SCANNING

Rapid Surface Cleanliness Verification Using Swab Sampling and Capillary Electrophoresis.

Mostafa A. Atia[1], Ria Marni Amuno[1], Umme Kalsoom[2], Samantha Ollerton[2], Alan Rhoden[3], Paul R Haddad[1], Michael C. Breadmore[1]

[1]Australian Centre for Research on Separation Science (ACROSS), School of Natural Science, University of Tasmania, Private Bag 75, Hobart, Tasmania 7001, Australia.

[2] GreyScan, Port Melbourne, Australia.

[3] Pfizer Global Technology & Engineering Manufacturing Intelligence, Peapack, NJ, United States.

Mostafa.Adel@utas.edu.au

Cleaning verification is mandatory in pharma production

- Required between each batch to ensure no cross contamination.
- Two ways:
  - **Collect and analyse rinse solution**
    - Easier, more repeatable, more representative to the whole system, but doesn't mean the surface is clean (things stick)
  - **Swab-based analysis**
    - Not as repeatable, but is better for things that stick and hardly reach sites.
  - Both require samples to be sent to the laboratory for analysis
  - This can take hours to days with significant loss in production capability until cleanliness has been verified.

At-site analysis

- Analysis of residue at-site would be quick and convenient
- Currently limited to optical spectroscopy methods
  - Mainly IR and Raman spectroscopy (although benchtop MS instruments are becoming more viable)
  - Point-and-shoot systems user friendly, they typically have a small 'field of view'
  - low sensitivity and selectivity (LOD ≤ 1µg/cm^2).
- Despite this, most samples are still sent to the lab for analysis

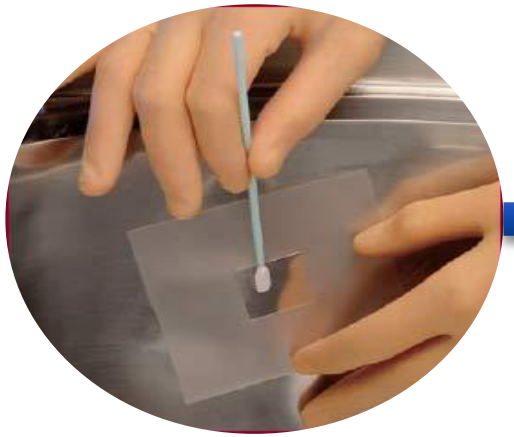
We know when speed is important…

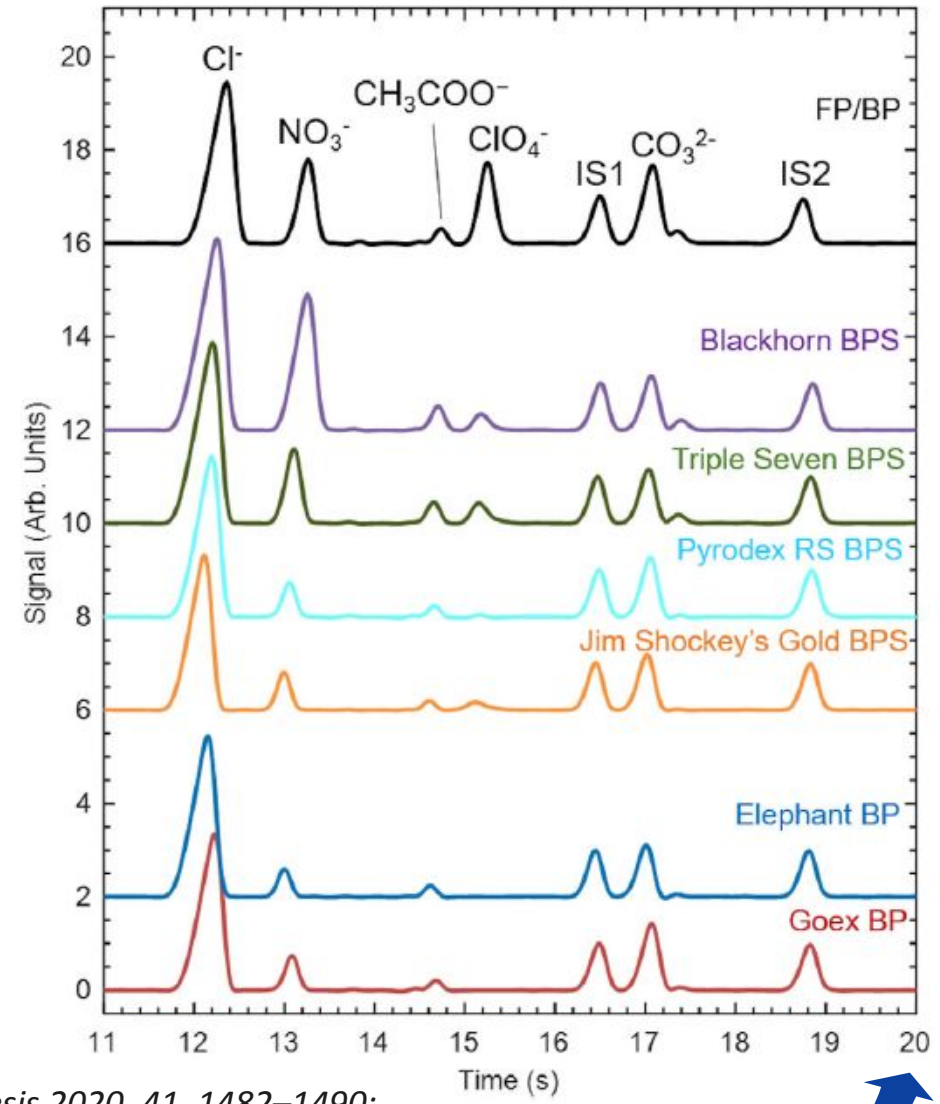
2019 Christmas list

"'five of the best' relate to some of the most exciting technologies I have seen that could enhance the security arsenal for any airport."
Philip Baum, Editor ASI

The GreyScan ETD-100

The GreyScan ETD-100



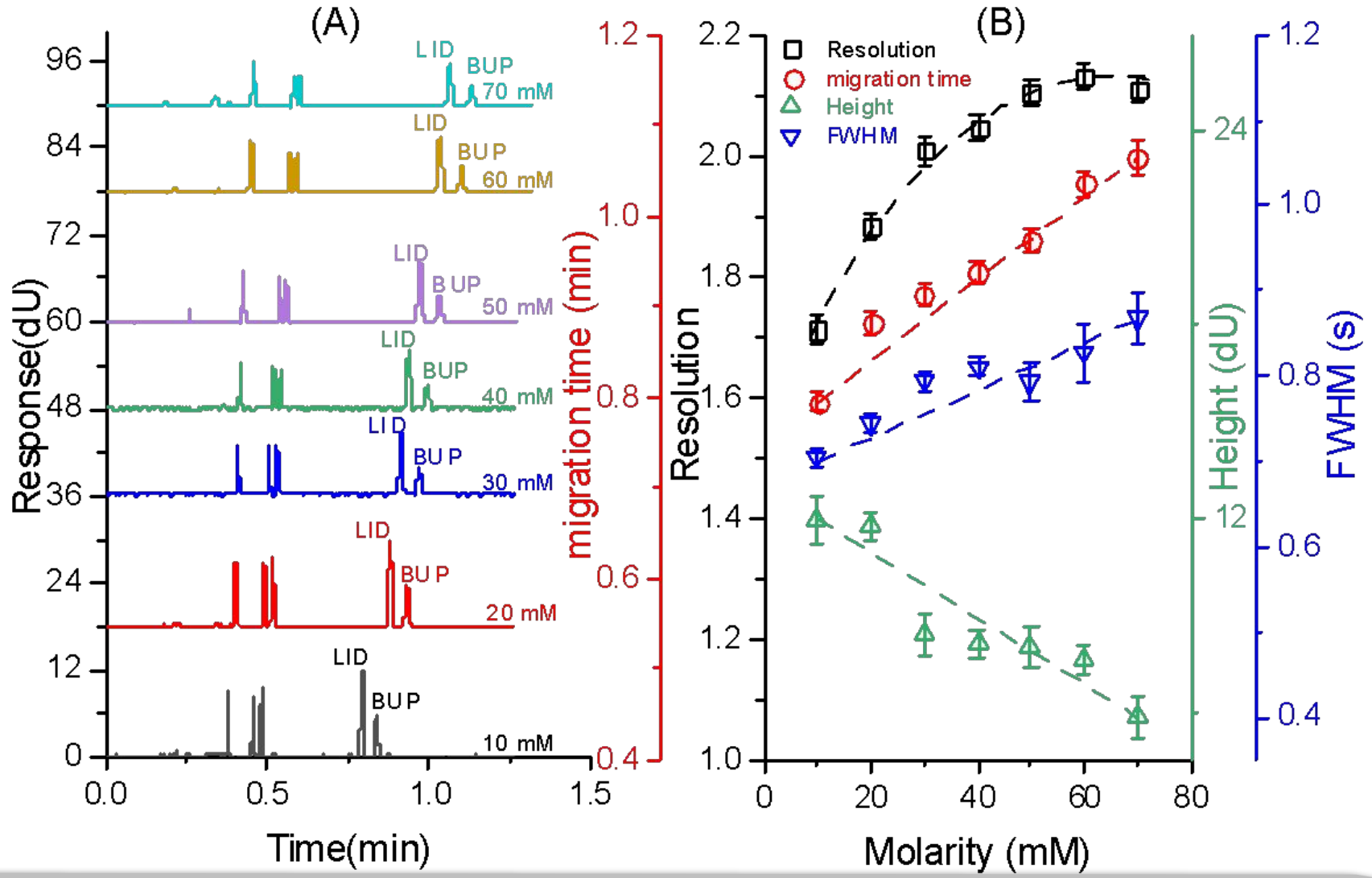


Krauss et al, Electrophoresis 2020, 41, 1482–1490;

Can the ETD-100 be used for trace pharmaceutical detection?

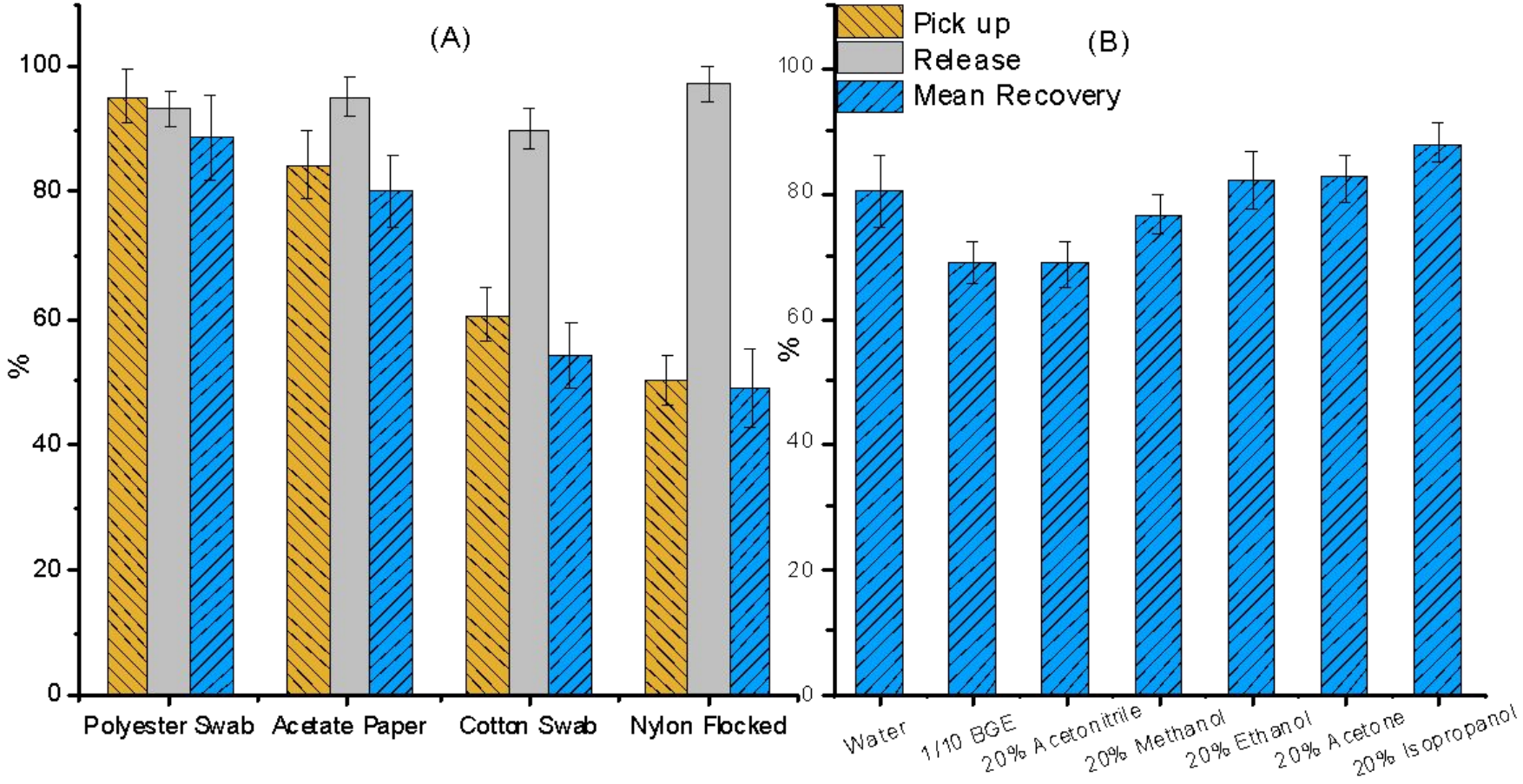
- Many papers on CE of pharmaceuticals
- Limitations of the ETD-100
  - C4D detection (charged drugs)
  - Some current components are not compatible with organic solvents
  - Single type of swab (acetate paper)
  - Destructive analysis (swab residue cannot be reanalysed)
- Benefits of the ETD-100
  - Portable system that can operate off battery for 6 hours
  - Completely integrated extraction system with the CE
  - Time saving with 1-2 min outcome after inserting the swab, Potential for 2-5 min turnaround on analysis
  - Has large surface coverage unlike other portable handheld techniques.

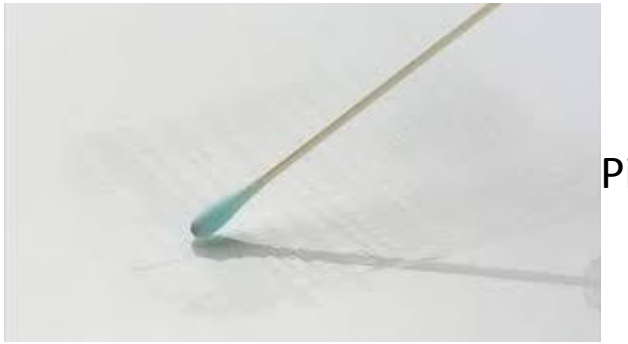
ETD-100 CE-C4D optimisation



(A) CE separation of 10 µg/swab Lidocaine (LID) and 5 ppm Bupivacaine (BUP) as at different concentrations of BGE
(B) Effect of different concentrations of BGE on LID height, FWHM, Migration time and Resolution between LID and BUP.

Extraction characterisation and optimisation





Pick up

Release

ETD-100 performance metrics

Parameter	GreyScan ETD-100	Agilent 7100 CE
Range (µg/swab)	0.50 – 20	0.50 - 20
Intercept (a)±SD	0.398 ± 0.024	1.05 ± 0.029
Slope (b)±SD	2.632 ± 0.053	0.246 ± 0.002
LOD (µg/swab)	0.133	0.312
LOQ (µg/swab)	0.403	0.946
R^2	0.997	0.998
% RSD of Peak Height	2.21	1.62
% RSD of Migration Time	0.187	0.200
Number of Theoretical Plates (N)	517×10^2	525×10^2

Calculation for a Swab Sample:

1. $\frac{\text{Lowest Dose (Product A)}}{\text{Safety Factor}} \times \frac{\text{Batch Size}}{\text{Max Daily Dose (Product B)}}$ – Maximum Allowable Carryover (MAC)

(Product A is the product being cleaned/Product B is the subsequent Product)

2. MAC/Total Surface Area = Surface Residue µg/cm²
3. Surface Residue/cm² × Area Swabbed = Residue on Swab (µg)
4. Residue on Swab(µg)/Dilution Volume (mL) = Residue level in swab sample (ppm)

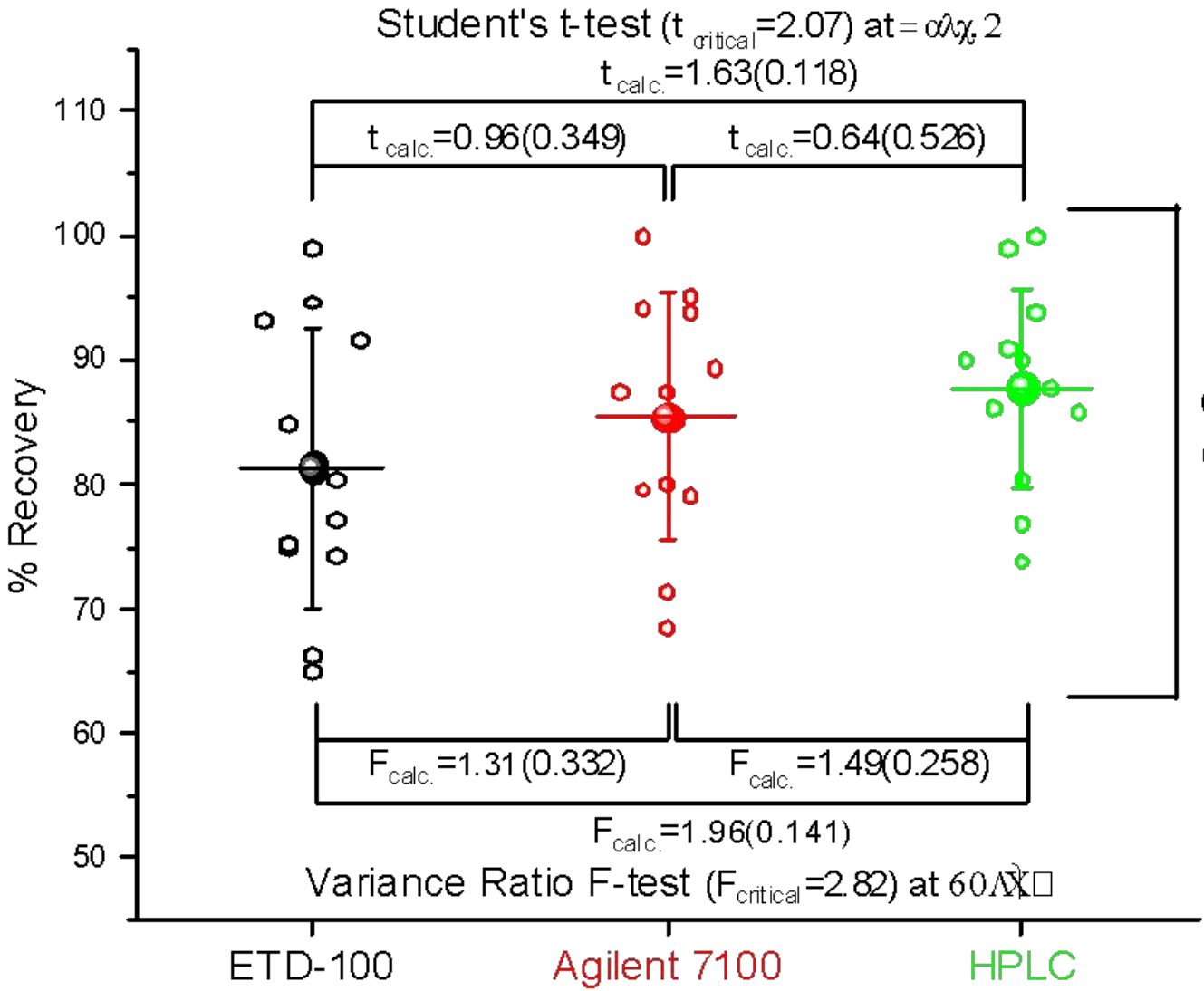
The table below shows the MAC values , Surface Residues, and PPM values in an Analytical Sample for all combinations of Lowest Dose (0.001 mg and 500 mg), Batch Size (15 kg and 50 kg), Maximum Daily Dose (0.05 gm and 5 gm), and total Surface Areas (1,000 cm2 and 100,000 cm2). A swab area of 100 cm2 and a swab recovery of 100% are assumed.

Lowest Dose (mg)	Batch Size (kg)	Max Daily Dose (gm)	MAC (mg)	Total Surface Area (cm²)	Surface Residue (µg/cm²)	ppm in 20 mL
0.001	15	5	0.003	100000	0.00003	0.0002
0.001	15	5	0.003	1000	0.003	0.02
0.001	1200	5	0.24	100000	0.0024	0.01
0.001	1200	5	0.24	1000	0.24	1
0.001	15	0.05	0.3	100000	0.003	0.02
0.001	15	0.05	0.3	1000	0.3	2
0.001	1200	0.05	24	100000	0.24	1
0.001	1200	0.05	24	1000	24	120
500	15	5	1,600	100000	15	75
500	15	5	1,500	1000	1,500	7,500
500	1200	5	120,000	100000	1,200	6,000
500	1200	5	120,000	1000	120,000	600,000
500	15	0.05	150,000	100000	1,500	7,500
500	15	0.05	150,000	1000	150,000	750,000
500	1200	0.05	12,000,000	100000	120,000	600,000
500	1200	0.05	12,000,000	1000	12,000,000	60,000,000

Table C Calculation for a swab sample limit and simulated results

Walsh, A. Pharm. Eng. 2011, 74–83.

Comparison with Normal CE and HPLC

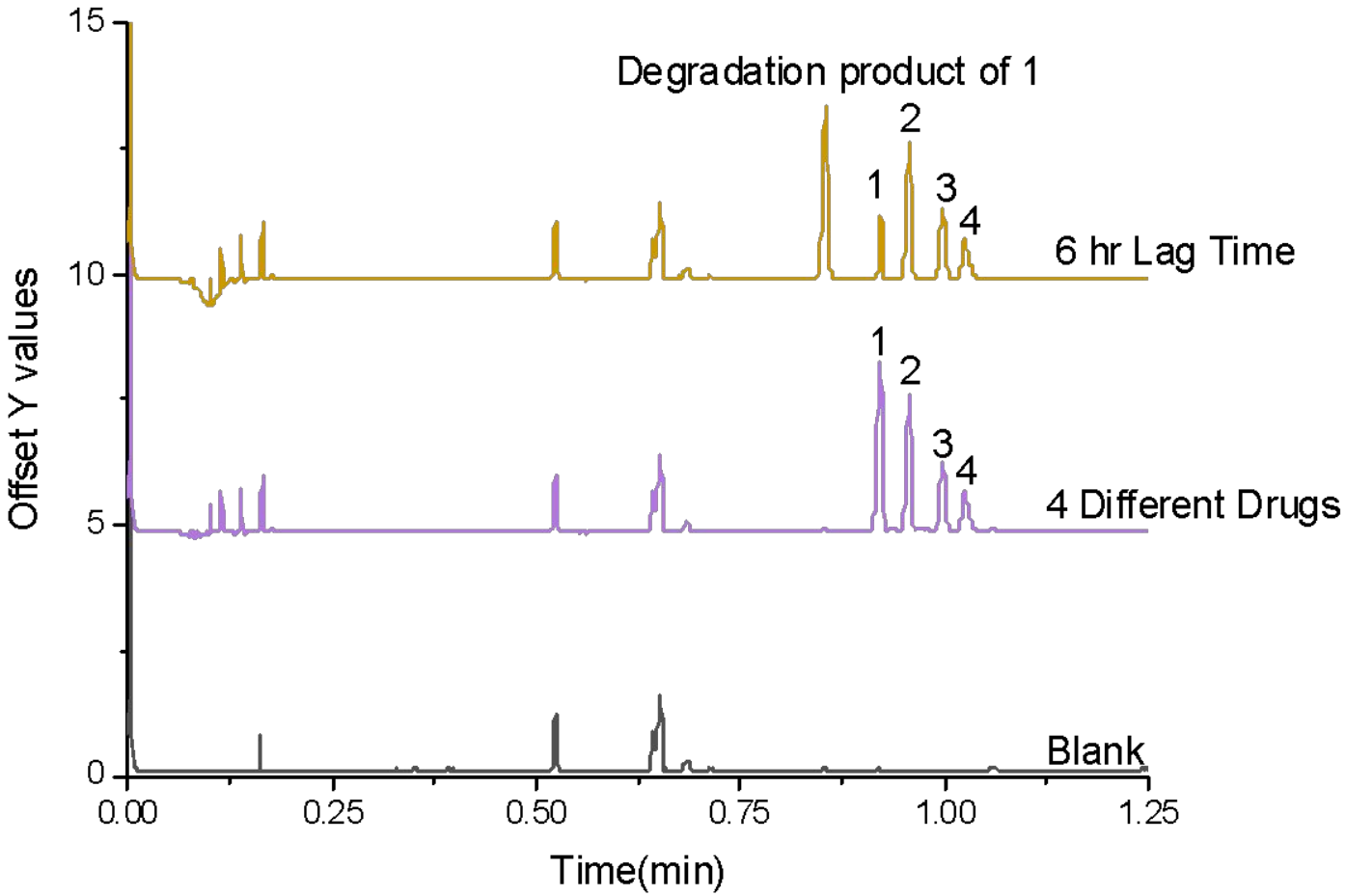


SD
Mean

One-Way ANOVA
($F_{critical}$=3.28) at τ
$F_{calc.}$=1.35(0.274)

The mean percent recovery for 12 spiked coupons with 5µg LID /10cm^{2,} using GreyScan ETD-100, Agilent 7100 CE and a reported HPLC method. The tabulated t and F values for Student's t-test, Variance ratio F-test and ANOVA are 2.07, 2.82 and 3.28 respectively at 95% confidence limit (α=0.05).

More Drugs.... less time



Where are we now?

- Capability of the ETD-100 for trace pharmaceutical detection has been demonstrated.
- Can reach all but the highest requirements for cleanliness testing in 2-3 min at-site.
- On-line concentration will allow lower limits to be achieved.
- Potentially applicable to other applications
  - Illicit drugs
  - Bacteria
  - viruses

Thanks to…

- Supervision and advice from:
  - Prof. Michael Breadmore, Prof. Paul Haddad.
- Sponsorship and scholarship from:
  - ARC, UTAS, Pfizer® and GreyScan®.
- All my colleagues