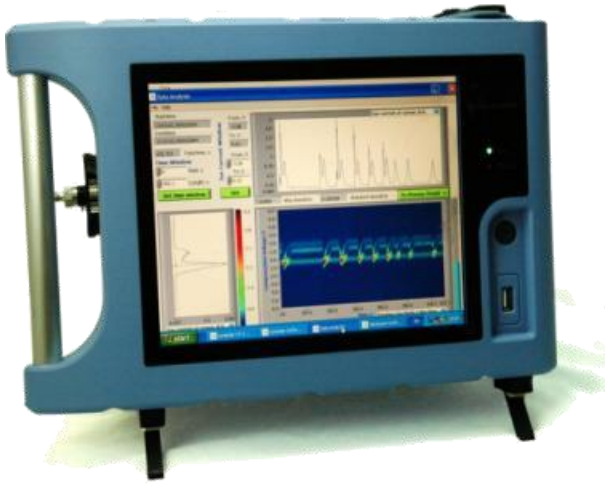
Testing for Residual Solvents in Pharmaceuticals Using a LONESTAR™ Portable Analyzer

Acetone, Chloroform, Diethyl ether, Ethanol, Hexane, Methanol,Toluene in Oxcarbazepine and Ropinipole



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Testing Objectives and Overview

The aim of the testing was to demonstrate the Lonestar platforms viability for making real-time quantitative measurements of residual solvent content in pharmaceuticals. The testing focused on two drugs, Oxcarbazepine and Ropinirole, spiked with various concentration levels of different solvents at the ppm level. Follow up tests were carried out at Owlstone's Cambridge, UK labs to show a wider range of solvent responses and mixtures of solvents using optimised sampling and FAIMS filter fields.

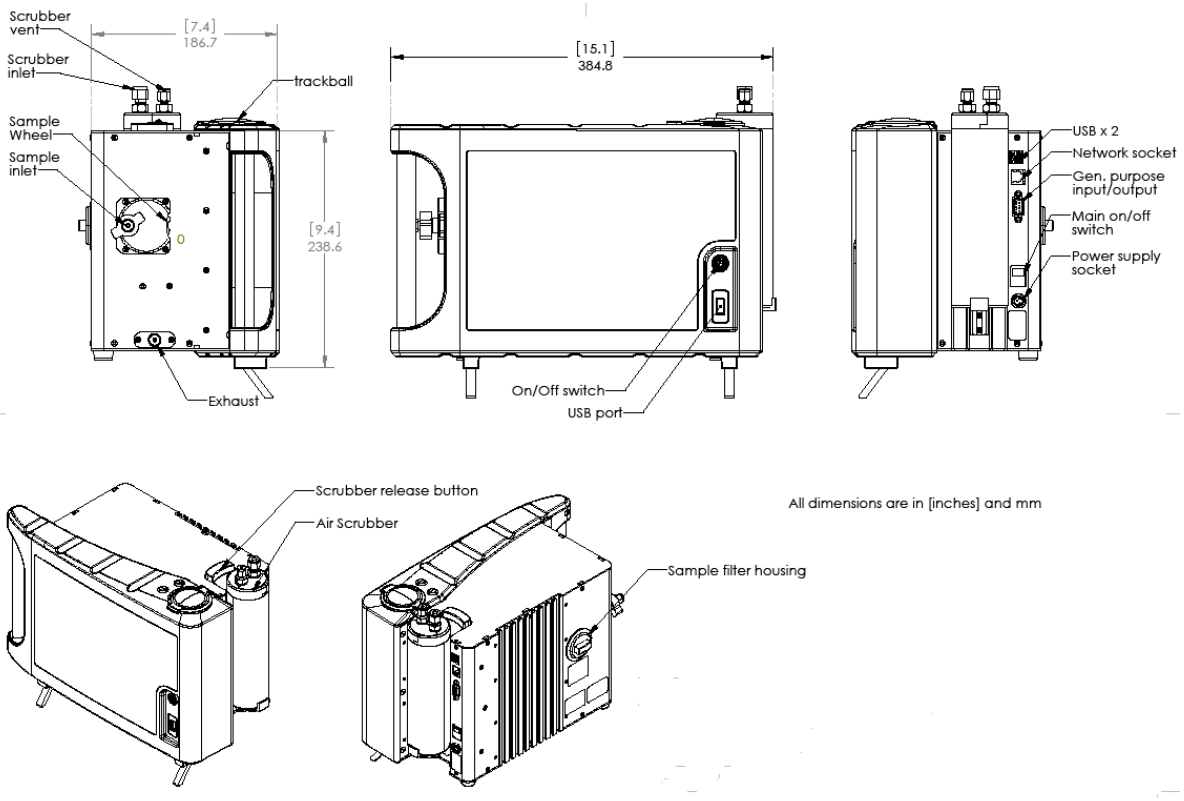
There are 60+ class 1, 2 and 3 solvents listed by United States Pharmacopeia USP which should not be present above set thresholds in any pharmaceuticals, though in practice the particular solvents used in the drug synthesis are the most likely to be present. Testing therefore focused on solvents associated with each drug, though all the solvents on the list should be detectable to sub ppm levels. For the two drugs tested the solvents were

- Ropinirole - methanol, ethanol, diethyl ether, acetone, toluene
- Oxcarbazepine - acetone, n-propanol, toluene

Other representative solvents were selected from USP list and tested, these were – chloroform and hexane to show the response to a halogenated compound and to a simple aliphatic hydrocarbon.

The Lonestar Platform

Lonestar is a powerful and adaptable chemical monitor in a portable self contained unit. Incorporating Owlstone's proprietary FAIMS technology (see Appendix A), the instrument offers the flexibility to provide rapid alerts and detailed sample analysis. It can be trained to respond to a broad range of chemical scenarios and can be easily integrated with other sensors and third party systems to provide a complete monitoring solution. As a result, Lonestar is suitable for a broad variety of applications ranging from process monitoring to lab based R&D.



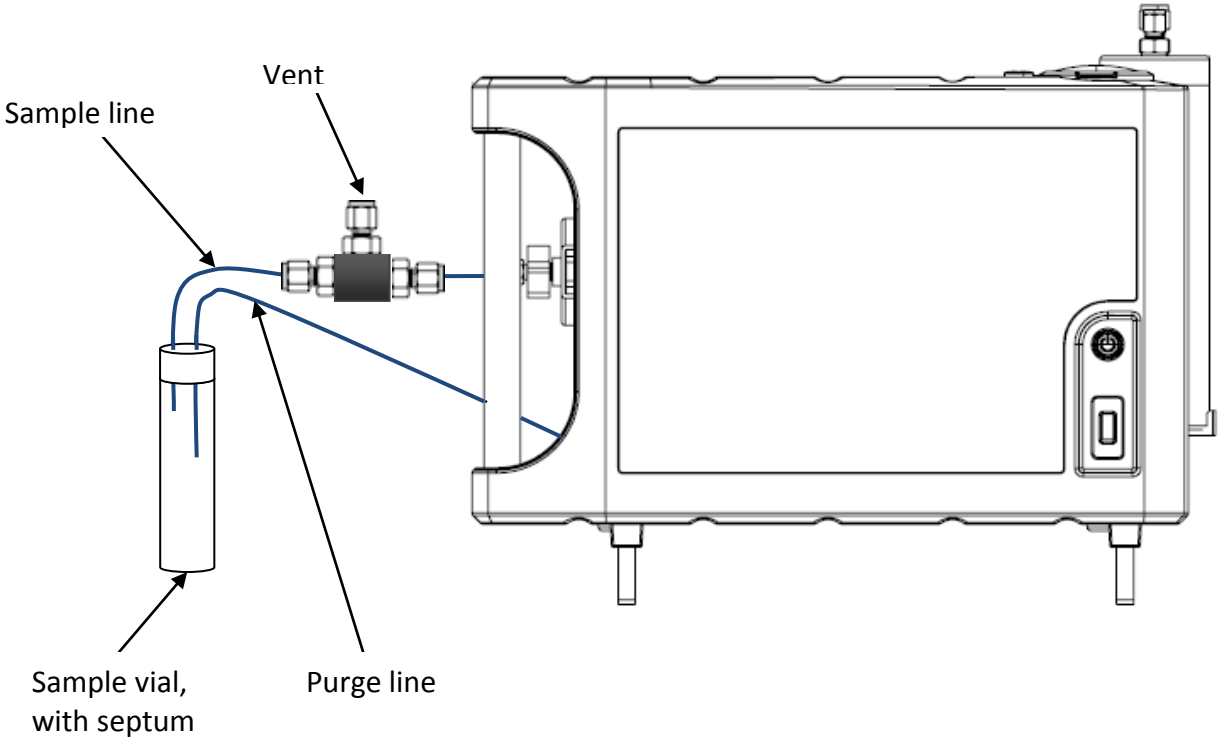
Lonestar connection figures

Testing Procedure overview

Testing was carried out using the basic configuration described below. To produce spiked samples 10g of sample drug in a powdered form was weighed out and placed in the vial then µl injections of the solvent to be tested were added to the vial to give high concentration samples.

Basic configuration

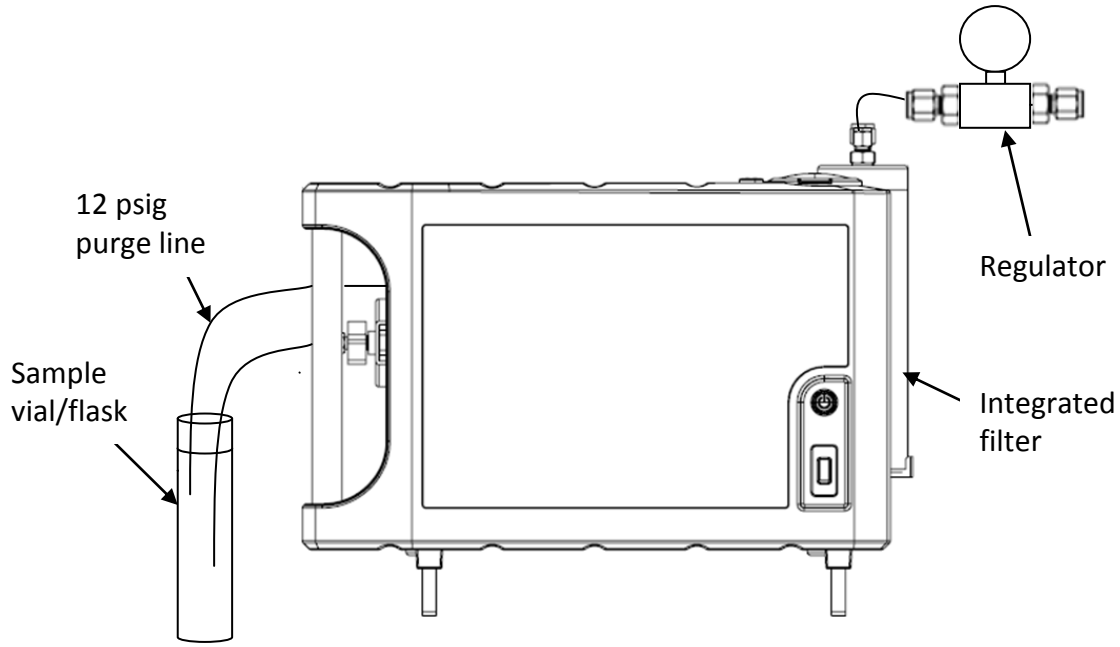
In order to make a gas phase measurement of the residual solvent content the vial is connected to the Lonestar inlet. The headspace of the vial is then flushed with clean air from the exhaust of the Lonestar. Due to the sensitivity of the instrument most of the sample gas is flushed directly out of an attached vent with only a small proportion being drawn in by the Lonestar.



Sampling system on front end

Alternative configurations

Selectivity can be improved and maintenance requirements can be reduced if a compressed air line is available, the system can then be run at a slight overpressure (which can help with selectivity) and the internal pump is no longer required. Some of the testing presented here is carried out with apparatus configured in this manner.

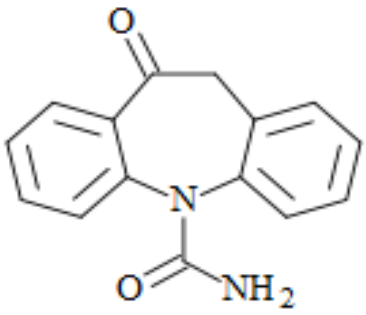


Alternative sampling system

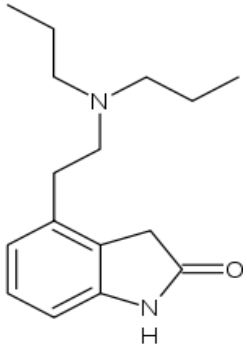
It is also possible to set up the Lonestar monitoring solvent drying process directly onto a vat if a real time indication of solvent level is required.

Results - Background Matrix

Two drugs were tested using the Lonestar in its basic sampling configuration - Ropinirole (4-[2-(dipropylamino)ethyl]-1,3-dihydro-2H-indol-2-one) and Oxcarbazepine (10,11-Dihydro-10-oxo-5H-dibenz(b,f)azepine-5-carboxamide).

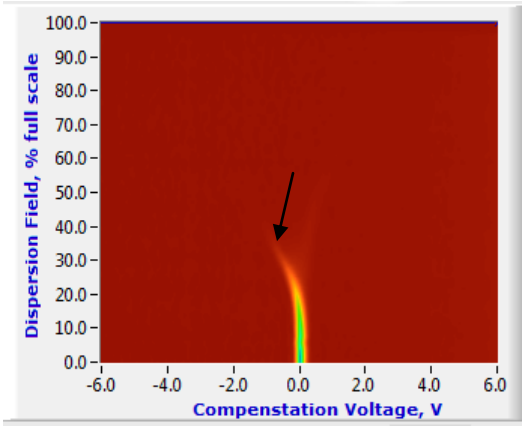


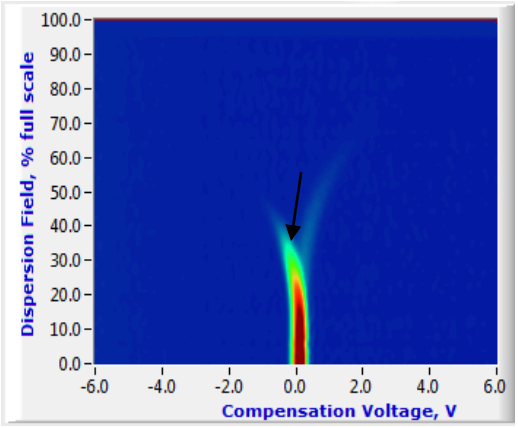
Oxcarbazpine



Ropinirole

Results showed that the two drugs had a low enough volatility that room temperature headspace sampling gives no response on the Lonestar.





Ropinirole response (negative ions left, positive ions right) – due to low volatility there are too few ions to detect, remaining highlighted peak on left is due to O_2- and right is H_3O+, (faint peak is contamination in air line and is present in blanks as well)

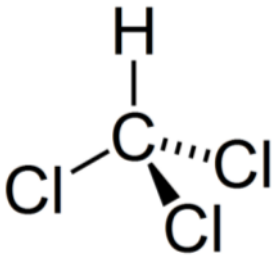
As no ions were detected from raw drug using this sampling method a detection algorithm could be very simple to implement; any detectable changes in the fingerprint obtained will signify the presence of an additional volatile compound.

Results - Individual solvent responses

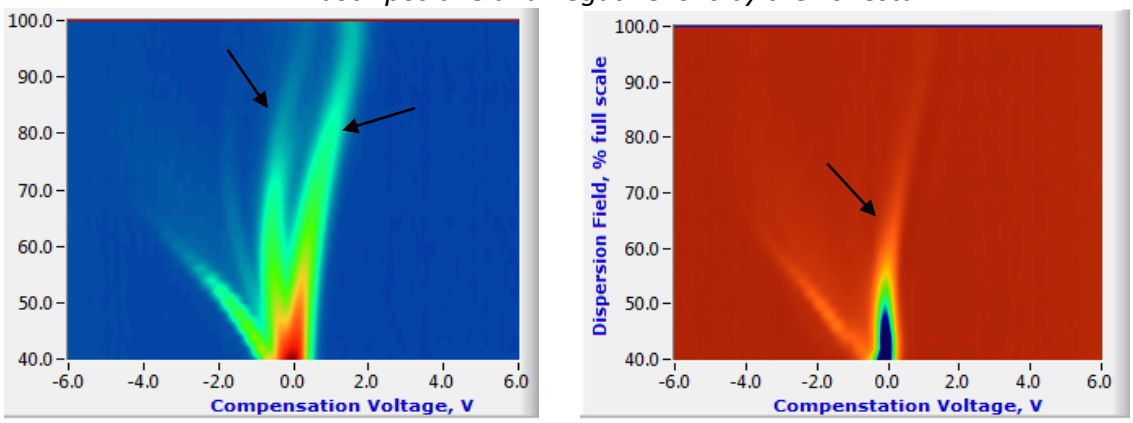
Tests were carried out on a range of individual solvents to obtain reference fingerprints and enable initial peak identification and show approximate dynamic range for quantification of concentration.

Chloroform

The first solvent on the USP list tested was chloroform ($CHCl_3$, CAS number 67-66-3) as an example of a halogenated solvent on the list. It produces stable negative and positive ions against which identification and quantification algorithms can be generated.

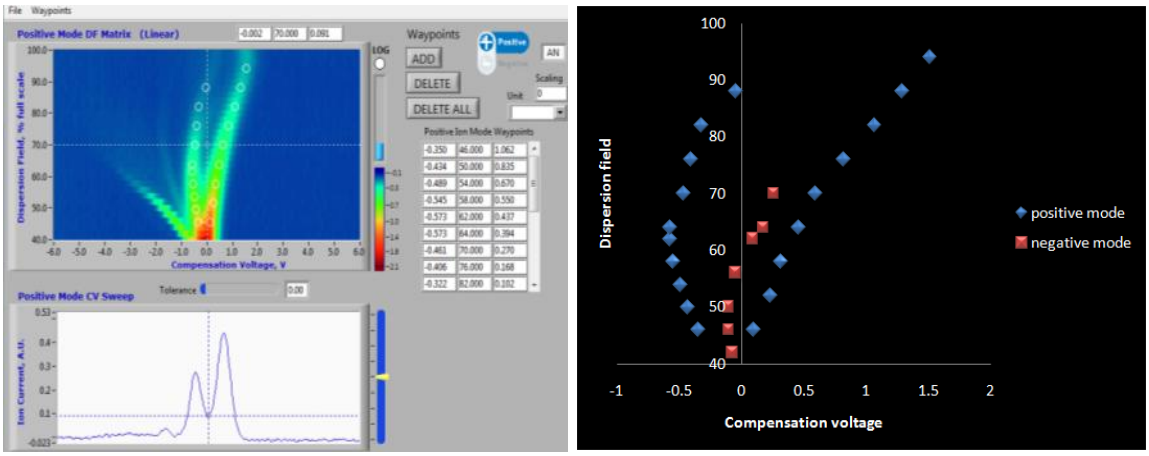


Trichloromethane – boiling point 61.2ºC, 119.38amu; chlorine can pick up a negative charge while the hydrogen can pick up a positive hydronium ion allowing detection via the presence of both positive and negative ions by the Lonestar



Positive(left) and negative (right) ion fingerprints of chloroform

The rule builder software provided with the Lonestar can be used to pick out a series of waypoints which can be then stored on a library to allow peak identification.

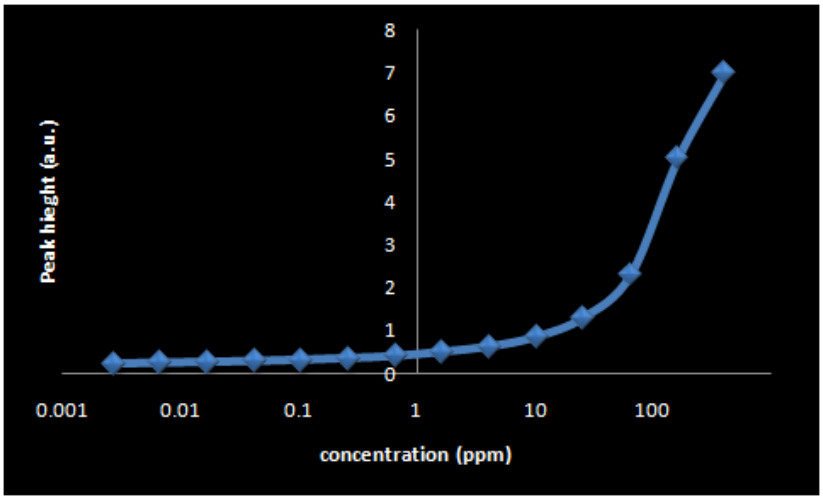


Identification waypoints selected using rule builder

Peak height can then be linked to concentration using various quantitative methods, in this case an exponential dilution was carried out. A flask held above the solvent boiling point is injected with the solvent and clean air is flushed through at a known rate so the concentration is dropping at a known rate. If the injection volume is known then an approximate concentration versus peak height relationship can be developed and used for real-time concentration calculations using the following equation.

$$[i]_T = [i]_{EDF} e^{-\frac{T \times F}{V}}$$

$[i]_T$ = concentration at time T, $[i]_{EDF}$ = Initial concentration, T = time (s), F = flow (litres/sec), V = Volume (litres)

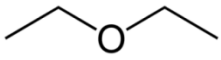


Peak height versus concentration for chloroform generated from an exponential dilution

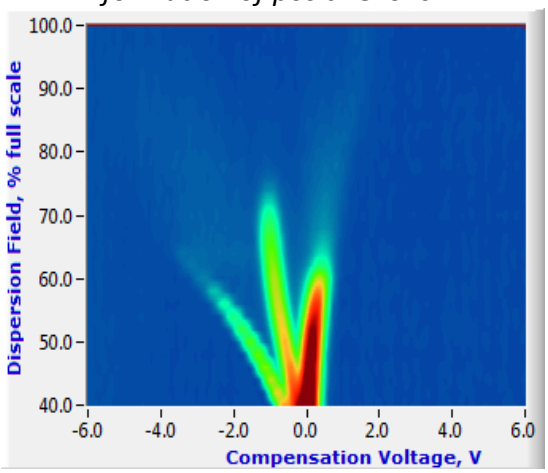
In practice the intrinsic errors in an exponential dilution means calibration by prepared standards should be used for accurate quantification, however this method is an effective way of quickly producing basic calibration curves.

Diethyl ether

The response to a trace amount of diethyl ether (C_4H1_0O, CAS number 60-29-7) was also tested; the fingerprint obtained is shown below.

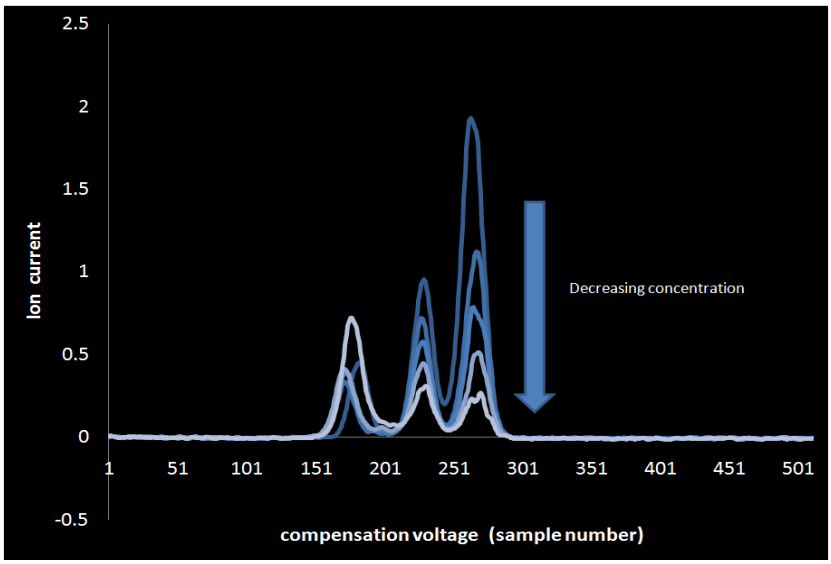


Diethyl ether – Boiling point 34.6, 74.12amu; 828kJ/mol proton affinity allows significant formation of positive ions



Diethyl ether fingerprint

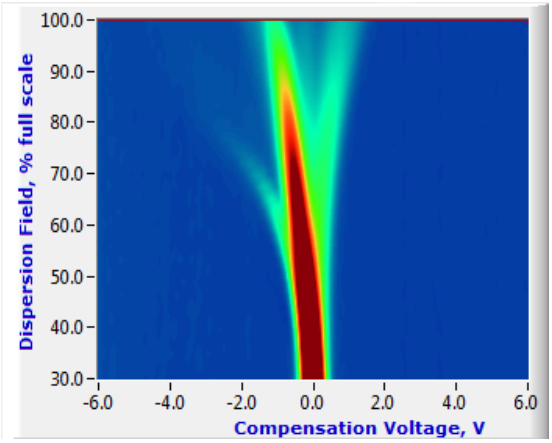
The double peak structure represents a monomer and dimer of the diethyl ether, this does need to be taken into account when quantifying the Lonestar response, at high concentrations the dimer peak (furthest right) dominates while at low concentrations the monomer peak (middle, left is air peak) is more significant. It is therefore necessary for some chemicals to produce two calibrations for different concentration ranges. Below is a plot of falling diethyl ether concentration, as the concentration drops the monomer (middle peak) becomes larger than the dimer peak.



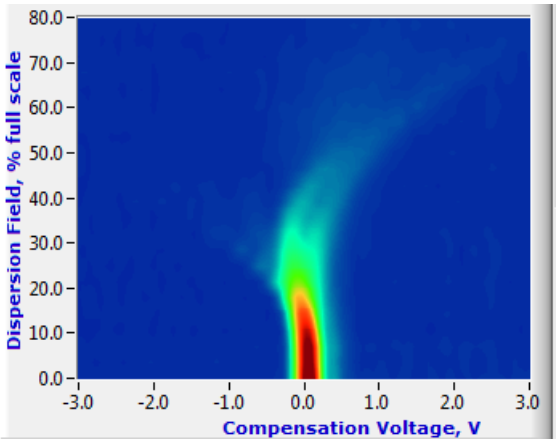
Monomer/dimer ratio changes as concentration decreases

Other solvents – Acetone, Ethanol, Hexane and Toluene

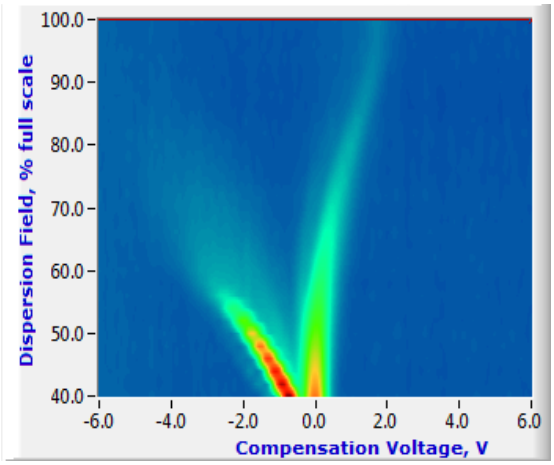
Below are example fingerprints for Acetone (C_3H_6O, CAS number 67-64-1), ethanol (C_2H_6O, CAS number 64-17-5), hexane (C_6H_{14}, CAS number 110-54-3) and toluene (C_7H_8, CAS number 108-88-3) at low ppm levels. This illustrates how the ion FAIMS fingerprint changes for different analytes.



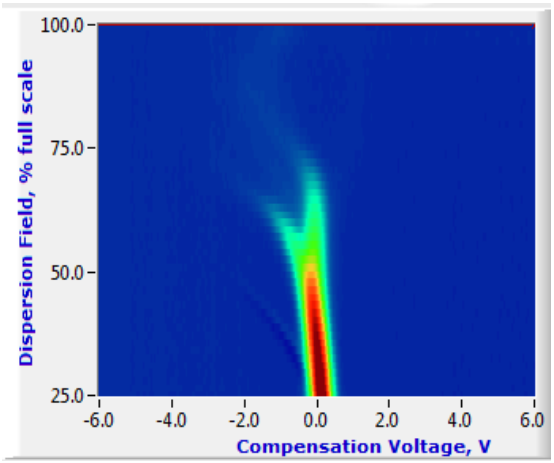
Ethanol



Hexane



Toluene



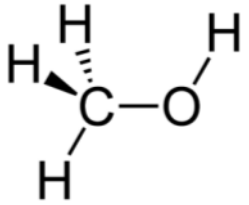
Acetone

Approximate limits of detection were found by a modified exponential dilution method. These detection limits could be exceeded with sampling optimisation but such a method may sacrifice the flexibility to detect all the solvents simultaneously.

Solvent	Approximate Limit of detection
methanol	100ppb
diethyl ether	<10ppb
chloroform	<10ppb
hexane	50ppb
Ethanol	30ppb

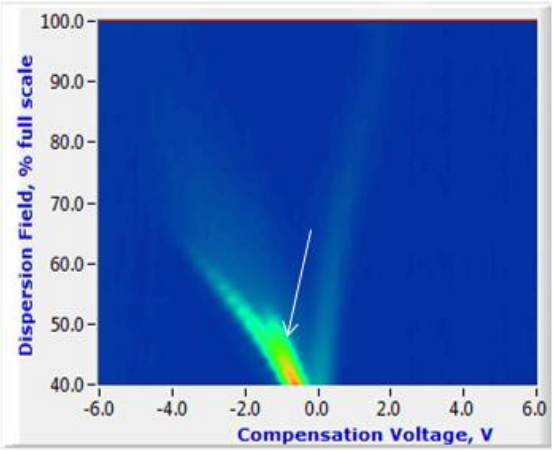
Methanol

Methanol (CH_3OH, CAS number 67-56-1) is the smallest solvent on the list it and consequently is one of the most difficult to detect. Methanol's mobility is similar to that of the air molecules which make up the reactive ion peak making resolving the ion peak challenging.

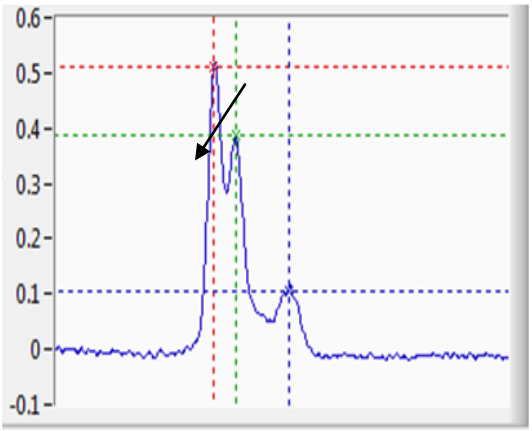


Boiling point 64.7, 32.05 amu, proton affinity 754 kJ/mol gives positive ion formation

The figure below shows the results of testing at a concentration of 4ppm methanol, the second plot shows a single slice of the fingerprint at 48% dispersion field with the methanol peak (middle peak) resolved from the reactive ion peak (left peak)



Methanol FAIMS fingerprint



Methanol peak separated from reactive ion peak (single slice of FAIMS spectra at 48% dispersion field)

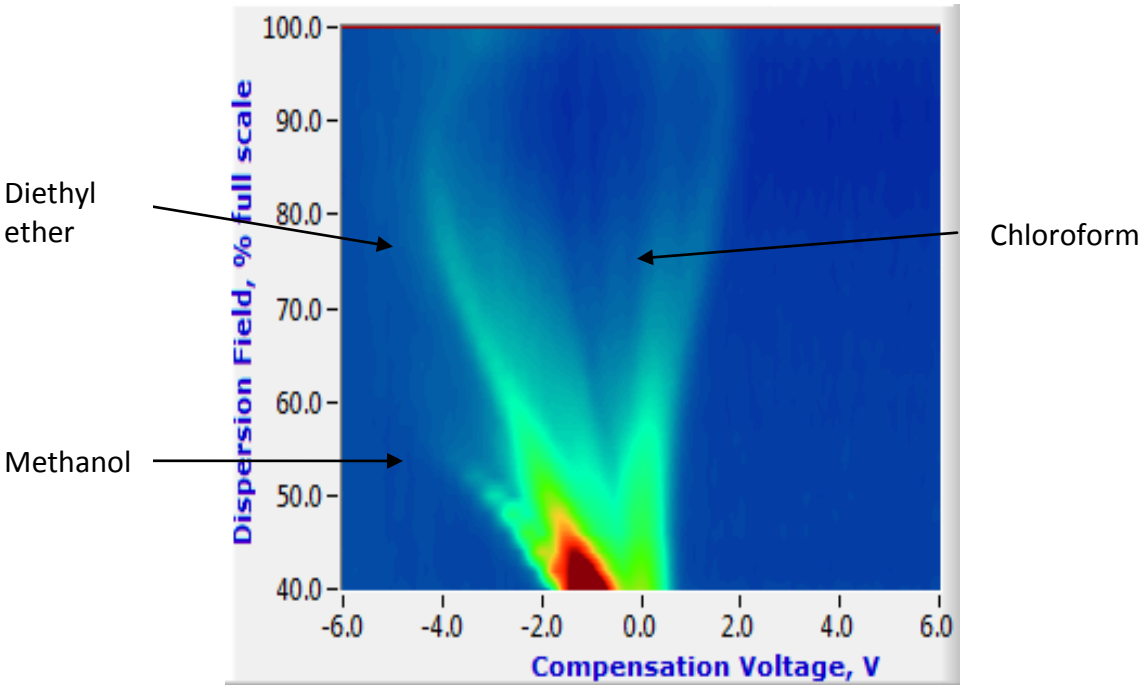
Results - Solvent drying

An effective away of illustrating the change in the Lonestar response to solvent content is to add a mixture of solvents to a flask and monitor the change in the headspace as clean dry air is flushed through.

Mix 1

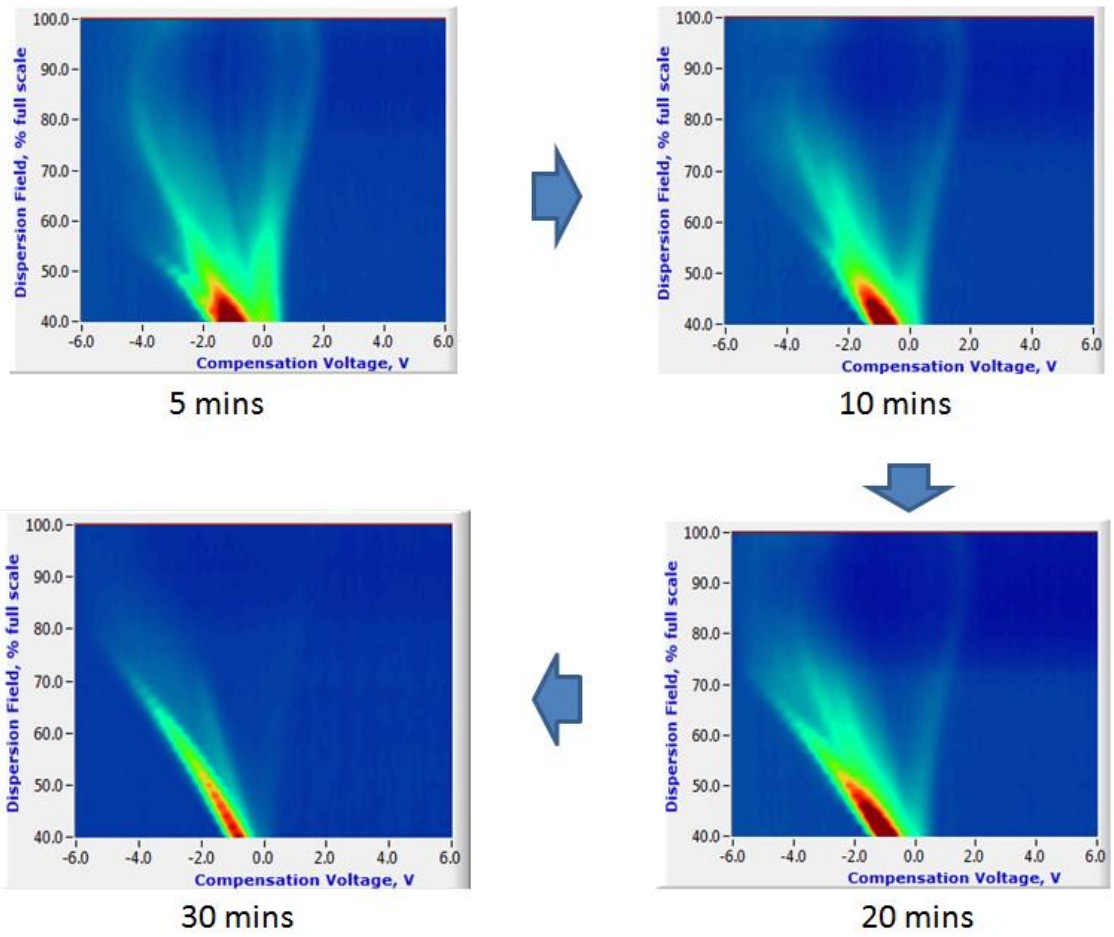
Methanol, diethyl ether and chloroform were added to a flask and clean dry air is flushed through at a rate of 5 flasks refreshes per minute.

Solvent	quantity
methanol	10µl
diethyl ether	10µl
chloroform	10µl



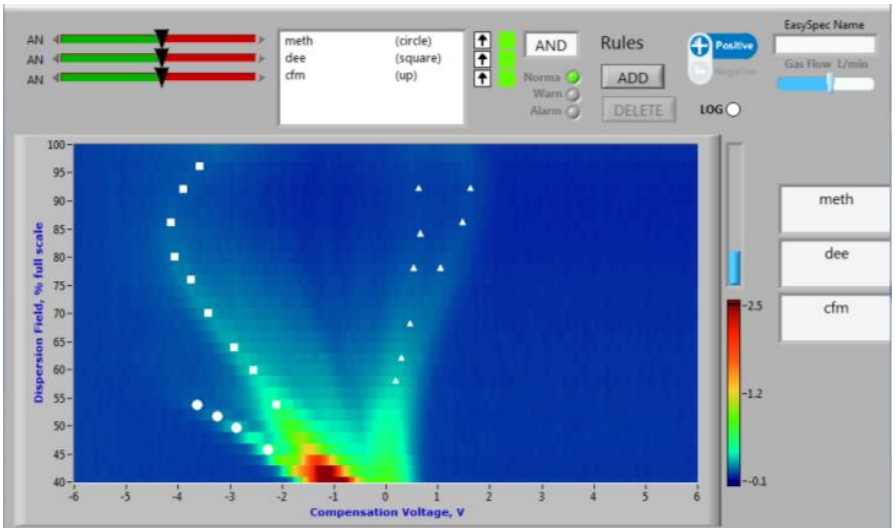
Initial plot after 5 minute showing the additive fingerprints of each solvent, peak magnitude indicates concentration and position on plot allows identification

Over time the peaks decay as the solvent dries/is diluted by the dry flush air. The figure below shows this evolution over time.



A mixture of three solvents drying over time as flushed with clean air till only the clean air peak is left.

The Lonestar software can be used to run simultaneous detection rules.

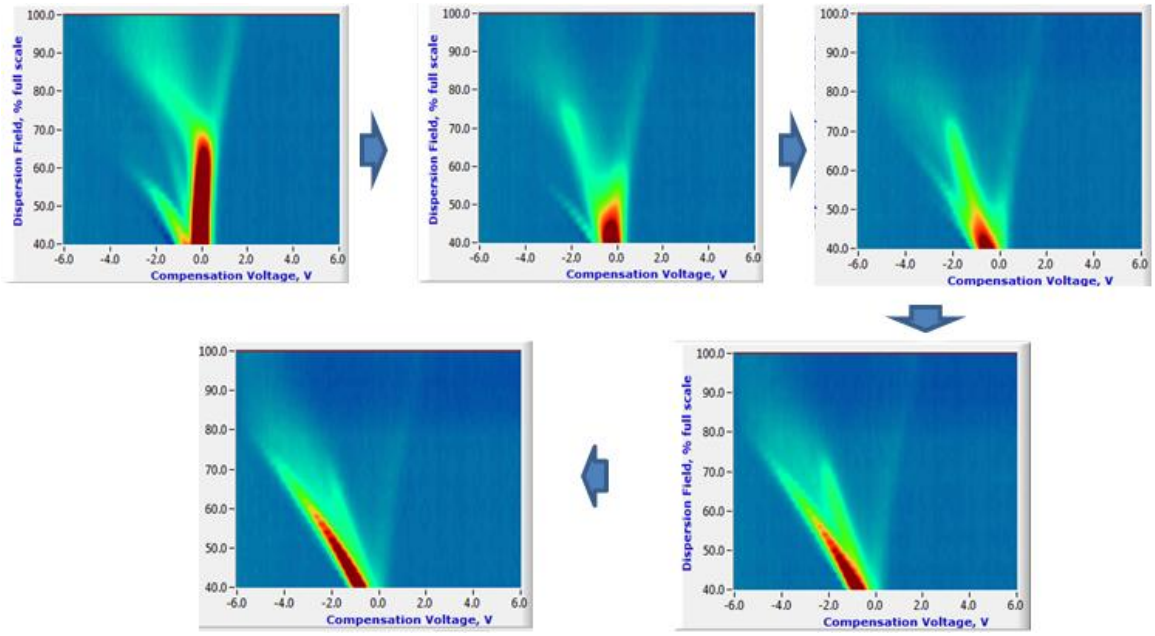


Integrated application builder used to identify and set threshold levels for multiple analytes

Mix 2

Adding toluene to the mix shows how dynamic range of the Lonestar can be limited, toluene high volatility puts lots in the headspace in the initial scans and masks other chemical responses, however once it drops to the low ppm concentrations the other peaks being masked become visible.

Solvent	quantity
methanol	10µl
diethyl ether	10µl
chloroform	10µl
toluene	10µl



Solvent drying of four solvents, masking of some analytes by strong toluene response

Masking by one solvent by another should not be a significant issue for pharmaceutical testing as the pass/green light requirement for the solvents will be no solvents above a certain concentration present. Also in practice the solvent levels should be low ppm or below at which point saturation masking is unlikely. Additional sample dilution with clean dry air can also be used to mitigate these issues.

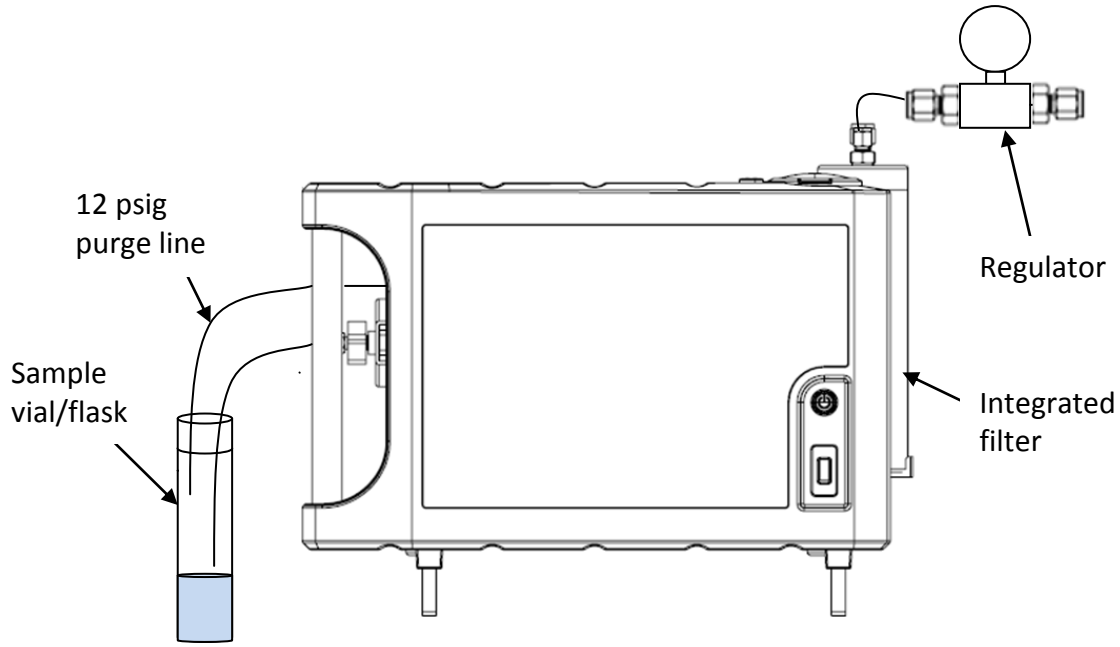
Future work

Other Solvents and selectivity

Depending on the application requirements, other solvent responses will need to be obtained and cross-sensitivity issues resolved. The thresholds for each solvent would need to be calibrated accurately (accuracy required will depend on the customer specification) and classification algorithms obtained. Cross sensitivity of some solvents (benzene/toluene pentane/heptane) would need to be investigated. In practice cross sensitivity issues should not be a significant problem as the the Lonestar function may be to highlight high solvent responses and a GC/LC-MS could be used to provide more specific information on suspect samples.

An alternative testing configuration – dissolving samples in water

An alternative sampling approach would be to dissolve the drug samples in water (if the particular drug is water soluble) and sample the headspace above the water as in the figure below.



Sampling a liquid headspace

Dissolving the sample in water has the advantage of removing the variability in the physical form of the sample, surface area is simplified to the circular water surface area, rather than depending on the powdered drug's packing density. The constant humidity generated can, in some cases, help with the detection of particular analytes. This sampling method would change the required identification and quantification algorithms. Consequently further investigation would be needed to evaluate its potential benefits and tradeoffs.

Summary

The testing showed that methods can be developed for making quick measurements of residual solvent content in pharmaceuticals

- The low volatility drugs tested give no measureable FAIMS response using a simple headspace measurement at room temperature. Consequently the detection of solvents is simplified as any ion response can be attributed to undesirable volatiles.

- Initial tests indicate that the solvents identified in the USP list should all be detectable down to sub 1ppm levels. Further testing would be required to confirm this but methanol which is one of the harder solvents to detect with FAIMS is detectable significantly below this concentration.

- Individual solvents can be identified and/or quantified to enable red light/green light checks on drugs for threshold solvents level. Alternatively calibrations of each solvent can be produced to enable absolute concentrations to be outputted.

- Typical fingerprints were obtained in approximately 2 minutes, however this has not been optimised, there is still redundant information which could be dropped by scanning less dispersion field values. Scan times of under a minute should be possible.

- Future work has been identified such as testing a wider range of solvents and quantifying response and cross sensitivity issues.

- Another future investigation would involve dissolving samples in water as a way of simplifying sample preparation and improving sample variability (variability from sampling a solid/powder). This method would need to be verified but has potential if solvent may be physically trapped in the drug or the sample form is variable.

Appendix A: FAIMS Technology at a Glance

Field asymmetric ion mobility spectrometry (FAIMS), also known as differential mobility spectrometry (DMS), is a gas detection technology that separates and identifies chemical ions based on their mobility under a varying electric field at atmospheric pressure. Figure 1 is a schematic illustrating the operating principles of FAIMS.

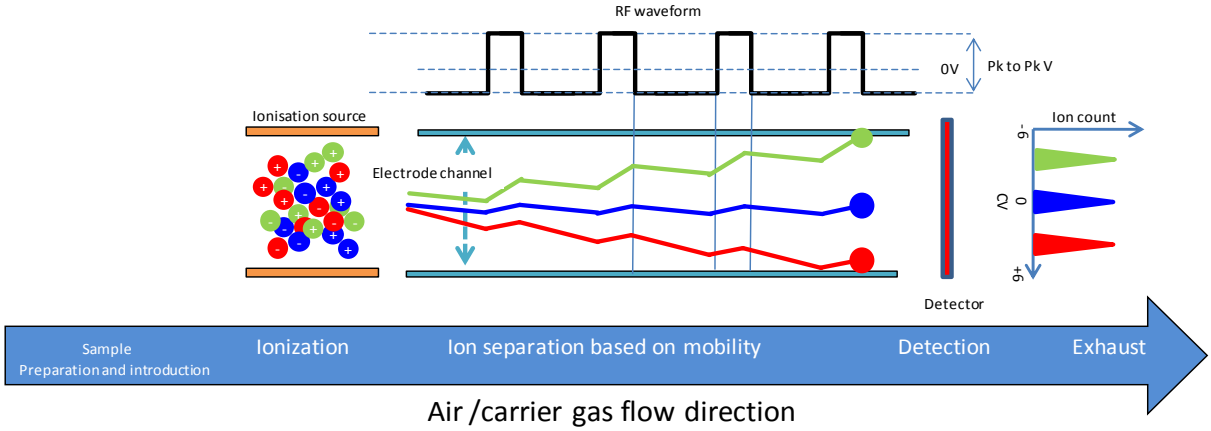


Figure 1 FAIMS schematic. The sample in the vapour phase is introduced via a carrier gas to the ionisation region, where the components are ionised via a charge transfer process or by direct ionisation, dependent on the ionisation source used. It is important to note that both positive and negative ions are formed. The ion cloud enters the electrode channel, where an RF waveform is applied to create a varying electric field under which the ions follow different trajectories dependent on the ions' intrinsic mobility parameter. A DC voltage (compensation voltage, CV) is swept across the electrode channel shifting the trajectories so different ions reach the detector, which simultaneously detects both positive and negative ions. The number of ions detected is proportional to the concentration of the chemical in the sample

Sample preparation and introduction

FAIMS can be used to detect volatiles in aqueous, solid and gaseous matrices and can consequently be used for a wide variety of applications. The user requirements and sample matrix for each application define the sample preparation and introduction steps required. There are a wide variety of sample preparation, extraction and processing techniques each with their own advantages and disadvantages. It is not the scope of this overview to list them all, only to highlight that the success of the chosen application will depend heavily on this critical step, which can only be defined by the user requirements.

There are two mechanisms of introducing the sample into the FAIMS unit: discrete sampling and continuous sampling. With discrete sampling, a defined volume of the sample is collected by weighing, by volumetric measurement via a syringe, or by passing vapor through an adsorbent for pre-concentration, before it is introduced into the FAIMS unit. An example of this would be attaching a container to the instrument containing a fixed volume of the sample. A carrier gas (usually clean dry air) is used to transfer the sample to the ionization region. Continuous sampling is where the resultant gaseous sample is continuously purged into the

FAIMS unit and either is diluted by the carrier gas or acts as the carrier gas itself. For example, continuously drawing air from the top of a process vat.

The one key requirement for all the sample preparation and introduction techniques is the ability to reproducibly generate and introduce a headspace (vapour) concentration of the target analytes that exceeds the lower limits of detection of the FAIMS device.

Carrier Gas

The requirement for a flow of air through the system is twofold: Firstly to drive the ions through the electrode channel to the detector plate and secondly, to initiate the ionization process necessary for detection.

As exhibited in Figure 2, the transmission factor (proportion of ions that make it to the detector) increases with increasing flow. The higher the transmission factor, the higher the sensitivity. Higher flow gives a larger full width half maximum (FWHM) of the peaks but also decreases the resolution of the FAIMS unit (see Figure 3).

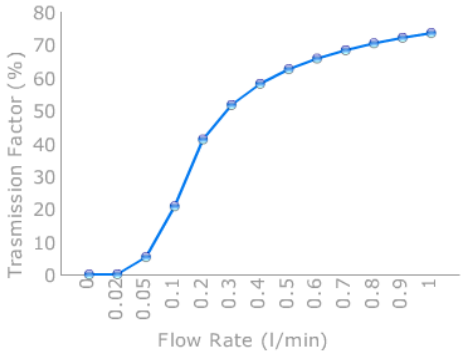


Figure 2 Flow rate vs. ion transmission factor

The air/carrier gas determines the baseline reading of the instrument. Therefore, for optimal operation it is desirable for the carrier to be free of all impurities (< 0.1 ppm methane) and the humidity to be kept constant. It can be supplied either from a pump or compressor, allowing for negative and positive pressure operating modes.

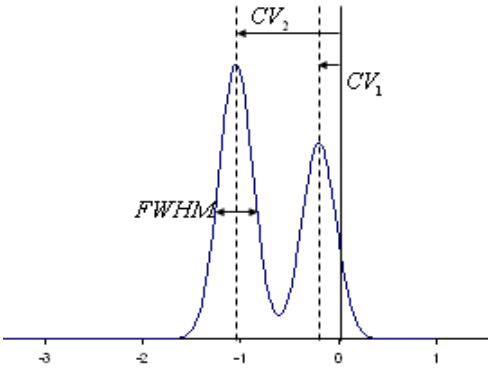


Figure 3 FWHM of ion species at set CV

Ionisation Source

There are three main vapor phase ion sources in use for atmospheric pressure ionization; radioactive nickel-63 (Ni-63), corona discharge (CD) and ultra-violet radiation (UV). A comparison of ionization sources is presented in Table 1.

Ionisation Source	Mechanism	Chemical Selectivity
Ni^{63} (beta emitter) creates a positive / negative RIP	Charge transfer	Proton / electron affinity
UV (Photons)	Direct ionisation	First ionisation potential
Corona discharge (plasma) creates a positive / negative RIP	Charge transfer	Proton / electron affinity

Table 1 FAIMS ionization source comparison

Ni-63 undergoes beta decay, generating energetic electrons, whereas CD ionization strips electrons from the surface of a metallic structure under the influence of a strong electric field. The generated electrons from the metallic surface or Ni-63 interact with the carrier gas (air) to form stable +ve and -ve intermediate ions which give rise to reactive ion peaks (RIP) in the positive and negative FAIMS spectra (Figure 4). These RIP ions then transfer their charge to neutral molecules through collisions. For this reason, both Ni-63 and CD are referred to as indirect ionization methods.

For the positive ion formation:

$N_2 + e^- \rightarrow \mathbf{N_2^+} + e^-$ (primary) + e^- (secondary)
$\mathbf{N_2^+} + 2N_2 \rightarrow \mathbf{N_4^+} + N_2$
$N_4+ + H_2O \rightarrow 2N_2 + \mathbf{H_2O^+}$
$H_2O+ + H_2O \rightarrow \mathbf{H_3O^+} + OH$
$H_3O+ + H_2O + N_2 \leftrightarrow \boldsymbol{H^+(H_2O)_2} + N_2$
$H^+(H_2O)_2 + H_2O + N_2 \leftrightarrow \boldsymbol{H^+(H_2O)_3} + N_2$

For the negative ion formation:

$O_2 + e^- \rightarrow \mathbf{O_2^-}$
$B + H_2O + \mathbf{O_2^-} \leftrightarrow \boldsymbol{O_2^-(H_2O)} + B$
$B + H_2O + O_2^-(H_2O) \leftrightarrow \boldsymbol{O_2^-(H_2O)_2} + B$

The water based clusters (hydronium ions) in the positive mode (blue) and hydrated oxygen ions in the negative mode (red), are stable ions which form the RIPs. When an analyte (M) enters the RIP ion cloud, it can replace one or dependent on the analyte, two water molecules to form a monomer ion or dimer ion respectively, reducing the number of ions present in the RIP.

Monomer Dimer

$$H^+(H_2O)_3 + M + N_2 \leftrightarrow M\boldsymbol{H^+(H_2O)_2} + N_2 + H_2O \leftrightarrow M_2\boldsymbol{H^+(H_2O)_1} + N_2 + H_2O$$

Dimer ion formation is dependent on the analyte's affinity to charge and its concentration. This is illustrated in Figure 4A using dimethyl methylphsphonate (DMMP). Plot A shows that the RIP decreases with an increase in DMMP concentration as more of the charge is transferred over to the DMMP. In addition the monomer ion decreases as dimer formation becomes more favourable at the higher concentrations. This is shown more clearly in Figure 4B, which plots the peak ion current of both the monomer and dimer at different concentration levels.

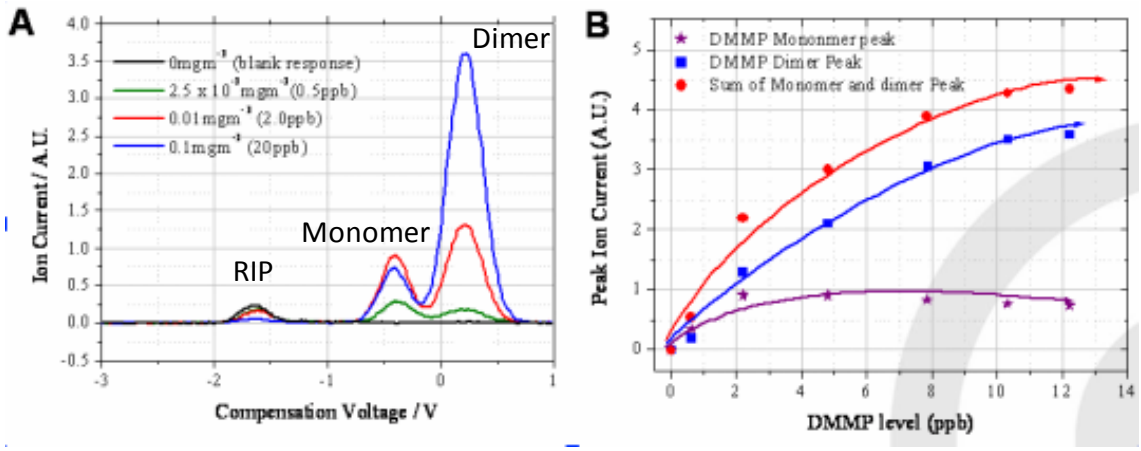


Figure 4 DMMP Monomer and dimer formation at different concentrations

The likelihood of ionization is governed by the analyte's affinity towards protons and electrons (Table 2 and Table 3 respectively).

In complex mixtures where more than one chemical is present, competition for the available charge occurs, resulting in preferential ionisation of the compounds within the sample. Thus the chemicals with high proton or electron affinities will ionize more readily than those with a low proton or electron affinity. Therefore the concentration of water within the ionization region will have a direct effect on certain analytes whose proton / electron affinities are lower.

Chemical Family	Example	Proton affinity
Aromatic amines	Pyridine	930 kJ/mole
Amines	Methyl amine	899 kJ/mole
Phosphorous Compounds	TEP	891 kJ/mole
Sulfoxides	DMS	884 kJ/mole
Ketones	2- pentanone	832 kJ/mole
Esters	Methly Acetate	822 kJ/mole
Alkenes	1-Hexene	805 kJ/mole
Alcohols	Butanol	789 kJ/mole
Aromatics	Benzene	750 kJ/mole
Water		691 kJ/mole
Alkanes	Methane	544 kJ/mole

Table 2 Overview of the proton affinity of different chemical families

Chemical Family	Electron affinity
Nitrogen Dioxide	3.91eV
Chlorine	3.61eV
Organomercurials	
Pesticides	
Nitro compounds	
Halogenated compounds	
Oxygen	0.45eV
Aliphatic alcohols	
Ketones	

Table 3 Relative electron affinities of several families of compounds

The UV ionization source is a direct ionization method whereby photons are emitted at energies of 9.6, 10.2, 10.6, 11.2, and 11.8 eV and can only ionize chemical species with a first ionization potential of less than the emitted energy. Important points to note are that there is no positive mode RIP present when using a UV ionization source and also that UV ionization is very selective towards certain compounds.

Mobility

Ions in air under an electric field will move at a constant velocity proportional to the electric field. The proportionality constant is referred to as mobility. As shown in Figure 5, when the ions enter the electrode channel, the applied RF voltages create oscillating regions of high ($+V_{HF}$) and low ($-V_{HF}$) electric fields as the ions move through the channel. The difference in the ion's mobility at the high and low electric field regimes dictates the ion's trajectory through the channel. This phenomenon is known as differential mobility.

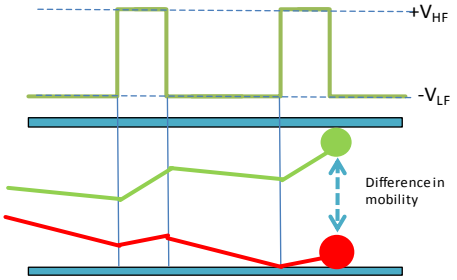


Figure 5 Schematic of a FAIMS channel showing the difference in ion trajectories caused by the different mobilities they experience at high and low electric fields

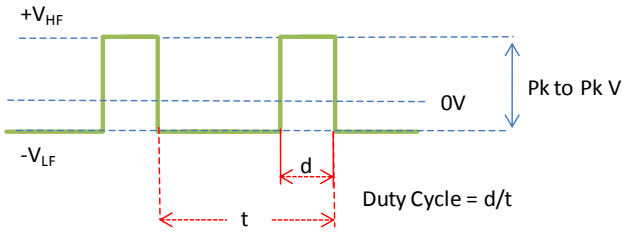


Figure 6 Schematic of the ideal RF waveform, showing the duty cycle and peak to peak voltage (Pk to Pk V)

The physical parameters of a chemical ion that affect its differential mobility are its collisional cross section and its ability to form clusters within the high/low regions. The environmental factors within the electrode channel affecting the ion's differential mobility are electric field, humidity, temperature and gas density (i.e. pressure).

The electric field in the high/low regions is supplied by the applied RF voltage waveform (Figure 6). The duty cycle is the proportion of time spent within each region per cycle. Increasing the peak-to-peak voltage increases/decreases the electric field experienced in the high/low field regions and therefore influences the velocity of the ion accordingly. It is this parameter that has the greatest influence on the differential mobility exhibited by the ion.

It has been shown that humidity has a direct effect on the differential mobility of certain chemicals, by increasing/decreasing the collision cross section of the ion within the respective low/high field regions. The addition and subtraction of water molecules to analyte ions is referred to as clustering and de-clustering. Increased humidity also increases the number of water molecules involved in a cluster ($MH^+(H_2O)_2$) formed in the ionisation region. When this cluster experiences the high field in between the electrodes the water molecules are forced away from the cluster reducing the size (MH^+) (de-clustering). As the low field regime returns so do the water molecules to the cluster, thus increasing the ion's size (clustering) and giving the ion a larger differential mobility. Gas density and temperature can also affect the ion's mobility by changing the number of ion-molecule collisions and changing the stability of the clusters, influencing the amount of clustering and de-clustering.

Changes in the electrode channel's environmental parameters will change the mobility exhibited by the ions. Therefore it is advantageous to keep the gas density, temperature and humidity constant when building detection algorithms based on an ion's mobility as these factors would need to be corrected for. However, it should be kept in mind that these parameters can also be optimized to gain greater resolution of the target analyte from the background matrix, during the method development process.

Detection and Identification

As ions with different mobilities travel down the electrode channel, some will have trajectories that will result in ion annihilation against the electrodes, whereas others will pass through to hit the detector. To filter the ions of different mobilities onto the detector plate a compensation voltage (CV) is scanned between the top and bottom electrode (see Figure 7). This process realigns the trajectories of the ions to hit the detector and enables a CV spectrum to be produced.

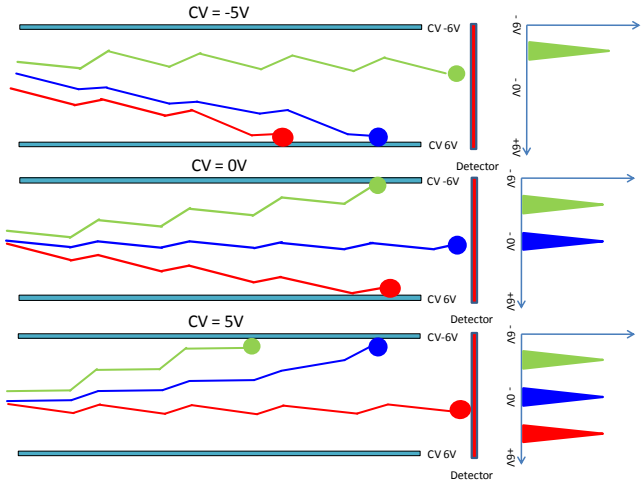


Figure 7 Schematic of the ion trajectories at different compensation voltages and the resultant FAIMS spectrum

The ion's mobility is thus expressed as a compensation voltage at a set electric field. Figure 8 shows an example CV spectrum of a complex sample where a de-convolution technique has been employed to characterize each of the compounds.

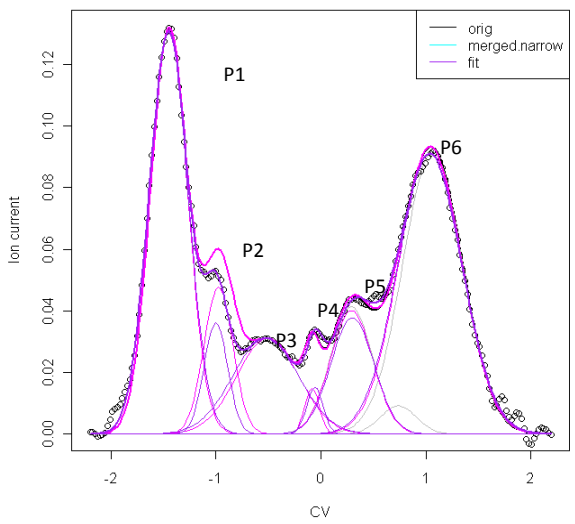


Figure 8 Example CV spectra. Six different chemical species with different mobilities are filtered through the electrode channel by scanning the CV value

Changing the applied RF peak-to-peak voltage (electric field) has a proportional effect on the ion's mobility. If this is increased after each CV spectrum, a dispersion field matrix is constructed. Figure 9 shows two examples of how this is represented; both are negative mode dispersion field (DF) sweeps of the same chemical. The term DF is sometimes used instead of electric field. It is expressed as a percentage of the maximum peak-to-peak voltage used on the RF waveform. The plot on the left is a waterfall image where each individual CV scan is represented by compensation voltage (x-axis), ion current (y-axis) and electric field (z-axis). The plot on the right is the one that is more frequently used and is referred to as a 2D color plot. The compensation voltage and electric field are on the x, and y axes and the ion current is represented by the color contours.

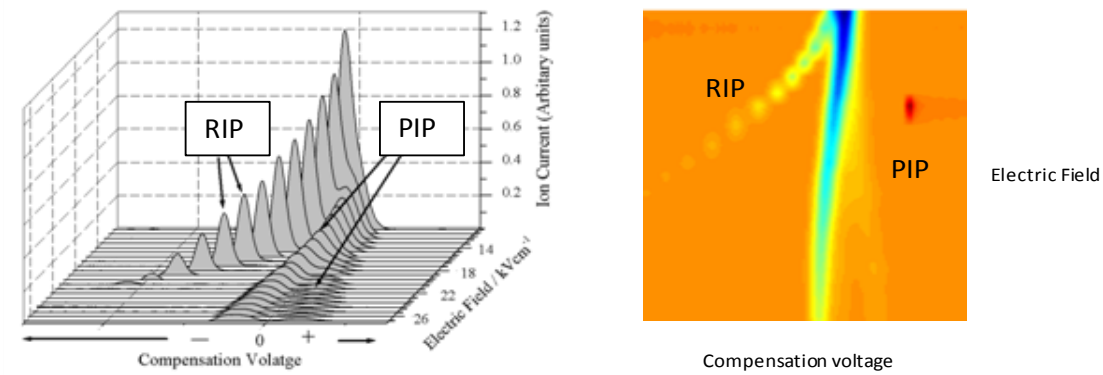


Figure 9 Two different examples of FAIMS dispersion field matrices with the same reactive ion peaks (RIP) and product ion peaks (PIP). In the waterfall plot on the left, the z axis is the ion current; this is replaced in the right, more frequently used, colorplot by color contours

With these data rich DF matrices a chemical fingerprint is formed, in which identification parameters for different chemical species can be extracted, processed and stored. Figure 10 shows one example: here the CV value at the peak maximum at each of the different electric field settings has been extracted and plotted, to be later used as a reference to identify the same chemicals. In Figure 11 a new sample spectrum has been compared to the reference spectrum and clear differences in both spectra can be seen.

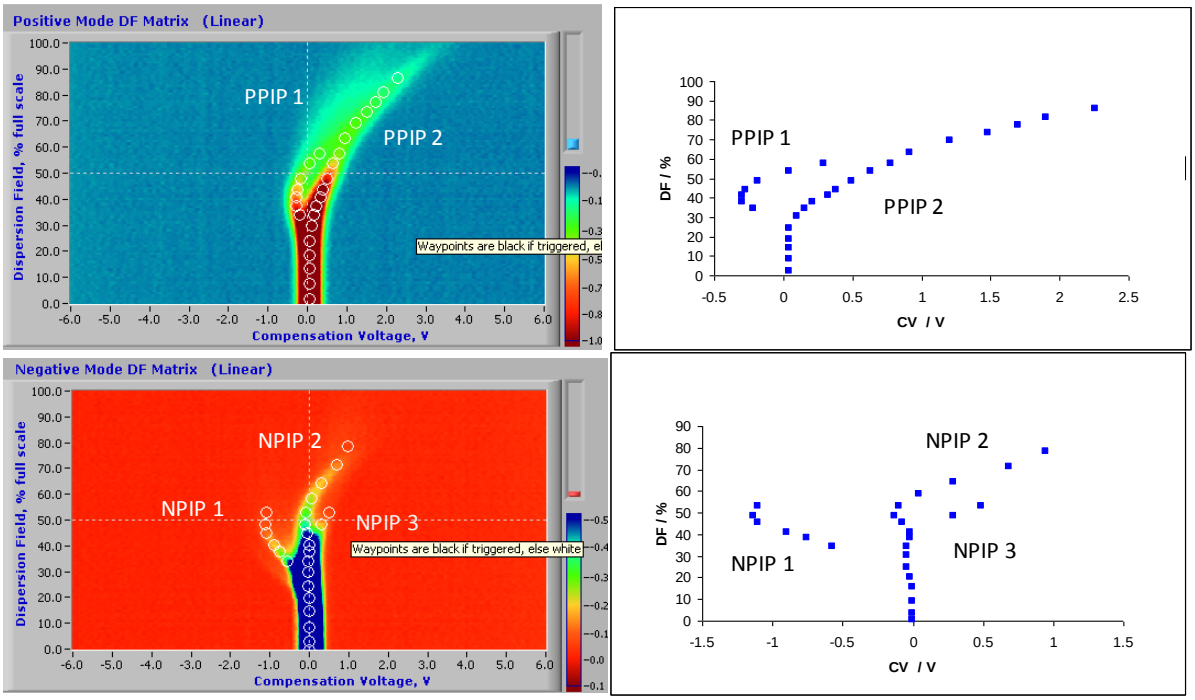


Figure 10 On the left are examples of positive (blue) and negative (red) mode DF matrices recorded at the same time while a sample was introduced into the FAIMS detector. The sample contained 5 chemical species, which showed as two positive product ion peaks (PPIP) and three negative product ion peaks (NPIP). On the right, the CV at the PIP's peak maximum is plotted against % dispersion field to be stored as a spectral reference for subsequent samples.

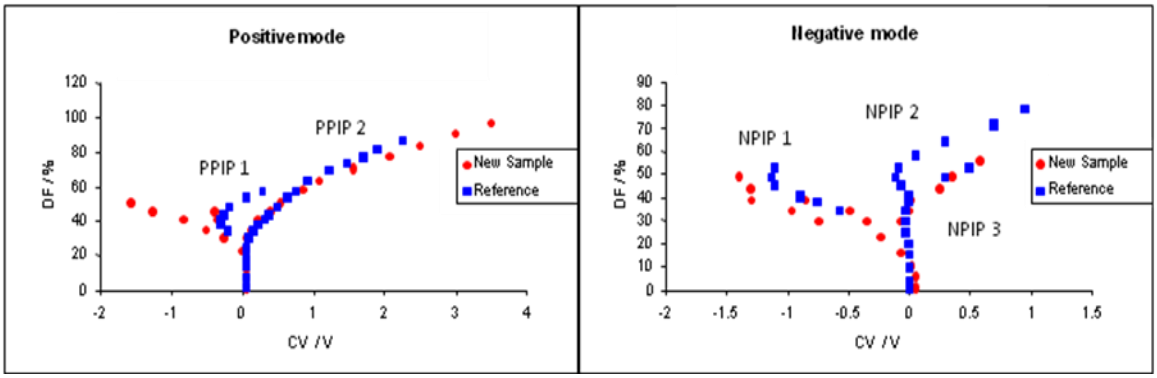


Figure 11 Comparison of two new DF plots with the reference from Figure 10. It can be seen that in both positive and negative modes there are differences between the reference product ion peaks and the new samples