A NOVEL SPRAY CONFINEMENT TECHNIQUE FOR MEDICAL SPRAYS: ADVANCED PROCESSING AND CORRELATIONS WITH TIMP MEASUREMENTS

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Abstract
Obtaining a sufficiently high inhalable fraction for metered dose inhalers is essential in the design and manufacturing of their atomizing devices and the corresponding confinement and mouthpiece configurations. In the current investigation, the inhalable fractions of six different spray configurations were measured using a "two stage twin-impinger (TIMP). The objective of this study is to establish a technique to correlate the data obtained by phase Doppler anemometry with the inhalable fraction results obtained by the TIMP. Three methods with varied complexity of calculating weighted averages of Stokes numbers for the mouthpiece outlet sprays, were adopted and high correlations values were obtained.

Introduction

"Spacer devices" are chambers that are placed between the drug issuing device (MDI) and the patient's mouth. They are increasingly used in the treatment of pulmonary diseases such as asthma [1], especially for children, [2], and [3], and those with poor inhalation technique, [4]. Spraying into the spacer before inhalation attenuates the problem of the high velocity of the aerosol and gives improved droplet sizes distribution, thus reducing the number of large particles impacting in the mouth, [5]. Furthermore the use of a spacer increases the respirable dose of fine particles (i.e. particles, smaller than 5µm, that reach the bronchial tree), [6]. An objective of the present research is to investigate whether some of the advantages of the spacer can be obtained by suitable design of a compact spray confinement chamber and mouthpiece, integral with the atomizing device.

Given the poor drug delivery of the pulmonary devices the prime objective would be to enhance the performance of delivery. This is done here by performing TIMP measurements of inhalable fraction and the results are correlated with PDA measurements for the six confined spray geometries, [7], by using parameters based on the Stokes Number.

Nomenclature

D	droplet diameter
D_{10}	numerical mean diameter
U	Axial component of the velocity
r	radial distance across mouthpiece exit
ρ	density
μ	dynamic viscosity
SN	Stokes Number, eqn (1)
Subscripts	
a	Air
L	liquid

Apparatus and Procedure

The use of a specially designed confinement chamber and use of a Dantec PDA system to obtain drop information at the outlet of the mouthpiece for a range of spray conditions has been described in [7]. A Glaxo Twin-Impinger apparatus was used to measure the inhalation efficiency of six of the sprays. A brief account on the TIMP apparatus is presented below.

The 'Twin Impinger', [8], is a two stage separation device for assessing the drug delivery from metered dose inhalers and other oral inhalation delivery devices. The discharged aerosol is fractionated by firing through a crudely simulated oropharynx and then through an impinger stage with an effective mean aerodynamic particle cut-off size of about 6.4 µm (depending on the flow velocity). The fine fraction is collected by a lower impinger. As shown in figure 1 the upper portion (stage 1, encompassing sections B, C and D) represents the throat, whilst the lower portion (stage 2, encompasses sections E, F, G and H) represents the rest of the respiratory system.

The then divides the dose emitted from the inhaler into the non-respirable dose impacting on the mouth and oropharynx, which is swallowed, and the remaining respirable dose that makes its way to the lungs. In normal use the emitted dose is drawn through the unit at 60 l/min, using a vacuum pump that provides a uniform suction. Both stages use the vertical impingement of the air stream onto a liquid surface (the solvent in the respective chambers) to form a "trap" for spray droplets which can then be removed for assay, using a spectrophotometer. The sprayed liquid must be tagged with a known concentration of marker chemical, in order that the spectrophotometer can be used to determine the volume collected in each stage. The aerosol deposits on three main impaction surfaces: (1) the back of the glass throat and (2) the upper impingement chamber, collectively described as Stage 1, (3) The lower impingement chamber which collects the remaining drug particles i.e. the respirable dose.

The TIMP measurements were carried out under time-varying "breathing" conditions as described in [7] and were repeated three times for each spray, which showed discrepancies less than 5%. The results presented in this paper are the averages of the replicate measurements. The TIMP measurements were made at different peak suction flow rates and the data for 60l/min. are presented here because this is the average person's inhalation rate. The outlet plenum, described in [7], was removed during TIMP measurements.

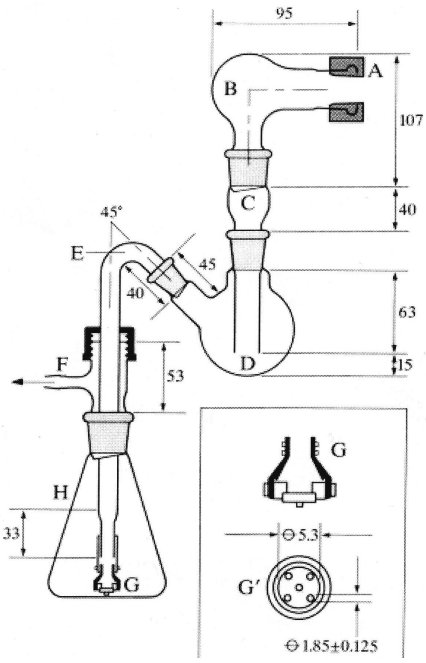

Figure 1. Schematic representation of Glaxo TIMP apparatus.

The PDA measurements were carried out, as described in [7], at 5mm downstream from the mouthpiece exit. For the purpose of correlating the PDA data with the concentration in stage 2 of the TIMP, only the data between -7 to +7mm from the axis of the mouthpiece were considered, the diameter of the mouthpiece exit being 14mm.

Results and Discussion

Figure 2 shows the results of the average TIMP concentrations for the two stages for 6 different mouthpiece spray cases with 2sec spray duration and 60L/min. peak air flowrate. The mouthpiece and confinement chamber configuration that produced these sprays have been described [7]. The highest second stage concentration was measure for case 3 whilst the lowest was that of case 2. Thus case 3 provides an inhaled fraction of 42% compared with 31% for case 2.

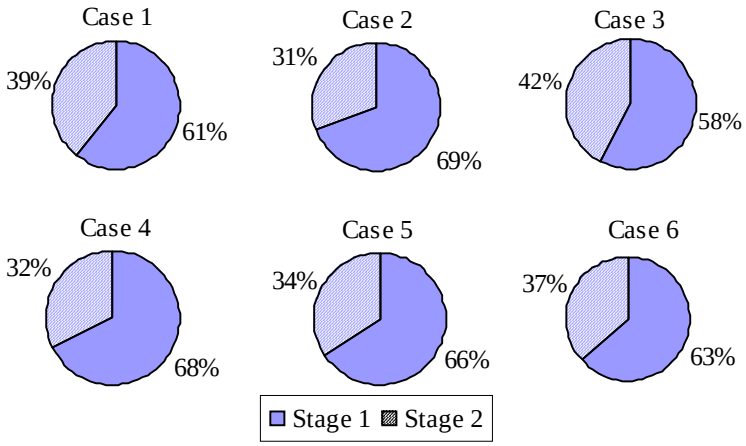

Figure 2. Graphical representation of the percentage concentration in both stages of the TIMP

An objective here is to analyse the structures of the aerosols leaving the mouthpiece in order to attempt to derive parameters based on these structures that are correlated with the observed inhalable fraction. Examination of the drop sizes, also shown in [7], indicates that the differences between, say, cases 2 and 3 are small so that the mean drop size is not a sufficient criterion for indicating inhalable fraction. Considering droplets of the same

size, both their initial velocities, when leaving the mouthpiece, and also the position at which they cross the mouthpiece outlet plane, must affect the likelihood of the droplets entering stage 2.

Considering figure 3 a droplet leaving the mouthpiece at "A" may negotiate the upper stage satisfactorily, leaving at point B. However the same size of droplet with a higher initial velocity, may impact the wall at B'. Also the same size of droplet, at the lower velocity and passing through C, may have insufficient distance to adjust to the streamlines and will impact on the wall at D. An obvious parameter to use for characterising the mouthpiece outlet spray, is a form of the Stokes number, suitably integrated across the mouthpiece outlet.

The definition of Stokes number is the stopping distance for a single spherical particle injected into ambient gas, when the Reynolds number does not exceed of the order unity. The assumption is that higher values of this parameter infer that a particle will have more difficulty in negotiating the pathways to the lungs, or at least to the second stage of the twin impinger.

$$SN = \rho_L D^2 U / 18 \mu_a \tag{1}$$

Three levels of complexity were established in calculating Stokes number which are referred to as method 1, 2 and 3 hereafter. As the liquid and gas properties are constants, the three methods of calculating Stokes number differ in the way of calculating D and U in equation 1:

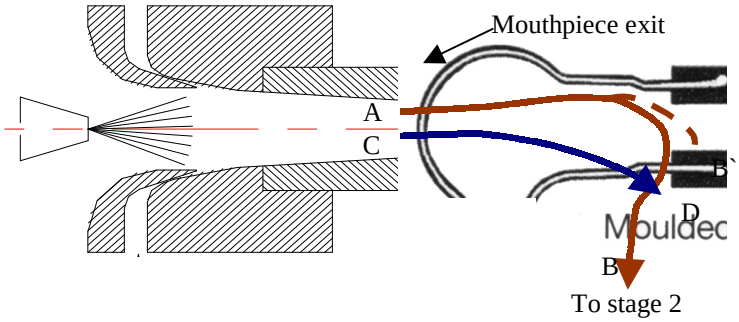

Figure 3. Drop paths in Twin-Impinger

Method-1, is the simplest, the values of D and U were calculated by averaging the values of the number mean diameter D_{10} and the average mean velocity U for 4sec of outlet flow as explained in [9] at each radial position. A single value of Stokes number was then obtained for each spray configuration by averaging the different radial values.

Method 2, has an intermediate level of complexity, the Stokes number was calculated taking into account its time dependency on the outlet spray, as this may vary significantly from case to case. The time varying values of D_{10} and U, at each radial position, were calculated by passing a 100 ms time window through the data and these were used to compute a time-dependant Stokes number. A characteristic Stokes number was then obtained by averaging with respect to both the time and radial position.

Method 3 was the most complex technique and this obtained a Stokes number for each individual droplet measured at each radial position for a 4sec period at each position.

The contour plots in figure 4 show the Stokes number time dependency for the six sprays using "Method 2". One can see that the Stokes number (stopping distance) reaches maximum values after about 2sec of the 4sec of the inhalation time. It can be seen that case 3 has clearly the lowest values of Stokes number throughout the inhalation period whilst case 1 has the highest peak values, concentrated in a narrow central zone in the mouthpiece. This can also be seen in figure 5 which show radial variations of Stokes number obtained by **Method 1**. Figure 6 shows, visually, the clear correlation between Stokes numbers, averaged using the three different methods, and the inhalable fraction. The correlation coefficients (all with a negative correlation) are, 0.972, 0.981 and 0.930 for Methods 1, 2 and 3 respectively.

Conclusions

The work reported has focused on establishing a method of correlation between Twin-Impinger inhalable fraction data and PDA data for an inhaler mouthpiece exit. This was possible using Stokes Number which links the droplet diameter and velocity in one relationship. This has been done using three different methods and the second method, based on both radial position and averaging time variation of Stokes number, is the most accurate because it considers the time dependency of the combined diameter and the velocity. It is appropriate to conclude, judging by the correlation factors which are close to unity, that the PDA and TIMP data correlate very well and hence there is a routine established for further experimental work using either of the two characterisation methods. However a larger number of tests conditions should be analysed in order to establish confidence in the methodology.

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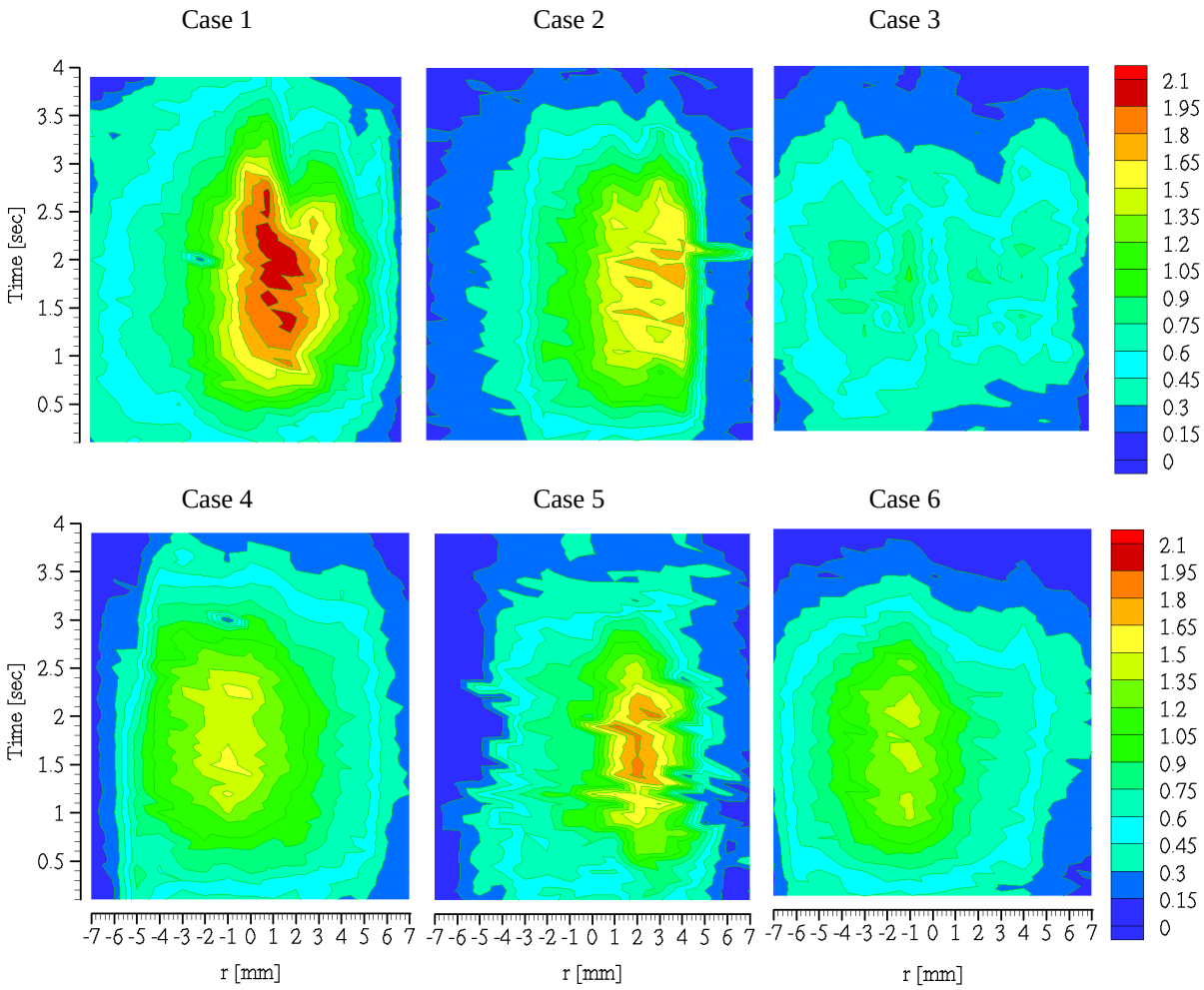

Figure 4. Contour plots of Stokes number for the six spray configurations computed using method 2.

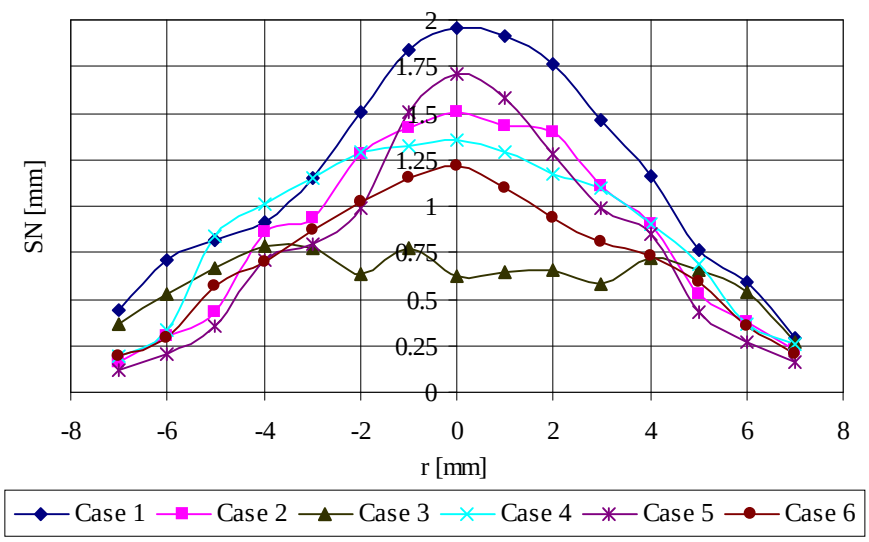

Figure 5. Radial variations of Stokes numbers obtained by Method 1 for the six cases

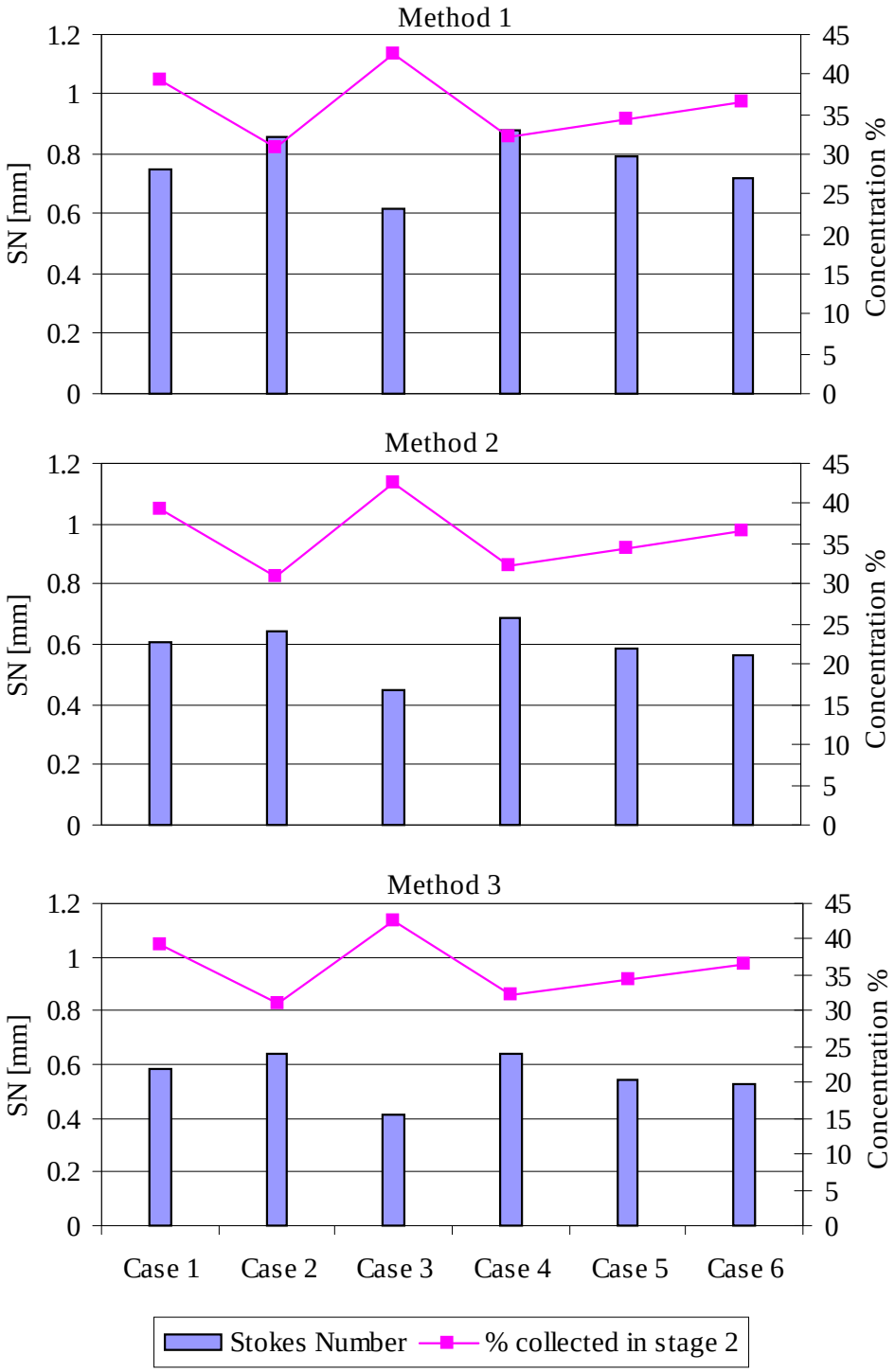

Figure 6. Correlation between TIMP concentration measurement and Stokes Number using the 3 methods.

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