Fast Residual Solvent Analysis (USP <467>) by MRR Spectroscopy

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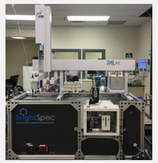
Motivation

The United States Pharmacopeia (USP) sets standards for permissible levels of residual solvents in pharmaceutical products. Current standard GC-FID methods to quantify these solvents at USP <467> limits can take between 60-90 minutes for a single measurement. Here we apply FT-MRR spectroscopy as an alternative quantification technique with simpler method development and faster cycle times (~8-12 minutes).

Why FT-MRR

Fourier **T**ransform – **M**olecular **R**otational **R**esonance (FT-MRR) produces unique, high resolution chemical fingerprints. Applications include impurities in gas mixtures, volatile impurities in pharmaceutical products, and structural identification of chiral molecules.



Advantages:

- Unmatched chemical specificity in complex matrices
- Direct analysis – no columns or chromatography
- Measurement and method development much faster than GC
- Automated measurements, on-line capable
- Easily identifies and quantitates all polar, volatile components

Complete measurement cycle	
Method Step	**Time**
Evacuate/ Clean Vial	5 min
Inject/equilibrate	2 min
Transfer headspace	5 sec
Measure	10 sec
Flush System	5 min
Total cycle time	12 min

Method Development

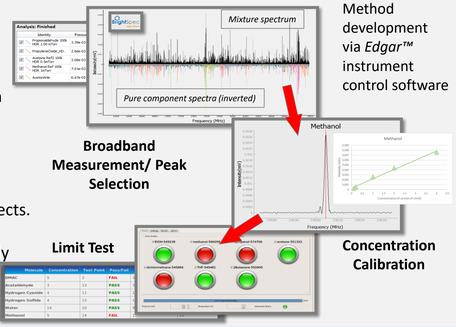
1. Broadband measurement and line selection

Automated composition analysis software IDs all MRR-amenable analytes and determines strong, clean lines of each analyte, even in very complex multi-component mixtures.

2. Standard Calibration

Characterizes instrument response to analyte concentration, headspace partitioning, and matrix effects.

After these steps are completed, the user can routinely run targeted quantification and/or limit tests to determine all selected individual analyte levels in unknown samples at once.



Method development via *Edgar*™ instrument control software

USP <467> Standard

To evaluate the technique for its applicability to residual solvent analysis, a mixture of United States Pharmacopeia <467> Class 2 (Mix A) solvents, diluted in water, was analyzed using the BrightSpec ONE static headspace method:

Procedure:

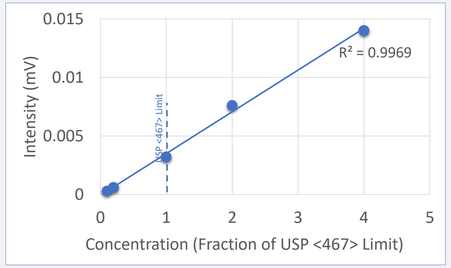
1. Broadband spectrum of mixture measured and used to identify clean, intense peaks for each analyte in complicated, multi-component spectrum
2. Mixture diluted down around USP <467> limits in water and analyzed at varying concentrations.

Conclusion:

- FT-MRR is capable of quantifying polar USP <467> solvents at 2-4000x lower levels than regulatory detection limits

FT-MRR Sensitivity for USP <467> Class 2 Mix A in Water (5 second measurement per analyte)		
Analyte	**USP 467 limit (mg/L)**	**Method LDL (mg/L)**
Acetonitrile	4.1	0.0096
Chlorobenzene	3.6	2.3
Cis-1,2-Dichloroethene	9.34	0.18
Dichloromethane	6	0.079
Methanol	30	0.69
Tetrahydrofuran	7.2	0.92

USP 467 limit values assume a daily product dose of 10 g/day and standard sample dilution methods (10 mg product per mL of diluent).



Calibration curve of *cis*-1,2-dichloroethene from 0.1x to 4x the required USP 467 detection limit (0.93 – 36 mg/L). The detection limit for this analyte is 0.18 mg/L.

Pharmaceutical Test Case: IV Solution Analysis

A spiked analysis was performed using the BrightSpec ONE static headspace method on an IV solution from a top-25 pharmaceutical company to quantify ethanol, methanol, and isopropanol:

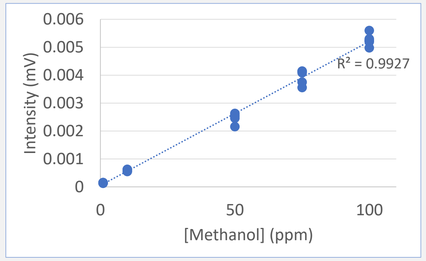
Procedure:

1. Reconstituted samples mixed and measured; Broadband spectrum used to identify clean peaks for targeted analysis.
2. To validate the method, we prepared standards at several concentrations ranging from 0 – 100 ppm of each analyte.
3. Experimental matrix spiked from 0 – 100 ppm and measured to quantify analytes of interest.

Conclusion:

- FT-MRR demonstrates detection and quantitation limits for ethanol, methanol, and isopropanol in a real Pharmaceutical IV matrix that are below required limits (10 mg/L)

IV solution was spiked and measured directly



◀ FT-MRR headspace analysis maintains linearity over 6 concentration gradient measurements

Limits for Pharmaceutical Test Case Experiment		
Impurity	**Amount (mg/L)**	**LDL (mg/L)**
Methanol	2.7	0.6
Ethanol	11.4	1.0
2-Propanol	< 6	6

▲ In IV solution, BrightSpec Method demonstrates quantitation below regulatory limits

Conclusions

1. FT-MRR spectroscopy provides a rapid, sensitive, convenient, and powerful alternative to GC in residual solvent analysis applications, with advantages including 5x faster cycle time than conventional USP headspace method, 5-10x faster method development, unmatched chemical specificity, no consumables, and less expensive instrumentation.
2. With simple 2-step method development, the BrightSpec ONE FT-MRR headspace method demonstrated linearity and sensitivity to directly quantify 6 USP<467> residual solvents below regulatory limits in water.
3. The BrightSpec ONE FT-MRR headspace enables accurate quantitation of ethanol, methanol, and isopropanol in a real pharmaceutical IV solution matrix below desired regulatory limits.

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