reach deep into the lungs is 49.90 mg and 51.66 mg, respectively, but nebulisation time is 42 min 30 and 16 min 30. In the experimental conditions used, the System 22 nebuliser associates a high quantity of α1 PI likely to reach deep into the lungs and a favourable nebulisation time for treatment compliance by patients.

The use of different nebulisers leads us to conclude that nebulising quality can be estimated in terms of quantity of drug likely to reach the lungs although nebulisation time is also to be taken into consideration. For the same operating conditions, it varies between 9 min and 42 min 30. These

Table 5
Influence of pressure on the percentage of α1 PI nebulised and the nebulisation time for three different nebulisers

		Peters Minineb	NL5	Up Draft HU 1705
% of α1 PI nebulised	16 l/min–0.5 bar	65.20%	32.50%	73.50%
	16 l/min–2.5 bars	67.40%	36.20%	79.5%
Nebulisation time	16 l/min–0.5 bar	17.5 min	32 min	42.5 min
	16 l/min–2.5 bars	10 min	18 min	16.5 min

differences suppose variations in patient compliance and the elimination of conditions for which nebulisation time is as high as 42 min 30.

It therefore seems interesting to define the characteristics of the constituent nebuliser elements in relation to the efficiency of these same nebulisers.

The shape and size of the reservoir have an effect on dead volume. Rounded or conical shapes allow for better recuperation of the non-emitted droplets which drip back to the base of the liquid tube, so making their reaspiration into the tube easier. Some nebulisers like System 22, Up Draft and Pari LC have rectangular parts vertically arranged around the liquid tube which improve the drip back of droplets into the reservoir. In this respect, a higher reservoir will cause greater drug loss because it will take more time for the liquid to trickle down the walls. However such a reservoir will be well-suited to highly nebulised doses.

The diameter of the air tube orifice influences upstream pressure in the nebuliser. When a non-adjustable compressor, the most usual kind, is associated with different nebulisers, the narrower the orifice, the higher the upstream pressure in the nebuliser. Some compressors have a low free airflow and are not powerful enough to ensure high upstream pressure in the nebulisers particularly if they have large air tube orifice. For example, in our study, with a free airflow of 8 l/min, it was not possible to obtain a pressure of 1.5 bars with NL5, Peters, System 22 and Rotaneb NA 10 nebulisers which present the largest air tube orifices: 1 mm for Rotaneb NA 10 and 0.75 mm for the others. The diameter of the air tube orifice also influences airflow at the outlet of the nebuliser. An increase in diameter increases outlet airflow, for the same conditions of pressure and free airflow of the compressor. Airflow after connecting four nebulisers with different air tube orifice is presented in Table 8 for the same conditions.

For some applications particularly as far as children are concerned, too high an airflow at the outlet of the nebuliser (for example 9 to 10 l/min) is not acceptable. This limitation of outlet airflow is one of the selection criteria of the nebuliser and of the pressure to be applied during nebulisation.

The diameter of the orifice of the liquid tube is also of importance. A large diameter leads to 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, it makes the disintegration of primary aerosol into lower-size droplets possible. In this case, the role of the impaction system is double: a retention effect of large particles, associated with a disintegration of primary aerosol. This is observed with nebulisers like System 22, Up Draft HU 1705 or Pari LC. When it is far away from the buzzard, the impaction system simply acts by retaining large droplets, without causing disintegration of primary aerosol. The quantity nebulised per unit of time decreases. This is the case for the NL5 nebuliser.

The shape of the impaction system must also be taken into consideration. Indeed, the rounded shape of an impaction bar will be less favourable to disintegration and retention of large droplets than a rectangular shape because droplets will be inclined to slide on it. On the other hand, some nebulisers possess chicanes as well as the im-

Table 6
Influence of nebuliser on the nebulising efficiency of α1 PI solution

Nebuliser	%<5.79 μm	% of α1 PI nebulised	Nebulisation time (min)
Peters Minineb	65.91%	67.43%	10
Euroneb RN 300	86.55%	66.04%	17
Misty Neb	56.75%	84.20%	11
Up Draft	64.86%	79.65%	16.5
System 22	84.66%	85.33%	11.5
Microneb NA 400	91.20%	58.27%	28
Microcirrus	99.80%	50.00%	42.5
Pari LC	71.82%	79.66%	9
Pari Baby	96.60%	63.66%	30
Rotaneb NA 10	89.95%	66.39%	14.5
NL5	95.66%	36.17%	18
Optineb	88%	69.25%	20*

Conditions for all nebulisers: 16 l/min–2.5 bars, except for Rotaneb NA 10: 16 l/min–1.5 bars; Optineb: 18 l/min–3.5 bars.
* For continuous working of the oxygen cylinder and uninterrupted nebulisation of the drug.

paction system. They act by changing airstream direction, which leads to the retention of large droplets. The size and shape of these chicanes are varied, which more or less modifies airstream direction.

Table 9 summarizes the relation between the characteristics of the constituent elements of nebuliser and nebulisation quality.

Table 7
Calculated quantity of α1 PI likely to reach the lower part of the respiratory tract after nebulisation of 100 mg α1 PI with different nebulisers

Nebuliser	Quantity (mg) of α1 PI likely to reach the lower part of the respiratory tract
Peters Minineb	44.44
Euroneb RN 300	57.15
Misty Neb	47.78
Up Draft HU 1705	51.66
System 22	72.20
Microneb NA 400	53.14
Microcirrus	49.90
Pari LC	57.21
Pari Baby	61.49
Rotaneb NA 10	59.71
NL5	34.60
Optineb	60.94

For all nebulisers: 16 l/min–2.5 bars, except for Rotaneb NA 10: 16 l/min–1.5 bars; Optineb: 18 l/min–3.5 bars

4. Conclusion

Our study was carried out with an α1 PI solution, chosen because of its therapeutic interest. It enabled us to define the influence of dynamic conditions and the characteristics of the constituent elements of a nebuliser on nebulisation quality. 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. It is interesting that the fraction likely to reach the lungs can be determined with a laser size analyser, its use being simpler than impactors.

Table 8
Airflow after connecting the nebuliser as a function of air tube orifice for some nebulisers in these conditions

Nebuliser	Air tube orifice (mm)	Airflow after the connecting of the nebuliser (l/min)
Rotaneb NA 10	1	7
NL5	0.75	4
Misty Neb	0.625	3
Pari Baby	0.5	2

Free airflow of the compressor: 16 l/min; pressure: 2.5 bars.

Table 9
Relation between the characteristics of the constituent nebuliser elements and nebulisation quality

	Liquid and air tube orifices	Shape and size of the reservoir	Shape and position of the impaction system
Droplet size	Influence	—	Influence
Total quantity of drug nebulised	—	Influence	—
Nebulisation time	Influence	Influence	Influence

This is possible only if the medicinal preparation droplets have a density close to 1 and are spherical. The association of high airflow and high pressure improves the respirable fraction and compliance by decreasing nebulisation time. However, these conditions have to be compatible with administration to patients. The characteristics of the constituent nebuliser elements, that is to say liquid and air tube orifices, size and shape of the reservoir, shape and position of the impaction system, are preponderant on nebulisation quality. In the case of favourable characteristics, a satisfactory granulometry can be obtained even if pressure is small. Nebulisation quality is the result of the association of dynamic conditions and nebuliser.

We think it is indispensable that solutions for nebulisation should be subjected to thorough pharmaceutical trials before use to define the best adapted nebuliser(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 for nebulisation the droplet size of which greatly influences drug therapeutic activity, it seems important to us to define, justify not only the formulation but also to associate with it the proper nebuliser(s) and the using conditions. This is the case for both specialities Pentacarinat[2] containing pentamidine and Pulmozyme[3] containing dornase alfa that obtained the Marketing Authorization Application file in 1989 and 1994.

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[2] Bellon (Rhône Poulenc Rorer), Neuilly sur Seine, France

[3] Produits Roche, Neuilly sur Seine, France