Understanding The Relationship Between Formulation Viscosity And Nebuliser Performance

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Summary

The use of nebulisers for aerosol drug delivery continues to be important, especially within a clinical environment. This has led to the continued development of novel nebuliser systems, with the goal of improving the drug delivery rate whilst maintaining the small aerosol droplet sizes required for drug deposition within the respiratory tract. In this study, we have employed the technique of laser diffraction system (Malvern Spraytec) to study the changes in particle size and concentration which occur during inhalation through a nebuliser, for solutions with different viscosities. The study shows how increasing the viscosity of the nebulised liquid has a significant impact on the particle size and concentration of the delivered aerosol, and helps to reveal the primary mechanisms for aerosolisation. This provides insight into how formulation and device parameters can be varied to achieve the desired performance.

Introduction

Aerosol inhalation is widely recognised as an important route of administration for the delivery of both locally and systemically acting drugs. Within this, the use of nebulisers continues to be important when treating young children and the elderly, especially within a clinical environment. Nebulisers allow for the delivery of a wide range of solution and suspension based formulations, and offer advantages over other aerosol delivery systems in that mechanical damage, which may cause degradation of 'fragile' drug compounds such as proteins and peptides, is minimised. Nebulisers also allow high doses of drug to be delivered, with minimal coordination effort required due to the fact that delivery occurs during unforced, tidal breathing conditions. These advantages have led to the continued development of novel nebuliser systems, with the goal of improving the rate of drug delivery whilst maintaining the small aerosol droplet sizes required for efficient drug deposition within the respiratory system.

Traditionally, characterisation of the output of nebuliser devices has been performed through a combination of dose collection (in order to understand the rate of drug delivery) and impactor analysis (for droplet sizing). Although the use of these techniques remains critical in understanding product performance, they do not provide any information regarding how the output of a nebuliser changes over the full duration of an inhalation manoeuvre. This can impact the ability to both understand how aerosolisation is achieved and link the performance observed to the formulation properties.

In this study, we employ on the technique of laser diffraction[1] (Spraytec, Malvern Instruments) to study the output of a breath-actuated, jet nebuliser in terms of the time-dependant droplet size and aerosol concentration, for three Newtonian liquids with different viscosities. A sinusoidal breath simulator (BRS1000, Copley Scientific) was used to set-up realistic breathing profiles, allowing the plume to be studied during both inhalation and exhalation.

Sample Preparation

Three liquids were prepared for nebulisation: deionised water (Newtonian viscosity = 0.89 mPa s), an aqueous solution of 0.5w/v% Polyvinylpyrrolidone (PVP) K90 (Newtonian viscosity = 0.92 mPa s) and an aqueous solution of 1.0w/v% PVP K90 (Newtonian viscosity = 1.9 mPa s). Each of these liquids was loaded into a gas-powdered, breath-actuated nebuliser, and the output of the nebuliser was measured at a driving gas flow rate of 4 l/min and 7 l/min using the technique of laser diffraction (Spraytec, Malvern Instruments). The time dependence of the droplet size and the aerosol concentration was determined for a simulated breathing rate of 20 breaths per minute, using a tidal volume of 500mls and an inhalation:exhalation ratio of 1:1; as generated by a sinusoidal breathing simulator (BRS1000, Copley Scientific). A 0.2 micron filter was placed directly after the laser diffraction measurement zone in order to capture any droplets prior to them reaching the breathing simulator.

Results and Discussion

A typical size history profile, recorded for nebulisation of deionised water at a driving gas flow rate of 7l/min, is shown in figure 2. The measured transmission level relates directly to the aerosol concentration, with lower transmissions correlating with higher concentrations. As can be seen, the aerosol concentration increases rapidly at the start of the inhalation manoeuvre, reaching a maximum after approximately 0.6 seconds. Some fluctuations in the measured Dv90 (particle size below which 90% of the volume of particles exists) are observed as the concentration increases, relating to the delivery of large particles which were probably trapped in the nebuliser mouthpiece following a previous inhalation cycle. By contrast, the Dv10 and Dv50 are relatively stable during inhalation. At the point where the exhalation cycle starts, another increase in concentration occurs, as aerosol in the void between the laser diffraction system and the filter is flushed back through the measurement zone. Coalescence of the droplets within this portion of the aerosol causes an increase in the Dv90 and Dv50 towards the end of the size history profile, until the aerosol concentration finally reaches the point where laser diffraction measurements are no longer possible.

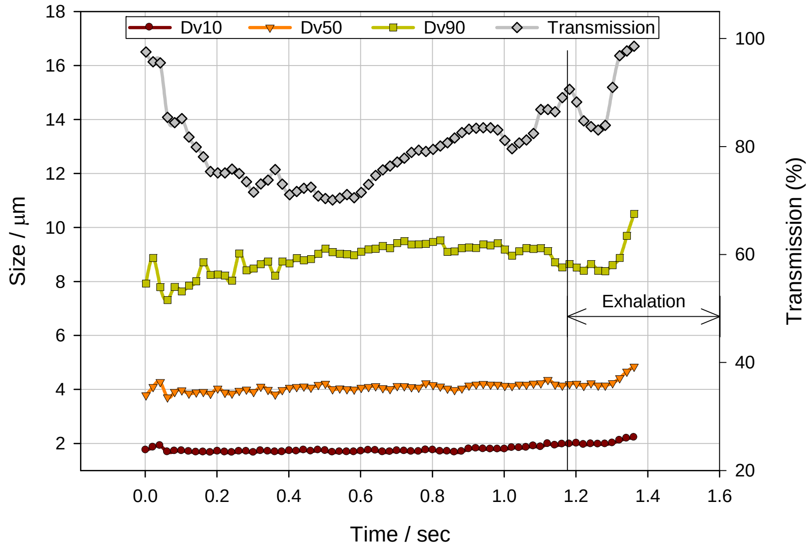

Figure 1: Size History profile recorded using laser diffraction for deionised water. The driving gas flow rate was set at 7 l/min. For clarity, every 10th data point is marked.

Viscosity Dependence

The changes observed in the output of the nebuliser as the PVP concentration is increased from 0w/v% to 1.0w/v% are show in figures 2 and 3 for driving gas flow rates of 4 l/min and 7 l/min respectively.

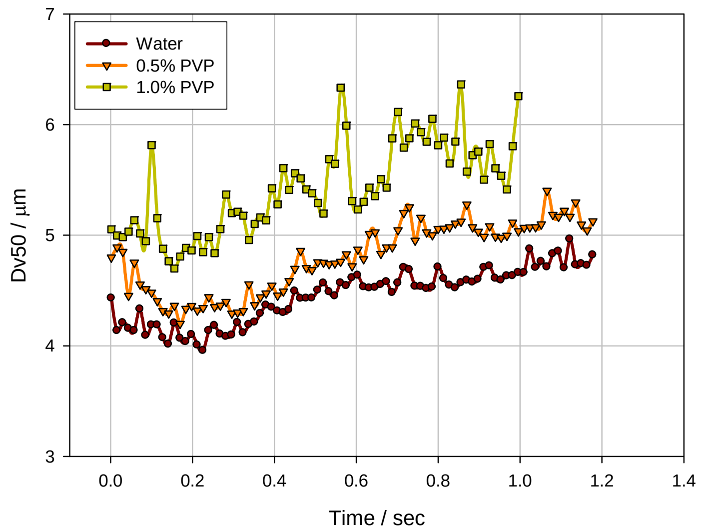

Figure 2: Dv50 profiles measured for each of the 3 nebuliser solutions, using a driving gas flow rate of 4lpm. Only data obtained during the inhalation part of the breathing profile are shown. For clarity, every 7th data point is marked.

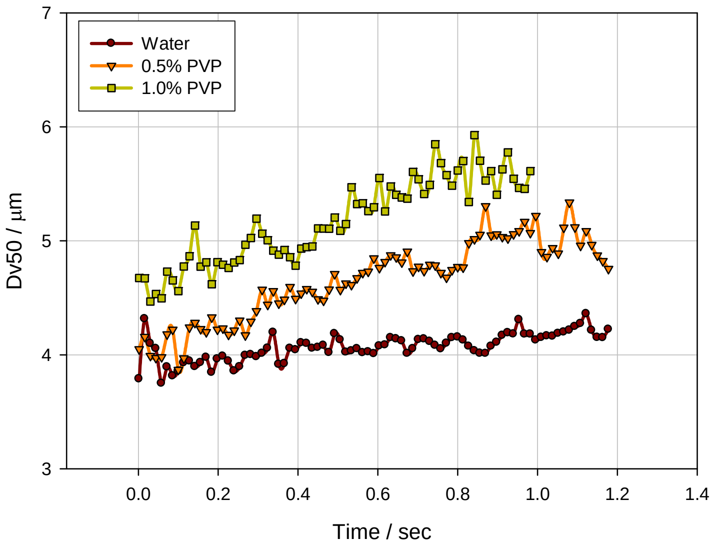

Figure 3: Dv50 profiles measured for each of the 3 nebuliser solutions, using a driving gas flow rate of 7lpm. Only data obtained during the inhalation part of the breathing profile are shown. For clarity, every 7th data point is marked.

A significant increase in the measured Dv50 is observed as the PVP concentration is increased, tracking the increase in the solution viscosity. The profiles obtained at 4 l/min are shifted to larger particle sizes compared to those observed at 7 l/min, as the energy available for nebulisation is less at lower gas flow rates. In both cases, droplets are observed throughout the inhalation process for deionised water and the 0.5w/v% PVP solution. However, for the 1.0% PVP solution the nebuliser delivers droplets over a significantly shorter time period, suggesting that the energy available for nebulisation is only just able to overcome the viscosity of the solution. Indeed, at 4 l/min driving gas, significant variations in the Dv50 are observed for this solution throughout the inhalation cycle, suggesting that the device is no longer operating well.

The above results are confirmed in table 1, where the concentration-weighted average and Relative Standard Deviation (RSD) for the Dv10, Dv50 and Dv90 delivered by the nebuliser for the entire inhalation time are reported, as measured over 3 repeat inhalations for each solution and driving gas flow rate. This confirms the reproducibility of the aerosol droplet size is generally better at 7 l/min, especially for the higher-viscosity solutions.

Driving Gas Flow Rate	PVP Concentration	Dv10		Dv50		Dv90	
		Size / µm	RSD (%)	Size / µm	RSD (%)	Size / µm	RSD (%)
4	0.0%	2.14	1.6	4.63	1.4	9.47	1.2
4	0.5%	2.30	2.2	4.84	2.1	9.79	3.2
4	1.0%	1.62	4.6	5.43	2.4	11.61	4.6
7	0.0%	1.75	0.8	4.03	1.1	8.84	2.2
7	0.5%	2.06	1.0	4.61	1.2	9.82	1.6
7	1.0%	2.22	0.7	5.07	1.3	10.96	2.6

Table 1: Average particle size delivered by the nebuliser for each liquid and driving gas flow rate.

Concentration Measurements

The efficiency of the nebuliser in delivering each of the liquids can be further understood by examining the changes in concentration which occur during the breathing manoeuvre. This is shown in figure 4 for the solutions nebulised using a driving gas flow rate of 7 l/min. Increasing the viscosity of the liquid causes the delivered concentration to decrease appreciably. An estimate of the total volume delivered can be obtained by calculating the cumulative concentration delivered for each solution (i.e. by calculating the area under each curve in figure 4). This suggests that the volume delivered for the 1.0w/v% PVP solution is only 12% of that observed in the case of deionised water. As such, the time required to deliver the entire volume of liquid loaded into the nebuliser would be expected to increase as the viscosity increases. Similar trends are observed when using a driving gas flow rate of 4 l/min, although the delivered aerosol concentration is always significantly lower than that observed at a flow rate of 7 l/min.

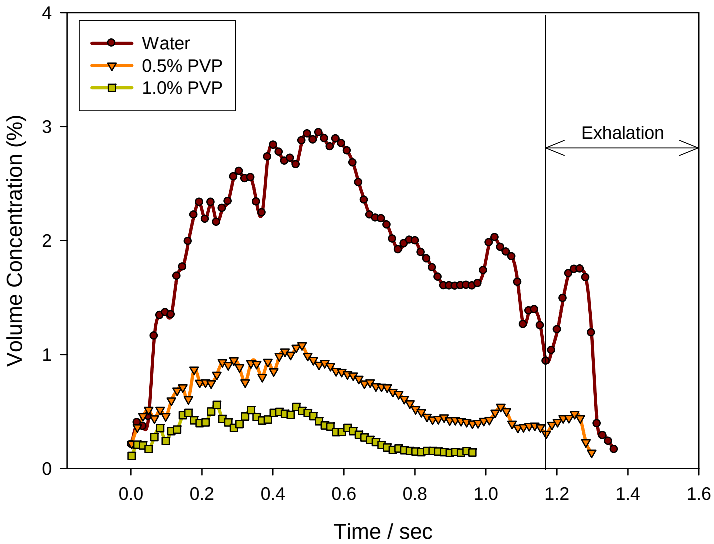

Figure 3: Time-dependant concentration measured for the 3 nebuliser solutions, using a driving gas flow rate of 7lpm. For clarity, every 8th data point is marked.

Discussion

By providing detail regarding the changes in droplet size and concentration delivered by a nebuliser during inhalation, this study is able to help describe how liquid atomisation changes as the viscosity of the nebulised solution increases. This methodology therefore shows potential to be a useful tool in aiding the development of nebuliser devices and formulations.

The results show that, as the viscosity of the formulation increases, significant changes in the droplet size and concentration profiles delivered by a nebuliser are observed. Increasing the driving gas flow rate, in order to provide additional energy input for atomisation via shear within the nebuliser venturi, can help to improve the reproducibility of the delivered aerosol. However, the aerosol particle size increases significantly as the formulation viscosity increases, whilst the concentration decreases. This would be expected to impact the efficiency of droplet deposition within the respiratory tract and will also lengthen the time taken to deliver the entire dose stored within the device.

References

[1] Mitchel, J.P., M.W. Nagel, S. Nichols and O. Nerbrick. 2006. Laser diffraction as a technique for the rapid assessment of aerosol particle size from inhalers. J. Aerosol Med. 19:409-433.