Molecular Rotational Resonance Spectroscopy: An Agile Solution for Residual Analysis in Pharmaceutical Products

Overview

Comprehensive assessments of leftover solvent levels in early-process chemistry can help expedite process development. This makes residual solvent analysis, where analytical techniques are leveraged to scrutinize and quantify the presence of trace solvents throughout manufacturing, critical for successfully bringing a drug to market. Although gas chromatography is a cornerstone in this effort, the technique is plagued by time-intensive and complex method development and is prone to error from laborious hands-on time. Thus, your development timelines can face weeks of delays and the unnecessary use of valuable resources.

The pharmaceutical industry has struggled to quickly and efficiently confirm and quantify problematic residual solvents without time-consuming method optimization—until now. Enter BrightSpec's isoMRR™ platform, the first commercially available molecular rotational resonance (MRR) spectroscopy instrument. Powered by headspace MRR, this technique is packaged in automated instrument form, offering a straightforward, breakthrough approach that gets you identity and quantitation data in a single measurement. No more tedious method development, drawn-out data analysis, and costly consumables. The isoMRR™ ensures unprecedented efficiency, allowing developers to navigate their manufacturing process with agility and ease. In this application note, we demonstrate the analytical performance of this novel platform, including method selectivity, repeatability, and performance in the drug substance.

The isoMRR™ Platform: A New Era in MRR

For decades, chemical analysis techniques in the pharmaceutical industry have remained mostly unchanged, mainly relying on chromatography-based systems. But MRR spectroscopy on the isoMRR™ platform is changing the game. Now, you can streamline lab operations and cut costs by reducing the need for expensive consumables and frequent requalification of new batches as with traditional methods. For starters, you'll get clear and precise compound information without the complexity of chromatography. The isoMRR™ technology amalgamates the strengths of nuclear magnetic resonance (NMR) and mass spectrometry (MS) – structure and speed, respectively – producing quick and complete structural characterization with unmatched specificity and equivalent sensitivity.

MRR Method Mastery

MRR uses microwave radiation to analyze vapor-phase components, resulting in unique three-dimensional structural fingerprints—making it easier to identify and quantify compounds, including isomers, within mixtures, without requiring chemical separation. The volatilized analytes travel through a heated line into a vacuum chamber creating a supersonic expansion, using high-purity neon as a carrier gas. This process rotationally cools the sample, boosting the MRR signal and enabling highly selective and quantitative analysis. With validated libraries of spectral signatures, you'll proceed confidently, knowing your results are consistent and reliable. The isoMRR™ technology meets the high standard for analytical performance in the pharmaceutical industry. This method covers a wide range of solvents and volatile impurities and excels with Class 2 Mixture C solvents, challenging due to their low volatility. The workflow (Figure 1) is easily adaptable to the unique needs of each analysis and supported by robust methods that are transferable across labs.

BrightSpec

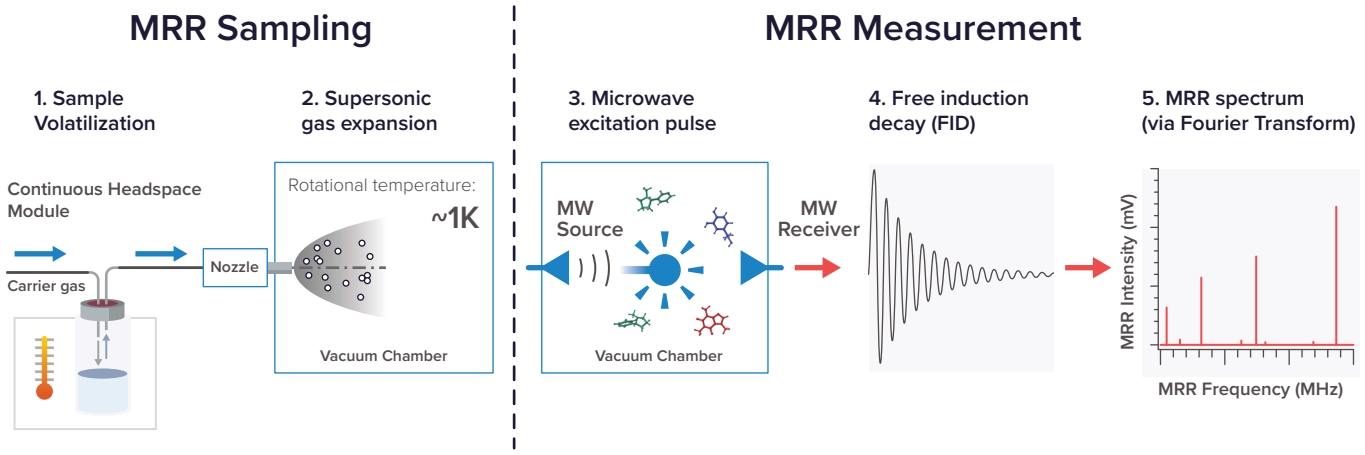

Figure 1. Schematic diagram of the continuous headspace isoMRR™ technology.

Results

Spectral Fingerprints: Unmatched Selectivity with MRR

MRR spectrometry is highly selective, with a typical full width at half-maximum (FWHM) for an individual transition being about 0.1 MHZ to 0.2 MHz and a broad instrument frequency range of 5000 MHz to 18500 MHz, resulting in approximately 10^5 measurement channels. Depending on the molecule's size and geometry, it can have anywhere from a few to several hundred detection frequencies, all of which are very narrow. This allows for the identification of unique, overlap-free detection frequencies for individual species, even within complex multi-component mixtures.

The highly selective nature of MRR spectroscopy is evident in its ability to distinguish between five diverse residual solvents from different the USP Class 2 mixtures, namely methanol (Class 2 mixture A), nitromethane (Class 2 mixture B), and 2-methoxyethanol and 2-ethoxyethanol (both Class 2 mixture C). Each spectrum is characterized by a distinct peak at a specific frequency, indicating the unique rotational transition for each compound.

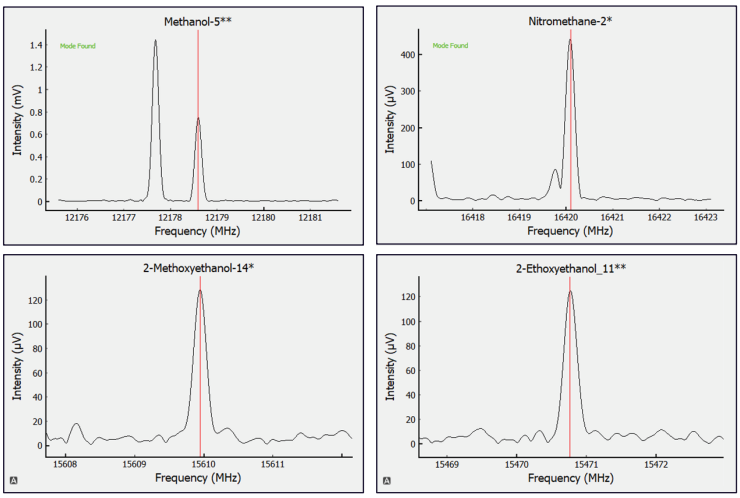

Figure 2. MRR selectively distinguishes between different compounds. The isoMRR™'s ultra-high resolution fully distinguishes spectral peaks from each other and the matrix components. BrightSpec has verified all frequencies shown and has made them available in the solvent library. Note that the additional peak in the methanol spectra is due to a non-molecular signal that can be identified and eliminated. The "shoulder peak" observed in the nitromethane spectrum is part of the peak and results from nitrogen splitting.

Nitromethane's high-intensity peak at 16420 MHz further demonstrates the isoMRR™'s capability to distinguish even closely related compounds clearly. Additionally, the unique spectral signatures of 2-methoxyethanol and 2-ethoxyethanol at 15610 MHz and 15471 MHz underscore the technique's superior selectivity in pinpointing specific molecular structures.

Intra-assay Repeatability Underpins MRR Accuracy

The analytical range of an MRR instrument is a crucial parameter that determines the accuracy and reliability of measurements within specified concentration limits. This range is often assessed by evaluating intra-assay repeatability percentages, which indicate the consistency of the instrument's performance when measuring the same sample multiple times under identical conditions. To that end, methanol has the best repeatability at 6.11% (Table 1), suggesting high precision in measurements within the confirmed linear range of 0 µg/mL to 150 µg/mL. Nitromethane (9.23%) is relatively good, with measurements consistent within the confirmed linear range of 0 µg/mL to 2.5 µg/mL. 2-methoxyethanol has a repeatability values of 13.96%, suggesting some variability within the confirmed linear range of 0 µg/mL to 20.5 µg/mL. 2-ethoxyethanol has the highest repeatability percentage at 19.03% (Table 1).

Methanol exhibits the highest precision and consistency in measurements, while 2-ethoxyethanol shows the highest variability and lowest precision. The linearity (R^2 values) for all solvents is generally high, indicating good linear relationships within the confirmed ranges.

Residual Solvent	Linear Range (µg/mL)	Linearity (R^2)	Repeatability (%)
Methanol	0–150	0.9971	6.1
Nitromethane	0–2.5	0.9983	9.2
2-Methoxyethanol	0–2.5	0.9830	13.9
2-Ethoxyethanol	0–8	0.9889	19

Table 1. The analytical range and repeatability of the isoMRR™ spectroscopy using various solvents from the USP Class 2 Mixture C designation.

Unwavering Linearity in Drug Substance

A linear assay response allows for reliable comparisons between solvents, ensuring that observed effects are due to the drug and not analytical inconsistencies. To ensure that a measurement of drug substance concentration accurately reflects its actual quantity, dose-response experiments were performed, and assay linearity was assessed (Figure 3). Data points for low to high concentrations of residual solvents (0–150 µg/mL) were taken from samples of acetaminophen, aspirin, and ibuprofen diluted in ionic liquid and compared with no substance controls. The linear relationship at low concentrations further supports the assay's sensitivity, implying that even small quantities of the analytes can be detected and quantified accurately.

The data points for residual solvents in acetaminophen, aspirin, and ibuprofen are closely aligned with the linear regression line (Figure 3, R^2 =0.997), and the isoMRR™ maintains its linearity and accuracy in the presence of different drug products. Moreover, the consistency of the response between substances means the matrix (the solution in which the drugs are dissolved) does not interfere with the MRR measurements, allowing for precise and reliable

quantification. The sensitivity is sufficient to detect and quantify low concentrations, suggesting a favorable LOD and LOQ. These data confirm the isoMRR™'s applicability to reliably analyzing drug products in a matrix without interference.

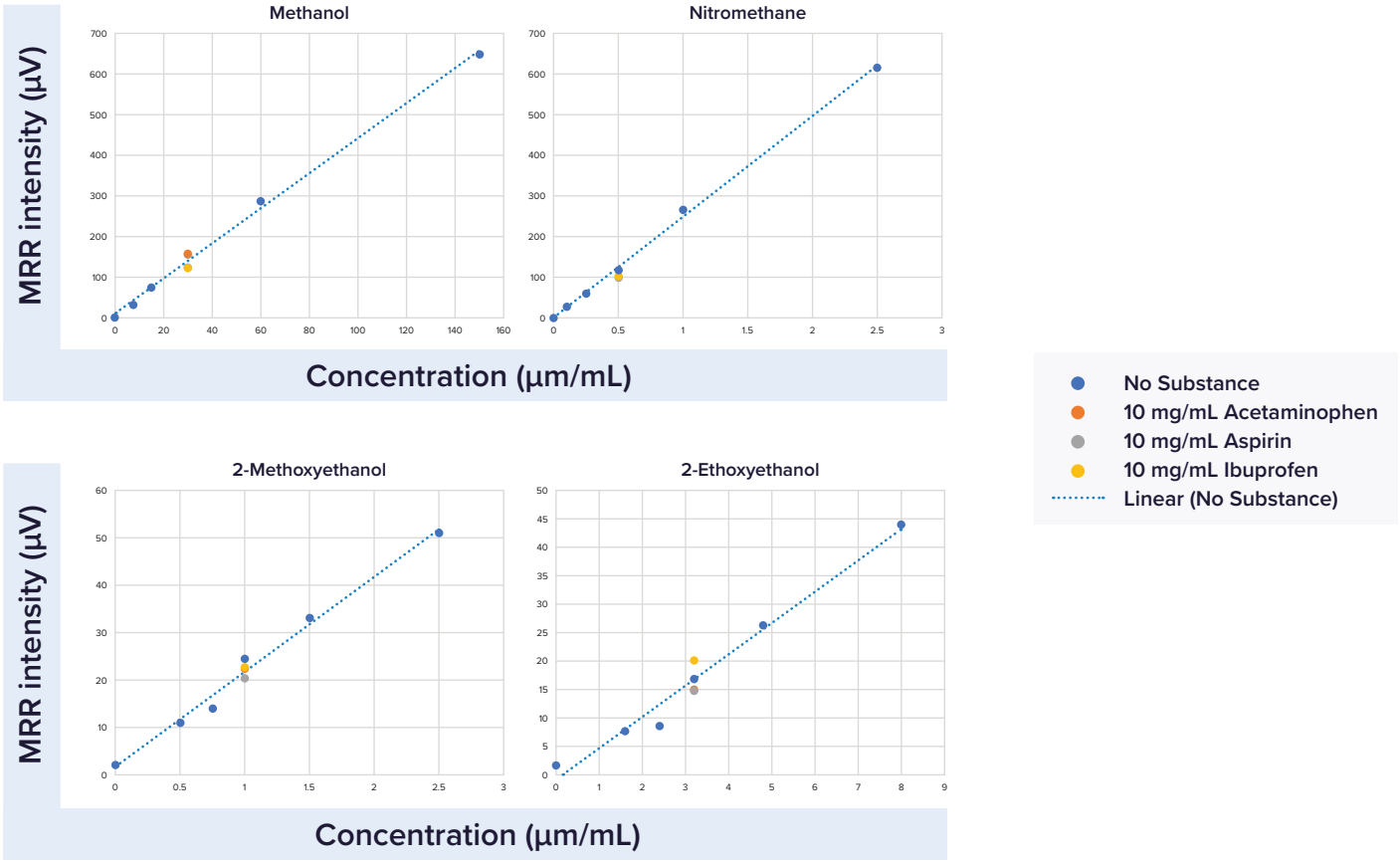

Figure 3. Relationship between MRR intensity (µV) and concentration (µg/mL) for various residual solvents in drug substances. The linear regression's high R^2 value (0.997) indicates an excellent linear correlation, suggesting that the isoMRR™ can reliably quantify the concentration of the substances over the tested range.

Demonstrating Percent Recovery in Drug Substance

Accurate percent recovery ensures the reliability of experimental results, indicating how much of the residual solvent is effectively recovered and detected from the sample. High percent recovery rates affirm the precision of the analysis, ensuring the safety and efficacy of pharmaceutical products. Recovery rates for methanol, nitromethane, 2-methoxymethanol, and 2-ethoxymethanol were assessed across three drug substances: acetaminophen, aspirin, and ibuprofen (Table 2).

Recovery rates for methanol and 2-methoxyethanol were excellent in each matrix, with all close to 100%. The lowest recovery rates were observed for nitromethane (79.42%, 82.44%, 86.11%) across the three drug substances, and 2-ethoxyethanol showed the most variable recovery (94.97%, 103.50%, 117.59%), suggesting the matrix may affect the recovery efficiency. Acceptable recovery is within the 80% to 120% range, and all solvents in the specified substances met these conditions. This analysis highlights the importance of validating the recovery efficiency for each residual solvent in different drug substances to ensure accurate quantification.

Residual Solvent	Acetaminophen (%)	Aspirin (%)	Ibuprofen (%)
Methanol	97.3	91.5	92.3
Nitromethane	86.1	82.4	79.4
2-Methoxyethanol	106.7	106.9	106.4
2-Ethoxyethanol	117.6	95	103.5

Table 2. Recovery rates of various residual solvents across three drug substances: acetaminophen, aspirin, and ibuprofen.

Concluding Remarks

The isoMRR™ platform, utilizing MRR spectroscopy, presents a momentous advancement in residual solvent analysis for pharmaceutical products. The innovative technology addresses longstanding challenges in the industry, providing a rapid, accurate, and highly selective method for identifying and quantifying residual solvents without the extensive method development required by traditional gas chromatography. The data presented in this application note demonstrate the isoMRR™'s exceptional performance in terms of method selectivity, repeatability, and linearity, as well as its robustness across various drug substances. By significantly reducing hands-on time and simplifying the analytical process, the isoMRR™ platform enhances operational efficiency, ensuring faster and more reliable results. It is a breakthrough, as it not only streamlines the workflow but offers a more sustainable and cost-effective solution, paving the way for its widespread adoption in pharmaceutical manufacturing and quality control.

BrightSpec, Inc.
770 Harris Street Suite 104b
Charlottesville, Virginia 22903