Macedonian Pharmaceutical Bulletin, 72 (Suppl 1) 307 - 308 (2026)
Online ISSN: 1857-8969
DOI: 10.33320/maced.pharm.bull.2026.72.03.148
Short communication

Development and validation of a headspace GC/MS method for residual solvents: overcoming the challenges of small molecule detection

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Introduction

GC-FID is the standard technique for residual solvent analysis; however, GC/MS (Sparkman et al., 2011) provides superior identification for unknown impurities. Detection of small-molecule solvents by MS presents unique challenges, including low-mass interference and limited fragmentation. This paper details a validated HS-GC/MS method for determination of residual solvents in Cannabis extracts, using selected ion monitoring (SIM) to improve sensitivity and specificity for small molecules, specifically addressing detector saturation and background noise to ensure compliance with ICH Q3C Guideline on impurities: guideline for residual solvents (ICH Q3C (R9) Guideline on Impurities: Guideline for Residual Solvents, 2024) and ICH Q2 Guideline on validation of analytical procedures (ICH Q2 (R2) Guideline on validation of Analytical Procedures, 2024). The validated method proved suitable for routine quality control analysis of residual solvents.

Cannabis (*Cannabis sativa* and *Cannabis indica*) is a plant that contains various groups of compounds like terpenes, flavonoids and probably the most characteristic among them cannabinoids. All compounds, especially terpenes and cannabinoids, can be extracted from the plant material by different approaches such as supercritical CO_2, or the most common classical extraction with a relatively apolar solvent - usually ethanol. The solvent (ethanol) can be detected as residue of such processing in the final products, and, in some cases, this impurity can be toxic. Ethanol belongs in Class 3 residual solvents, with low toxic potential and is limited to 5000 ppm or 0.5%.

In addition to ethanol, other organic solvents such as methanol, acetonitrile, isopropanol, and acetone may be present as residual impurities. These solvents can originate from various stages of the manufacturing process, including extraction, purification, and equipment cleaning. According to the ICH Q3C guideline, methanol and acetonitrile are classified as Class 2 solvents due to their higher toxicity, with concentration limits of 3000 ppm and 410 ppm, respectively, whereas acetone and isopropanol are classified as Class 3 solvents with lower toxic potential and higher permitted limits of 5000 ppm.

Residual solvents are volatile organic chemicals that must be monitored to ensure patient safety. It is crucial to ensure that, during the manufacturing process of cannabis extracts, the levels of the above-mentioned solvents are minimized and controlled within the acceptable limits established by the ICH Q3C guideline.

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Traditional methods, such as Ph. Eur. 2.4.24 (European Pharmacopoeia, Chapter 2.4.24. Identification and Control of Residual Solvents Strasbourg: Council of Europe), primarily utilizes Flame Ionization Detection (FID) due to its wide linear range and robustness for small molecules. However, FID lacks the qualitative power to identify co-eluting unknown peaks versus GC/MS (Sparkman et al., 2011) that provides superior selectivity and identification capability, especially in complex matrices, such as cannabis extracts. Transitioning to Mass Spectrometry (MS) introduces complexities: small molecules often have fragment ions that overlap with atmospheric background (N_2, H_2O, CO_2) and can easily saturate the detector at the high ppm levels allowed for Class 3 solvents. This study presents a method that balances these MS-specific challenges with the need for high-sensitivity quantification.

Materials and methods

The main challenge in GC-MS analysis of residual solvents is the detection of low molecular weight compounds (e.g. methanol, ethanol), which produce low m/z fragments that may overlap with background signals (air, water, CO_2).

To mitigate background noise, the MS was operated in Selected Ion Monitoring (SIM) mode for qualification, focusing on characteristic ions for Acetone, Methanol, Acetonitrile, Ethanol and Isopropanol to avoid atmospheric interference. Higher m/z ions were monitored when possible.

A high split ratio (75:1) was employed to ensure that high-concentration solvents (Class 3) remained within the MS detector's linear range and to avoid detector saturation.

This approach enabled reliable identification and quantification of all analytes.

Results and discussion

The primary obstacle in method development was the limited fragmentation of solvents like Methanol (m/z 31, 32) and Ethanol (m/z 31, 45). By optimizing the solvent delay and ion source temperature, we minimized the "air-peak" interference that often masks these low-mass signals in MS.

Specificity: MS provided definitive peak identification through mass spectral matching, a critical advantage over FID when matrix interferences were present.

Linearity & Range: Despite the narrower dynamic range of MS compared to FID, linearity was achieved ($R^2 \geq 0.999$) by optimizing injection volumes and split ratios.

Accuracy & Precision: Recovery rates (85–110%) and RSD (<5%) for all solvents confirmed that the MS detector, when properly tuned, provides the same quantitative reliability as FID.

The validated method demonstrated high specificity due to MS detection, adequate sensitivity for regulatory limits, good repeatability, and reproducibility.

Compared with GC-FID, the method provides improved identification capability without compromising quantitative performance.

Conclusion

Developing a GC/MS method for residual solvents requires a strategic approach to overcome the limitations of small-molecule mass spectrometry. By utilizing SIM mode and controlled split injections, we developed a method that provides both the quantitative rigor of FID and the qualitative certainty of MS, making it ideal for complex pharmaceutical matrices.

References

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ICH Q2(R2): Guideline on validation of Analytical Procedures (2024) ICH Q2(R2) Guideline on validation of analytical procedures Step 5

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