Ultrafast Analysis of Pressurised Metered Dose Inhaler (pMDI) by MS

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Pat Ref –WO/2008088270

AstraZeneca
life inspiring ideas

Overview

- The current inhaler test landscape
  - DDU/Cascade impactor methods
  - Limitation of current screening techniques
- Introduce potential new screening technique
  - Capable of API specific detection
- How the technique works
- Current applications/results
- Future developments

Introduction

- The speed of inhaled pharmaceutical products developed often compromised labour intensiveness of the the test procedures required
  - Delivered dose/Cascade Impaction methods are time consuming
- A current lack of a discriminatory technique screening inhaler performance
  - DDU/ACI
- Current screening techniques like APS/ELPI lack specificity to drug components in the formulation
- Decided to look into the potential for using the selectivity offered by Mass Spec as a solution to these issues

Method Requirements (URS)

- Fast analysis technique
  - Minimal sample preparation
- Real time monitoring capability
- Compound specific

Could Mass Spectrometry be an option?

If so how would we approach it?

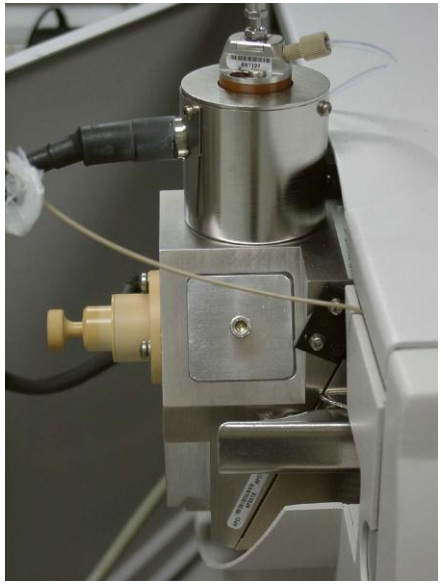
- LC-MS?
  - No chromatography?
- Or possibly direct sample induction?

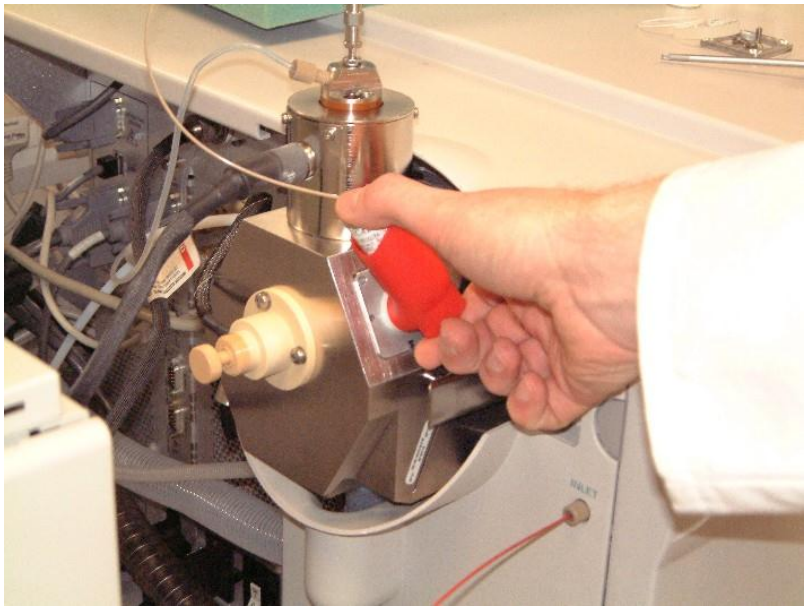
Direct Spray MS (direct sample induction)

- Droplet size range from pMDI similar to that produced by an LC-MS nebuliser spray
- Decided to investigate the possibility of spraying the pMDI directly into the MS spray chamber

How it works

- Very Simply!
- The pMDI actuated directly into the spray chamber of an LC-MS





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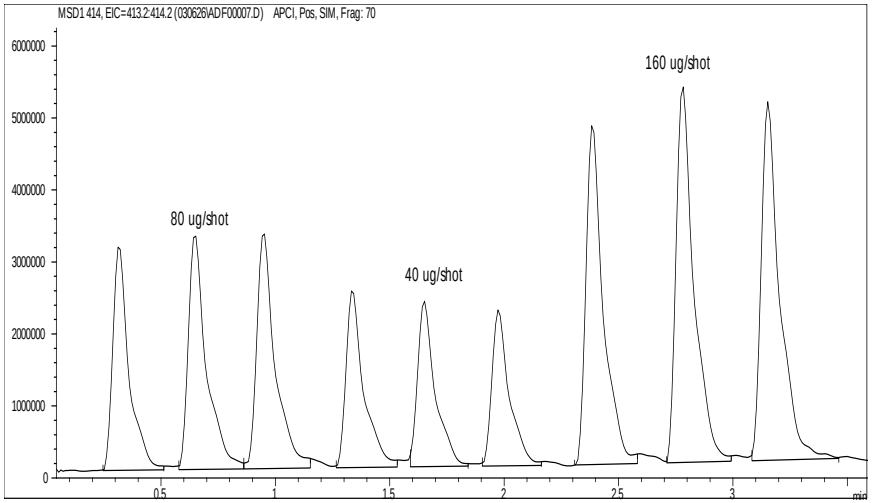
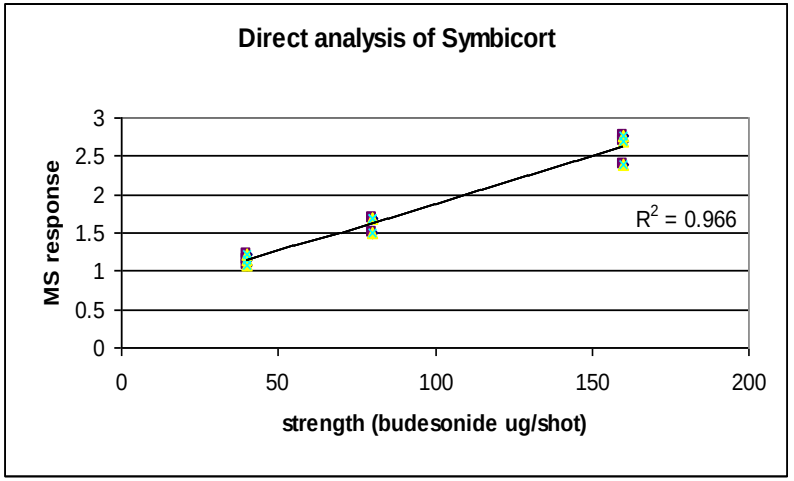
Initial Results

- Reproducibility
  - Better than 10%
- Linearity - Symbicort 40/4.5, 80/4.5, 160/4.5





POTENTIAL FOR A QUANTITATIVE TECHNIQUE EXISTS

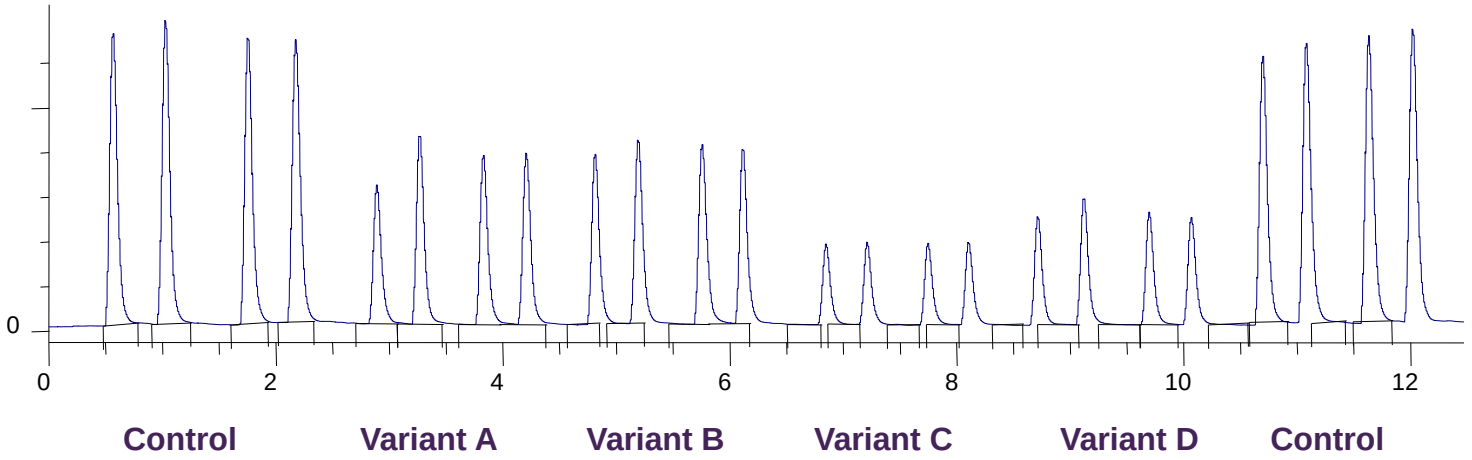
Current Applications

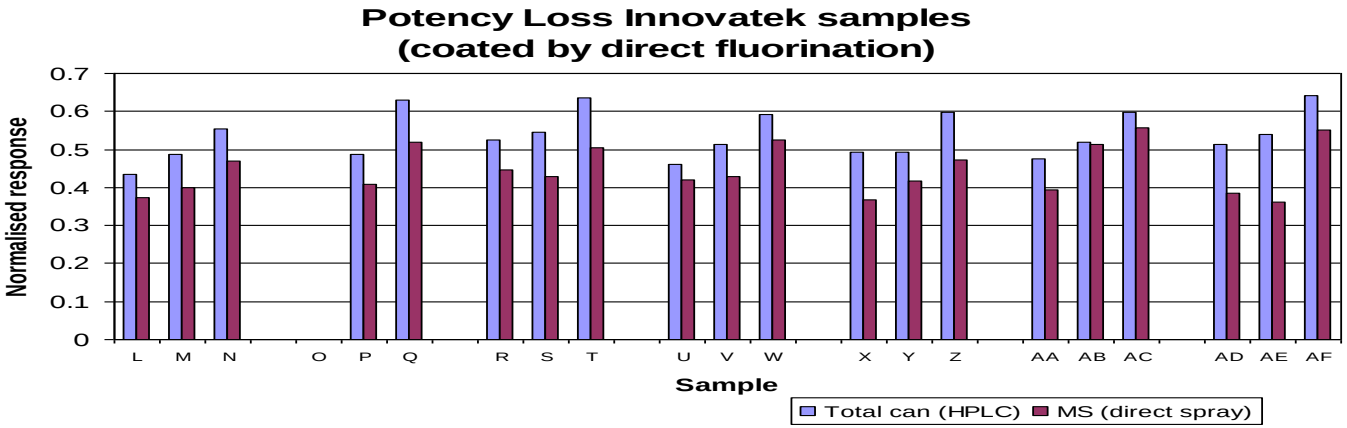
- Compatibility
  - Device formulation interaction
  - Currently Semi quantitative
- In-use leachables studies
  - From valve and actuator
  - PBT Monomer
  - Anti-Oxidants eg Irgafos 168
- Excipient Detection
  - PEG
  - Depends upon levels (LOQs)
- Degradent screening

Compatibility – Material Screening

- No sample prep
- Ultra fast analysis with high selectivity
- Excellent screening technique
- Add extra material to the pMDI
  - Fill with formulation
- Heat to 60°C for 1 week, valve up
- Analysis by direct spray MS

Compatibility





- Direct Spray characterisation was completed in 15 minutes
- One weeks work using Direct Spray equivalent to 5 weeks Total Can Analysis

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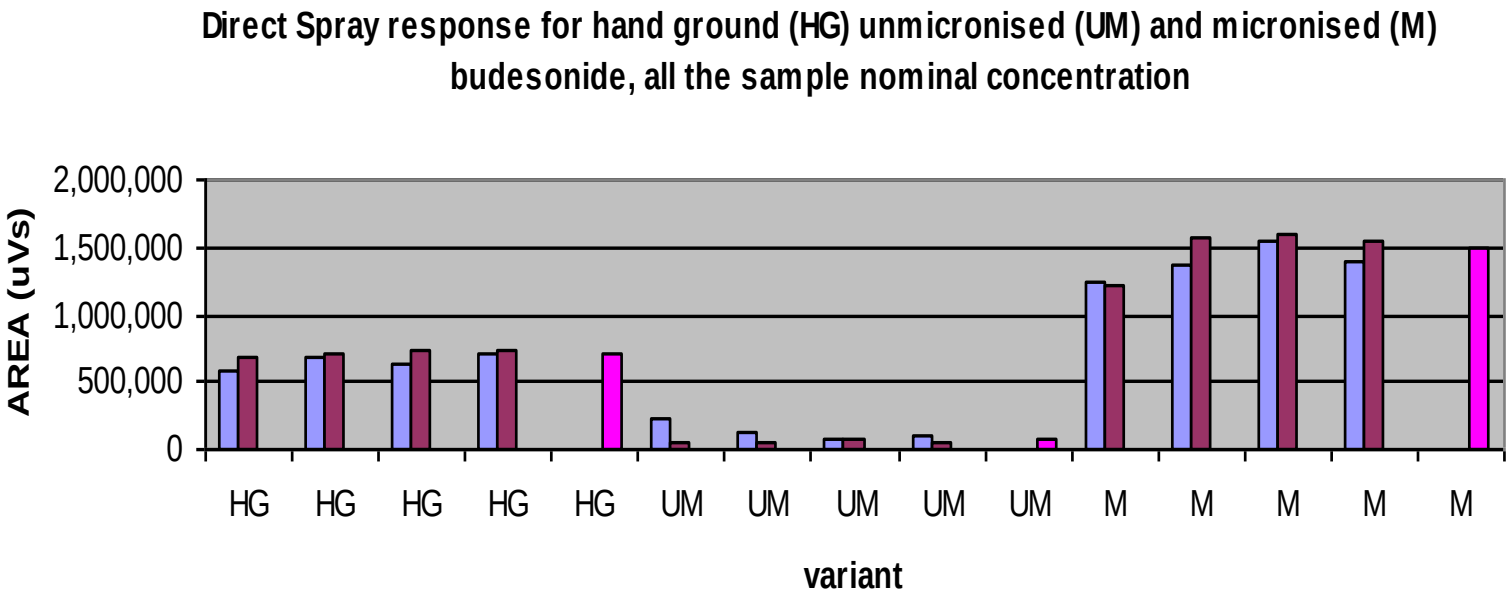
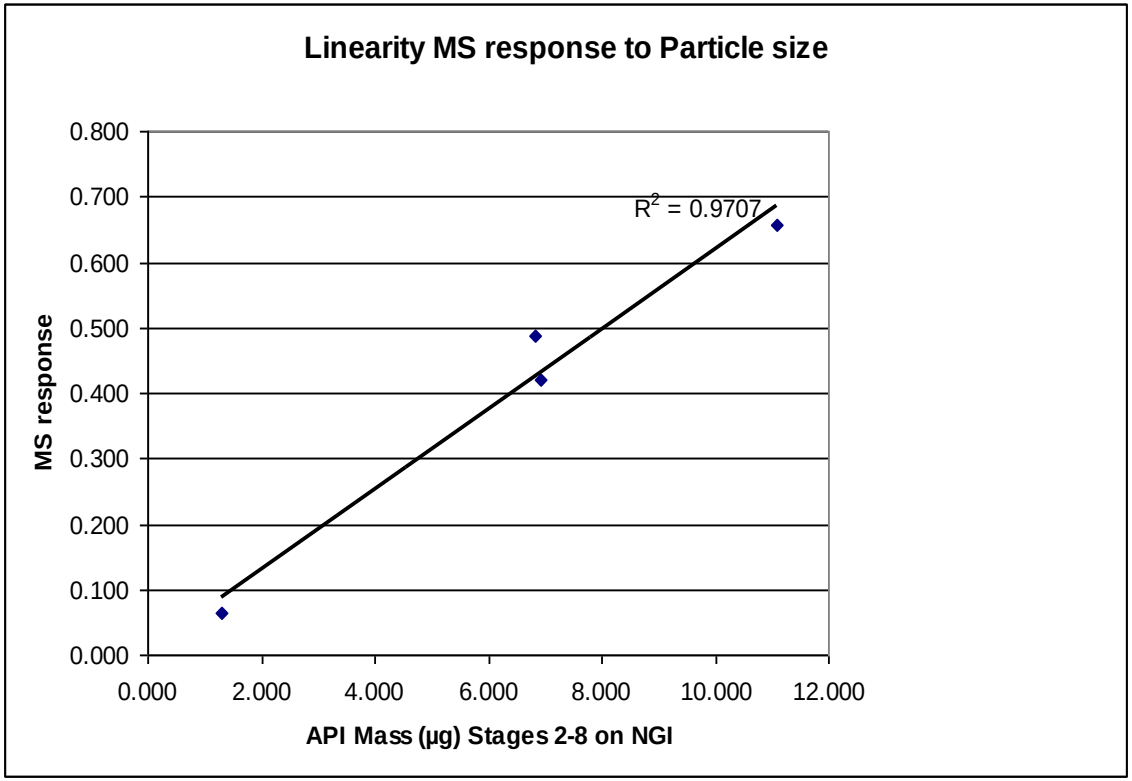
Sensitivity to Particle Size

- The MS has shown a degree of proportionality to large differences in particle size



Sensitivity to Particle Size

- Analysing prepared pMDIs with differing particle size material and comparing direct spray response with with NGI mass per stage data (stages 2-8)
  - Linear response with good correlation



Future work

- Optimise Mass Spectrometer test equipment for direct analysis of pMDI, DPI and nebulisers
  - Optimise sample induction techniques
  - Understand/Optimise airflow into the Spray Chamber
  - Minimise impaction effects/losses
  - Lead to Hardware optimisation?
- Assess the capability of the technique to become a fully quantitative analytical technique for pMDIs
- Develop technique for assessment of Fine Particle dose
- Suitable for any ionisable species

Reduction in pMDI development cycle times

Conclusion

- Direct spray could provide the pharmaceutical industry with a useful screening technique for evaluating inhaler performance
- Demonstrates a degree of analyte specificity not seen with other inhaler screening techniques that are currently available
- Further work is required to optimise the system hardware and to assess it’s potential as a fully quantitative technique

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