EXAMINATION OF PRIMARY DROPLET GENERATION AND ATOMIZATION PERFORMANCE IN PNEUMATIC NEBULIZERS

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ABSTRACT

This research is concerned with the investigation of the flow systems set up within pneumatic medical nebulizers that bring about the generation of liquid droplets. The research has been motivated by the possibility to improve the efficiency of nebulizer atomization design and therefore the suitability of the usage of macromolecule containing drug formulations. Four commercially available pneumatic nebulizers were tested to see how differing nebulizer designs performed.

Volumetric median diameter, D_{v05}, as measured by a Malvern laser diffraction instrument. Respirable volume fraction was measured using a multistage liquid impinger apparatus, the twin impinger (TIMP). Flow visualization was performed on each test nebulizer using a high speed video camera at frame rates up to 4500 fps to gain an understanding of the flow structures experienced by the nebulizing liquid.

From flow visualization the droplet formation for the nebulizers was found to occur both through a coarse atomization of gas and liquid jet interactions and fine atomization occurring through droplet stripping from a liquid film formed on the solid inner surfaces of the nebulizer nozzle and baffle. It was also observed that secondary baffle structures and the inner walls of the nebulizer served to filter out the larger droplets back into the nebulizer reservoir. Laser diffraction measurements indicate a high volumetric proportion of droplets of inhalable diameter; however liquid impingement measurements showed a shortfall in the total deep lung liquid volume deposition compared with the laser diffraction measurement. The results presented form a basis for further analysis regarding nebulizer design in view of how atomization would affect sensitive drug formulations.

INTRODUCTION

Recent advances in the biotechnology industry have now made it possible to treat a wider range of diseases using protein drugs and gene therapy. Previously the delivery of such drugs has taken the form of injections that can prove to be an unsuitable and uncomfortable mode of administration. The prospect exists that these drugs can be delivered to the body via inhalation delivery, which is often a more convenient mode of administration. The utilization of medical nebulizers to treat various respiratory diseases such as asthma is already a well-known method of delivering suitable drugs. The realization that inhalation delivery could be extended to treat a more diverse variety of medical conditions, such as cystic fibrosis or diabetes, is very much a recent and innovative concept.

Nebulizers atomize solutions or suspensions of drugs into a fine mist of droplets that can be inhaled by the patient. Nebulizers traditionally use compressed air to produce drops, most of which are collected by baffles and continually recirculated, such that only respirable sized droplets can emerge from the nebulizer to the patient. New inhalation treatments using therapeutics that contain long chain molecules will require a method of atomization that will not injure these molecules. It is necessary that in the development of pulmonary delivery systems, both the drug formulation and the device technology be considered in parallel for the research to progress efficiently.

Previous research into the subject of reducing damage to sensitive nebulized macromolecular medications has mainly concerned itself with the modification of the drug formulation whilst using conventional, commercially available nebulizers. The alteration of drug formulations, such as the use of liposomes Khatri et al [1], or surfactant additions Niven et al [2], is subject to a large quantity of research. The development of different designs of nebulizers that, in themselves, could offer more efficient and less stressful alternatives to current devices in use is still a field of research to be explored. Indeed there have been many studies of nebulizer performance Waldrep et al [3], nebulizer design Nerbrink et al [4], and nebulizer atomization Corcoran et al [5]. There is still further study that can be carried out in relation to nebulizer design with regard to how the atomization physics affects the formulation.

Therefore experimental work is needed to analyse the effect that the device design has upon the atomizing forces experienced by the nebulized fluid, whilst retaining high nebulizer performance. This information can then be applied to the development and study of the design of atomization devices that are less physically harmful to long molecule containing drugs [6].

EXPERIMENTAL APPARATUS AND PROCEDURES

In this study four designs of pneumatic nebulizers were examined, they were selected because of their availability, difference in design and because they represent typical nebulizers on the market. Each of the nebulizers operate using the same basic principle in that a high speed air flow draws liquid up from a reservoir into contact with the air flow causing a coarse primary atomization, a series of baffle surfaces then act to cause finer secondary atomization and recirculate larger droplets back to the reservoir. The four test nebulizers used here were; Pari Plus and Pari Star (both Pari GMBH), Ventstream (Profile Therapeutics plc UK) and Microneb III (Lifecare UK) and their designs can be seen in figure 1.

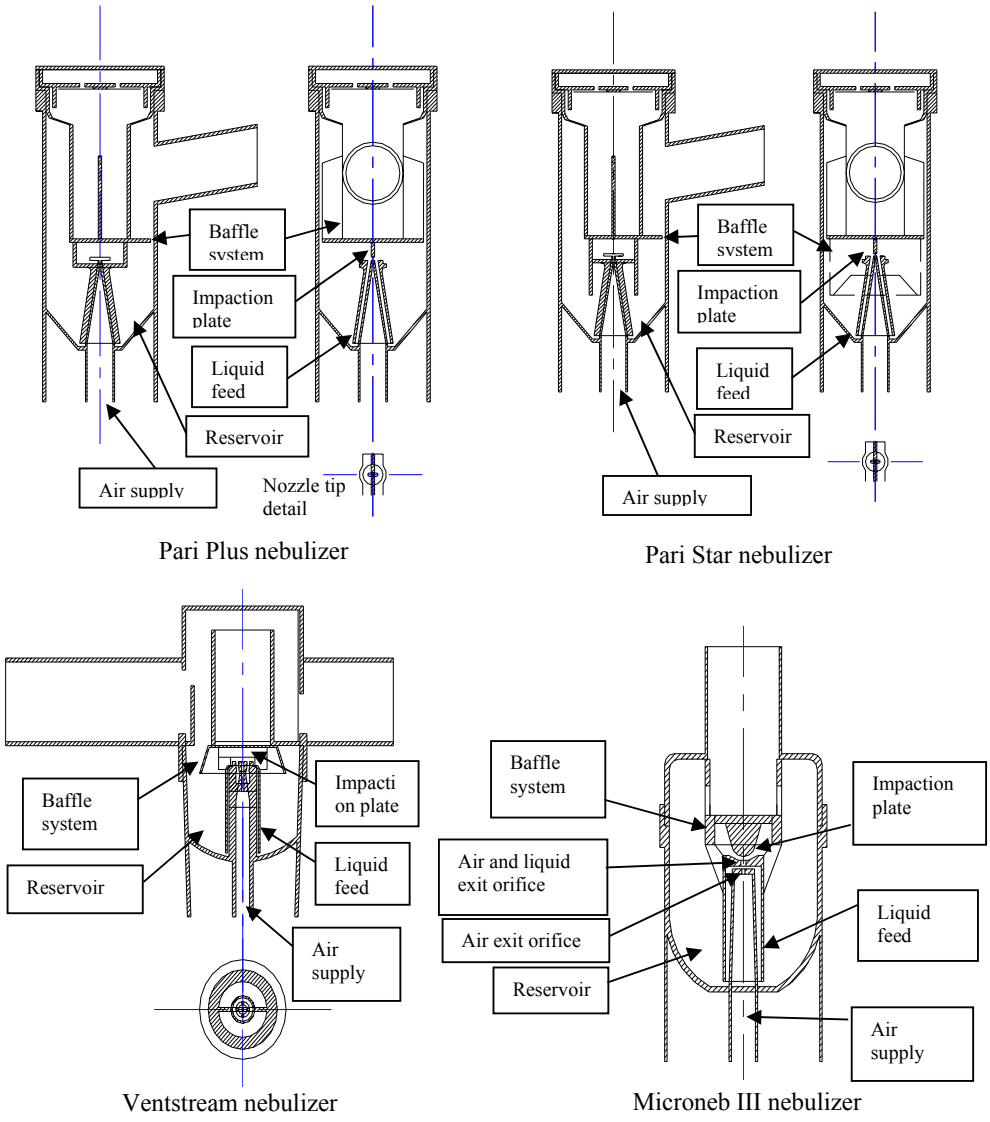

Figure 1, Designs of test nebulizers

In this study three main experimental procedures where used to assess the performance of the medical nebulizers. Laser diffraction droplet sizing using a Malvern 2600 instrument was used to obtain volumetric median diameter and droplet size distributions by volume delivered by the test nebulizers. Nebulizers were operated with initial 5ml reservoir volume fills, at air inlet gauge pressures of 1, 1.5 and 2 bar, at a distance of 4cm from the measurement laser. The 63mm measurement lens was used and the distance to this lens was such that the spray plume was within the collecting lens focal length. Inertial liquid impaction using the GlaxoSmithKline twin impinger apparatus (TIMP) [7] was used to obtain deep lung volume dose delivered by the nebulizers. The TIMP was operated for 5minutes and with a suction of 60 L/min with the nebulizers' output coupled to the entrance of the TIMP head. The water soluble dye methylene blue was used as the indicator, and the TIMP stage volume fractions were determined by solution concentration analysis using a Beckman DU640i spectrophotometer. Each measurement was carried out three times and the average reading was calculated, the standard deviation of this data set was also calculated and found to be within the accepted error range for the respective techniques. High speed video footage using a Kodak Ektapro Motion Analyser Model 4540 system was used to obtain flow visualization of the primary atomization structures set up within the nebulizers. For this parts of the nebulizers' wall and baffle systems were cut away.

RESULTS AND DISCUSSION

Figure 2 shows frames from the high speed video footage of the nebulizers with the baffle sections cut away. Also Shown is a schematic of the mode of primary atomization observed in each test nebulizer design. Generally it can be seen that ligaments and droplets are stripped from liquid surfaces formed upon the solid surfaces found in each of the nebulizers. There is a variation between these modes between nebulizers according to the geometry of the nebulizers liquid / air feed and primary impaction plate baffles. The design of the Pari nebulizer shows a flow structure set up whereby the liquid film that is drawn onto the primary impaction plate and thus the air flow is most efficiently flowing across the liquid and is therefore the most efficient at producing droplets. The Ventstream device exhibits a structure whereby the liquid is drawn across the exit orifice surface to the airflow, but the droplet formation from this less efficient air / liquid co-flow is less effective at producing small droplets. The Microneb III device sets up a larger liquid film which whose geometry gives an efficient surface for droplet formation but flooding of this region causes much recirculation. Further observation shows that it is a combination of the secondary baffle systems and mostly the nebulizer walls that act to filter out the larger droplets.

Figure 3 shows the results from the TIMP tests. The TIMP stage 2 represents the percentage by volume of droplets below the cut off diameter of 6.63μm. This is effectively the fraction of dosage delivered to the deep lung by the nebulizer. The TIMP stage 1 represents the fraction of delivered dose that will impact in the patient's mouth and upper airways. The fraction uncollected is accounted for by the evaporation of solution occurring within the nebulizer and the particles produced by the nebulizer that are likely to be too small and therefore exhaled. Shown is the general trend that the higher the nebulizer operating pressure the greater the deep lung penetration the device is supplying. Also of note is the fact that there is a high fraction of liquid volume that is either evaporated or not captured by the TIMP apparatus, this suggests that a large quantity of the drug dose would be wasted. Examining the results obtained from the Malvern data, D_{v05} as in figure 4, there is a clear correlation between TIMP 2 deposition and D_{v05} as expected. However the %volume of droplets under 6.63mm as measured by the Malvern instrument overestimates the % volume as measured using the TIMP apparatus, this shortfall is likely to be the droplets too small to be captured by the TIMP apparatus along with other volume evaporated within the nebulizer device. Indeed although the Ventstream nebulizers produces a lower D_{v05} than the Pari nebulizers, this device perhaps produces too small droplets, droplets that are likely to be exhaled by the patient. The Ventstream device also consumes a higher air flow rate which also indicates a higher likelihood that evaporation would occur within the device. Of the two Pari models examined, the Pari Star produces the smaller droplets, although the mode of the primary atomization nozzle is the same, this is because of the larger secondary baffle system acting to filter out more of the larger droplets produced by the primary atomization. The fact that the Pari Star has the larger baffle system is also reflected in the lower flow rates that it exhibits. The Microneb III nebulizer has a particularly different primary impaction plate baffle compared with the other test nebulizers. The lower liquid flow rate is because of the larger quantity of liquid recirculated as can be seen from figure 2. This design does prove to set up a flow structure that proves to produce small droplet sizes. It is also important to consider the liquid output flow rate along side the deep lung dose delivered by the nebulizer. The product of these values is an indication of the deep lung dose delivered to the patient per unit time. This is an important consideration for patient usage time.

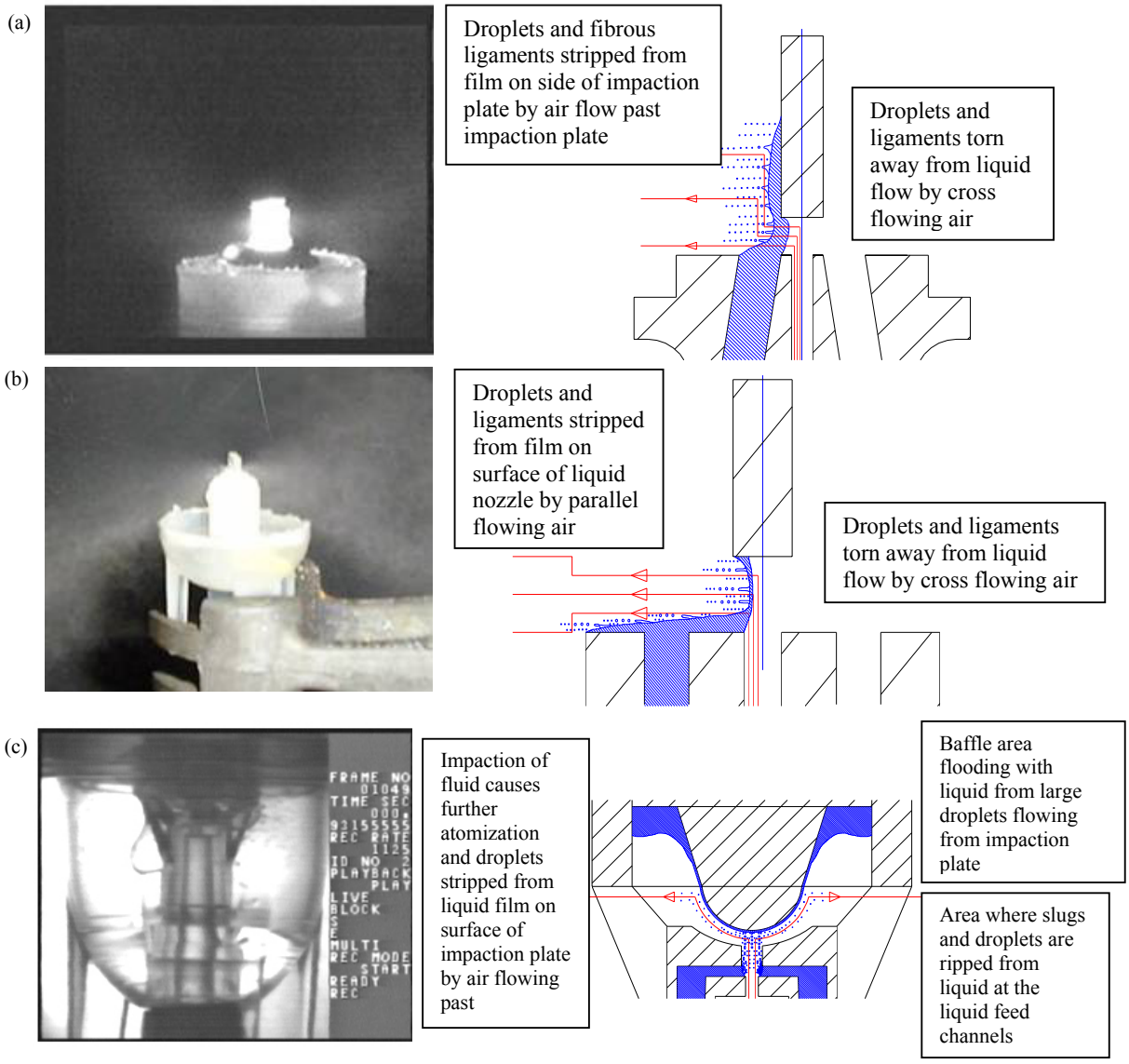

Figure 2, High speed camera frames of primary nebulizer atomization, along with schematic of droplet formation for; (a) Pari nebulizer, (b) Ventstream nebulizer, and (c) Microneb III nebulizer. As a sense of scale the central fluid supply column diameter of each nebulizer is approximately 9mm

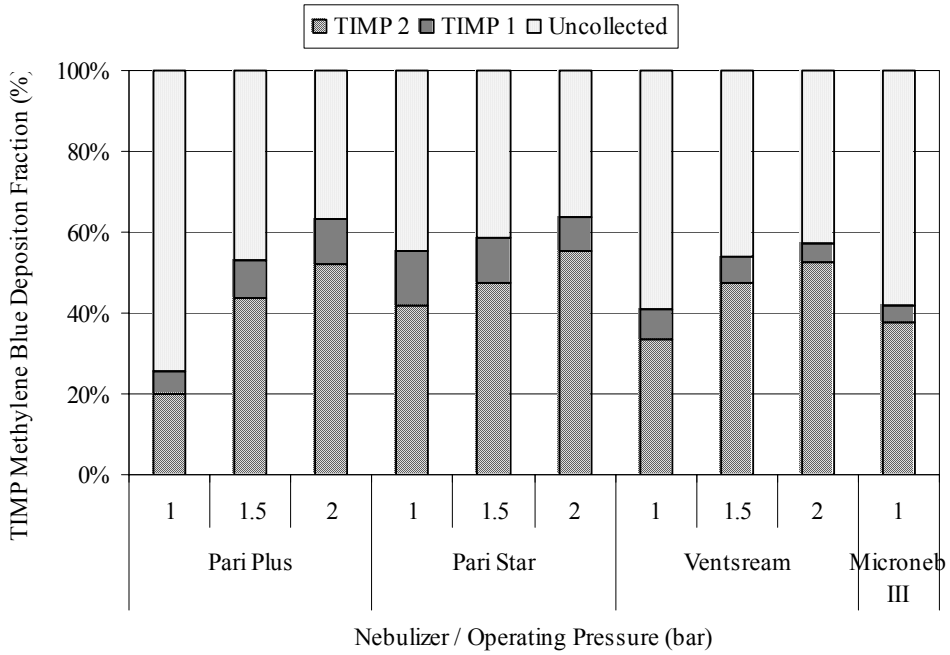

Figure 3, Twin Impinger Deposition of Test Nebulizers at Various Operating Pressures

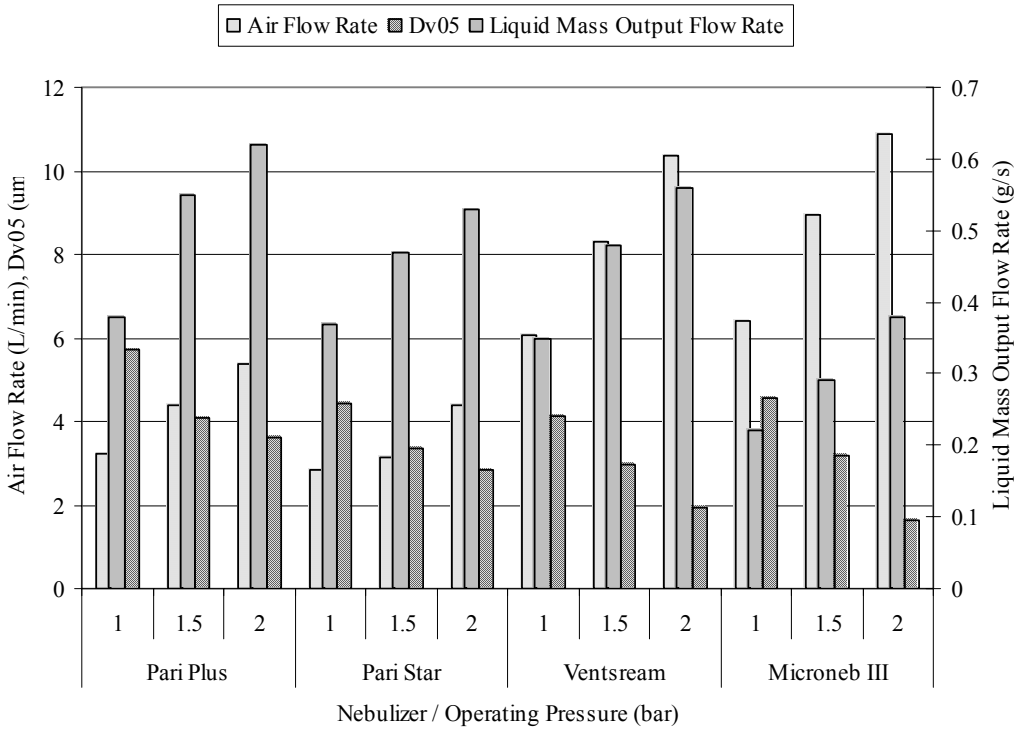

Figure 4, Volume Median Diameter, Liquid Output Flow rate and Air Flow rate Performance of Test Nebulizers

CONCLUSION

This study has examined the physical flow structures set up within medical nebulizers that bring about primary atomization. Important features such as mode of primary droplet formulation design and baffle and orifice geometries are significant. Also presented are factors that should be considered when selecting nebulizers, in terms of deep lung dose, and time of nebulization. When selecting and designing a device for use with sensitive formulations one should bare in mind these factors as well as the importance of the flow of the fluids within the nebulizer.

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