Tracking Ethylene Oxide and Acetaldehyde in PEG-3350

How Molecular Rotational Resonance Spectroscopy Outpaces Gas Chromatography

Overview

Polyethylene Glycol (PEG) is a cornerstone excipient across pharmaceuticals, consumer products, and food. Its versatility comes from its solubility, stability, and generally straightforward use in formulations. Though for higher-molecular-weight grades like PEG-3350, the material's viscosity—which makes it effective in laxatives, ointments, and tablets—also makes it challenging to handle in analytical workflows. This complexity further compounds contamination risk, with residual ethylene oxide (EtO) and acetaldehyde having triggered recalls and heightened regulatory scrutiny. Because EtO is flagged as a Group 1 human carcinogen and acetaldehyde as Group 2B, even trace levels raise red flags for compliance, patient safety, and trust.

Gas chromatography-mass spectrometry (GC-MS) is the regulatory mainstay for EtO and acetaldehyde detection. But its application to PEG-3350 presents well-known challenges: viscous matrices that demand dilution, extra prep, and meticulous handling, all while throughput slows and variability creeps in. As regulators push for container-by-container testing, those inefficiencies are getting harder to justify.

Molecular rotational resonance (MRR) spectroscopy is the smart alternative. Instead of wrestling with tedious prep, you can measure EtO and acetaldehyde directly in PEG-3350. The workflow is straightforward, and this application note demonstrates that the results are clear, with sensitivity meeting regulatory standards without any compromise.

Clear Gains with Clear Signals

MRR simplifies impurity testing in PEG-3350 by cutting out the extra steps that slow down conventional approaches. Instead of wrestling with injections and complex method setup, MRR uses headspace sampling to analyze samples directly and efficiently. The BrightSpec isoMRR™ platform delivers clear spectral fingerprints for EtO and acetaldehyde, reducing ambiguity and shortening the path to results. Runs are quick—typically less than ten minutes per vial—with the ability to process multiple samples in parallel. This combination of speed, clarity, and minimal preparation makes MRR a practical alternative to GC-MS when accuracy and throughput both matter (**Table 1**).

	MRR	GC-MS
Method Complexity	Validated spectra provide unambiguous EtO and acetaldehyde detection with minimal setup.	Requires matrix-specific method development to separate analytes from PEG, increasing time and operator effort.
Sample Handling	Headspace sampling requires no direct injection, making it well-suited for challenging matrices.	Direct injection is required, making it difficult to work with challenging matrices.
Specificity and Speed	Quick screening with direct, specific identification of EtO and acetaldehyde.	Separating EtO and acetaldehyde from other volatiles demands careful optimization, lengthening run times.
Sample Preparation	EtO and acetaldehyde in PEG-3350 can be measured directly, with no extensive prep.	Requires dilution with methanol for injection, along with filtration to remove any particulates.

Table 1. **Comparison of MRR and GC for EtO and acetaldehyde detection in PEG-3350.** MRR enables direct measurement of EtO and acetaldehyde in PEG-3350 with minimal preparation, whereas GC requires complex method development, direct injection, and extensive sample handling.

BrightSpec

Methods

Sample Preparation

PEG-3350 stock solutions were prepared at 100 mg/mL in formamide. Calibration curves were generated by spiking these solutions with known concentrations of EtO and acetaldehyde to demonstrate linearity. No derivatization was performed. Approximately 1 mL of each calibration solution was transferred into a 20 mL headspace vial and loaded into the autosampler.

Measurement Conditions

- Headspace equilibration: 10 min (up to 8 samples simultaneously)
- EtO measurement: 60 s at 11,385.91 MHz, and 45 °C headspace temperature
- Acetaldehyde measurement: 40 s at 8,243.47 MHz, and 80 °C headspace temperature
- Automated vial replacement ensures continuous operation without downtime

Results

Strong calibration performance is central to showing that an analytical method can deliver reliable quantitation across the required range. In **Figure 1**, calibration standards were prepared by spiking PEG-3350 solutions with known amounts of EtO and acetaldehyde, enabling direct evaluation of method response. The resulting curves show a clear linear relationship between concentration and MRR signal ($R^2 > 0.99$), highlighting the precision and reproducibility of the BrightSpec isoMRR platform. That kind of linearity is especially important when regulatory acceptance depends on accurate detection of impurities at trace levels. After all, even small deviations can carry big compliance and safety consequences, underscoring the importance of methods like MRR that achieve both regulatory confidence and real efficiency.

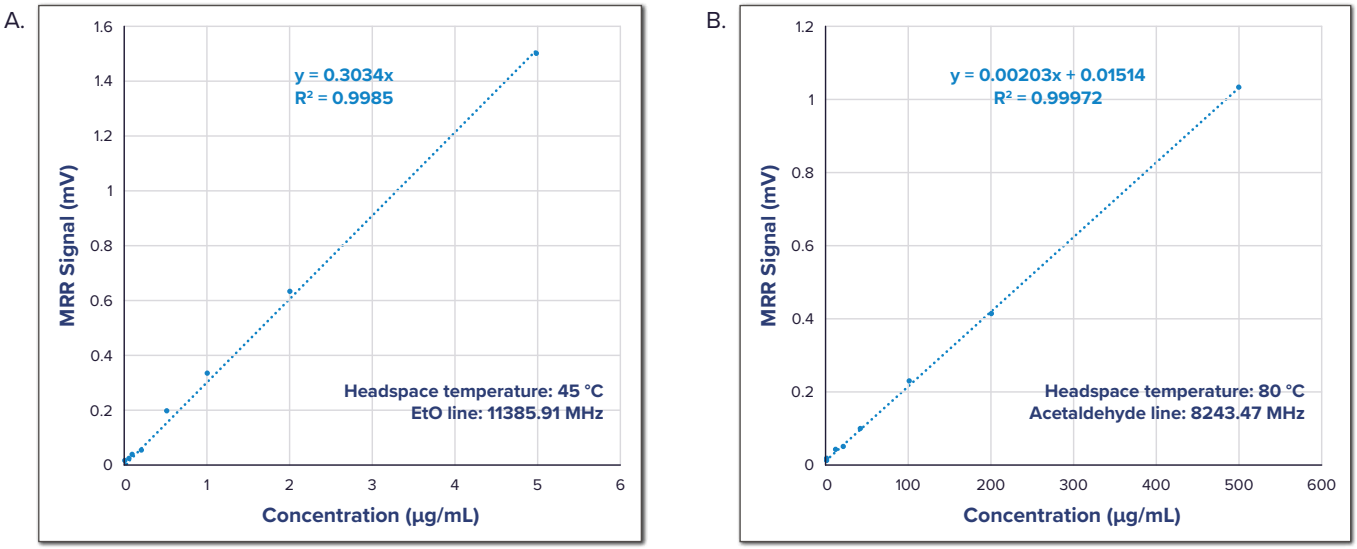

Figure 1. Calibration curves for EtO and acetaldehyde in PEG-3350 by headspace-MRR. Calibration plots demonstrate linear response of MRR signal to analyte concentration in 100 mg/mL PEG-3350 solutions prepared in formamide. **A.** Ethylene oxide, measured at 11,385.91 MHz with headspace equilibration at 45 °C ($R^2 = 0.9985$). **B.** Acetaldehyde, measured at 8,243.47 MHz with headspace equilibration at 80 °C ($R^2 = 0.9997$). Both analytes show strong linearity across the tested ranges, confirming method suitability for impurity quantification.

The dataset in **Table 2** demonstrates that MRR achieves the precision and sensitivity required to meet impurity thresholds established for PEG excipients. Both EtO and acetaldehyde show excellent linear response ($R^2 > 0.99$), indicating the method can reliably quantify across the regulatory range. The ability to reach low limit of quantitation (LOQ) values that align with pharmacopoeial acceptance criteria confirms the suitability of MRR for compliance testing. Importantly, the short measurement times—under a minute for each analyte—highlight a clear advantage in throughput compared with more traditional methods. This speed, combined with direct headspace analysis, minimizes sample preparation and reduces

opportunities for error. The data also illustrate that MRR can handle the unique challenges of viscous PEG matrices while still generating clean, reproducible signals. The results reported in Table 2 position MRR as a highly efficient option for routine monitoring of EtO and acetaldehyde in PEG-3350, balancing accuracy, sensitivity, and operational simplicity.

PEG Impurity	Boiling Point (°C)	Linearity (R^2)	PEG-3350 in Formamide (mg/mL)	Analyte in Solution (µg/mL)	USP Acceptance Limit*		MRR Measurement Time to Reach LOQ** NMT USP Acceptance Limit
					In pure PEG-3350	In corresponding PEG-3350 solution	
EtO	10.7	>0.99	100	0.05-5.0	NMT 1 µg/g	NMT 0.1 (µg/mL)	~60 seconds
AcH	20.2	>0.99	100	10-500	(FA + AA) NMT 200 µg/g	NMT 17-20 (µg/mL)	~40 seconds

Table 2. Analytical performance of MRR for detecting EtO and acetaldehyde in PEG-3350. Summary table showing method parameters and performance metrics for PEG-3350 impurities. Both EtO and acetaldehyde exhibit strong linearity ($R^2 > 0.99$) across the tested ranges. Headspace-MRR achieved LOQs corresponding to USP acceptance thresholds: EtO measured down to ~0.1 µg/mL (~1 µg/g in pure PEG-3350) with ~60 s acquisition time; Acetaldehyde measured down to 17–20 µg/mL (~200 µg/g in pure PEG-3350, combined with formaldehyde allowance) with ~40 s acquisition time.

***NMT*; not more than**
*** According to USP Notice C290515-M7189-CE2020, rev. 01 20201125, Dec 1, 2020**
**** Estimated as: LOQ = 10 x (standard deviation of blank / slope)**

Conclusion

By eliminating the need for sample dilution, preparation, and complex method development, headspace-MRR enables direct analysis with minimal set-up time. The method achieves low LOQs that align with USP acceptance criteria, while maintaining strong linearity ($R^2 > 0.99$) across relevant concentration ranges. Equally important, measurement times of less than one minute per analyte deliver significant improvements in throughput without sacrificing accuracy or reproducibility. These results establish MRR as a robust, efficient, and compliance-ready solution for routine monitoring of PEG excipients, combining sensitivity, precision, and operational simplicity in a single platform.

References

USP Convention. *PEG-3350 Revision Bulletin / Notice*, USP-NF, 1 Dec. 2020, **uspnf.com/sites/default/files/usp_pdf/EN/USPNF/revisions/peg-3350-rb-notice-20201125.pdf**

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