Effects of viscosity, pump mechanism and nozzle geometry on nasal spray droplet size

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Abstract

In this work the atomization behaviour of a nasal spray system has been investigated by laser diffraction. The effects of formulation viscosity, pump mechanism and nozzle geometer on the droplet size produced by a nasal spray were investigated. The droplet size was also investigated as a function of actuation conditions as this is a critical factor in determining potential patient use.

Introduction

Droplet size is a critical parameter in the performance of a nasal spray as it determines the location of deposition within the nasal cavity and hence the bioavailability and bioequivalence of the drug. The range of treatments delivered using nasal sprays has widened from locally acting drugs, for example treating allergic rhinitis, to molecules for systemic activity such as vaccines which are more difficult to deliver non-invasively. However, although these molecules can be delivered by a nasal route, the absorption of the drug may be hindered by the rate of mucociliary clearance [1-3]. Therefore the viscosity of the formulation is critical in retaining the drug in the nasal cavity for long enough to achieve sufficient absorption. Hence there is a requirement to increase the viscosity of the formulation to improve adsorption. However, this increase in viscosity will affect the droplet size produced by a nasal spray. This creates a delicate balance between increasing the viscosity in order to improve retention and reducing viscosity to provide good atomisation behaviour. Therefore, the formulation, pump mechanism and nozzle geometry of the nasal spray must be optimised in order to obtain the appropriate droplet size.

As the nasal spray must be actuated by a patient, it is critical that the performance of the nasal spray is evaluated using a range of actuation conditions. Ideally a nasal spray should produce a similar droplet size over a reasonable range of actuation conditions, and hence deliver the same dose independently of the actuation conditions and therefore be suitable for use by a greater number of patient groups. In this work, three formulations with different viscosities have been tested using two different pump mechanisms and two non-standard orifice diameter nozzles. Each system has been tested at a range of actuation velocities in order to assess the dependence of droplet size on actuation conditions for these systems.

Critical parameters in atomization include the liquid flow within the nozzle and the interaction between the jet produced and the ambient gas. The liquid flow within the actuator and nozzle can be described by the Reynolds number;

$$\text{Reynolds number} \quad R_e = \frac{\rho V d}{\eta} \tag{1}$$

Where V is the fluid velocity, d is the diameter of the actuator or jet, ρ is the fluid density, and η is the viscosity of the liquid. The Reynolds number determines whether the liquid flow is dominated by viscous (low R_e) or inertial forces (high R_e) and hence whether the flow is generally laminar or turbulent. The Reynolds number has been used to describe three mechanisms of jet breakup [4]. Firstly at low Reynolds numbers large uniform droplets are produced according to the Raleigh mechanism of jet breakup. At intermediate Reynolds numbers breakup is achieved by oscillation of the jet with respect to the jet axis until the jet disintegrates. This second region produces a wide range of droplet sizes. Finally at high Reynolds numbers the complete atomization of the jet is achieved within a short distance from the orifice. In this work the effect of the fluid velocity on the droplets size will be investigated through variation of the actuation velocity. Secondly the viscosity of the formulation will be varied by using increasing concentrations of a viscosity modifier and the effect of actuation velocity on these different viscosity fluids investigated. Following primary atomisation the droplet size may be further reduced by secondary atomisation. The level of droplet break up in secondary atomisation depends on the size of

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the initial droplets, the relative velocity of the droplets in air, and the physical properties of the system (e.g. surface tension). The dependence of secondary atomisation on relative velocity and physical properties of the system is described by the Weber number. The Weber number is the ratio of the inertia of a fluid to its surface tension and is hence important in the process of droplet formation.

$$\text{Weber number} \quad W_e = \frac{\rho V^2 l}{\sigma} \tag{2}$$

Where l is the characteristic length or droplet diameter and σ is the surface tension. Therefore the further breakup of droplets is expected to be strongly dependent on the liquid velocity. Hence, secondary atomisation is expected to affect the dependence of the nasal spray droplet size on the actuation velocity.

Materials and Methods

Model formulations were studied in order to examine how the rheological properties affect the atomisation behaviour of a nasal spray. The model formulations consist of varying concentrations of polyvinylpyrrolidone (PVP) in water. PVP is used in the model formulations to increase the Newtonian viscosity of the formulation with only a small change to the elasticity of the sample and therefore allowing the effect of viscosity on the droplet size to be investigated. Investigations were made using concentrations of PVP in the range 0% to 1.5%.

The three model formulations were tested in a range of different nasal spray systems. The nasal spray systems comprised two commercially available pumps, VP3 and Equadel (Valois S.A.S). The VP3 is a standard pump design where as the Equadel pump uses a mechanism dependent on pressure to release the actuation energy and thereby deliver a consistent droplets size. These pumps were used in combination with a standard nozzle and two non-standard nozzles with small and large orifice diameters, where the difference in diameter between the two nozzles is 200µm. Each of these combinations was then tested under a range of actuation conditions. The actuation of the nasal sprays was controlled using a velocity controlled actuator (Proveris Scientific). Each combination was actuated using a slow (40mm/s), medium (70mm/s) and fast (100mm/s) actuation profile, in each case the nasal spray hold time was 500ms.

The atomisation dynamics of these systems were assessed using droplet size measurements carried out by laser diffraction (using a Malvern Spraytec). This technique measures the intensity of light scattered by the sample as a function of angle and by using an appropriate scattering model the particle size distribution can be calculated. Laser diffraction is a suitable technique for investigating atomisation dynamics as highly time resolved data can be obtained, in this work data was acquired at a rate of 2.5kHz. This enables the three phases of the atomisation of a nasal spray (formation, fully developed and dissipation) to be characterised in detail and thereby enabling a greater understanding of the atomisation dynamics. Droplet size measurements were carried out at a distance of 30mm and each combination (formulation, pump and nozzle) was measured over three actuations. The laser diffraction measurements produce an average size profiles for each combination; these size profiles show the variability in the droplet size parameters (e.g. median size, Dv50) over the duration of the spray event. This allows the effect of the formulation, pump and nozzle on the duration of the stable phase, and therefore the proportion of drug that would be delivered at an appropriate droplet size to be investigated.

Results and Discussion

Firstly the effect of pump mechanism will be considered, the VP3 is a standard nasal spray nozzle where as the Equadel has been designed to deliver a consistent dose under a wider range of actuation conditions. Figure 1 shows the median particle size (Dv50) plotted as a function of time for the standard pump (a), VP3, and the Equadel pump (b). Figure 1(a) shows that using the VP3 pump for the lower viscosity formulations (water, 0.25% PVP and 0.5% PVP) produces a well defined fully developed phase and that an increase in the droplet size within the fully developed phase is observed with increasing viscosity. However as the viscosity is increased further, the 1% PVP formulation, a fully developed phase is only achieved toward the end of the actuation and with a significant increase in the droplet size. Finally at 1.5% PVP the droplet size remains large throughout the actuation and a well defined fully developed phase is not achieved. In comparison the Equadel pump produces a fully developed phase of much longer duration and a fully developed phase is retained up to 1% PVP. However, using the 1.5% PVP formulation with the Equadel pump shows a large and variable droplet size suggesting that complete atomization has not occurred.

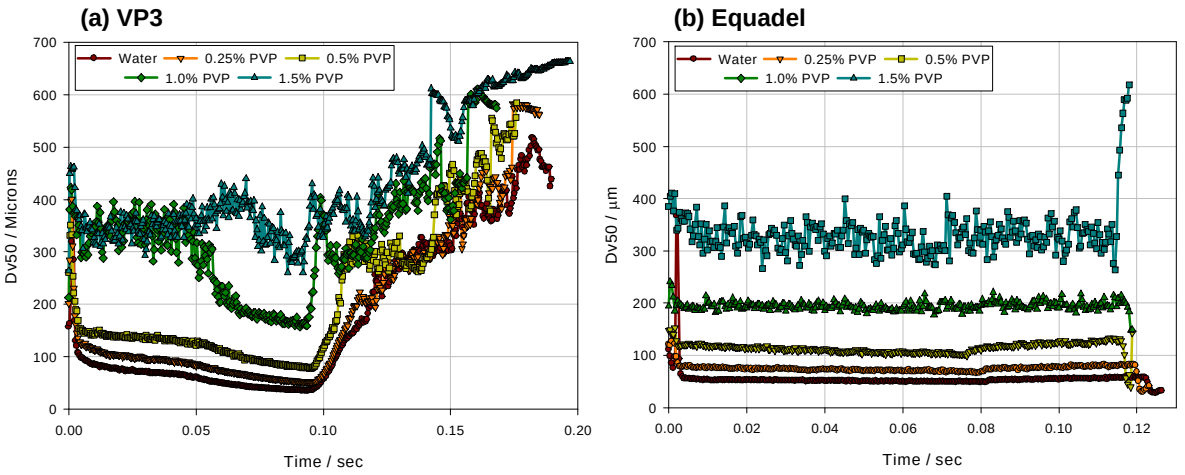

Figure 1. Size profiles for (a) VP3 and (b) Equadel at a range of formulation viscosities

The improved fully developed phase achieved using the Equadel pump is due to differences in the pump mechanism. In the Equadel pump the actuation energy is stored and then released according to the pressure of the liquid in the actuator. This allows for a more reproducible fully developed phase to be achieved for a wider range of formulation viscosities. In the rest of this work the effect of actuation conditions on the droplet size produced by the Equadel pump will be investigated using three formulations (water, 0.5% and 1% PVP) and using two non-standard nozzle orifice diameters (small and large) where the orifice diameters are separated by 200µm.

The effect of actuation velocity on the droplet size produced by the Equadel pump was investigated using the small orifice nozzle. Figure 2 shows the droplet size produced using water, 0.5% PVP, and 1% PVP actuated under the slow (40mm/s), medium (70mm/s) and fast (100mm/s) actuation profiles. From which it becomes apparent that the Equadel pump produces a droplet size which is independent of actuation velocity for each formulation. However an increase in droplet size is still observed as the viscosity of formulation is increased. This suggests that for each formulation the variation in the velocity due to the actuation conditions is not sufficient to change the mode of atomisation and a consistent droplet size is produced. However as the viscosity is increased the droplet size produced in the fully developed phase is shifted to slightly larger sizes although independent of actuation velocity.

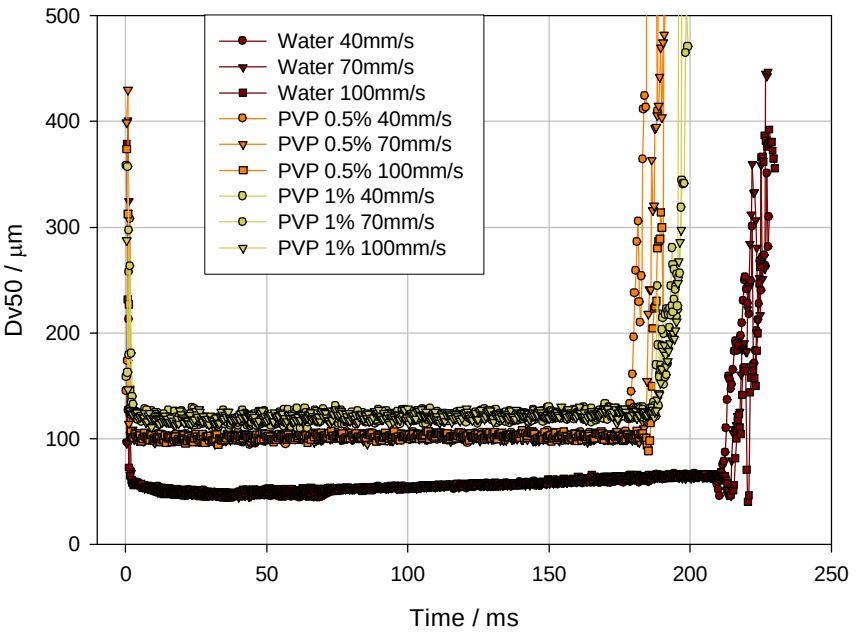

Figure 2. Equadel pump with small orifice diameter for different viscosities and velocities

The droplet size profiles were then measured for the Equadel pump using a larger orifice nozzle. Again the droplet size was measured using the three model formulations of increasing viscosity and using the three actuation profiles. Figure 3 shows the median droplet size produced by the Equadel pump using the large orifice nozzle actuated using the slow, medium and fast actuation profiles. This shows that a consistent droplet size is produced using the two higher velocity profiles however a larger droplet size is produced using the slow actuation profile. The duration of the spray event is also reduced for the slow actuation profile suggesting that a lower volume of the metered liquid has atomised under these conditions. This suggests that the reduction in actuation velocity from 70mm/s to 40mm/s has changed the mode of atomisation produced by the pump.

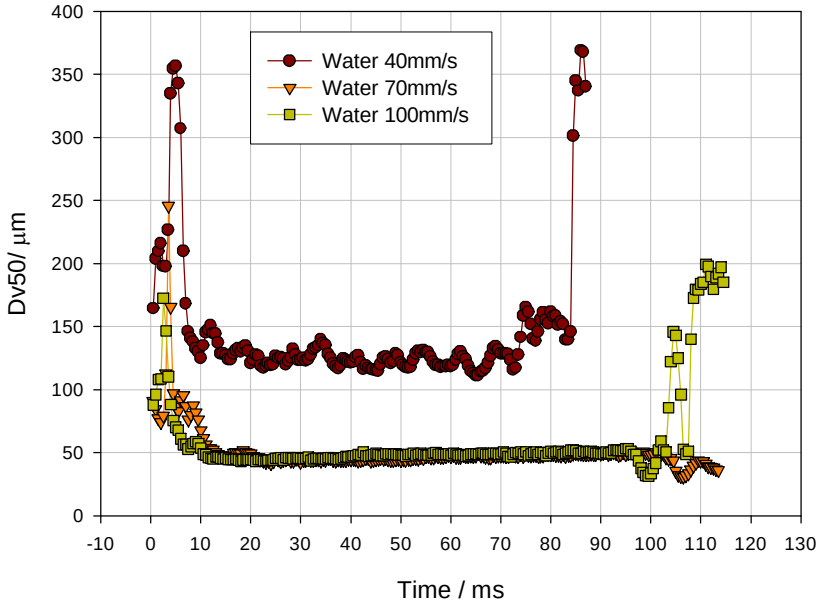

Figure 3. Equadel pump using water and the large orifice nozzle

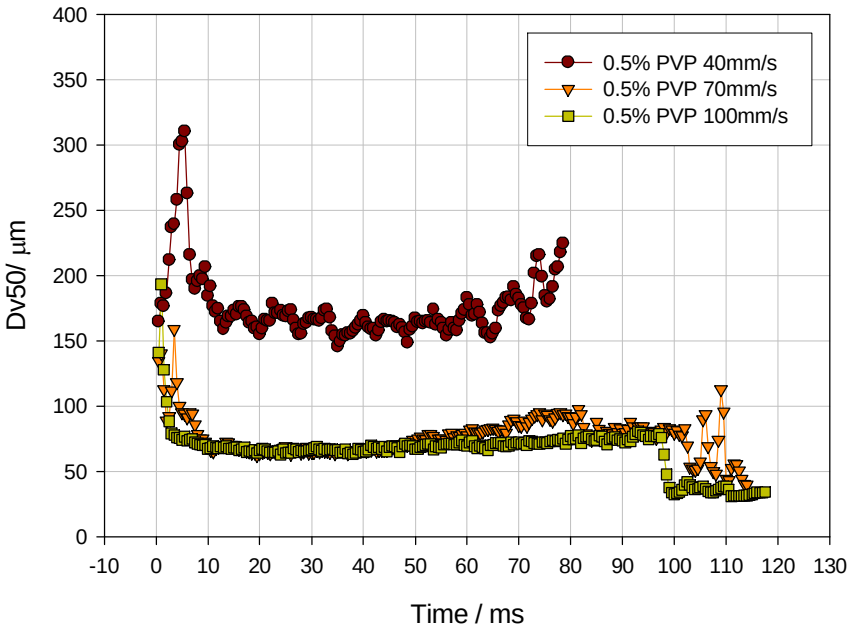

Figure 4. Equadel pump using 0.5% PVP and the large orifice nozzle

Figure 4 shows the median particle size produced by the larger orifice nozzle using the 0.5% PVP formulation. For this formulation there is a small increase in the droplet size produced using the medium actuation conditions towards the end of the fully developed phase (compared to the droplet size produced using the fast actuation profile). This indicates that the increase in viscosity is beginning to affect the mode of atomisation at this actuation velocity. Similarly to the measurements of water using the large orifice nozzle the droplet size produced at 40mm/s is much larger and the pump is no longer fully atomising the formulation.

Finally the results of the 1% PVP solution using the large orifice nozzle, Figure 5, show that the droplet size produced during the fully developed phase using the medium actuation profile is larger than that produced using the fast actuation profile for the majority of the fully developed phase. The fact that the droplet size is larger for most of the fully developed phase indicates that the viscosity is beginning to reduce the pressure drop such that the mode of atomisation is being affected even at the higher actuation velocities. Finally using the slow actuation profile, the droplet size is significantly larger and very variable through the profile indicating that poor atomisation is achieved using the higher viscosity formulation at slower actuation profiles.

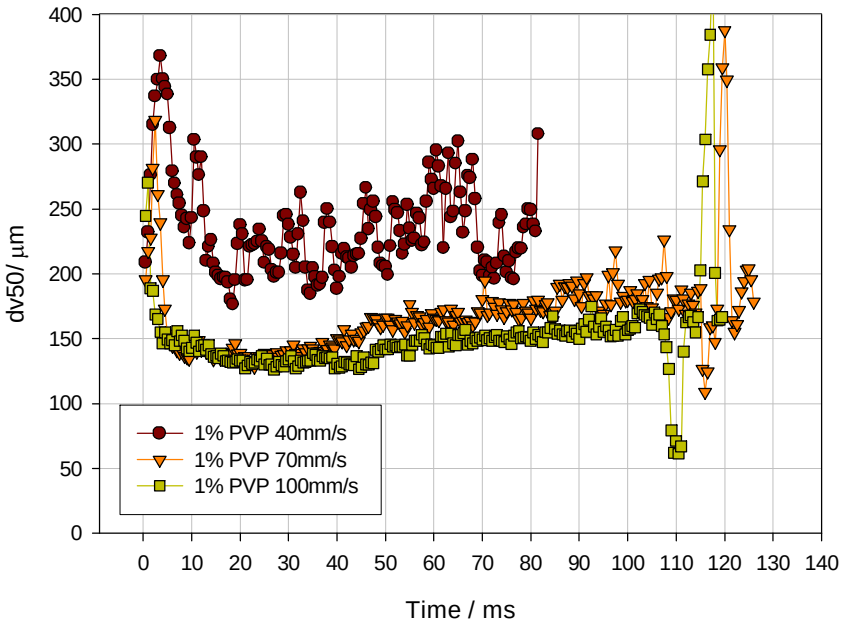

Figure 5. Equadel pump using 1%PVP and the large orifice nozzle.

In general the large orifice nozzle shows the same increase in droplet size as a function of formulation viscosity as observed for the small orifice nozzle. However when the large orifice nozzle is used, the droplet size produced is no longer independent of actuation velocity for a given formulation, suggesting that the diameter of the nozzle orifice is affecting the pressure of the liquid within the nozzle. The droplet size is consistent at higher velocities when water is used. However, as the viscosity of the liquid increases differences in the droplet size produced at 70mm/s and 100mm/s are observed. The greatest difference between the droplet sizes produced at 70mm/s and 100mm/s are observed for the highest viscosity formulation, 1% PVP. When the low velocity actuation profile is used a significantly larger droplet size is produced and the duration of the spray is shorter, this is due to insufficient pressure within the actuator causing a change in the mode of the pump and poor atomisation.

Conclusions

These results show that the mechanism of releasing the actuation energy employed by the Equadel pump, which is dependent on the pressure within the actuator, can be affected by the combination of the nozzle orifice diameter and the formulation viscosity. If the small orifice nozzle is used then the droplet size produced is independent of the actuation velocity for a given formulation viscosity. In this case the pump mechanism is operating as designed, such that a consistent droplet size is produced independently of the actuation conditions. The model formulations show an increase in the droplets size with increasing viscosity although the droplet size remains independent of actuation conditions. The droplet size increases with increasing viscosity as the viscous forces within the formulation become more significant compared to the inertial forces supplied by the actuator.

The situation is more complex for the large orifice nozzle, where the actuation independence of the droplet size is lost. In this case a significantly larger droplet size is produced at lower actuation velocities suggesting that the pressure achieved within the actuator is not sufficient to produce good atomization using this orifice diameter. Some dependence of droplet size on actuation velocity was also observed at higher velocities for the higher viscosity formulations.

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