BrightSpec
Molecular Rotational Resonance Spectroscopy

Characterization of Volatile Impurities in Solid Pharmaceutical Products by FT-MRR Thermal Evolution

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Highlights

- Thermal evolution provides simple ID and quantification of small volatile impurities in solid products, without chromatography.
- FT-MRR can characterize both known and unknown impurities using the BrightSpec Spectral Library.
- Typical detection limits are 100 ppb or less.

Introduction

Identification and quantification of small molecular weight impurities in solid products is a need at all stages of pharmaceutical manufacturing, starting at the R&D stage and going through quality control. These impurities might include residual solvents, mutagenic impurities, and other products that at high concentrations might impede the drug formulation process or pose a public health risk. Also, some of the impurities may be unintended side products of the manufacturing process and therefore identifying the observed compounds may be a significant challenge requiring multiple analytical techniques.

Fourier Transform Molecular Rotational Resonance (FT-MRR) spectroscopy is extremely well suited to tackle the challenges of unknown identification and quantification. Molecules with permanent dipole moments have characteristic fingerprint spectra consisting of highly resolved frequencies and a relative intensity pattern, giving an extraordinarily low rate of false positives and the capability for analyzing multi-component mixtures.

In this Application Note, we describe the FT-MRR Thermal Evolution analysis, by which any impurities in the FT-MRR niche (volatile, polar compounds with masses 150 amu or less) that are liberated from the product can be rapidly identified and quantified with no need for solvents or carrier gases (other than nitrogen gas used for cleaning the system between runs). Since the typical minimum detectable quantity for the BrightSpec instrument is 0.1-1 ng or less, impurities at the ppb level are measurable using this method from a 10-100 mg sample.

Methods

The FT-MRR thermal evolution method is performed using the BrightSpec One spectrometer shown in Figure 1 with headspace module attached. A small amount of the product under study (typically between 10-100 mg) is weighed directly into a standard 20 mL headspace vial. The vial is crimp-capped and briefly evacuated to remove the ambient atmosphere in the vial. Then, the bottom of the vial is heated to liberate volatile impurities. Typically the sample is heated past its melting point, although often some impurities are released before melting. The sides of the vial are kept cooler so that nonvolatile components (including the API) condense before transfer to the spectrometer.

After sufficient equilibration time, a vacuum loop transfer mechanism is used to transfer a fixed volume of the vial headspace into the FT-MRR sample cell for analysis. Since most products have volatiles content (including water) less than 1%, the pressure delivered to the vacuum chamber is 10 mTorr or less. This allows a collision-free environment for the FT-MRR measurement, which is necessary to maintain high resolution.

Fig 1: *BrightSpec One FT-MRR spectrometer with headspace module used for thermal evolution analyses.*

Results

An impurities analysis of commercially obtained diphenhydramine hydrochloride (DPH) is presented in Fig. 2. This sample is a secondary standard traceable to USP and European Pharmacopeia, obtained from Sigma-Aldrich. From heating 50 mg of solid product, a strong signature attributable to ethanol is observed. We measured both a broadband spectrum (revealing all impurities with sufficient intensity) as well as targeted spectra of a number of common Class 2 and Class 3 regulated residual solvents. The BrightSpec Spectral Library (~200 species as of February 2017) is used to screen measured spectra for identifications.

For each identified impurity, the partial pressure in the spectrometer is determined through comparison to the experimental spectral library and is accurate to within 15%. This partial pressure is directly relatable to the impurity's partial pressure in the vial, and therefore to the mass of the impurity in the original sample. This assumes complete liberation of the volatile impurity, which can be directly assessed by increasing the temperature, equilibration time, or both, and verifying that the impurity is not further liberated. Additionally, decomposition products (common ones include sulfur dioxide and formaldehyde) are sometimes observed and can usually be distinguished on the basis of their temperature liberation profile. In this case, we observed a weak signal of chloromethane at a temperature of 225°C that is believed to be a decomposition product.

Table 1 shows a comparison of the results of the thermal evolution method to the same sample by static headspace FT-MRR, where the sample is diluted in water and analyzed through an equilibrium headspace method. We highlight two key points in this table:

(1) the headspace method, by which quantification is performed through an external standard calibration curve, gives agreeable results with thermal evolution within measurement errors (n=3 relative standard deviations are 10% for the solution headspace, and 20% for solids headspace);

(2) for the same product, thermal evolution yields a lower detection limit by a factor of ~200 with roughly the same amount of sample consumed (within a factor of 2).

The difference in sensitivity is due to the fact that in thermal evolution, the dominant components of the powder have negligible vapor pressure and so nearly complete separation of the volatile analytes can be performed; on the other hand, in an equilibrium headspace measurement, ethanol is only moderately concentrated in the headspace over a water solution. The solutions headspace does have better repeatability at this time; work is underway to automate the vial temperature control to improve these results.

Conclusion

FT-MRR's key advantage over other techniques for volatile impurities analysis is its absolute specificity and resolution, which eliminates the need to separate analytes from each other via chromatography in order to perform analyses. The thermal evolution method described in this white paper captures these advantages to yield a simple and sensitive method for providing quantitative identifications of volatile impurities in dry powders. By streamlining method development, FT-MRR instruments designed by BrightSpec can enable rapid chemical insights into pharmaceutical manufacturing processes.

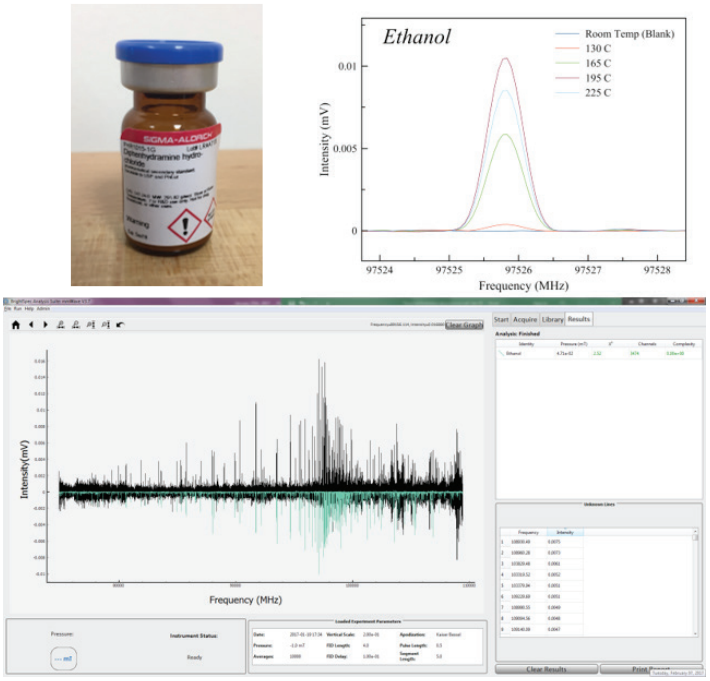

Figure 2: *Thermal evolution analysis of diphenhydramine hydrochloride (top left). Top right: signal of evolved ethanol in relation to vial temperature. Bottom: broadband spectrum showing a clear match to the FT-MRR signature of ethanol.*

Table 1: *Comparison of ethanol quantification in DPH by thermal evolution and static headspace.*

Thermal Evolution				**Static Solution Headspace**			
Trial #	Solid Wt. (mg)	EtOH Signal (μV)	EtOH Conc. in DPH (ppmw)	Trial #	DPH Conc. (mg/mL)	EtOH Signal (μV)	EtOH Conc. in DPH (ppmw)
1t	50	2.8	55	1s	104.2	0.049	72.6
2t	48	3.4	69	2s	105.0	0.060	88.4
3t	54	4.6	84	3s	102.5	0.052	78.4
		Average (ppm)	**70.0**			**Average (ppm)**	**79.8**
		RSD (%)	**20%**			**RSD (%)**	**10%**
		MDL (ppm)	**<0.1**			**MDL (ppm)**	**20**

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