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Investigation of the aerodynamic characteristics of inhaler aerosols with an inhalation simulation machine

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Abstract

An experimental facility comprising of an inhalation simulation machine and a laser-Doppler anemometer has been developed to investigate the aerodynamic characteristics of inhaler aerosols. The machine has been used to simulate transient inhalation flows with different degrees of inspiratory effort. Measurements of the mean flow and of the turbulence levels and time scales have been obtained for three commercially-available dry powder inhalers at different inhalation pressures. The results provide an extensive characterisation of aerosol aerodynamics and can aid the assessment of inhalers under various inhalation conditions.

Keywords: Dry powder inhaler; Aerosol characteristics; Turbulence; Inhalation simulation

1. Introduction

There are numerous and inter-dependent factors that affect respiratory drug delivery from dry powder inhalers; these include powder formulation and carrier/drug particle size, design of the inhaler, inhalation technique, velocity and turbulence of the inspired air, etc. (Byron, 1990; Timsina et al., 1994). The design of an inhaler is a complex and time consuming task as all these factors have to be taken into account. A new design must be subjected to many different stages of pharmaceutical and clinical testing in order to determine its overall efficiency.

Although it is generally accepted that the aerodynamic properties of dry powder inhaler (DPI) aerosols have an important role in improving the efficiency of respiratory drug delivery (e.g. meshes have been used to increase the turbulence level of the flow emerging from inhaler mouthpieces), there was relatively little effort made in the past to tackle this aspect of inhaler design due to lack of available technology to determine the detailed flow characteristics of inhaler aerosols. This was also partly due to the fact that pharmaceutics and fluid dynamics represent two distinguished fields

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of expertise and joint efforts for inhaler optimisation have been lacking.

In recent years the importance of adopting an integrated approach has been recognised. Much effort has been directed towards the design of DPI in an effort to optimise the flow produced by investigating the flow characteristics and correlating them with the design features of the inhaler as well as with physiological and pharmaceutical aspects. Such an approach can help identify systematically the effects of DPI design modification at an early stage and thus minimise expensive and time-consuming in vitro and in vivo testing.

A number of investigators have employed purpose-designed facilities generating transient flow through inhalers in order to achieve dynamic sampling of the aerosol clouds. For example, Hindle et al. (1994) utilised a three-way solenoid valve attached to a twin-stage impinger to generate transient flows through DPI while Brindley et al. (1994) employed a computer-controlled motor-driven piston for the same purpose. Such studies have been concerned with the measurement of pressure drop, dose emission and related parameters. Efforts have been made to determine the velocity characteristics of aerosols with flow-measurement techniques (see, for example, Clifford et al., 1990), but these have not been concerned with the flows generated under transient or controlled inhalation conditions.

Inhalation is a transient and complex process which may be broken down into three parts: an accelerating flow followed first by a short period of near-constant flow and then by a decelerating flow. The duration of the inhalation process and the total flow volume vary from person to person, especially among asthmatic sufferers. Using the same device different patients might achieve varying results because their inhalation effort might be affected by the higher or lower flow resistance produced by each device (Timsina et al., 1993). This suggests that inhalers should be optimised through testing under a wide range of conditions.

As different devices generate varying resistances to the patient-induced flows, it is necessary to use inhalation pressure rather than inhalation flow rate as the characteristic parameter. A constant flow rate condition through an inhaler with a high flow resistance will necessitate an extremely high inhalation pressure, far higher than those that can be achieved by most humans, whether healthy or asthmatic, and therefore constant flow rate testing may be an inappropriate means of assessing the performance of an inhaler device.

An experimental facility has been developed to study the aerodynamic properties of inhalers of different designs. It consists of a laser-Doppler anemometer (LDA) and an inhalation simulation machine (ISM). Laser-Doppler anemometry is an optical technique which is employed to measure the velocity characteristics of the flows produced by inhalers. The purpose-built inhalation simulation machine is used to simulate the inhalation processes of healthy and asthmatic persons.

This paper describes in detail the techniques and the instrumentation, namely the ISM and LDA, used for the determination of aerodynamic parameters of relevance to DPI design. Characteristic results obtained with three commercially available inhalers at different inhalation pressures are presented to illustrate the information that can be obtained and its relevance for inhalation flows.

2. Experimental methods

2.1. ISM and device resistance measurements

In order to ensure reproducible inhalation flows are generated, an ISM was designed and manufactured. The ISM is capable of simulating inhalation through an inhaler device by a patient as well as producing continuous flow. A photograph and a schematic diagram of the ISM are shown in Fig. 1 and Fig. 2, respectively; the ISM is essentially a mechatronic (mechanical/electronic) device and comprises a mechatronic lung, a fan and a cavity.

Air flow through the mechatronic lung is generated by the fan and the peak inhalation flow rate is regulated by a throttle upstream of the fan. The lung consists of a cam-driven double-seated valve mechanism. The cam is traversed by means of a ratchet and pinion mechanism driven by a variable speed motor via a magnetic clutch. Traversing the cam causes the valve to move from position 1 to position 2 (see Fig. 2), which corresponds to the start and finish of an inhalation

Fig. 1. General view of the inhalation simulation machine.

process, respectively. The transient flow variation, i.e., the inhalation pattern produced, is governed by the cam profile, while the inhalation duration is determined by the traversing speed of the cam. By altering the cam profile and/or the motor speed, various inhalation profiles can be simulated. The total inhaled volume is a function of cam shape and speed as well as of valve throttle position.

Two limit switches aligned with positions 1 and 2 shown in Fig. 2, are fitted on the traversing rod on which the cam is located. These limit switches are triggered as the valve moves from position 1 to 2, giving two reference pulses for the determination of the start and finish, hence the duration, of an inhalation process.

A rectangular cavity made of clear acrylic plastic is used to simulate the mouth cavity. The cavity is of square cross-section and fixed to the ISM to allow optical access for velocity measurements with laser techniques. The inhalers are mounted to the cavity using purpose-made adaptors and air-tight contact is ensured with a spring-loaded mechanism so that air enters the cavity only via the inhaler.

The flow rate through the inhaler being tested is measured by a Vitalograph® Spirometer Compact II flow head fitted at the entrance of the mechatronic lung. The flow head is essentially a viscous flow meter. The pressure difference between two pressure tappings on the flow head varies linearly with flow rate and it is measured by means of a differential pressure transducer. With suitable calibration at the onset of the experiments, measurement of the flow rate is obtained.

Three types of inhaler device were tested in the present work: Rotahaler® (Glaxo), Intal Spinhaler® (Fisons) and Turbohaler® (Astra). The first two are single-dose and the third a multi-dose device. In order to compare the performance of the devices when used by patients with varying inspiratory efforts, tests are made at various fractions (25–100%) of a control value of inhalation pressure for each device. The control value (termed the maximum inhalation pressure, p_{imax}) of each device was determined as the average of

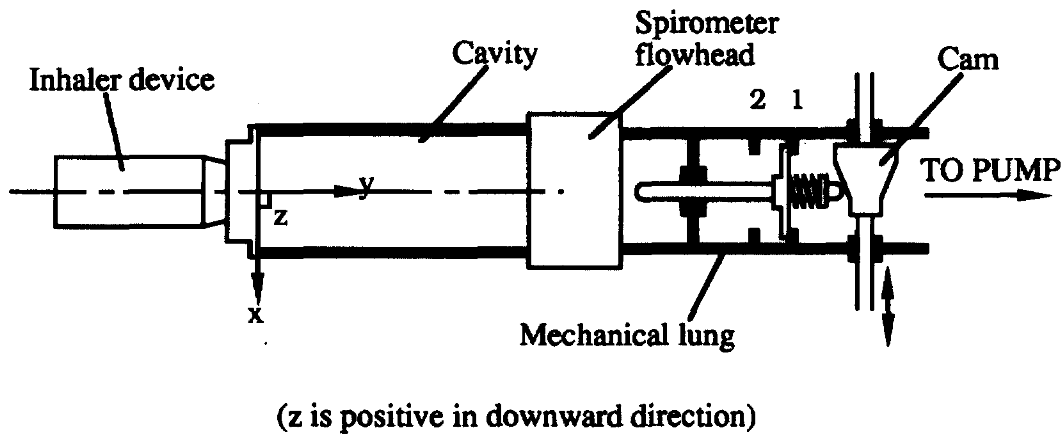

Fig. 2. Schematic cross-section of the cavity and mechanical lung.

the maximum pressure drop generated across each device through inhalation tests with 15 'healthy' human volunteers obtained in a previous experiment (Timsina et al., 1993). The average maximum inhalation pressures measured were 1.3 kPa for the Rotahaler and the Spinhaler and 1.44 kPa for the Turbohaler device.

The inspiration flow profiles obtained from the Spirometer recordings of the 15 healthy volunteers were used as a guide for the design of the cam and cam follower. These profiles varied significantly from person to person and therefore an average profile was used as a baseline or standard inhalation profile. As a result of this averaging process, the constant/maximum flow rate part of the profile is longer than in individual recordings. However, virtually all possible inhalation flow profiles can be simulated with the ISM.

The devices were mounted to the ISM with the mouthpiece axes aligned with the centre-line of the cavity and the variation of inspired flow rate (F) with inspired volume (V), of F with time and of V with time were determined with the pressure transducer. Characteristic variations are shown in Fig. 3(a)–(c). These traces were obtained with the Turbohaler attached to the ISM which operated at 100% of the maximum inhalation pressure for the device (1.44 kPa). The inhaled volume was 1.057 l, the peak inhalation flow (PIF) was 0.756 l/s and the duration of inhalation was 1.56 s.

As different devices generate varying resistances to patient-induced flows, measurements were made in order to quantify their respective resistances to flow. The ISM was set to generate continuous flow and the peak inhalation flow rates produced by various inhalation pressures were then measured for each device. Fig. 4 shows the relationship between inhalation volumetric flow rate, F, and inhalation pressure, p_i, obtained for the three devices tested. It can be observed from this figure that the least resistance to the flow is produced by the Rotahaler, followed by the Spinhaler and the Turbohaler. This indicates that a constant flow rate condition through an inhaler with a high flow resistance, such as a Turbohaler, will necessitate extremely high inhalation pressures, far higher than those that can be achieved by most humans, regardless of their inspiratory capability. Therefore, inhalation pressure rather than inhalation flow rate was used as the characteristic parameter in this work, as the former can represent better the inspiratory effort exerted by patients (see also Lee et al., 1993a).

2.2. LDA and measurement procedure

LDA is an optical technique which utilises the Doppler effect by which waves from a given source reach an observer with an increased frequency if the source and observer are approaching each other and a reduced frequency if they recede

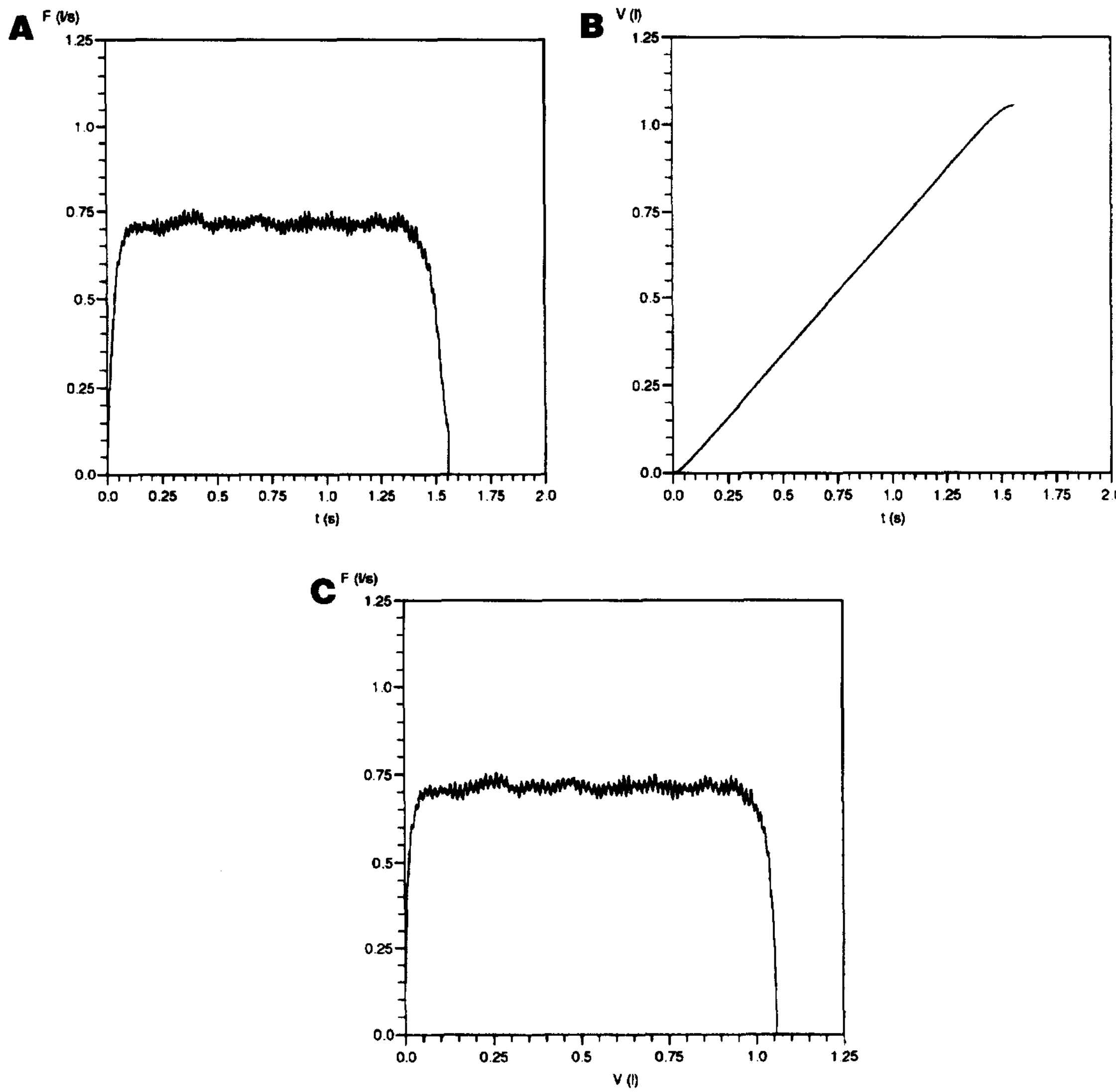

Fig. 3. Indicative variation of (a) flow rate F with time, (b) volume V with time and (c) flow rate F with volume V. Results obtained with Turbohaler DPI operated at 1.44 kPa inhalation pressure.

from one another. LDA is suitable for a wide range of velocities, varying from mm/s to hundreds of m/s and both the velocity and turbulence at a location in a flow can be determined with considerable accuracy.

In the most common form of laser-Doppler anemometer such as that employed for the present investigation, the beam from a laser is split into two. These two beams are deflected by mirrors or lenses to intersect and form a measurement volume within the flow. Within this measurement volume, a set of interference fringes are formed. The distance λ^* between successive fringes is given by:

$$\lambda^* = \frac{\lambda}{2\sin\left(\frac{\kappa}{2}\right)} \tag{1}$$

where λ is the wavelength of the laser light and κ is the intersecting angle of the beams. A particle in the flow moving with a velocity component U in the plane of the two beams and perpendicular

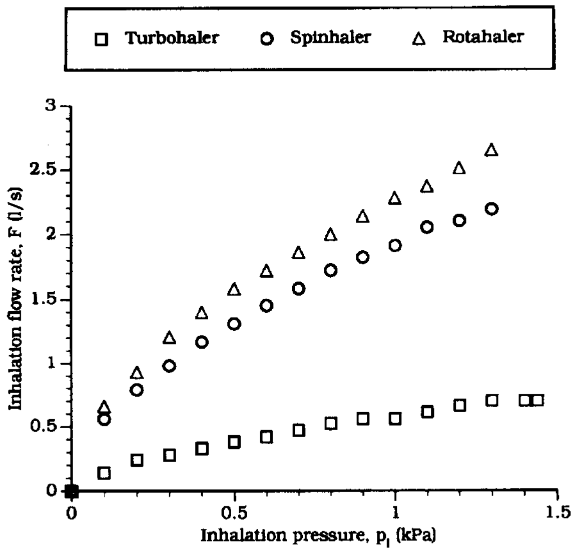

Fig. 4. Variation of inhalation flow rate through the ISM with inhalation pressure for the Rotahaler, Spinhaler and Turbohaler DPI devices.

to the bisector of the angle κ will scatter light as it moves through the fringes. This scattered light is collected with a photodetector and its amplitude is modulated with a frequency, f_D:

$$f_D = \frac{2U \sin\left(\frac{\kappa}{2}\right)}{\lambda} \tag{2}$$

By measuring this frequency, U can be determined. In order to measure velocity components in different directions, the measurement volume is moved so that the bisector of the angle between the beams coincides with the direction concerned. If particles cross the fringes in rapid succession, the variation of the velocity with time at the measurement location can be accurately determined and the turbulence level and other parameters important for the quantification of the turbulence field can be obtained.

LDA offers two major advantages: no obstructions (e.g., probes) need be inserted into the flow and no calibration is required. The main requirements for the application of the technique are laser beam (optical) access to the flow and the presence of scattering particles. It is ideally suited for multiphase flows such as aerosols. However, the instrumentation involved is complex and extreme care is necessary in order to obtain meaningful results. In addition, the velocities of each of the two phases (dispersed/solid particles and continuous/gas) must be unambiguously determined.

The variation of velocity with time for the transient flows produced by different DPI (time-resolved velocity measurements) was measured using an anemometer comprising a 2W Argon-Ion laser, a diffraction grating, a photomultiplier, a frequency counter and associated optics. Smoke particles of sufficiently small size (a few μm in diameter) were introduced into the environment upstream of placebo inhalers in order to obtain a high data collection rate for the characterisation of the turbulence structure of the continuous phase (air). Measurements at various locations within the cavity were made at 25, 50, 75 and 100% of the maximum inhalation pressure for each inhaler in order to simulate inhalation by patients with varying inspiratory difficulty.

The signal outputs from the frequency counter and from the pressure transducer, together with the reference pulses indicating the start and finish of an inhalation cycle were input into a multi-channel analogue-to-digital (A/D) converter interfaced with a computer. These signals were simultaneously sampled and digitised by the A/D converter at a rate of 1500 Hz, and stored on the computer. The differential pressure transducer signal was used for monitoring purposes and, together with the two reference pulses, to record the total inhaled volume, the peak inhalation flow rate and the inhalation duration. The values of these three parameters obtained from each simulated cycle were compared with the corresponding values for the specific device and inhalation pressure so that reproducibility was ascertained.

From the recorded data, the variation of instantaneous velocity with time in an inhalation cycle is obtained by extracting the velocity data recorded between the two reference pulses. A characteristic velocity-time trace obtained with the Rotahaler is shown in Fig. 5(a).

Since all turbulent flows essentially consist of fluctuations of velocity superimposed on the mean velocity, any instantaneous value of the velocity, U, can be considered as comprising of two components:

$$U = \bar{U} + u \tag{3}$$

where $\bar{U}$ is the mean velocity and u is the fluctuation velocity. In order to quantify the magnitude of the mean and fluctuation velocities of the flows generated by each device, the original velocity recording (U) is decomposed into $\bar{U}$ and u by means of a Fast Fourier Transform (FFT). Through the FFT a frequency spectrum is obtained and the low frequency ($\bar{U}$) and high frequency (u) contributions to this spectrum can be separated. Two inverse FFTs are then performed to obtain a mean velocity-time trace and a fluctuation velocity-time trace, shown in Fig. 5(b) and Fig. 5(c) respectively. The turbulence level, u', generated during an inhalation process is then estimated by obtaining the ensemble-averaged root-mean-square value of u when the mean velocity $\bar{U}$ is near-uniform, e.g. between 0.25 and 1.35 s in Fig. 5(b):

$$u' = \sqrt{\bar{u}^2} \tag{4}$$

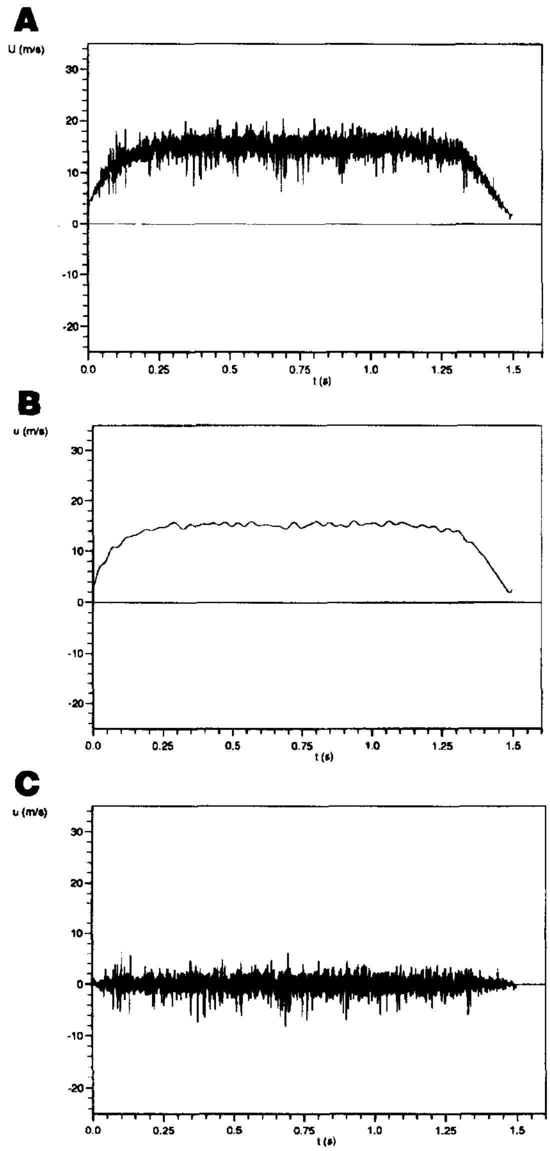

Fig. 5. Variation of the (a) instantaneous, (b) time-resolved mean and (c) fluctuating velocities measured at $x = 0$ mm, $y = 5$ mm and $z = 0$ mm downstream of a Rotahaler DPI. $p_i = 1.3$ kPa.

The temporal and spatial scales of turbulence are important features of the turbulence structure, which can be used to characterise the drug de-aggregation performance of each device. Although the interpretation of the effect of turbulence scales on inhaler performance is not straightforward, in general smaller scales might be expected to result in better de-aggregation characteristics. The micro time scale of turbulence provides a measure of the most rapid changes in the turbulent fluctuations, while the integral or macro time scale is a rough measure of the longest connection in the fluctuations (Hinze, 1975). Temporal scales of turbulence were determined at each measurement location. The integral time scale L_t was obtained using the following equation:

$$L_t = \int_0^{\infty} R(\tau)\,d\tau \tag{5}$$

Where $R(\tau)$ is the autocorrelation function and is given by:

$$R(\tau) = \frac{\overline{u(t)u(t+\tau)}}{u'^2} \tag{6}$$

and the micro time scale λ_t was obtained by:

$$\frac{-2}{\lambda_t^2} = \frac{-1}{u'^2}\overline{\left(\frac{\partial u}{\partial t}\right)^2} \tag{7}$$

The micro length scale λ_x may be considered as a measure of the average dimension of the eddies that are mainly responsible for the dissipation of turbulence energy, while the integral length scale L_x is a measure of the longest correlation distance between the velocities at two points of the flow field. When $\bar{U}$ is constant and $\bar{U} \gg u'$, these two spatial scales may be related to the temporal scales as follows:

$$\lambda_x = \lambda_t \bar{U} \tag{8}$$

and

$$L_x = L_t \bar{U} \tag{9}$$

However, since the turbulence intensities (defined as $u'/\bar{U}$) in the aerosols investigated in the present work were high in many parts of the flows, the condition $\bar{U} \gg u$ was not satisfied and spatial scales of turbulence could not be determined accurately.

The magnitudes of the measurement errors vary from one location to another as they depend partly on the local velocity gradients; they were calculated to be around 1–5% for the mean velocities and 5–10% for the turbulence levels. The errors in the determination of the time scales are more difficult to determine accurately; they were estimated at around 20% for the values reported here.

3. Results and discussion

In this section characteristic mean velocity, turbulence level and integral time scale results obtained with the three inhalers are presented and discussed to indicate the spatial and termporal variation of these quantities.

The velocity recording presented in Fig. 5(a) was obtained with the Rotahaler operated at the maximum inhalation pressure (1.3 kPa) at a location on the centreline of the cavity and at a distance of 5 mm downstream of the inhaler mouthpiece. The mean and turbulence velocity variations obtained from this recording by means of FFT techniques are shown in Fig. 5(b) and Fig. 5(c), respectively.

It can be observed from Fig. 5(a) that the velocity rises from zero as the inhalation process starts, fluctuates about a mean velocity of about 15 m/s for most of the inhalation duration and subsequently drops to zero as the cycle is completed. The velocity fluctuates during the inhalation cycle, reaching values as low as 6 m/s and as high as 20 m/s. By subtracting the mean velocity variation (Fig. 5(b)) from the instantaneous velocity recording (Fig. 5(a)), the fluctuating velocity variation is obtained (Fig. 5(c)). The turbulence level u' was calculated by ensemble-averaging these fluctuations and this value is discussed below.

Velocity recordings obtained further downstream along the cavity centreline, at 15 mm and 25 mm from the mouthpiece for the maximum

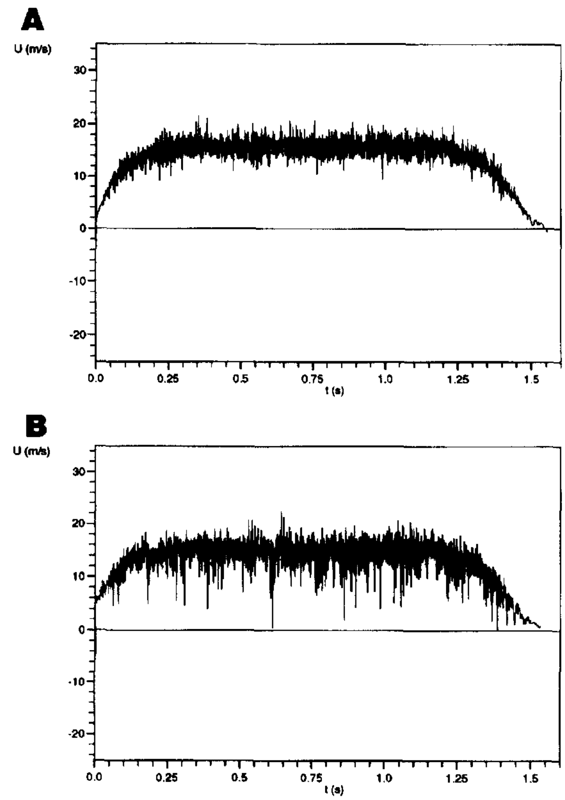

Fig. 6. Variation of the instantaneous velocities measured at $x = 0$ mm and $z = 0$ mm downstream of a Rotahaler DPI at $p_i = 1.3$ kPa. (a) $y = 15$ mm and (b) $y = 25$ mm.

inhalation pressure condition, are shown in Fig. 6(a) and (b), respectively. The mean velocity value at $y = 15$ mm is similar to that at $y = 5$ mm (Fig. 5(a)), but at $y = 25$ mm it decreases to 14 m/s. The velocity fluctuations are slightly lower at $y = 15$ mm than at $y = 5$mm, but considerably higher at 25 mm. This indicates that in order to assess the axial turbulence levels generated, it is necessary to consider their distribution across the cavity. In Fig. 7, the variation of u' with distance from the mouthpiece (y) is shown along three lines parallel to the centreline: $x = -5$, 0 and 5 mm, for the maximum inhalation pressure condition. Along $x = 0$ and 5 mm u' increases with downstream distance. However, at $x = -5$ mm, u' decreases near the centre of the cavity and subsequently increases further downstream. These results indicate clearly that the flow produced by the inhaler is three-dimensional and measurements at a single

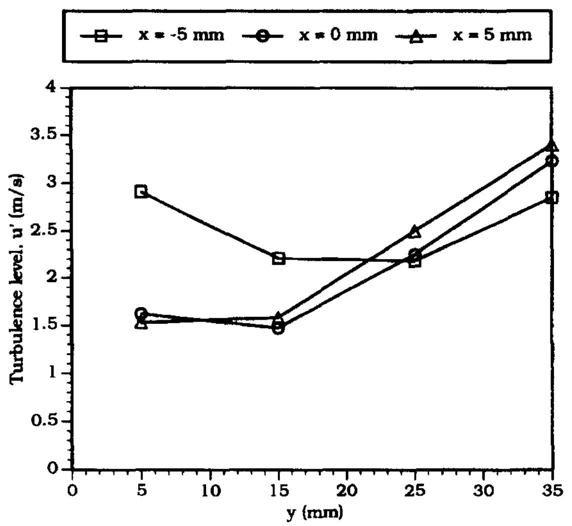

Fig. 7. Variation of the turbulence levels generated by a Rotahaler DPI device with location in the $z = 0$ mm horizontal plane. $p_i = 1.3$ kPa.

location may provide a misleading assessment of the velocity and turbulence characteristics.

A similar observation can be made for the distribution of the integral time scales which is presented in Fig. 8. The values of T across the cavity vary from 3 to 6 ms. There are significant variations near the mouthpiece which in general tend to decrease with downstream distance.

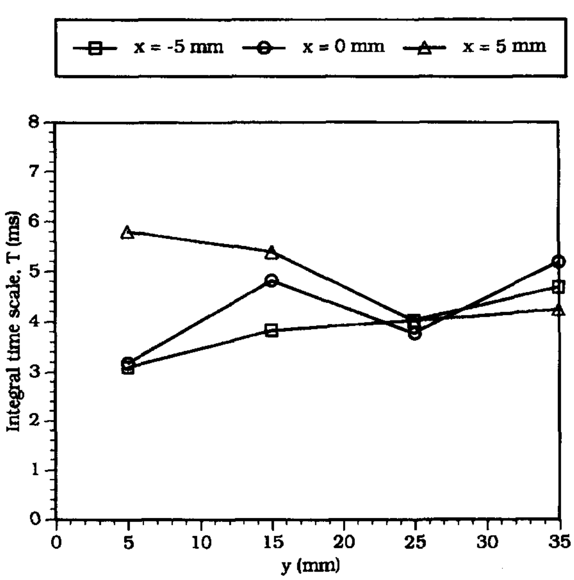

Fig. 8. Variation of the integral time scales generated by a Rotahaler DPI device with location in the $z = 0$ mm horizontal plane. $p_i = 1.3$ kPa.

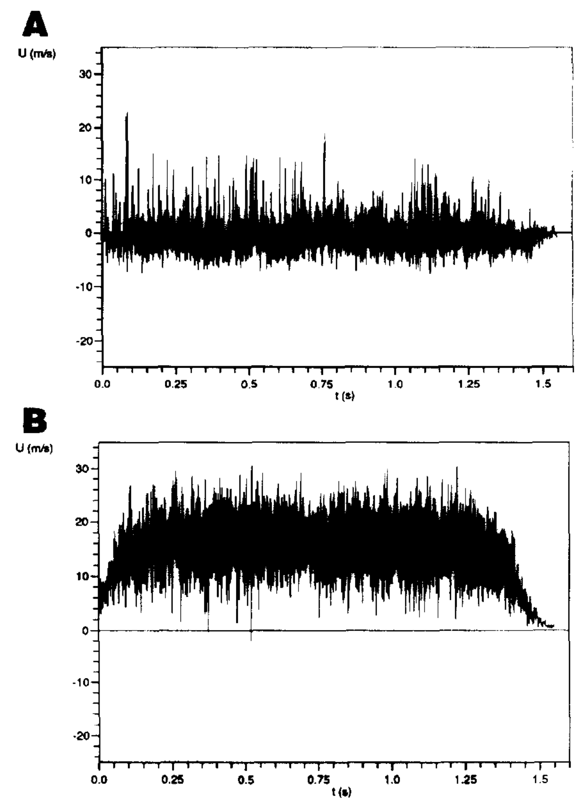

Fig. 9. Variation of the instantaneous velocities measured at $x = 0$ mm, $y = 5$mm and $z = 0$ mm downstream of a (a) Turbohaler ($p_i = 1.44$ kPa) and (b) Spinhaler ($p_i = 1.3$ kPa) DPI device.

Measurements obtained with other devices showed considerable differences in both the mean velocity and turbulence level distributions. Characteristic recordings obtained along the centreline at $y = 5$ mm with the Turbohaler and Spinhaler devices, at their corresponding maximum inhalation pressure conditions, are shown in Fig. 9(a) and (b), respectively.

The Turbohaler result (Fig. 9(a)) reveals a very low mean velocity (around 0 m/s) but with high fluctuations, from -7 m/s to 23 m/s. Again, this distribution is characteristic of the flow produced by the particular device. The swirling flow generated at the outlet of the Turbohaler mouthpiece is accompanied by low axial mean velocities and occassionally local flow reversal near the cavity centreline, a characteristic of most swirling flows. The steep velocity gradients at the edges of the swirling jet result in the generation of considerable amounts of turbulence.

The variation in Fig. 9(b) is typical of the Spinhaler results obtained: significant levels of turbulence are generated with the device across most of the cavity. Although the mean velocity (15 m/s) is not dissimilar to that measured with the Rotahaler in the same location, fluctuations from − 2 m/s to 30 m/s can be observed. The turbulence level (u') values at this location are 5.25 m/s and 3.6 m/s with the Spinhaler and Turbohaler, respectively and they may be compared with the corresponding value of 1.6 m/s for the Rotahaler. However, it must be recalled that it is the average value of the turbulent levels of all three velocity components in the x-, y- and z-directions across

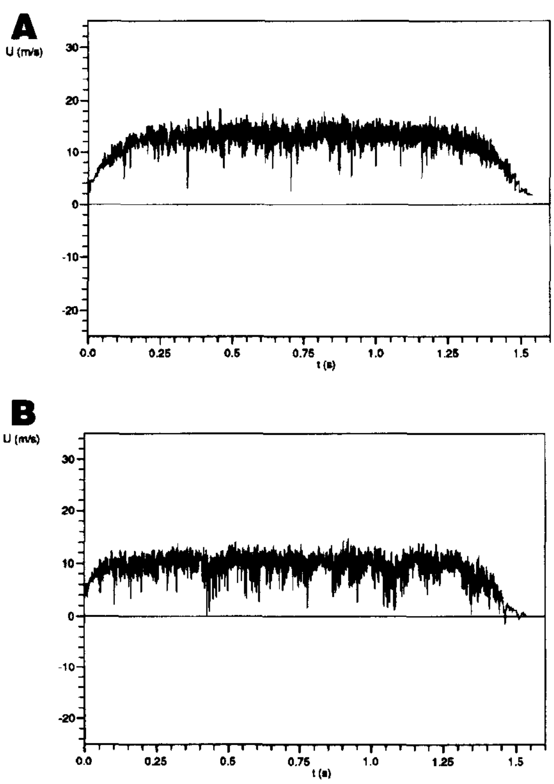

Fig. 10. Variation of the instantaneous velocities measured at $x = 0$ mm, $y = 5$ mm and $z = 0$ mm downstream of a Rotahaler DPI. (a) $p_i = 0.98$ kPa and (b) $p_i = 0.65$ kPa.

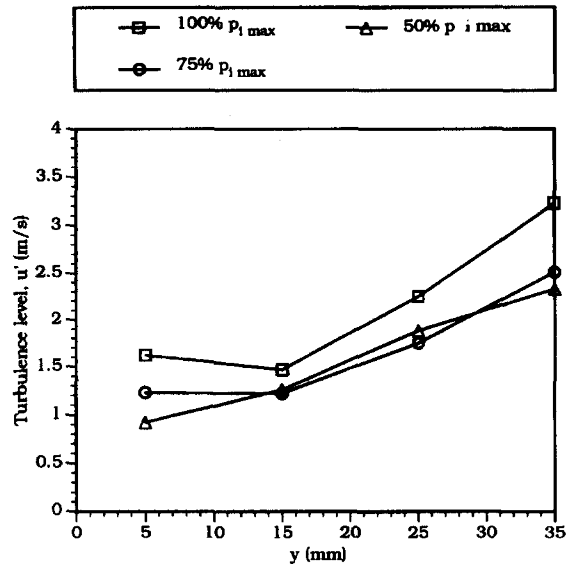

Fig. 11. Variation of the turbulence levels generated by a Rotahaler DPI device with inhalation pressure along $x = 0$ mm in the $z = 0$ mm horizontal plane.

the whole cavity that must be used for the assessment of the turbulence-generating properties of different devices (see also Lee et al., 1993b).

Variation of the inhalation pressure was also simulated with the ISM and it was found to affect the mean velocity and turbulence characteristics of the aerosols. Fig. 10(a) and (b) present recordings obtained with the Rotahaler operated at 75% (0.98 kPa) and 50% (0.65 kPa) of the maximum inhalation pressure. The results shown may be compared with Fig. 5(a) obtained at 1.3 kPa at the same location. The mean velocities decrease with inhalation pressure, as might be expected, to 13 m/s at 75% and 10 m/s at 50% of maximum pressure. The decrease of mean velocity with inhalation pressure is non-linear but very similar to the decrease in flow rate with p_i indicated by the steady (constant) flow tests (Fig. 4). This result indicates that steady flow tests can provide a useful indication of the mean flow performance of a DPI.

The u' turbulence levels also decrease with inhalation pressure; values of 1.6, 1.2 and 0.9 m/s were calculated for inhalation pressures of 100, 75 and 50%, respectively. The decrease in u' with inhalation pressure is also non-linear. The turbulence level values must however be assessed with care due to the variation of the trajectory of the flow leaving the inhaler with flow rate and the aforementioned three-dimensionality of the flow: comparatively high values in one location may be accompanied by lower values in others. A better assessment can be made by considering the distribution of the u' turbulence levels across the cavity for the three inhalation pressures considered. Such a variation of u' along the centreline is shown in Fig. 11. It can be seen that, in general, u' is highest at the maximum inhalation pressure but there are no clear trends evident at the lower pressures.

Because of such local variations, the average u' level across the whole cavity may be a better indication of the overall turbulence producing characteristics of the device. For the Rotahaler, this was calculated to be 1.25, 1.8, 2.0 and 2.4 m/s for inhalation pressures of 25, 50, 75 and 100% of p_{imax} respectively. An increase in the average u' values with inhalation pressure was also measured with the Spinhaler, with values of 2.0 m/s at 25% and 4.3 m/s at 100% of p_{imax}. The Turbohaler results also showed u' increasing with p_i, from 0.8 m/s at 25% to 1.9 m/s at 75% of p_{imax}; however the average u' values for 75 and 100% of p_{imax} were similar. This difference may be related to the nature of the flow produced. As the Rotahaler and the Spinhaler generate flows which are primarily axial, the average axial turbulence level should provide an adequate assessment of turbulence generation. The Turbohaler, however, generates a strongly swirling flow and measurements of the average turbulence levels in the other two directions may also be required to quantify the flow adequately.

4. Concluding remarks

The ISM has proved to be an accurate and useful means for accurate in vitro simulation of different inhalation conditions. Detailed characterisation of the mean flow and turbulence characteristics of DPI inhalers can be carried out in the machine with laser anemometry techniques and in this way the aerodynamic performance of the devices can be ascertained under repeatable conditions. Such devices are widely accepted as providing an efficient method of delivering drugs to the lungs. The results obtained can enable a more thorough characterisation of DPI performance, taking into account the distribution and structure of the mean flow and turbulence generated by a device. The present work has indicated that the assessment of the aerodynamic performance of DPIs is not straight-forward and systematic studies of the effect of inhalation pressure and design device on the flow properties are required. Clearly, powder formulation and clinical and pharmaceutical tests are of the utmost importance and therefore a multi-disciplinary approach may be necessary for the effective optimisation of the design of inhaler devices.

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