FTIR Chemometrics Applied to E-liquids Quantitative Analysis

TSRC 08.18.2018

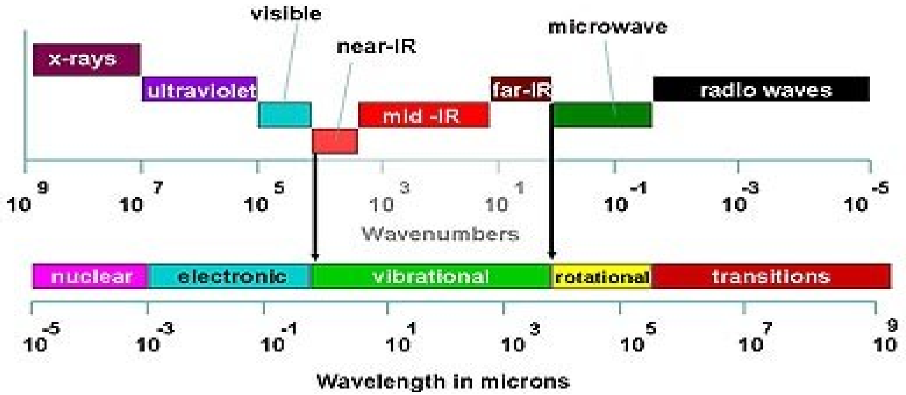
Frank S. Higgins, E. Kate Thorn, and Mark J. Rusyniak

Altria
Altria Client Services

What is FTIR?

Fourier Transform Infrared (FTIR) spectroscopy

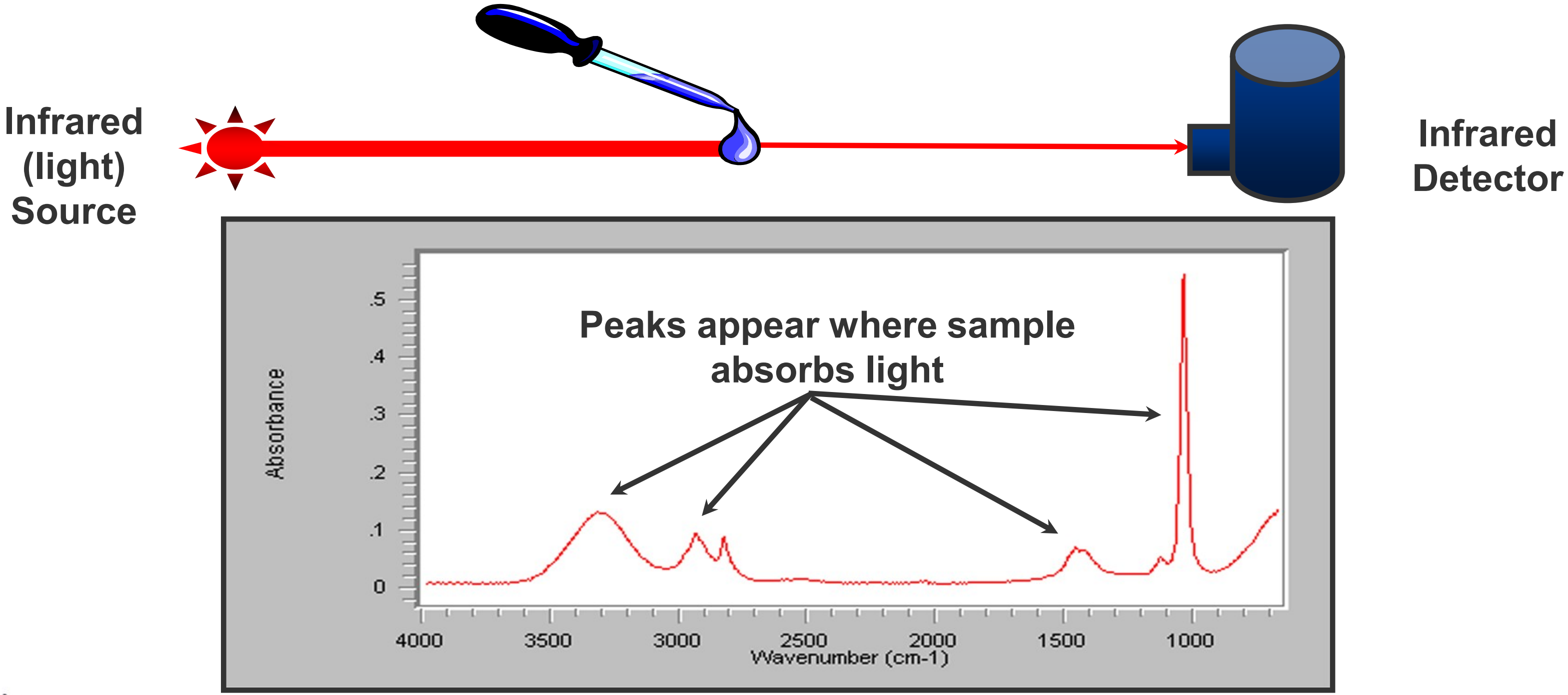
- Measures the absorption of infrared light in the 2.5-25μm wavelength range of the EM spectrum (4000-400cm^{-1})



Altria
Altria Client Services

Infrared Spectrum

A spectrum is a graph of how much infrared light is *absorbed* by molecules at each *wavenumber* of infrared light



What is FTIR

Advantages

- Specificity - fingerprint technique
- High optical throughput – all wavelengths of light are measured simultaneously
- High signal to noise
- Fast
- Easy to use

FTIR is Trending

Advances in optics and chemometrics

- Industries are taking a second look at FTIR
- Replacing or supplementing existing techniques

Organizations accepting FTIR methods

- FDA
- US Pharmacopeia (USP)
- American Oil Chemist Society (AOCS)
- AOAC International
- ASTM International
- International Organization for Standardization (ISO)

Existing E-liquid Methods

Currently gas chromatography (GC) is the conventional method to measure the principle components of e-liquids (CORESTA CRM 84)

- Water, nicotine, propylene glycol (PG), vegetable Glycerin (VG), menthol, and ethanol
- Ion chromatography (IC) for acids
- Karl Fischer (KF) is now the primary technique for water

FTIR e-liquids method includes all these components in a single measurement

FTIR Advantages Over GC & KF

FTIR Advantages

- Better PG and VG measurements
- Improved low water measurements
- Low cost of operation
  - No consumables
  - No expensive gases
  - No solvents
  - Low instrument maintenance
  - Low cost instrumentation
- No dilution or sample preparation
- No post analysis data processing
- Time per sample 2 minutes

Why FTIR for E-liquids Analysis

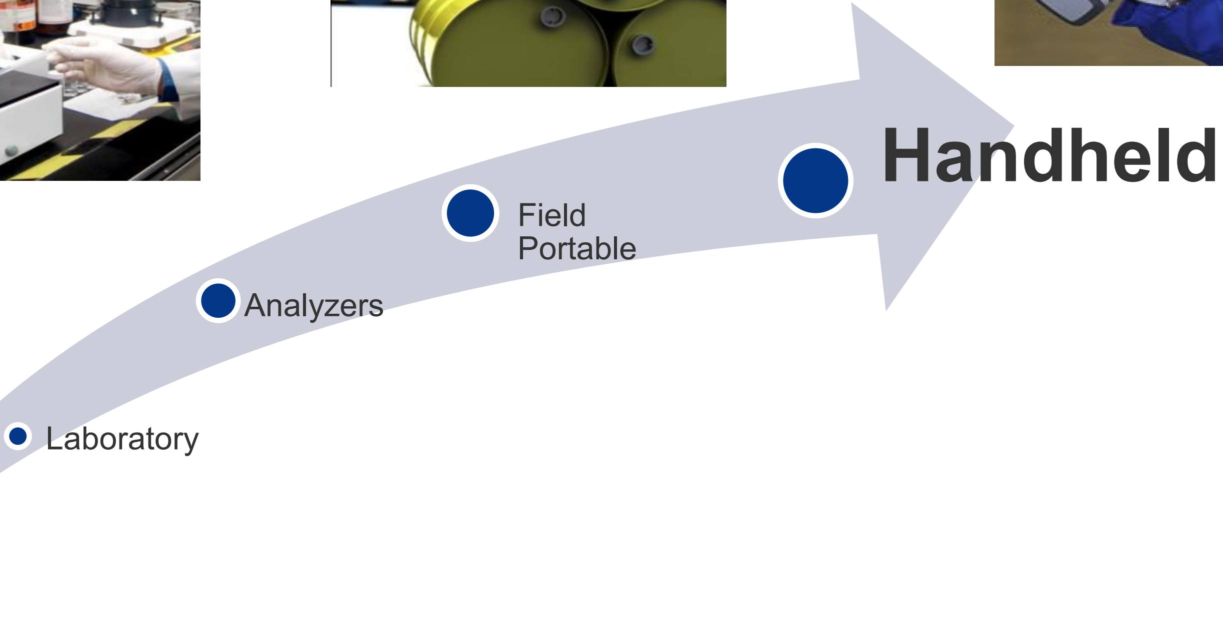
Ideal screening technique

- Reduces product development bottle necks
- Can be rolled out to high throughput manufacturing online or at-line applications

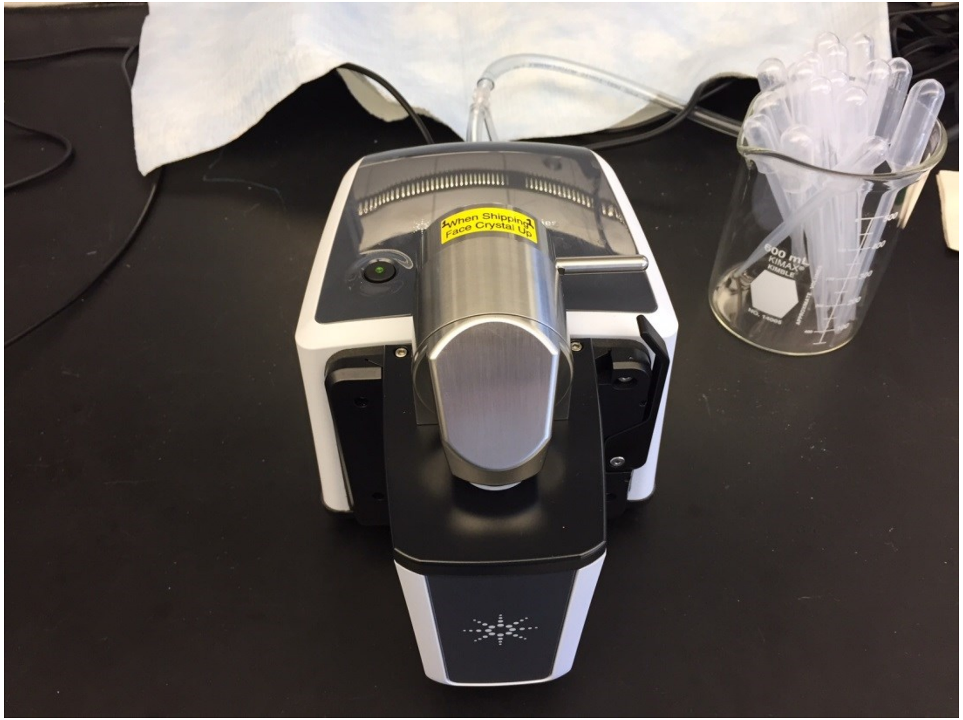
Factory QA/QC

- Incoming raw materials (i.e. Glycerol, PG)
- Could be used to quickly identify and possibly prevent out of spec batches

New FTIR Technology Available



Agilent Cary 630 FTIR Innovations

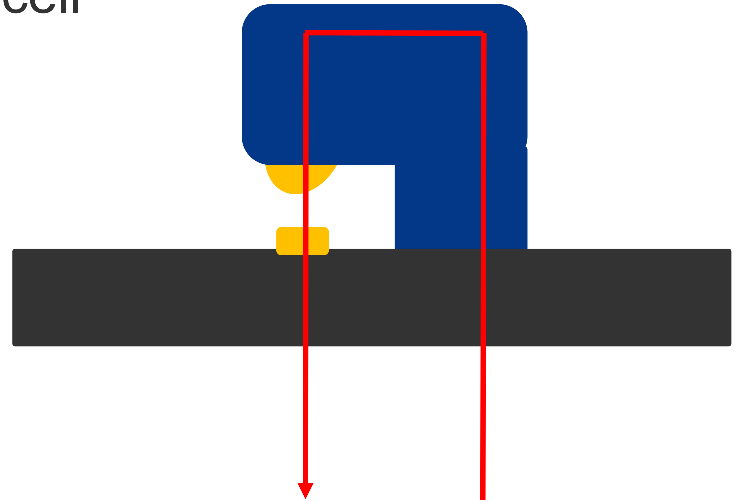


- Compact and portable
- Connects to most laptops
- True Michelson Interferometer ensures full wavenumber range capabilities (DTGS Detector)
- High signal to noise – equivalent performance to full size FTIR instruments

TumblIR Liquids Cell

Single Transmission Cell

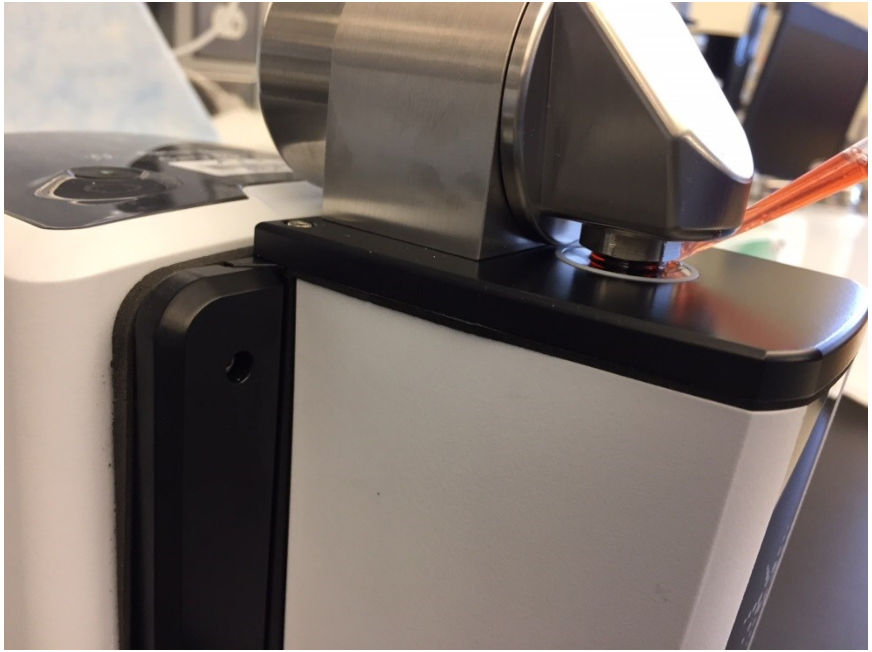
- Fixed path length liquid transmission cell
  - Standard 100µm
  - Can be factory Set to 30µm
- Liquids only
- Quantitative analysis
  - 100 ppm to 100%
- Reproducible and easy to use
- Easy to clean
- Ideal for viscous liquids like e-liquids



TumblIR Liquids Cell

Cell empty - background

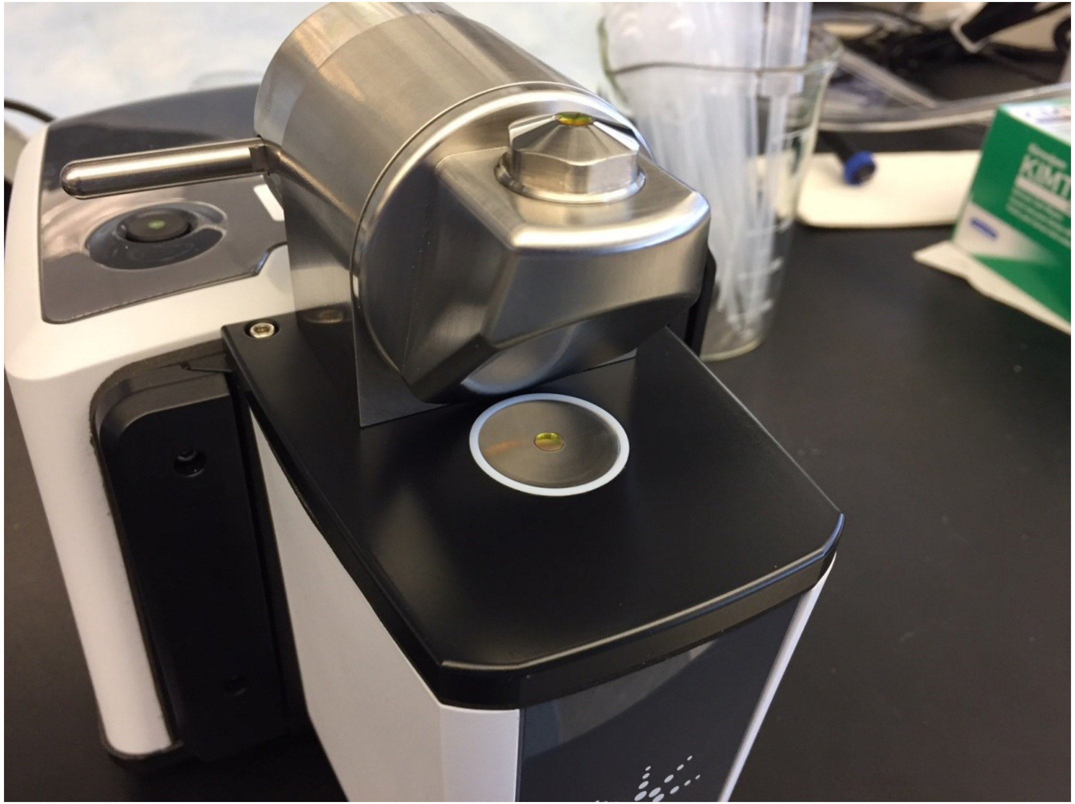
Cell full – ready for scanning



Altria
Altria Client Services

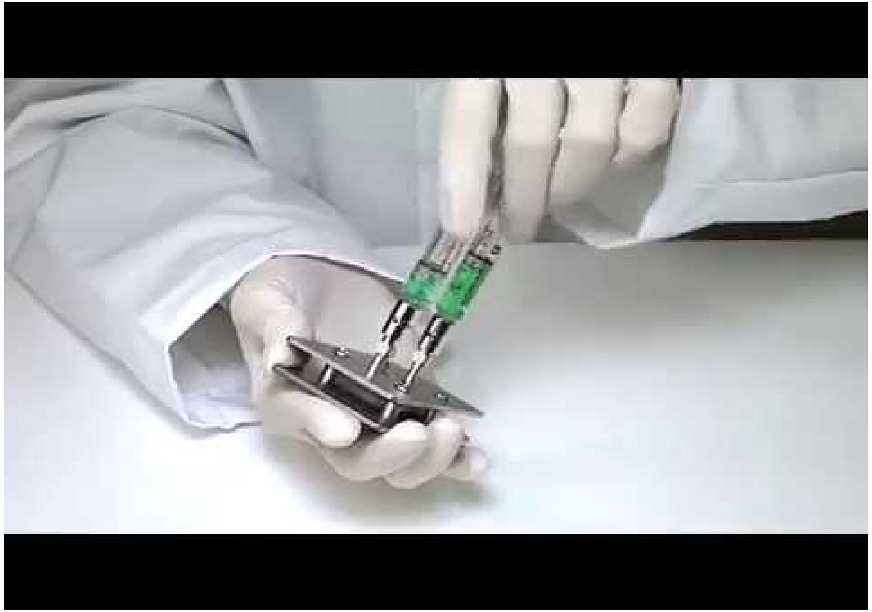
TumblIR Liquids Cell

Cell open - cleaning

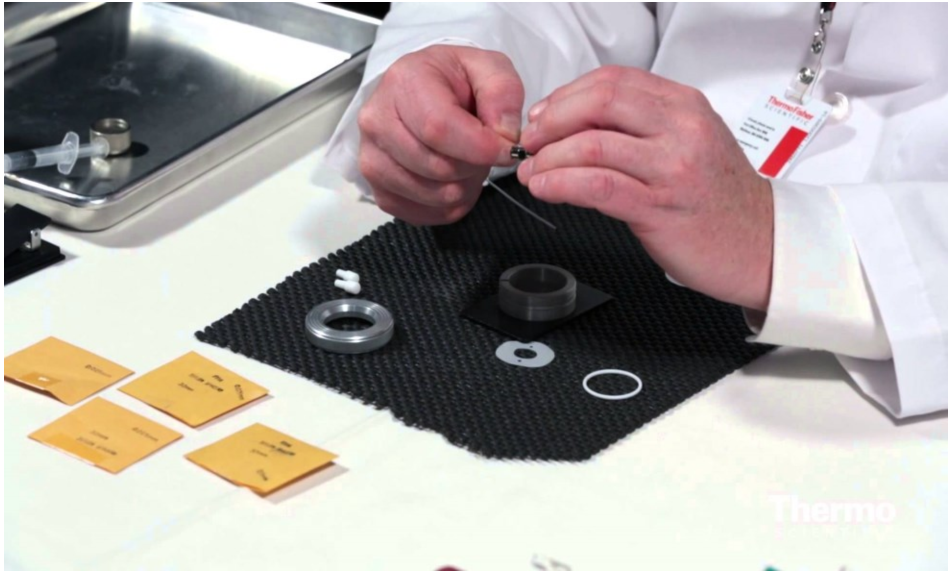


Traditional IR Liquid Transmission Cell

Filling: Messy



Cleaning: Not always this bad



Calibrating the method

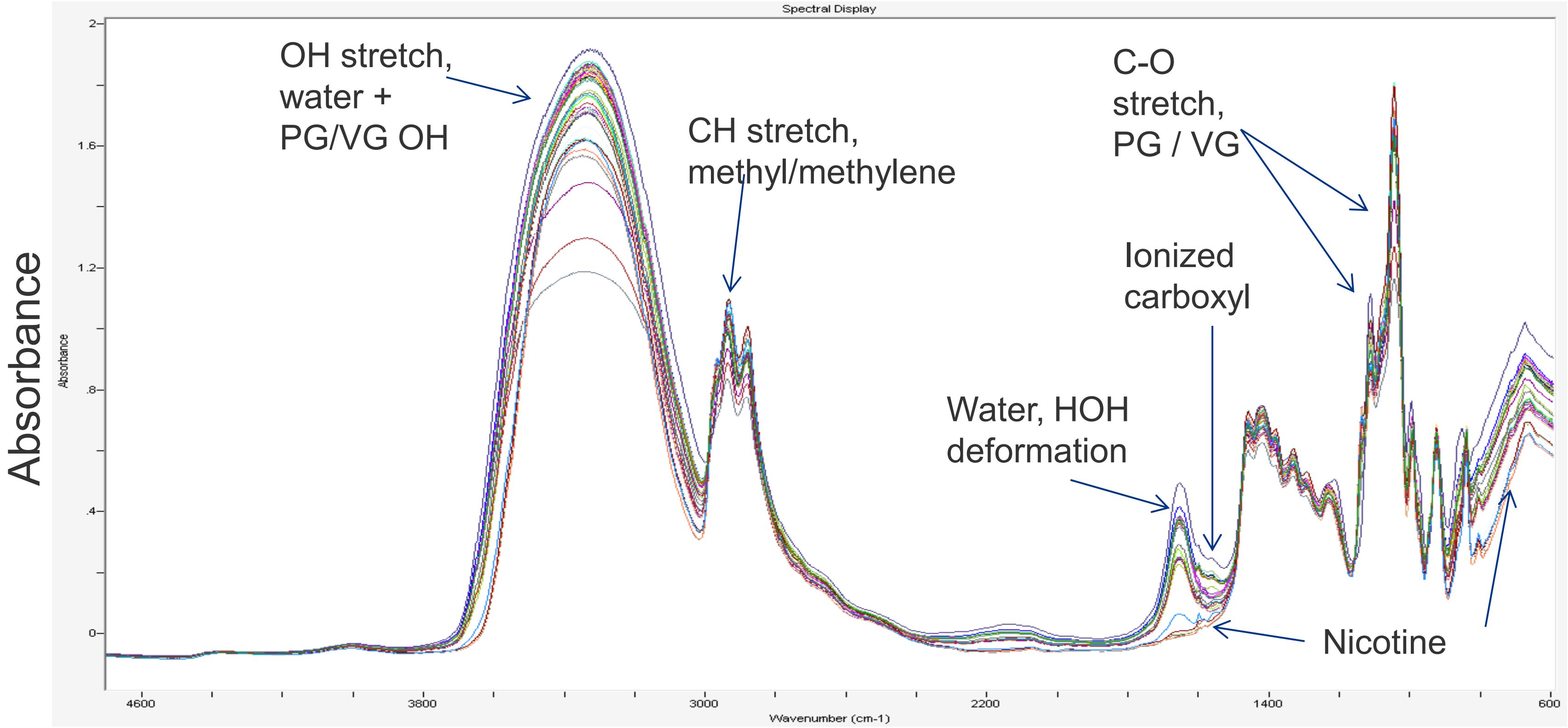
Partial Least Squares (PLS) Chemometrics

- Great for complex mixtures
- Allows multiple regions of the IR spectrum to be used in the calibration
- Preprocessing algorithms can be used to improve the calibration
    - Mean centering
    - First and second derivatives
    - Ideal for calibrations using bands that over lap
- Standard Error of Cross Validation (SECV) is a PLS feature to evaluate the performance of the calibration.

Large sets of e-liquids are measured

- Known values for each analyte are obtained
    - KF, GC, and IC values are used for each sample in the calibration
    - Preprocessing and regions are selected to optimize each analyte

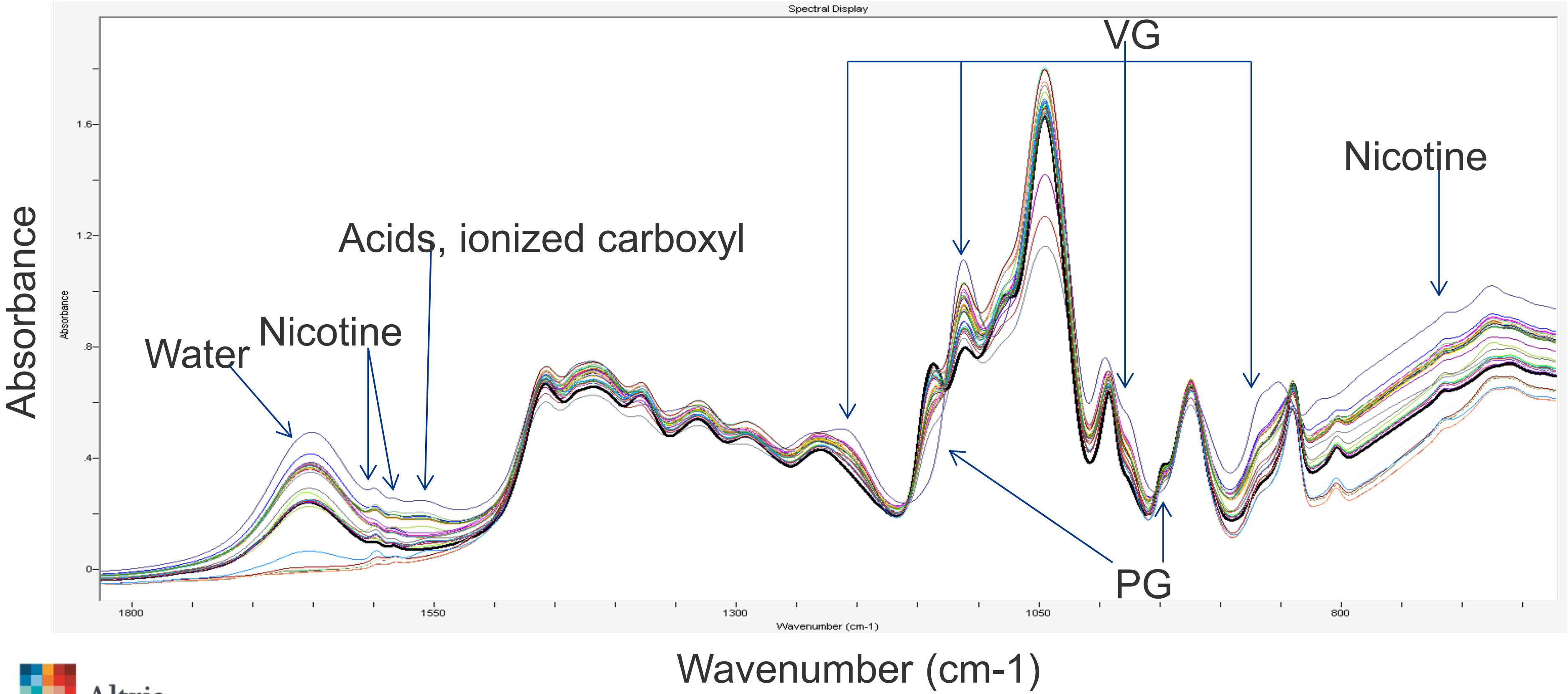
FTIR PLS Spectral Overlay



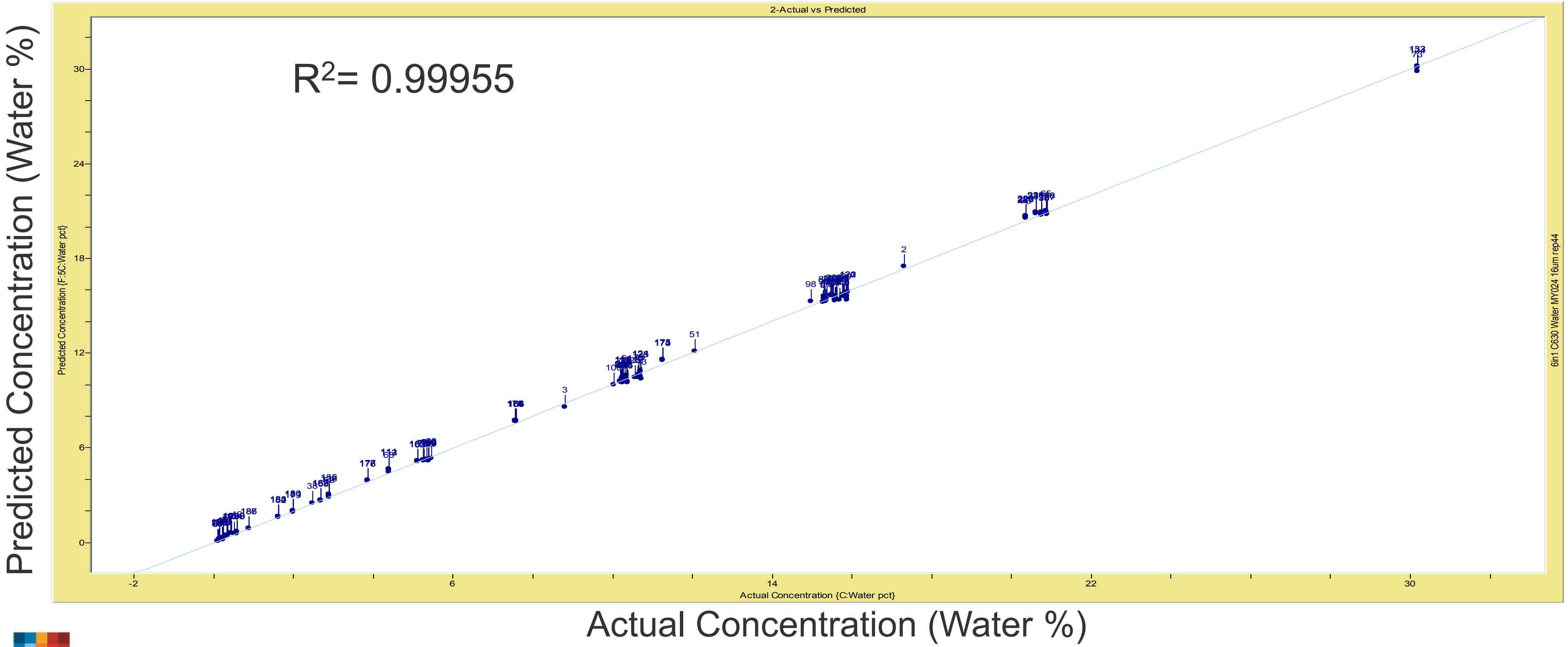
Wavenumber (cm^{-1})

Altria
Altria Client Services

FTIR PLS Spectral Overlay (Fingerprint Region)



Water: FTIR PLS Actual vs. Predicted Calibration Plot



FTIR Method Accuracy and Precision: Low Water

Accuracy - Individual aliquots of the same e-liquid sample were measured (N=10). The sample was measured by validated "gold standard" techniques as shown in the "Actual %" column. The percent water LOD (3x SD) and LOQ (9x SD) are shown.

E-Liquid 1	Average (%)	St.Dev. (%)	%RSD	Actual % (GC, KF, IC)	Accuracy (% Difference)	LOD %	LOQ %	KF St.Dev. (%)	KF %RSD
Water (%)	0.147	0.010	7.080	0.144	1.883	0.031	0.094	0.032	20.071
Propylene Glycol (%)	37.692	0.102	0.270	37.853	-0.427				
Glycerol (%)	57.504	0.181	0.314	57.598	-0.163				
Nicotine (wt %)	2.486	0.015	0.607	2.461	1.028				
Menthol (%)	0.000	0.000	NA	0.000	NA				
EtOH (%)	0.617	0.010	1.646	0.614	0.456				
Acids (%)	0.000	0.000	NA	0.000	NA				

Precision – The same aliquot of E-Liquid 1 measured consecutively (N=9).

E-Liquid 1	Average (%)	St.Dev. (%)	%RSD
Water (%)	0.157	0.002	1.474
Propylene Glycol (%)	37.627	0.039	0.104
Glycerol (%)	57.419	0.067	0.116
Nicotine (wt %)	2.489	0.016	0.637
Menthol (%)	0.000	0.000	NA
EtOH (%)	0.607	0.004	0.717
Acids (%)	0.000	0.000	NA

FTIR Method Repeatability Test: High Water

Individual Aliquots = Same E-liquid 2 sample with replicate ~0.25mL aliquots measured.
Same Aliquot = Same E-liquid 2 sample and aliquot measured 5 consecutive times.

Individual Aliquots	E-Liquid 2 Rep1	E-Liquid 2 Rep2	E-Liquid 2 Rep3	E-Liquid 2 Rep4	E-Liquid 2 Rep5	**Average**	**Std. Dev.**	**%RSD**	KF Average (%)	KF St. Dev. (%)	**KF %RSD**
Water (%)	15.590	15.640	15.540	15.600	15.610	15.596	0.036	0.234	15.583	0.107	0.682

Same Aliquot	E-Liquid 2 Rep1	E-Liquid 2 Rep2	E-Liquid 2 Rep3	E-Liquid 2 Rep4	E-Liquid 2 Rep5	**Average**	**Std. Dev.**	**%RSD**
Water (%)	15.590	15.600	15.590	15.580	15.590	15.590	0.007	0.045

E-liquid 2 Air Exposure Experiment

Same Aliquot	E-Liquid 2 Avg	E-Liquid 2 30 Mins	E-Liquid 2 3hours
Water (%)	15.60	12.36	11.96
Propylene Glycol (%)	23.98	24.78	24.82
Glycerol (%)	55.89	57.80	58.22
Nicotine (wt %)	3.64	3.84	3.86
Menthol (%)	0.00	0.00	0.00
EtOH (%)	0.84	0.52	0.39
Acids (%)	0.74	0.87	0.88

Altria
Altria Client Services

FTIR Method Accuracy and Precision: Propylene Glycol

The lowest PG calibration sample (E-liquid 3) was measured to determine LOD and LOQ (N=6).

E-Liquid 3	Average (%)	St.Dev. (%)	%RSD	Actual % (GC, KF, IC)	Accuracy (% Difference)	LOD	LOQ
Water (%)	15.565	0.023	0.149	15.583	-0.119		
Propylene Glycol (%)	23.336	0.020	0.088	23.386	-0.215	0.061	0.184
Glycerol (%)	56.339	0.067	0.118	56.644	-0.538		
Nicotine (%)	3.502	0.021	0.614	3.490	0.339		
Menthol (%)	0.000	NA	NA	NA	NA		
EtOH (%)	0.736	0.009	1.233	0.754	-2.431		
Acids (%)	0.706	0.002	0.237	0.723	-2.284		

FTIR Method Accuracy and Precision: Glycerol

The lowest glycerol calibration sample (E-liquid 4) was measured to determine LOD and LOQ (N=6).

E-Liquid 4	Average (%)	St.Dev. (%)	%RSD	Actual % (GC, KF, IC)	Accuracy (% Difference)	LOD	LOQ
Water (%)	15.060	0.025	0.164	15.000	0.398		
Propylene Glycol (%)	66.719	0.100	0.150	67.950	-1.812		
Glycerol (%)	17.417	0.016	0.092	17.050	2.153	0.048	0.144
Nicotine (%)	0.000	NA	NA	NA	NA		
Menthol (%)	0.000	NA	NA	NA	NA		
EtOH text	0.000	NA	NA	NA	NA		
Acids (%)	0.000	NA	NA	NA	NA		

Altria
Altria Client Services

FTIR Method Accuracy and Precision: Nicotine and Menthol

The lowest nicotine and menthol calibration sample (E-liquid M4) was measured to determine LOD and LOQ (N=6).

E-Liquid M4	Average (%)	St.Dev. (%)	%RSD	Actual % (GC, KF, IC)	Accuracy (% Difference)	LOD	LOQ
Water (%)	3.487	0.012	0.334	NA	NA		
Propylene Glycol (%)	53.147	0.058	0.109	52.993	0.290		
Glycerol (%)	40.659	0.051	0.125	41.273	-1.487		
Nicotine (%)	0.580	0.021	3.679	0.599	-3.172	0.064	0.192
Menthol (%)	0.542	0.025	4.567	0.481	12.613	0.074	0.223
EtOH (%)	0.169	0.007	4.253	0.208	-18.590		
Acids (%)	0.000	NA	NA	NA	NA		

FTIR Method Accuracy and Precision: Ethanol

The lowest ethanol calibration sample (E-liquid M17) was measured to determine LOD and LOQ (N=6).

E-Liquid M17	Average (%)	St.Dev. (%)	%RSD	Actual % (GC, KF, IC)	Accuracy (% Difference)	LOD	LOQ
Water (%)	11.571	0.028	0.238	11.253	2.825		
Propylene Glycol (%)	27.031	0.032	0.117	27.197	-0.609		
Glycerol (%)	56.097	0.058	0.104	56.429	-0.588		
Nicotine (%)	3.674	0.016	0.439	3.661	0.334		
Menthol (%)	0.000	NA	NA	NA	NA		
EtOH (%)	0.146	0.006	3.930	0.155	-5.853	0.017	0.051
Acids (%)	0.713	0.003	0.359	0.713	-0.038		

Altria
Altria Client Services

FTIR Method Accuracy and Precision: Total Acids

The lowest total acids calibration sample (E-liquid M21) was measured to determine LOD and LOQ (N=6).

E-Liquid M21	Average (%)	St.Dev. (%)	%RSD	Actual % (GC, KF, IC)	Accuracy (% Difference)	LOD	LOQ
Water (%)	0.919	0.010	1.042	0.889	3.337		
Propylene Glycol (%)	36.719	0.050	0.137	37.138	-1.128		
Glycerol (%)	56.868	0.082	0.145	57.520	-1.132		
Nicotine (%)	2.526	0.014	0.563	2.541	-0.597		
Menthol (%)	0.000	NA	NA	NA	NA		
EtOH (%)	0.566	0.005	0.960	0.583	-3.033		
Acids (%)	0.050	0.001	1.690	0.048	3.452	0.003	0.008

Altria
Altria Client Services

FTIR Method Calibration Summary

E-Liquids	SECV %	R2	LOD %	LOQ %
Water (%) High	0.156	0.9996	NA	NA
Water (%) low	0.094	0.9985	0.031	0.094
Propylene Glycol (%)	0.305	0.9994	0.061	0.184
Glycerol (%)	0.510	0.9990	0.048	0.144
Nicotine (wt %)	0.037	0.9993	0.064	0.192
Menthol (%)	0.052	0.9983	0.074	0.223
EtOH (%)	0.030	0.9950	0.017	0.051
Acids (%)	0.014	0.9974	0.003	0.008

Conclusions

- Current FTIR technology makes analysis of viscous liquids, such as e-liquids, faster and easier.
- FTIR methods can provide immediate results for e-liquids research and manufacturing applications.
- FTIR analysis is a less expensive and easier to maintain compared to other techniques.
- Chemometric PLS calibration to “gold standard” techniques, such as GC, KF, and IC, produces accurate and precise measurement of e-liquids by FTIR.
- FTIR e-liquids results indicate comparable performance to GC, KF, and IC techniques, and in some cases better performance.

Acknowledgments

- Special Thanks for the Karl Fischer, GC, and IC data, samples, and background knowledge of e-liquids formulations
  - Robert Ragland
  - Sean Platt
  - Charnise Jackson
  - Xue Luo
  - Geniya Prepelitskaya

www.altria.com/ALCS-Science