

INTRODUCTION

Research indicates that as a nebulised plume passes through an NGI, heat transfer from the impactor causes evaporation of the nebulised solution, resulting in an inaccurate distribution of particles¹. It has been suggested that cooling the NGI will help to reduce this evaporation². Currently there are limited data that consider this issue with respect to different nebuliser formulations, and how different methods for cooling the impactor affect performance of the test.

This study was performed to look at the effects of temperature on aerodynamic particle size of both solution and suspension formulations and to consider the effect of continuous cooling throughout nebulisation versus 'a fridge method'³. The NGI Cooler (Copley Scientific, Nottingham UK) will be used to produce a range of controlled temperatures required for testing.

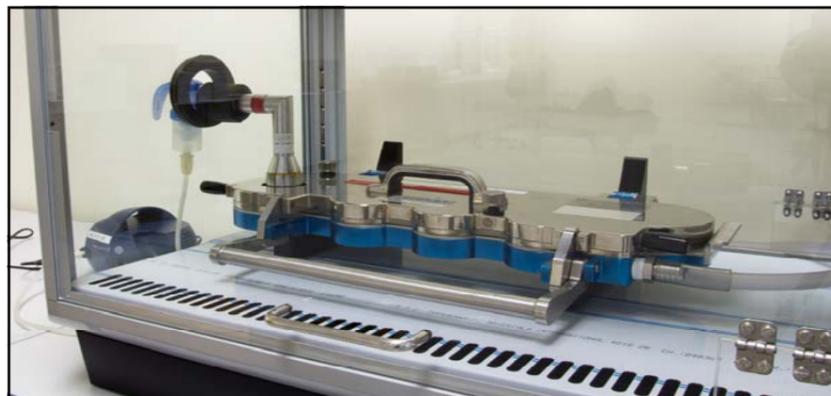
METHOD

NGIs were performed in triplicate at the following conditions:

- Ambient laboratory conditions (23±2°C and 45-75% RH),
- NGI placed in the fridge for 90mins at 2-8°C (nebulisation was started within 5mins of removal from the fridge)
- 5°C, 7.5°C and 10°C in the NGI cooler.

A commercially available jet nebuliser was used. The flow rate was maintained at 15L/min and nebulisation was continued until the sample had been exhausted.

Two formulations were tested at each condition: A Salbutamol sulphate solution (2.5mg/2.5ml) and a Fluticasone Propionate suspension (0.5mg/2ml). After nebulisation the amount of drug in the throat, cups and filter was quantified using HPLC.



References:

- 1) Finlay WH, Stapleton KW. Undersizing of droplets from a vented nebulizer caused by aerosol heating during transit. *Journal of Aerosol Science*. 1999. 30. 1. p 105-109.
- 2) Berg E, Mitchell J, Dennis J, Kreher C, Jauernig J, Lamb P, Karlsson M, Nikander K, Tservistas M. The Nebuliser Sub-Team of the European Pharmaceutical Aerosol Group. *Drug Delivery to the Lungs* 18. 2007.
- 3) Berg, E and Asking, L (2004) Nebulizer Droplet Size Distribution – Refrigerated NGI at 15l/min – RDD IX 2004
- 4) *Pharmeuropa* Vol 18. No. 2. April 2006. 2.9.44

RESULTS

The data show that there is a clear trend demonstrating that with a decrease in temperature a corresponding decrease in the FPF of Salbutamol is observed (Fig.1). This indicates there is a reduction in evaporation of the solution at lower temperatures.

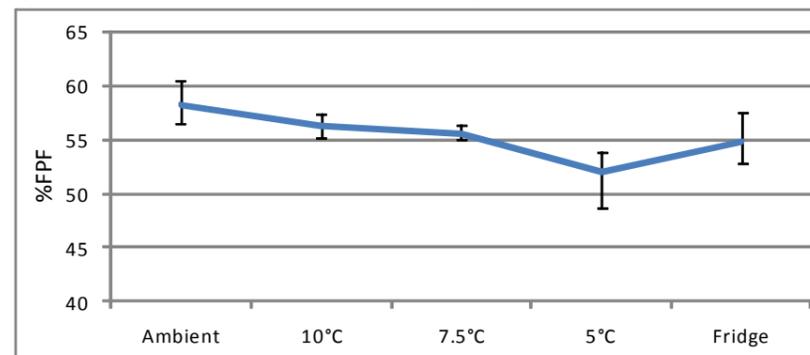


Figure 1. Comparison of the mean %FPF of the Salbutamol solution at various temperatures

This trend is not as apparent for the FP suspension (Fig.2), although the FPF is lower at the cooler temperatures compared to the ambient condition. The relative consistency of results at the lower temperatures for the FP suspension compared to the Salbutamol solution may be a consequence of the size of the particles in the suspension limiting any further evaporation.

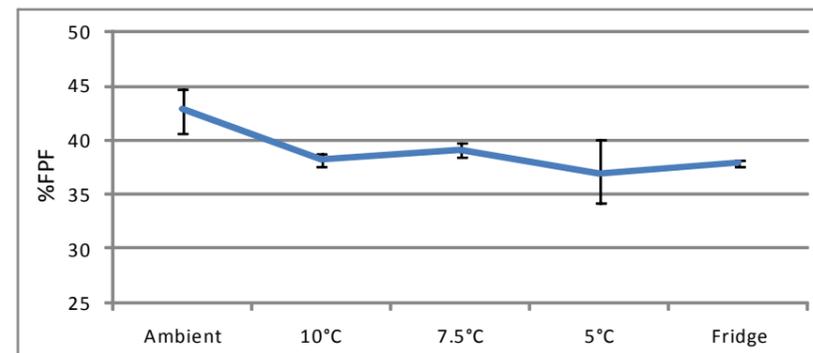


Figure 2. Comparison of the mean %FPF of the FP suspension at various temperatures

There is a significant difference between the mean FPF for the Salbutamol solution at 5°C in the cooler, compared with the fridge. This indicates that the NGI cooler is more effective than the fridge at reducing evaporation of the nebulised solution. The use of the NGI cooler is also a more efficient process than using the fridge to cool the NGI, as it requires 90mins in the fridge to equilibrate, whereas the NGI body remains in the cooler during nebulisation, which means the equilibration time is much shorter.

DISCUSSION

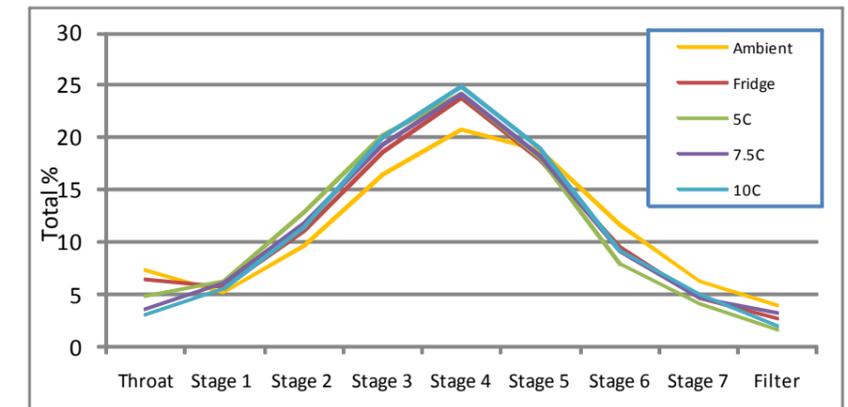


Figure 3. Mean Salbutamol distribution as % of total drug

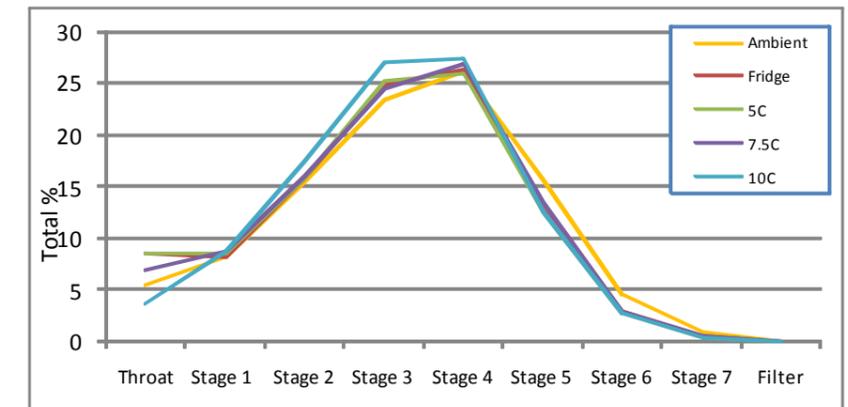


Figure 4. Mean FP distribution as % of total drug

This investigation has shown that as the temperature of an NGI reduces, a decrease in the FPF is observed for both a solution and a suspension formulation; however the effect is more pronounced in the solution formulation examined.

The profiles show there is a bias towards the smaller particle sizes at ambient conditions (Fig.3 and 4) and cooling the NGI assists in minimising this effect as a result of reduced droplet evaporation.

In conclusion, the nebuliser monograph in the *Pharmeuropa*⁴ suggests that the NGI needs to be cooled to 5-10° to reduce evaporation and the data obtained here indicate this to be justified; however this would need to be validated on a product-by-product basis.

There are many types of nebulisers, and the particle distribution may not be affected by evaporation in the same way for each one and should therefore be evaluated on a case-by-case basis. As a follow up experiment the effect of ambient air drawn into the device and NGI will be investigated.