

The Quantitative Assessment of Vape Devices as Novel Pulmonary Drug Delivery Systems Using Fluorine-18 Radiolabelled Drug Molecules

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Summary

Positron emission tomography (PET) is a highly sensitive and quantitative modality that can be employed for the efficient and informed development of novel pulmonary drug delivery devices. Vape devices present an alternate drug delivery system whereby the performance and formulation can be personalised for the end-user to improve experience and compliance. A novel molecule was designed, synthesised and radiolabelled to allow efficient radiolabelling of vape liquid. This probe was used to understand the influence of device settings on output. It was concluded that a high a temperature setpoint (315°C), low coil resistance (< 0.3 Ω) and short vape duration (≤ 4s) greatly increased output whilst flow rate (2.3 – 35 L/min) and glycerol content (0 – 100%) had little influence. Optimal settings were used to demonstrate marked increase in output efficiency of vape devices (10.91%/s) compared to jet nebulisers (0.18%/s). Using these settings, two known radiolabelled drug candidates ([¹⁸F]Fluticasone propionate and [¹⁸F]Fleroxacin) were assessed for their respective output and stability. [¹⁸F]Fluticasone propionate demonstrated good output (4.08%/s) and stability at the highest temperature setting; these promising results warrant further investigation. [¹⁸F]Fleroxacin was unstable at higher temperature and required vaping at 100°C to maintain drug integrity; output was compromised and it was concluded that this drug class was unsuitable for vape delivery. A mass median aerodynamic diameter of 1 µm and comparative activity distribution of vaped radiotracers confirmed uniform dispersion within the vape liquid and the capability for deep lung delivery using vape devices.

Key Message

The sensitive and quantitative properties of fluorine-18 radiolabelling were used to validate vape devices as novel drug delivery systems. The parameters for optimal output were determined and used to demonstrate significantly improved performance compared to a jet nebuliser. Favourable output and stability were observed for a clinically relevant radiolabelled corticosteroid.

Introduction

The pulmonary route allows for high doses of drug to be achieved in the lung for both local and systemic treatment of disease. The success of pulmonary drug delivery is dependent on the device aerosolization efficiency and ability to deposit sufficient drug concentrations within the lung. Conventional pulmonary delivery relies on one of four devices; pressurised metered dose inhalers, dry powder inhalers, nebulisers or soft mist inhalers. Despite their many clinical successes, these devices possess various drawbacks including the use of ozone depleting gases, high patient effort needed to efficiently aerosolise the drug, long user interaction times and varied deposition profiles.¹ These issues should be addressed to ensure the most sustainable, efficient and effective pulmonary drug delivery is available to patients.

Vape devices present a novel alternative pulmonary drug delivery system which can offer high drug output from short operation periods and minimal patient effort. Furthermore, these devices can be personalised for the end-user resulting in an improved compliance. This can be achieved by the addition of flavourings to the formulation in order to mask the bitter taste of drugs or by reducing the output for patients experiencing hypersensitivity in the upper airways. The success of these devices in the delivery of nicotine for smoking cessation highlights their popularity yet they remain underexplored in terms of the effect of device settings on output, aerosol properties and drug compatibility and safety.

To increase the efficiency of device development and speed up the bench to bedside translation of new technology which could offer significant patient benefits, non-invasive imaging can be employed. Positron emission tomography (PET) is a highly sensitive and quantitative medical imaging modality

which has been previously successfully used to validate novel drug delivery systems.² Drug candidates can be transformed into radiotracers by substituting specific atoms with their radioactive isotope. This ensures the physiochemical properties of the drug are not altered and the study results are clinically relevant. Of the radioisotopes available, fluorine-18 benefits from high positron yields and low positron energies, promoting sensitive measurements. Studies using radiolabelled drug candidates will yield real-time quantitative results that can be employed in preclinical proof-of-concept *in vitro* studies and more complex *in vivo* studies focussing on pulmonary penetration, deposition and clearance. In all, these studies can be used to optimise performance by making informed changes to the device or formulation for maximum drug output, stability and safety.

The project aimed to characterise device output and use this to investigate the potential for the pulmonary delivery of drugs using vape devices. To demonstrate clinical relevance, known radiolabelled drug candidates (fleroxacin and fluticasone propionate) were assessed for their vape output and stability.^{3,4} The results from vaping these radiolabelled drug molecules can be used to predict the suitability of other drug candidates from their representative classes (fluoroquinolone antibiotics and corticosteroids) for pulmonary delivery using these devices.

Experimental Materials & Methods

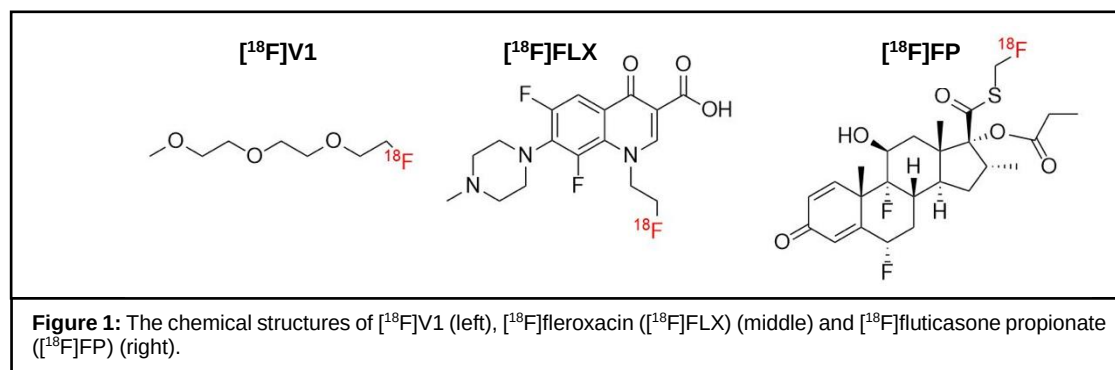
Vape operation was controlled using a custom-made rig which included; a variable temperature control vape device, rebuildable atomisers, coils (26, 28 or 32 AWG), a Raspberry Pi 4, a mass flow regulator and a vacuum pump. Vape liquid was created in-house using varying proportions of vegetable glycerol and propylene glycol. Vape aerosol was measured using a Dekati ELPI+, Dekati eDilutor Pro, air compressor and dehumidifier which were all supplied by Scielutions Limited.

The radiochemistry precursor and non-radioactive fluorinated reference compound of [¹⁸F]V1 were prepared in-house in a two-step synthetic procedure from triethylene glycol, sodium hydride, methyl iodide, toluene sulfonyl chloride and tertiary butyl ammonium fluoride. Intermediates, radiochemistry precursors and reference compounds were confirmed using ¹H, ¹³C and ¹⁹F NMR, HPLC and MS. Radiolabelling of [¹⁸F]V1 was achieved using a standard [¹⁸F]KF/K₂₂₂ complex in acetonitrile at 95°C for 15 minutes. The desired product was isolated by distillation and confirmed by HPLC. Radiochemistry precursors for [¹⁸F]fleroxacin and [¹⁸F]fluticasone propionate were prepared in house following established protocols and radiolabelling of these compounds was carried out as described previously.^{3,4} Non-radioactive fluorinated reference for fluticasone propionate and fleroxacin, obtained from Carbosynth and TCI respectively, were used to confirm identity of the radiolabelled product by HPLC.

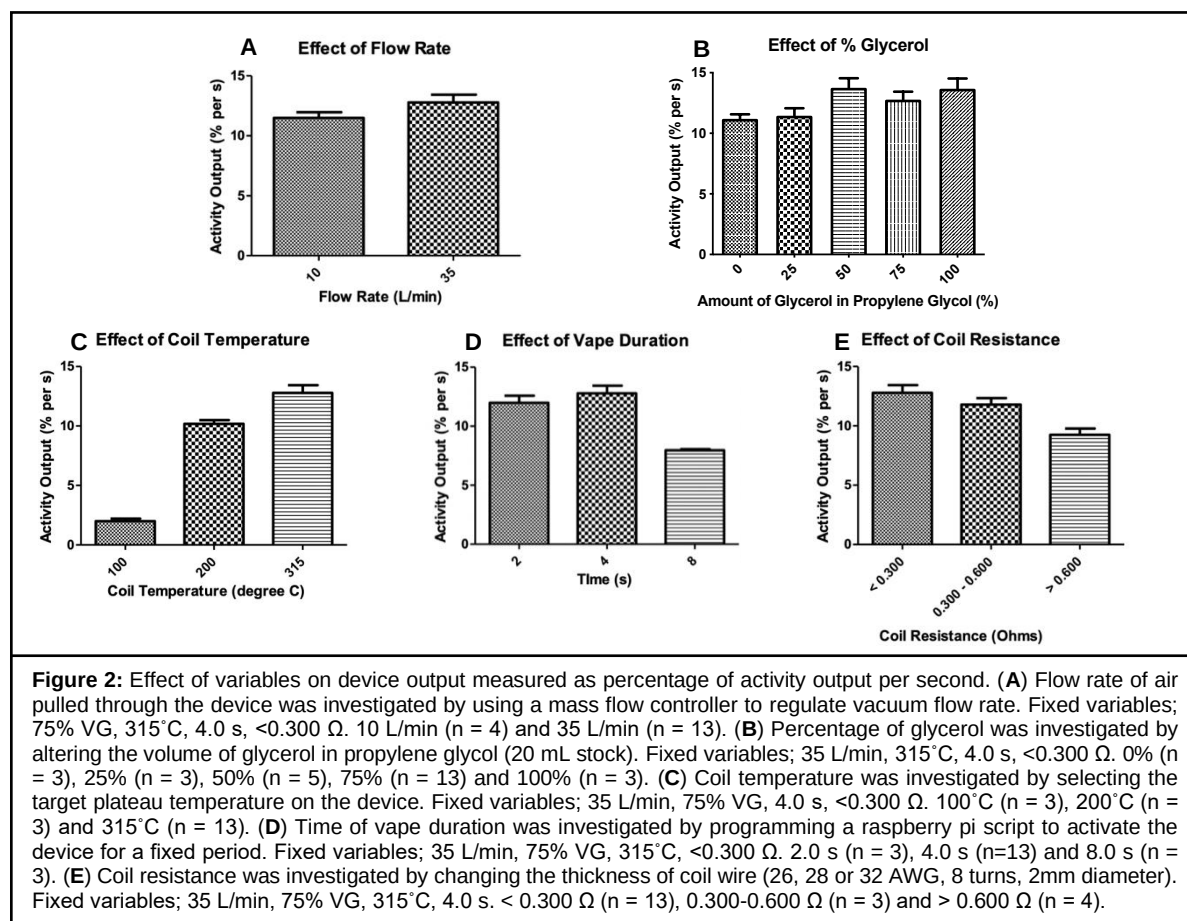
Formulated radiotracers were aliquoted and concentrated. Homemade vape liquid was added and the mixture was shaken for 120s followed by a 300s rest period. Radiolabelled vape liquid was pipetted onto cotton wicks within the coils and these were attached to the vape device. Vaping was performed remotely using a command script to run the Raspberry Pi and activate device. Activity concentration of the vape device was measured before and after vaping to determine output. Tracer stability was determined by HPLC analysis of vaped tracer extracted from in-line filters.

Results & Discussion

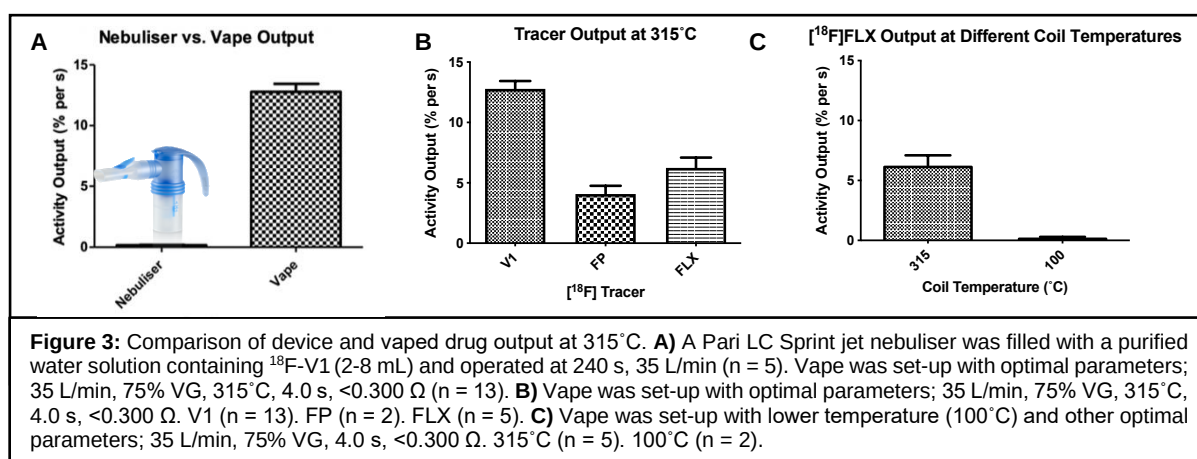
Variable temperature control vape devices were used in conjunction with rebuildable atomisers in order to control temperate setpoint and coil resistance. A custom rig was developed to allow for control over device operation flow rate and ensure radiation protection of the end user. The vape activation was controlled by a RaspberryPi unit that allowed tight control over device operation times (± 0.1 second).



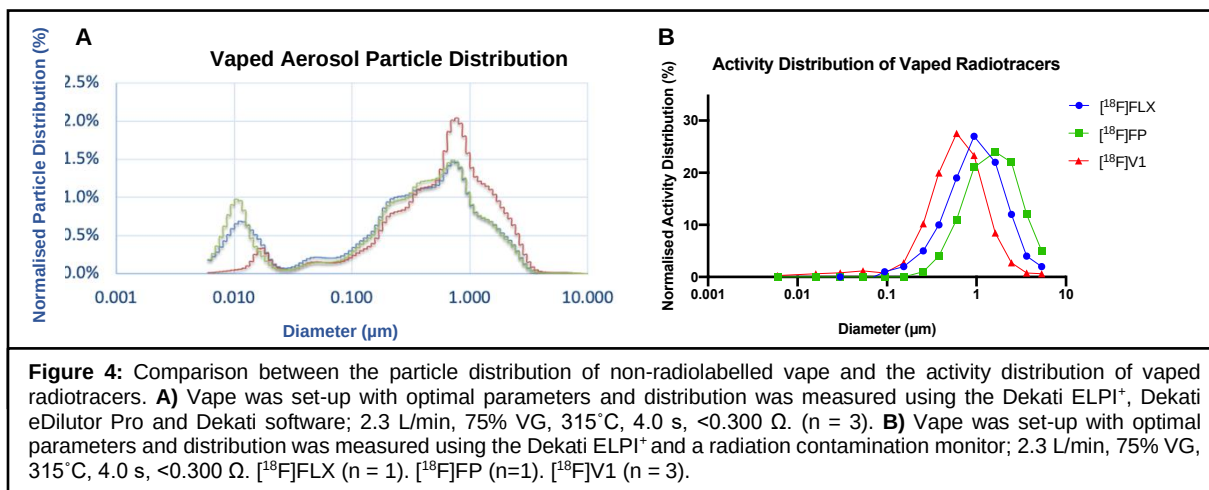
A custom probe, [^{18}F]V1 (figure 1), was designed and synthesised with the efficient radiolabelling of vape liquid in mind. [^{18}F]V1 was radiolabelled using a [^{18}F]KF/K₂₂₂ complex then the volatile nature of [^{18}F]V1 was exploited and the tracer was purified by distillation. [^{18}F]V1 was isolated in variable but good yield and high radiochemical purity (decay corrected RCY $43.8 \pm 16.6\%$, $n = 17$, RCP $> 98\%$, synthesis time = 102 ± 12 minutes).



[^{18}F]V1 was used to radiolabel vape liquid and subsequently investigate the effect of device and user variables on output. In order to ascertain the optimal parameters for drug output a study was performed to understand the effect of each variable. The graphs shown in figure 2 illustrate the results of this screening study. For maximal output it was concluded that high coil temperatures, low resistance coils, and short-period vapes were favourable. Flow rate had little effect as did VG percentage. Higher percentages of PG are associated with 'throat hits' so to ensure better patient compliance 75% was employed. These optimal settings were then used to assess drug output.



To provide comparison, a Pari LC Sprint jet nebuliser was characterised for output using an aqueous solution of [^{18}F]V1. Vape devices offer a much improved output per second compared to a jet nebuliser (10.91 vs. 0.18% per second) (figure 3, A). [^{18}F]Fluticasone propionate showed good output (4.08% per second) and remained stable after vaping at the highest temperature setting (315°C) (figure 3, B). After vaping at the same temperature, [^{18}F]fleroxacin exhibited 60% decomposition and required vaping at 100°C to maintain stability. At these lower temperatures, the output was greatly compromised (0.2% per second) (figure 3, C).



Non-radiolabelled vape was assessed using a Dekati ELPI⁺ equipped with a Dekati eDilutor to determine the MMAD of the vape device using the optimal settings as determined previously. The observed MMAD was ~1 μm (figure 4, A) which favours deep lung distribution and supports the use of vape devices for pulmonary drug delivery. To confirm uniform distribution of drug molecules within the aerosol, the vape liquid radiolabelled with [^{18}F]FLX, [^{18}F]FP or [^{18}F]V1 and was passed through the Dekati ELPI⁺. The device was dismantled and activity at each stage of the impactor was measured using a radiation contamination monitor. The results were decay corrected and normalised to provide comparison to unlabelled vape; the observed overlapping distribution profile confirms uniform drug distribution (figure 4, B).

Conclusion

A novel molecular probe was successfully synthesized and radiolabelled, allowing for the quantification of vape device output. Fluticasone propionate demonstrated good output and favourable stability at the highest temperature set-point which warrants further investigation. The observed instability of fleroxacin above 100°C and reduced output at low temperatures, indicates vape delivery is non-ideal for the fluoroquinolone class of drug. A mass median aerodynamic diameter of 1 μm and comparative activity distribution of vaped radiotracers confirmed uniform dispersion within the vape liquid and the capability for deep lung drug delivery using vape devices. The promising results to date warrant the extension of this study to understand how clinically relevant concentrations of fluticasone propionate may influence output. Further, we hope these formulations can be assessed *in vivo* once the device and formulation has been optimised to ensure the three R's of animal-based research are adhered to.

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