AN ALTERNATIVE SPRAY PRODUCTION METHOD FOR PRESSURIZED METERED DOSE INHALER

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Abstract
Methods for producing fine sprays at low flow rates, whilst minimising compressed gas use, are of interest particularly, but not exclusively, for medical inhalation therapy. In this study a simple atomizer geometry is found to operate particularly satisfactorily for liquid flow rates less than 3ml/min. This consists of a hypodermic tube, with internal bore typically 125μm, injecting liquid into an air jet produced by a choked gas orifice typically with diameter 200μm. The orientation and shape of the liquid orifice, and its position in the gas jet, for optimum atomization quality are examined. Inhalable fraction measurements show that, as expected, changes in flow rates and geometry which reduce drop size generally tend to increase inhalable fraction. Phase Doppler Anemometry measurements and high-speed imaging show that a narrow, nearly axisymmetric spray rapidly develops near the atomizer even though the atomizer geometry is asymmetric. It was found that this nozzle configuration is performing similarly to devices with CFC or HFC propellants.

Nomenclature

$SMD = D_{32}$	Sauter mean diameter.
D_{30}	Volume mean diameter.
HFC	Hydrofluoroalkane propellant
CFC	Clorofluoroalkane propellant
U_{mean}	The mean stream wise component of the velocity.
U_{rms}	The root mean square value of U.

Interlocution

The pressurized metered-dose inhaler (pMDI) is a device designed to dispense finely dispersed drug formulation for the treatment of various pulmonary diseases through oral intake of multiple doses. The spray issued from these devices is traditionally generated by flash evaporation of CFC-based propellants. However, in response to the Montreal Protocol [1] which phased out the production of ozone depleting substances in 1987 and was implemented in the European Union to ban production of all CFCs from the 1st January 1995, pharmaceutical firms and others evaluated potential non-CFC propellants that could be used safely and effectively in MDIs. In the course of this extensive review, HFCs emerged as the only propellant suitable for pharmaceutical use. No other compound has been proven to meet the stringent criteria1 for a medical gas to be used for inhalation by patients. The HFCs used in asthma inhalers meet these criteria. HFCs 134a and 227 are the only proven alternatives to CFC propellants for MDIs. These propellants are non-flammable and have been shown to be safe for human inhalation through extensive toxicity testing, which has been to the same detailed level as a new drug. Both have vapor pressures suitable for MDI usage, and both are essentially biologically inert. HFCs do not deplete the ozone layer, and they have significantly lower global warming potentials than the CFCs that they replace in pharmaceutical applications. The HFCs while they are much lower in the global warming severity they are nevertheless a contributing factor. Therefore an alternative method of producing more "ozone and environmentally friendly" sprays, having an MDI spray like profile has to be developed. A possible alternative is to use compressed (inert)gas and two fluid atomization. Widger et. al. [2] have introduced a method of producing very fine liquid sprays at low liquid flow and using low throughputs of compressed gas. This is referred to as the "UMIST" atomizer, in which a liquid nozzle has a beveled orifice immersed in the air jet from the air nozzle. The angle between the two nozzles (with diameters from 125-200 μm) can be varied. Figure 1

1 Correct propellants used in medical inhalers must:
be a liquefied gas, have appropriate solvent properties, have very low toxicity, have appropriate density, chemically stable, compatible with a wide range of medicines, acceptable to patients (taste and smell) and non-flammable

shows the UMIST 200/125 atomizer using hypodermic tubes of 200 and 125 μm internal diameter for gas and liquid respectively. Note that the nozzles in figure 1b are not in their optimum respective positions.

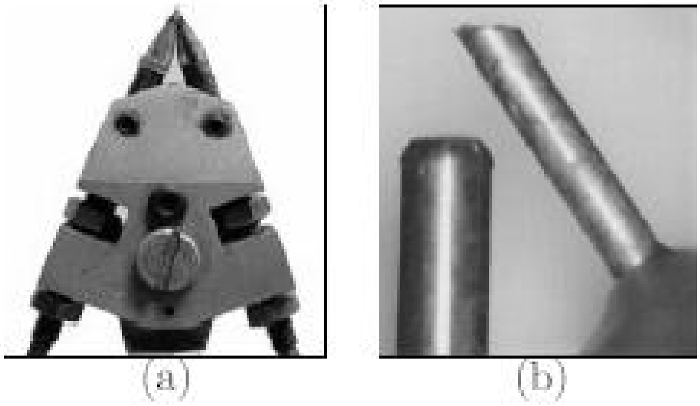


Figure 1. UMIST twin fluid hypodermic atomizer (a) atomizer and supports, (b) enlargement of the tip showing the beveled liquid hypodermic (right) and the gas hypodermic (left).

Apparatus

The philosophy of the atomizer is that the sharp edge of the liquid nozzle projects into the high velocity gas stream such that the gas streamlines converge at the periphery of the liquid orifice. Provided that the liquid orifice is beveled, as shown, the liquid emerges from the orifice at the periphery of the liquid nozzle where it leaves as a sheet, with subsequent ligament formation. It is immediately subjected to the highest gas velocities that prevail in the flow. The quality of the spray is very sensitive to the relative positions of the two hypodermics and the area of the gas outlet covered (obscured) by the beveled tube.

In this paper further development of this atomizer arrangement is described to produce SMD's of 2-4 µm but still retaining a pMDI like spray pattern. The criteria of SMD together with percentage droplets, by volume, smaller than 7 µm are crucial to the pharmaceutic industry to give an indication of the inhalable fraction

The UMIST atomizer essentially utilizes the principle of an air blast atomizer. The angle separating the nozzle centrelines is 45^o. Different ratios of gas to liquid orifice diameters, gas orifice obscuration and combinations of liquid and gas flow rates were examined. The best spray is produced at obscuration of about 85 %, i.e. the sharp tip of the liquid orifice projects 85% across the projected area of the gas orifice. Therefore the tests were conducted at this obscuration.

The liquid (water in the tests reported here) was supplied to the atomizer by means of pressurized reservoir. The flow rates of gas and liquid were controlled using needle valves. Volume flow rate was measured using two miniature rotameters which were pre- and post-calibrated and provided measurement to within ±0.05ml/min for 0.8ml/min$\leq Q_L \leq$20L/min. Calibrated pressure gauges were used to measure the liquid and gas pressures 1m upstream of the atomizing nozzle. A change in atomizer pressure was an indicator should the liquid hypodermic undergo a blockage. The tests were done with continuous spray.

Parameter	UMIST nozzle Gas/Liquid hypodermics diameter			
	150/150	200/125	200/150	200/200
SMD (μm)	11.12	08.81	09.90	08.24
% <7.16 (μm)	16.20	19.80	17.40	22.50

Table 1. Sauter mean diameter and droplet percentage by volume less than 7.16 (μm)

Results and Discussion

Before a detailed study of the 200/125 atomizer, other combinations of the nozzle were studied. Table 1 summarises Malvern 2600 data for tests made with 600 and 2.0 mL/min air and liquid flow rates respectively. For the 200/125 atomizer liquid flow rate was varied between 1.3 and 3.0 mL/min, whilst that of the air was in the range of 600 to 2300 mL/min (NTP). The air supply pressure with respect to the ambient pressure was 0.2 MPa (2 bar) at 600 mL/min, and 0.8 MPa at 2300 mL/min. A summary of the findings is depicted in figures 2 and 3, which show the SMD and percentage by volume less than 7.16 µm respectively as functions of water flow rate and atomizing air supply pressure. Measurements were made, using steady sprays of water, at 60mm downstream with the laser beam penetrating through the centre of the spray. The optimum spray was found to occur for the 8 bar air pressure. Although the 2.2 mL/min liquid flow rate gave the lowest SMD (about 2.0 µm), 2.0 mL/min was more satisfactory judging by the inhalable fraction, criterion (droplet % <7.16).

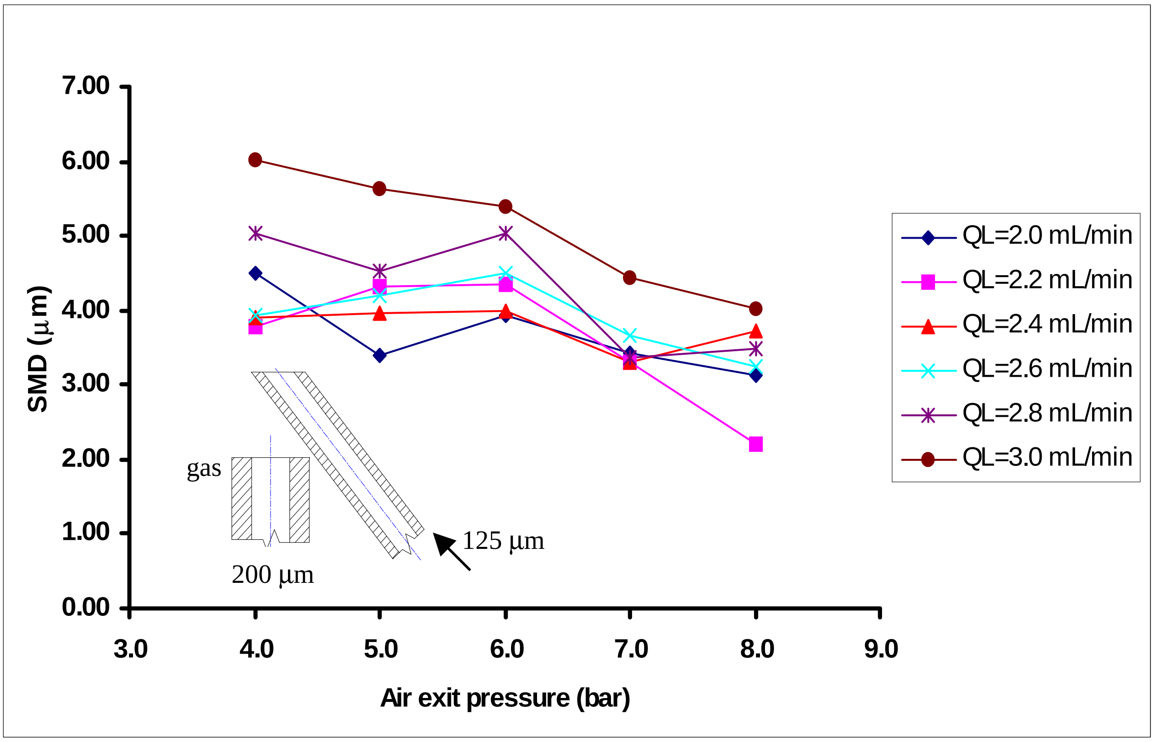


Figure 2. SMD against air pressure for different liquid flows, 200/125 atomizer

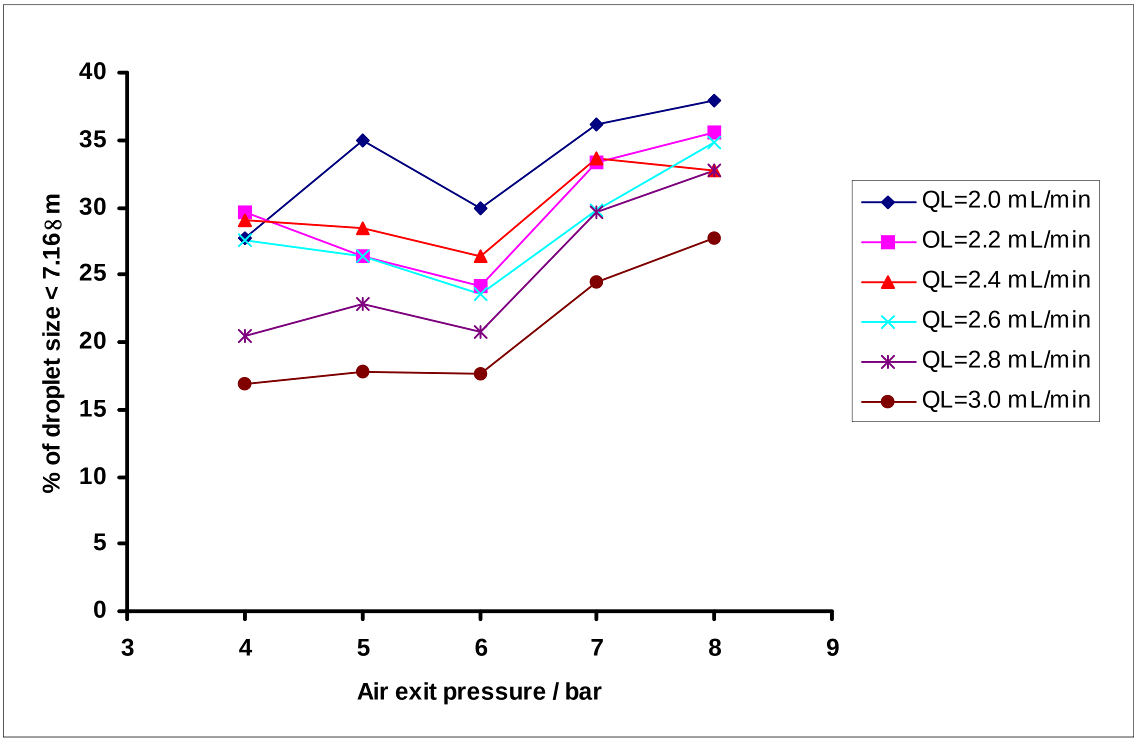


Figure 3. % of droplet size <7.16 µm against air pressure for different liquid flows, 200/125 atomizer

The spray was also characterized using Dantec PDA instrument using laser power 100 mW and with a collection angle 72^{o}. Figures 4-7, are the traverses across the free spray for different distances downstream for SMD, mean droplet velocity (U), the R.M.S. of droplet velocity variations divided by the local mean velocity, and droplet mass flux. The results are representative of those expected for a narrow angle, turbulent, finely atomized spray. The mean drop size is uniform across a central zone, but with larger droplets tending to concentrate at the outer edges, where their velocities are very low or negative in places. The PDA provides larger mean drop diameters than the Malvern instrument. This is because the laser power used was not sufficient for detecting the droplets around 1 μm diameter without giving biasing effects.

The average total spray angle, in the first 60mm, is 19^{o}, as measured to the edge of the velocity profile. Peak velocity and droplet mass flux are at the spray centre, featuring a typical profile of free jet. High speed videos were taken using Kodak 4540 camera operating at “1/4 frame” giving 18000 fps. Close ups of the near-atomizer region, although relatively poor in resolution, showed that the spray angle in the first few millimetres was greater than 19^{o}, and air entrainment caused the subsequent narrowing of the angle. An example frame is shown in figure 8. As seen in figure 5 the centre of the spray is off-axis, where the axis is here based on the centreline of the air nozzle. This is due to the deflection effect of the liquid nozzle immersed in the gas jet.

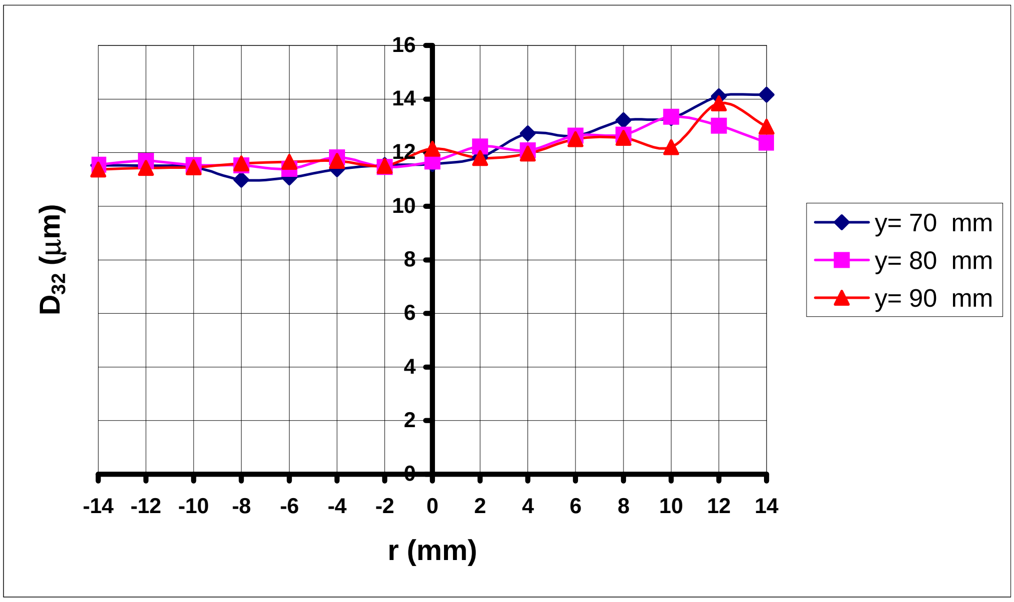


Figure 4. SMD distribution in free spray from 200/125 atomizer (8 bar)

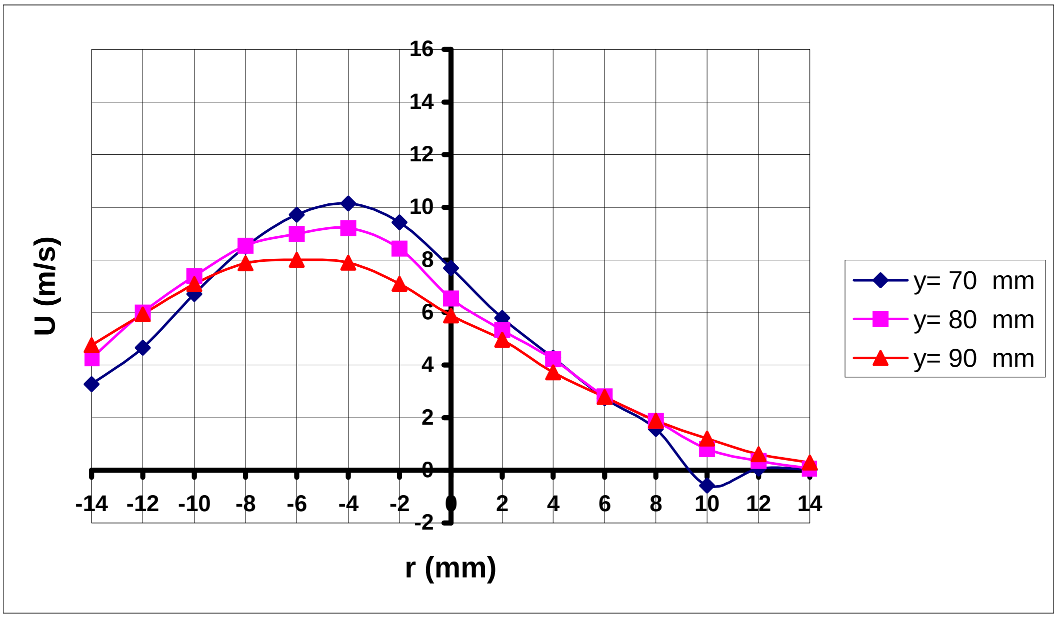


Figure 5. Mean droplet velocity distribution in free spray from 200/125 atomizer (8 bar)

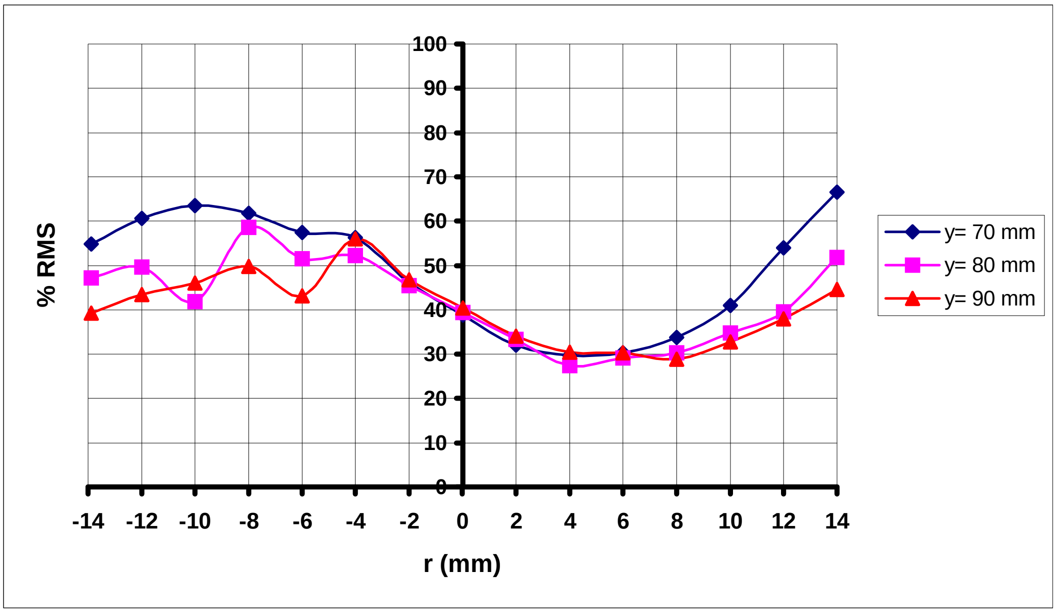


Figure 6. Relative turbulence intensity in free spray from 200/125 atomizer (8 bar)

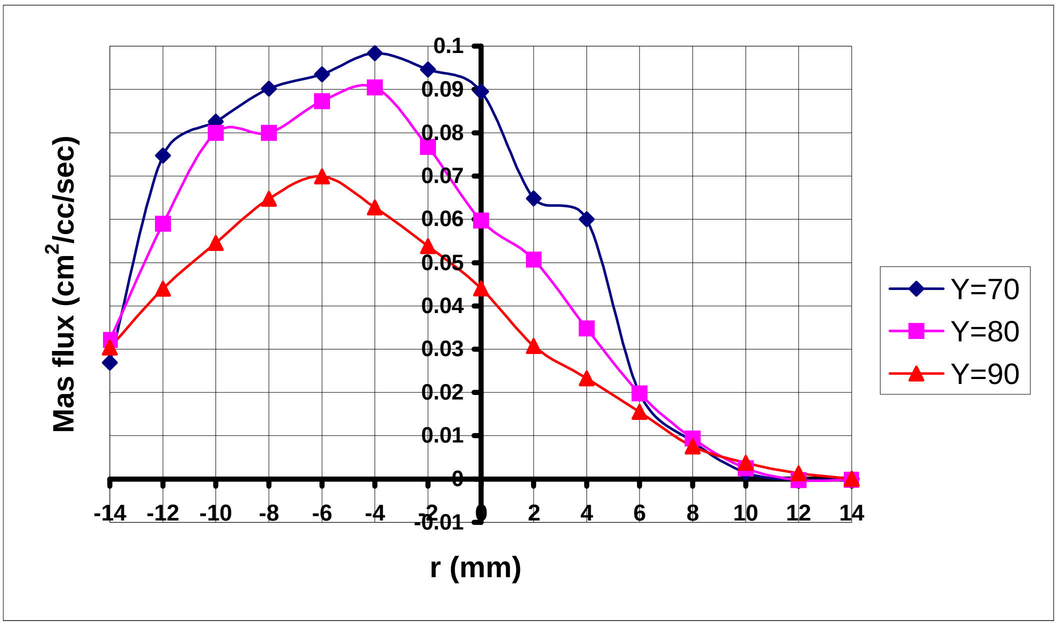


Figure 7. Droplet mass flux distribution for free spray from 200/125 atomizer (8 bar)

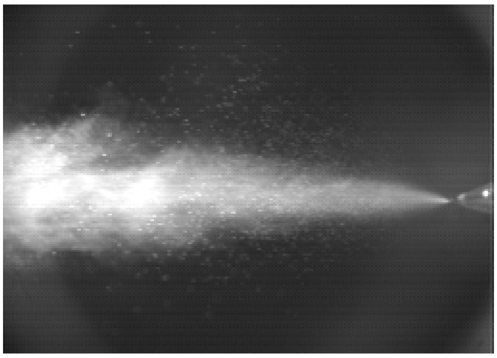
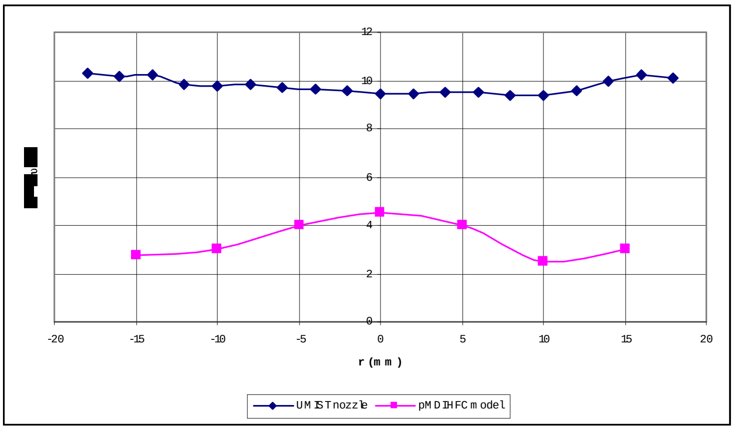


Figure 8. UMIST twin fluid hypodermic



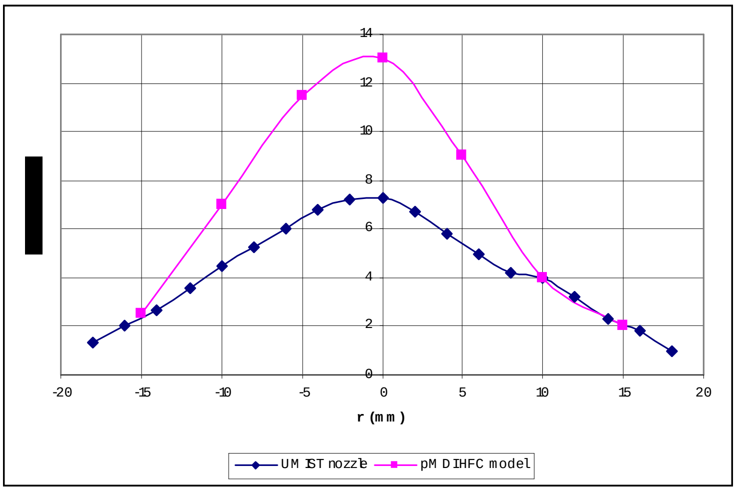


Figure 9. Comparison of pMDI HFC model (Dunbar et. al.) and UMIST nozzle; profile of D_{30} (top) and profile of U_{mean} (bottom).

Discussion and Concluding Remarks

Dunbar et. al. [3], have performed PDA investigation of sprays of drugs from pMDIs using HFC propellant. Their result at 100 mm downstream are in Figure 9, where the mean diameter D_{30} was measured. As seen in figure 9 the UMIST atomizer at the same distance downstream has a much lower velocity profile but higher Volume Mean Diameter (D_{30}). However, the drug with surfactant sprayed by Dunbar et. al. had lower effective surface tension than the untreated water used in the present tests and , for example, sprays of ethanol using the present atomizer, gave D32 and D30 values 60 to 70 % of those when using water. The low velocity, and thus low momentum, of the spray is an advantage for MDI usage: inhalability does not depend only upon drope size but also upon initial spray momentum as it leaves the mouthpiece [4]. Excessive momentum can result in unwanted deposition in the upper respiratory path, even for fine sprays.

Acknowledgment

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Refrences

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[3] Dunbar, C.A., Watkins, A.P. and Miller, J.F., “An Experimental Investigation of the Spray Issued from a pMDI Using Laser Diagnostic Technique”, Journal of Aerosol Medicine.10 (4), 351-368, (1997).

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