Fourier Transformed Infrared (FTIR) Method For Continuous Real-Time Aerosol Characterization For *In Vivo* Studies

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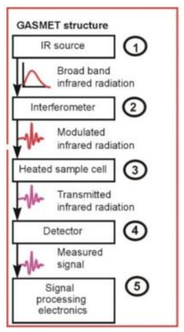
Introduction and Objectives

The conduct of *in vivo* studies, as recommended by test guidelines (e.g., TG413) from the Organization for Economic Cooperation and Development, requires the test atmosphere to be held as constant as practicable. This is nontrivial, especially in cases where the test items are complex multi-phase and multi-constituent aerosols from Reduced-Risk Products or e-liquids.

Classical methods for quantification of nongaseous key constituents, such as nicotine concentration in the test atmosphere, typically involve sample trapping in an appropriate medium followed by offline analysis. This is resource-intensive and provides only cumulative averages over the period of sample collection. For a more immediate assessment, a real-time aerosol characterization method has been developed to quantify key aerosol constituents using Fourier Transformed Infrared (FTIR) spectroscopy.

System and Principle of Operation

Hardware: Gasmet CX4000



Interior of the Gasmet CX4000

Source: https://www.gasmet.com/wp-content/uploads/2018/03/Gasmet-CX4000-Technical-Data-ID-7082.pdf

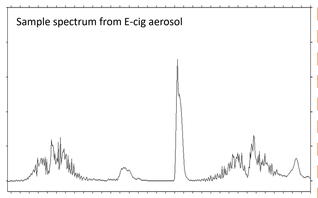
Spectrometer	
Resolution:	Recommended 8 cm^{-1} or 4 cm^{-1}
Scan frequency:	10 scans / s
Detector:	Peltier cooled MCT
Source:	SiC, 1550 K
Beamsplitter:	ZnSe
Window material:	ZnSe
Wave number range:	900 - 4 200 cm^{-1}

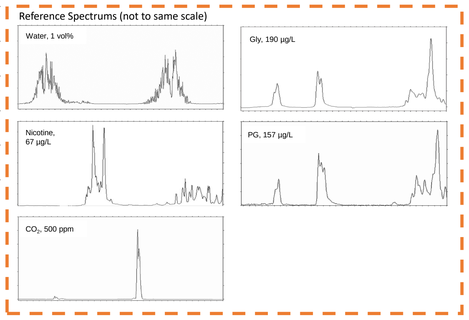
Sample cell	
Structure:	Multi-pass, fixed path length 5.0 m
Standard material:	100 % rhodium coated aluminium
Mirrors:	Fixed, protected gold coating
Volume:	0.4 liters
Connectors:	Inlet Swagelok 6 mm Outlet Swagelok 8 mm
Gaskets:	Viton® O-rings
Temperature:	180 °C, maximum
Window material:	BaF_2

The instrument selected for the real-time aerosol characterization is the Gasmet CX4000. The CX4000 is an industrial multicomponent gas analyzer for continuous application monitoring, such as continuous emission monitoring. The CX4000 works in the following steps:

1) The infrared (IR) source produces broadband IR radiation.
2) The IR radiation is modulated in the interferometer through an optical inverse Fourier transform.
3) The modulated IR radiation passes through the sample cell, which is heated up to 180˚C. The sample gas within the sample cell absorbs certain wavelengths of the IR radiation.
4) The detector detects the transmitted IR radiation.
5) The signal is digitized by an analogue to digital converter. The computer performs a mathematical Fourier transform on the digitized modulated signal, and a spectrum is obtained.

Software: Calcmet



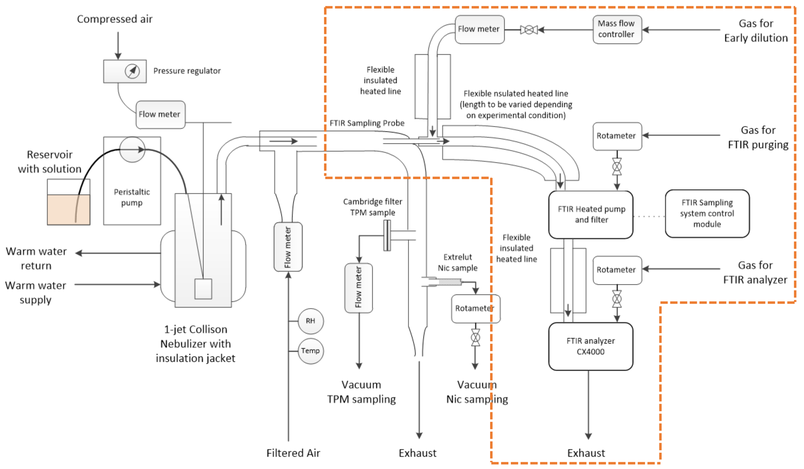


Analysis:

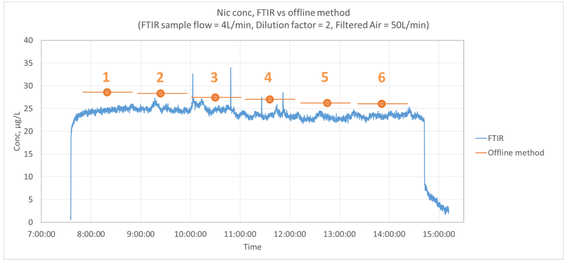
0.925 * Water 1 vol-%	=	**0.925 vol% Water**
0.762 * Nicotine 67 µg/L	=	**51.10 µg/L Nicotine**
0.809 * Gly 190 µg/L	=	**153.8 µg/L Gly**
1.791 * PG 157 µg/L	=	**281.6 µg/L PG**
0.765 * CO_2 500 ppm	=	**382.7 ppm CO_2**

The Calcmet software compares the actual spectrum generated from the CX4000 with a spectrum computed by assigning different weightage to reference spectra of pure compounds generated at different concentrations. An optimization procedure minimizes the difference between the actual and computed spectrum. When an optimized solution is obtained, the weightage assigned to the reference spectra is used to quantify the concentrations in the actual spectrum simultaneously.

Results – Factory Recommended Setup

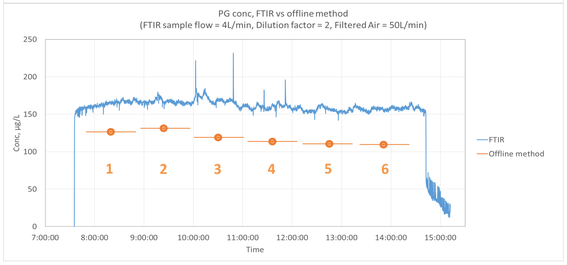


- Aerosol was generated from a solution containing nicotine, propylene glycol (PG), and glycerin (Gly) using a Collison nebulizer.
- Offline samples collected are:
  - Nicotine: Trapped using H2SO4 impregnated Extrelut® NT3 sorbent tube and analyzed using GC FID.
  - Gly and PG: Trapped on 44 mm glass fiber filter and analyzed using GC FID.
- Real-time (using FTIR) and offline samples were collected simultaneously and compared against each other.



Sample no.	Offline method, µg/L	FTIR, µg/L	Ratio FTIR : Offline method
1	28.60	24.62	0.86
2	28.32	24.93	0.88
3	27.45	24.98	0.91
4	27.02	23.59	0.87
5	26.22	22.95	0.88
6	26.05	23.40	0.90

Sample no.	Offline method, µg/L	FTIR, µg/L	Ratio FTIR : Offline method
1	205	234	1.14
2	208	234	1.13
3	190	263	1.39
4	180	233	1.29
5	178	228	1.29
6	177	230	1.30

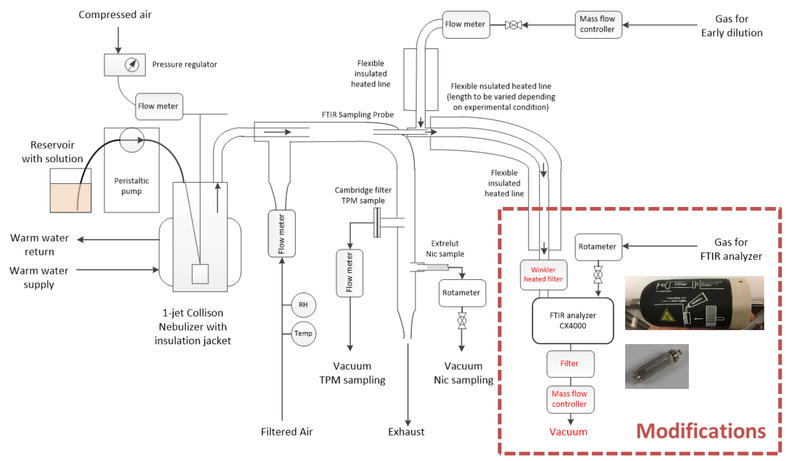


Sample no.	Offline method, µg/L	FTIR, µg/L	Ratio FTIR : Offline method
1	126	164	1.30
2	131	167	1.27
3	119	169	1.42
4	114	160	1.41
5	111	156	1.41
6	110	157	1.43

Observations:

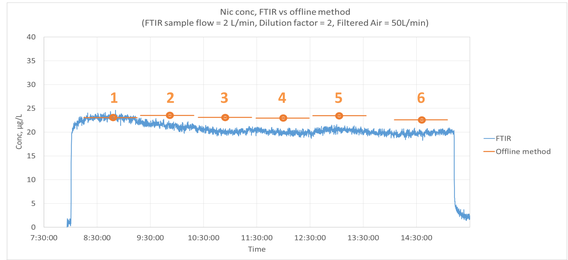
- FTIR results on average 12% lower than offline method for nicotine, up to 30% higher for Gly, and up to 40% higher for PG.
- Presence of concentration spikes due to sudden release of condensed aerosol within the heated pump and filter module.
- Nicotine and PG take longer to clear from the system.

Results – PMI Modified Setup



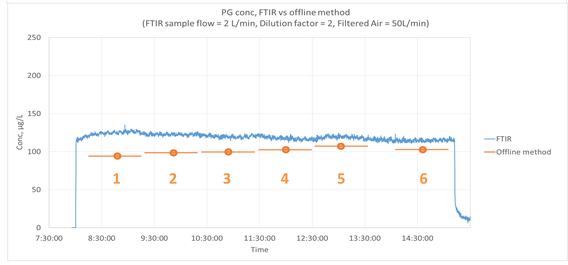
The following modifications were made to the setup to minimize the condensation of aerosol and, in this manner, to avoid the formation of concentration peaks during continuous analysis.

- Removal of the heated pump and filter module. A Winkler heated filter with a 2 µm metallic filter was installed before the CX4000 to protect the analyzer from nongaseous components in the sample.
- With the removal of the heated pump, the sample gas is drawn into the CX4000 using vacuum instead of being pushed into the CX4000. The sampling flow rate is controlled using a mass flow controller and allows adjustments to be made to the sampling flow rate.



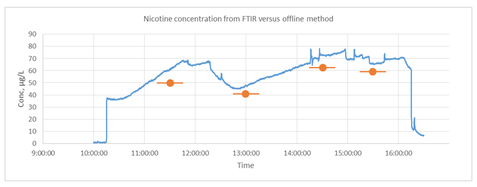
Sample no.	Offline method, µg/L	FTIR, µg/L	Ratio FTIR : Offline method
1	23.06	22.99	1.00
2	23.52	21.42	0.91
3	23.07	20.25	0.88
4	22.94	20.01	0.87
5	23.43	20.37	0.87
6	22.57	19.77	0.88

Sample no.	Offline method, µg/L	FTIR, µg/L	Ratio FTIR : Offline method
1	164	247	1.51
2	164	240	1.46
3	164	234	1.43
4	162	234	1.44
5	163	240	1.47
6	160	233	1.45

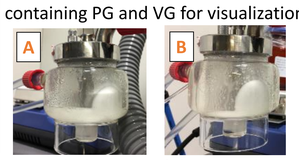


Sample no.	Offline method, µg/L	FTIR, µg/L	Ratio FTIR : Offline method
1	94	125	1.32
2	98	123	1.25
3	100	120	1.20
4	102	118	1.15
5	107	119	1.11
6	103	115	1.12

Application 1 – Influence of Solution Level on Nebulizer Efficiency

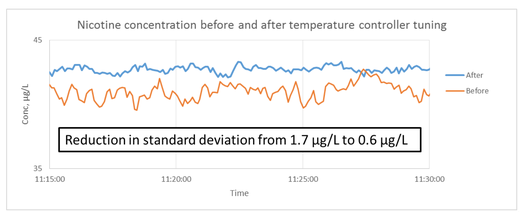


Pictures generated from solution containing PG and VG for visualization.



Aerosol was generated using a Collison nebulizer from a solution containing nicotine and phosphate-buffered saline. Offline methods for nicotine quantification showed unstable nicotine concentrations (orange dots). Real-time quantification using FTIR showed that the fluctuations were related to changes in the solution level within the nebulizer jar. At the beginning, the solution level tends to be high and causes more of the aerosol to be entrained in the solution (Picture A). As the solution is consumed, the level decreases, reducing the entrainment of aerosol material (Picture B) and increasing the aerosol concentration. When solution level gets too low, solution will be pumped to the nebulizer jar, and the cycle repeats.

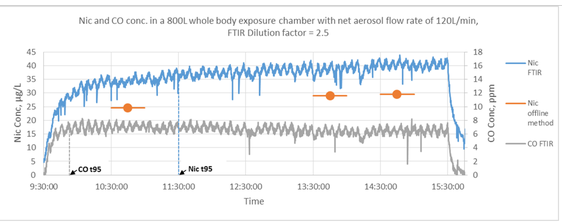
Application 2 – Verification of CAG Temperature Controller Configuration



Results from the FTIR showed the reduction in the standard deviation of the nicotine concentration in the aerosol before and after the tuning. Using offline methods, more samples will need to be collected to verify the effectiveness of the tuning.

Aerosol was generated using a Capillary Aerosol Generator (CAG) from a solution containing nicotine, PG, and vegetable glycerin (VG). Aerosol is generated from the CAG by first vaporizing the solution, pumped through a heated capillary, followed by condensation of the vaporized solution when mixed with air of a lower temperature. The stability of the temperature of the heated capillary has a direct impact on the consistency of the aerosol generated. The configurations of the temperature controller for the CAG were tuned and verified for effectiveness using real-time quantifications from the FTIR.

Application 3 – Estimation of Time to Equilibrium (t95)



Real-time quantifications of carbon monoxide and nicotine concentrations in a whole-body exposure chamber using the FTIR provided more accurate t95 values. The data also showed that t95 is related to the phase where the compound resides in the aerosol.

Discussions and Conclusions

The FTIR enables real-time quantification of multiple components in the aerosol generated for *in vivo* studies. The key advantage of the FTIR over offline methods is the generation of results in real time and simultaneous quantification of multiple components. This is particularly useful during the optimization of aerosol generation parameters and troubleshooting. Differences between results from FTIR and offline methods could be reduced by:

- Calibrating the FTIR with the sample being pulled through the analyzer using vacuum instead of being pushed through the FTIR.
- Adjusting the parameters and components used by the Calcmet program in the analysis.
- Improving the trap for PG and VG. It was found that there was ~10% breakthrough of PG from filter pads.

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Competing Financial Interest

Philip Morris International is the sole source of funding and sponsor of this project.