BrightSpec
Molecular Rotational Resonance Spectroscopy

Residual Solvent Analysis: Static headspace – FT-MRR spectroscopy

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Abstract

This note introduces a fast molecular spectroscopy technique for residual solvent analysis that utilizes FT-MRR (Fourier transform molecular rotational resonance). FT-MRR can be used to both identify and quantify volatiles in a mixture in less than a minute without chromatography. A simple, static headspace sampling method is used here to demonstrate FT-MRR for residual solvent analysis.

Introduction

The global pharmaceutical industry adopts ICH guidelines that limit residual solvent content.[1] The United States Pharmacopeial Convention (USP) enforces the ICH guidelines with a gas chromatography (GC) analytical method that can take hours to complete (USP 467).[2] Although GC methods are adaptable to address a wide range of chemical mixtures, the chemical separation step limits the throughput capability, and frequent chemical calibration is required. GC is costly in terms of time, technical labor, consumables, and the number of instruments required to meet throughput requirements. They are not compatible with the process analytical technology (PAT) initiative to incorporate fast methods for process analysis.[3]

With typical measurement times of 10 seconds per analyte to reach regulated detection levels (0.005 – 0.5% by mass of solid), FT-MRR offers a fast solution for solvent analysis. The intrinsic advantage of FT-MRR for chemical analysis is the operational simplicity enabled by the absolute molecular structure specificity and the high resolution of the fingerprint. In combination with a double resonance identity verification technique, matrix interference and cross-talk between analytes is not a concern for FT-MRR. As a result, chromatography is not required for mixture analysis. One FT-MRR spectrometer can detect a wide range of volatiles with the subset chosen by the user and easily modified. Room temperature FT-MRR is most sensitive to small, polar volatiles (< 150 amu) that generally make up the list of commodity chemicals and common solvents for chemical synthesis. These characteristics also make FT-MRR capable of quantitative water analysis.

Experimental

The static headspace FT-MRR method for residual solvent analysis was developed using ethanol solutions in water and in DMAC in order to benchmark the basic performance. To prepare a headspace sample, a dry 27 mL headspace vial was sealed with a rubber septum and evacuated via needle as a part of the spectrometer sampling module. Using a syringe, 1 mL of solution was injected into the vial and allowed to vaporize/equilibrate for 2 minutes before transfer to the measurement cell. The pressure after transferring the sample is typically between 1-5 mTorr. See Fig. 1 and Table 1 for the measurement cycle description.

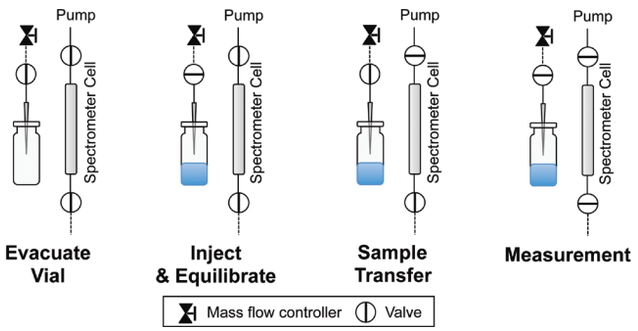

Fig 1: *Mass flow control sample transfer.*

Table 1: Measurement cycle time

Evacuate vial	2 minutes
Inject and equilibrate	2 minutes
Transfer headspace sample	5 seconds
Measure FT-MRR spectrum	10 - 40 sec
Total	~ 5 minutes

A linear correlation analysis was performed using serial dilutions of ethanol in water and in dimethylacetamide (DMAC) across a concentration range of 15 – 800 µg/mL (or 0.15 - 8% by mass of dissolved solid according to USP 467). The measurement chamber was maintained at 60 °C (to reduce carry-over effects) and pressurized with 5 mTorr of sample (15 µL STP gas). The FT-MRR ethanol signal intensity at 281279.8 MHz was recorded for each sample after 10 seconds of signal averaging. Signal intensity is calibrated against an internal power curve that is automatically generated by the spectrometer.

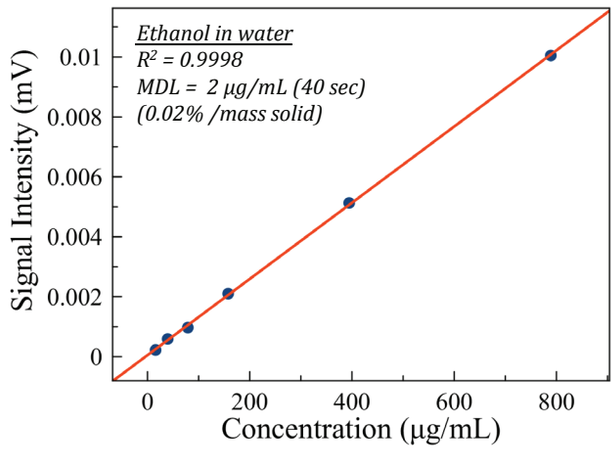

Fig 2: *Results for ethanol/water headspace*

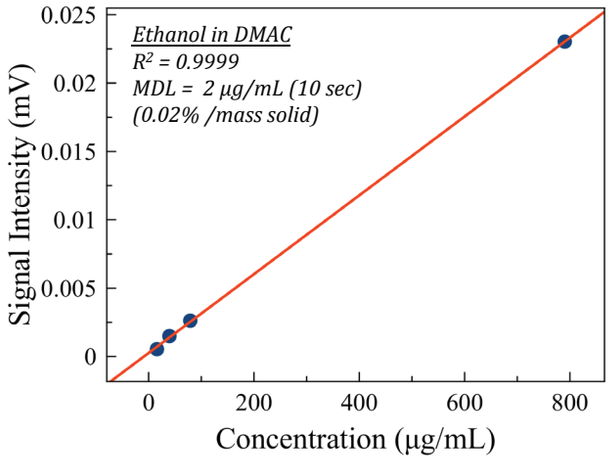

Fig 3: *Results for ethanol/DMAC headspace*

Results

The linear correlation analyses are displayed in Fig. 2 (for water solubles analysis) and Fig. 3 (for water insoluble analysis). Both results show a linear correlation (R^2) of greater than 99.95% and detection levels of 0.02% without having to utilize headspace enhancement techniques (heating and salt addition) or purge and trap methods. The detection limits are reported in terms of percent mass of solid in a solution prepared at a concentration of 10 mg/mL per USP 467. Since only a milliliter of solution is used for this method, only 10 mg of solid sample are required to run a single analysis. The regulated levels for solvent content vary from 0.005 – 0.5% depending on the solvent. With detection levels of 0.02%, FT-MRR meets the quantitative performance required to monitor ethanol, a class III solvent limited to < 0.5%.

Even in the presence of a DMAC or water matrix, FT-MRR spectra are sufficiently resolved to identify and quantify a mixture of analytes at low concentration. The simple, bench top method for headspace analysis presented here has a sample-to-sample cycle time of approximately 5 minutes. With a spectrometer analysis time of less than a minute, the throughput advantage can be improved with auto sampling techniques. For in-line drying analysis, a vacuum line can be sampled directly for FT-MRR analysis and results can be reported every 10 seconds for each analyte of interest.

Conclusions

The performance of the static headspace FT-MRR method using dilute solutions of ethanol in water and in DMAC meets the quantitative need for process monitoring of residual solvent below 0.05% and the 5 minute overall cycle time has a throughput advantage over GC methods that can take hours. The primary advantages of FT-MRR for process analysis are derived from the high-speed, software controlled FT-MRR spectrometer and the direct analysis capability. The advantages include:

- Fast, Quantitative analysis
- User selectable detection targets
- Simple operation
- Free from carrier gases or cryogens
- Free from chromatography or chemometrics

BrightSpec FT-MRR instruments bring new, direct measurement capabilities for analytical method development and process analysis in pharmaceutical manufacturing. Since FT-MRR is broadly applicable to volatiles analyses, other compatible applications for FT-MRR include, residual solvent analysis by TGA, potential genotoxic impurity analysis (PGI), leachables/extractables analysis, drying analysis, and water analysis.

1. ICH. Impurities: Guideline for Residual Solvent Q3C(R5), February 2011.

2. USP-NF. General Chapter 467: Residual Solvents, 2007.

3. U.S. Food and Drug Administration, Guidance for Industry, PAT-A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance, September 2004