

A Harmonized GC–FID Method for Multi-Product Residual Solvent Analysis in Diagnostic and Therapeutic Radiopharmaceuticals

Sarko Jabari

Karolinska University Hospital

Noemi Molina

Karolinska University Hospital

Jenny Gröhn

Karolinska University Hospital

Thuy A. Tran

Karolinska Institutet

Mohammad Mahdi Moein

Mohammad.moein.2@ki.se

Karolinska Institutet

Research Article

Keywords: Radiopharmaceuticals, Residual solvent, GC-FID, Quality control, GMP

Posted Date: October 12th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-11150380/v1>

License:   This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Additional Declarations: No competing interests reported.

Abstract

Residual solvent analysis in radiopharmaceutical manufacturing often relies on product-specific gas chromatography methods, increasing routine QC complexity. We developed and validated a harmonized single-column GC–FID method for five target solvents: ethanol, acetone, acetonitrile, tetrahydrofuran, and dimethyl sulfoxide. Baseline separation was achieved within an 11 min 40 s chromatographic run. Low-concentration ethanol and acetonitrile analysis was additionally validated for diluted [^{18}F]FDG samples. The method was evaluated across three formulation matrices and applied to routine QC samples representing ^{11}C -, ^{18}F -, ^{68}Ga -, and ^{177}Lu -labeled products, demonstrating the feasibility of a common platform for GMP radiopharmacy QC.

Introduction

Residual solvents in radiopharmaceuticals may originate from radionuclide production, radiolabeling reactions, purification, and formulation processes. Although these solvents are often essential during synthesis and processing, they provide no therapeutic benefit and may pose toxicological risks, including neurotoxicity, hepatotoxicity, and effects on the central nervous system [1–3]. Their concentrations are therefore controlled according to international guidelines, including ICH Q3C, and relevant pharmacopoeial requirements [4, 5]. According to ICH Q3C, solvents are classified according to their toxicological potential into three categories: Class 1 (solvents that should be avoided), Class 2 (solvents that should be limited), and Class 3 (solvents with low toxic potential) [2, 4, 5]. In radiopharmaceutical manufacturing, most residual solvents belong to Classes 2 and 3 and include ethanol (EtOH), acetonitrile (MeCN), acetone, methanol (MeOH), dimethyl sulfoxide (DMSO), tetrahydrofuran (THF), dichloromethane (DCM), and N,N-dimethylformamide (DMF) [6–8]. EtOH is frequently used as a stabilizer to mitigate radiolysis and may also be introduced during synthesis, purification, and other manufacturing steps.

Residual solvent analysis in radiopharmaceuticals presents challenges because the short half-lives of radionuclides impose strict time constraints on Quality control (QC) testing before product release [9]. In addition, small batch sizes and low production yields may limit the amount of sample available for analysis. In routine practice, radiopharmaceuticals such as [^{18}F]FDG are often produced at high radioactive concentrations, requiring dilution of QC samples before analysis to reduce radiation exposure to personnel. This dilution can substantially decrease residual solvent concentrations and consequently challenge their reliable detection and quantification [9–12]. Consequently, analytical methods for residual solvent determination must be sensitive, rapid, robust, and suitable for routine use under Good manufacturing practice (GMP) QC requirements.

Gas chromatography–flame ionization detection (GC–FID) is widely used for residual solvent determination because of its suitability for volatile organic compounds and its established application in pharmaceutical quality control [13–21]. However, the direct application of pharmacopoeia methods can be challenging because radiopharmaceuticals often have complex and variable matrices, typically consisting of aqueous buffered solutions containing stabilizers, excipients, and residual precursors [11, 22]. These matrix components can affect analyte volatility and chromatographic behavior, potentially resulting in co-elution, reduced resolution, or variability in detector response. Furthermore, differences in formulation composition

can complicate the application of a single standardized method across different products, highlighting the need for generalized analytical approaches suitable for multiple radiopharmaceuticals.

Although validated GC-based methods have been reported for individual radiopharmaceuticals, including [^{18}F]FDG and L-[^{11}C]methionine [23–26], these methods are generally developed for specific products, solvent panels, or formulation matrices. More generalized approaches have also been described, including methods demonstrating multi-analyte and multi-product applicability [27, 28]. However, the practical implementation of a single validated method across radiopharmaceuticals with different radionuclides, formulation compositions, and routine QC requirements remains insufficiently addressed. In particular, the combined evaluation of matrix effects, low-concentration analysis following sample dilution, application to routine GMP products, and comparability with an established product-specific analytical procedure has received limited attention.

The use of multiple product-specific methods can increase the operational burden associated with method validation, periodic review, instrument maintenance, analyst training, and controlled documentation. A common analytical platform could reduce this method-specific complexity by allowing multiple radiopharmaceutical products to be analyzed using shared chromatographic conditions and a consistent validation framework. However, such an approach requires evidence that analytical performance is maintained across relevant solvent concentration ranges and formulation matrices, including the conditions encountered in routine radiopharmaceutical QC. Therefore, the aim of this study was to develop and validate a generalized single-column GC–FID method for the quantitative determination of ethanol, acetone, acetonitrile, tetrahydrofuran, and dimethyl sulfoxide across multiple diagnostic and therapeutic radiopharmaceuticals. This study presents a common chromatographic platform validated for five residual solvents across relevant concentration ranges, with additional low-concentration validation of ethanol and acetonitrile in diluted [^{18}F]FDG samples. The platform was further evaluated across three representative formulation matrices and applied to routine QC samples representing ^{11}C -, ^{18}F -, ^{68}Ga -, and ^{177}Lu -labeled products. The developed method was also compared with an established product-specific GMP GC–FID procedure to assess analytical comparability under the investigated conditions. Collectively, these evaluations assessed whether a single validated chromatographic platform could support multiple radiopharmaceutical QC applications while reducing reliance on separate product-specific methods.

Theory

The chromatographic behavior and quantitative performance of residual solvent analysis depend on factors including column chemistry, oven temperature program, carrier-gas flow, injection conditions, and sample composition. For radiopharmaceutical QC, these parameters must provide sufficient chromatographic separation and analytical sensitivity within a short analysis time compatible with routine product-release testing. The present study therefore investigated whether a common chromatographic configuration could provide adequate analytical performance across multiple radiopharmaceutical formulation matrices.

In GC–FID, organic compounds eluting from the chromatographic column are introduced into a hydrogen–air flame, where ionization processes generate an electrical signal. Under appropriate operating conditions, the detector response can be used for quantitative determination through calibration against reference

standards. GC–FID is therefore particularly suitable for the determination of volatile organic residual solvents.

Gas chromatographic separation of residual solvents is based on differences in analyte volatility and interactions with the stationary phase. Following injection and vaporization, analytes are transported through the column by the carrier gas and undergo repeated partitioning between the mobile gas phase and stationary phase. Differences in these interactions result in compound-specific retention and enable chromatographic separation.

Experimental

Chemicals and Instrumentation

Ethanol (EtOH), acetonitrile (MeCN), acetone, tetrahydrofuran (THF), dimethyl sulfoxide (DMSO), methanol (MeOH), dichloromethane (DCM), and N,N-dimethylformamide (DMF), all with reported purities of $\geq 99.5\%$, were obtained from VWR International AB, Sigma-Aldrich, Merck (Darmstadt, Germany), and Thermo Fisher Scientific. Reference solvent materials were stored at 2–8°C and allowed to equilibrate to room temperature before use. Stock solutions were considered stable for up to three months when stored under the specified conditions. Working solutions were prepared by diluting the corresponding stock solutions with ultrapure water produced using a Milli-Q® Direct water purification system (Merck Millipore, Burlington, MA, USA).

Gas chromatographic analyses were performed using an Agilent 7890B gas chromatograph (Agilent Technologies, Santa Clara, CA, USA; serial no. CN17093115) equipped with a flame ionization detector (FID; G3462A), an automated liquid sampler (ALS 7693), and a split/splitless injector. Chromatographic separation was achieved using a DB-624 capillary column (30 m $\times$ 0.53 mm i.d., 3.00 μ m film thickness; Agilent Technologies, part no. 125–1334). An Ultra Inert inlet liner packed with glass wool (Agilent Technologies, part no. 5190 – 2295) was used throughout the study.

Instrument control, data acquisition, and data processing were performed using Laura software (version 6.1.4.62 SP1). Standard and validation solutions were prepared using an Ohaus Explorer EX2202 analytical balance (OHAUS Corporation, Parsippany, NJ, USA). The GC system was supplied with hydrogen (99.9999%), helium (99.9999%), and synthetic air (99.9999%), all obtained from Linde Gas AB (Solna, Sweden).

Preparation of Calibration Standards and Validation Samples

Standard solutions used for method development and validation were prepared by diluting the respective organic solvents with ultrapure water. For the general method, stock solutions were prepared at concentrations of 80.00 mg/mL for EtOH, 5.00 mg/mL for acetone, 0.27 mg/mL for MeCN, 0.36 mg/mL for THF, and 3.30 mg/mL for DMSO. Calibration and linearity were evaluated using seven concentration levels prepared by serial dilution of the respective stock solutions. The investigated concentration ranges were 5.00–100.00 mg/mL for EtOH, 0.42–8.33 mg/mL for acetone, 0.05–1.09 mg/mL for MeCN, 0.03–0.60 mg/mL for THF, and 0.21–4.22 mg/mL for DMSO.

The calibration ranges were selected to encompass the expected residual solvent concentrations in radiopharmaceutical products while providing adequate sensitivity and linearity for routine QC analysis. The validated method was subsequently applied to the radiopharmaceuticals described below.

For application to [^{18}F]FDG, separate stock solutions of EtOH and MeCN were prepared at concentrations of 0.80 mg/mL and 0.066 mg/mL, respectively. Because QC samples are routinely diluted prior to analysis to reduce radiation exposure, additional low-concentration calibration ranges were established for these analytes. Calibration and linearity were evaluated using five concentration levels covering 0.10–1.20 mg/mL for EtOH and 0.02–0.24 mg/mL for MeCN.

The potential influence of formulation matrix composition on analytical performance was evaluated using reference standards prepared in representative radiopharmaceutical formulation matrices corresponding to [^{18}F]FDG, L-[^{11}C]methionine, and [^{68}Ga]FAPI-46. Equivalent reference standards prepared in Milli-Q water were used for comparison.

The applicability of the developed method was further evaluated using routine QC samples from [^{18}F]FDG, [^{18}F]FE-PE2I, L-[^{11}C]methionine, [^{68}Ga]FAPI-46, [^{68}Ga]ATH001, and [^{177}Lu]ABY-271 produced at Karolinska University Hospital. Formulation compositions were obtained from the corresponding Investigational Medicinal Product Dossiers (IMPDs) and GMP manufacturing documentation.

Method Validation

Method validation was performed in accordance with the ICH Q2(R2) and ICH Q14 guidelines. The following performance characteristics were evaluated: range, linearity, specificity, limit of detection (LOD), limit of quantification (LOQ), repeatability, intermediate precision, and accuracy. LOD and LOQ were calculated from the standard deviation of the response and the slope of the calibration curve. Precision was evaluated in terms of repeatability (intra-day precision) and intermediate precision (inter-day precision) at selected concentration levels. Accuracy was assessed based on recovery, expressed as the percentage of the measured concentration relative to the nominal concentration. Unless otherwise stated, all measurements were performed in triplicate.

Formal validation was performed for ethanol, acetone, acetonitrile, tetrahydrofuran, and dimethyl sulfoxide. For ethanol and acetonitrile, additional low-concentration calibration ranges were separately evaluated and validated for diluted [^{18}F]FDG samples. The applicability of the chromatographic conditions to methanol, dichloromethane, and N,N-dimethylformamide was investigated separately through an exploratory separation assessment and was not included in the formal validation.

For comparison with the established analytical procedure, representative reference solutions and radiopharmaceutical QC samples were analyzed using both the established GMP GC–FID system (GC-01) and the newly developed system (GC-02). GC-01 employed validated product-specific methods, whereas GC-02 used the generalized chromatographic method described in this study. The two systems differed in chromatographic conditions and instrument components, including column configuration. This comparison

was conducted to assess the comparability of the two analytical setups and was not intended to constitute a formal method-transfer or interlaboratory validation study.

Results and Discussion

GC Method Development and Optimization

Due to the wide range of boiling points of the investigated residual solvents (56.1–189.0°C), a temperature-programmed oven method was employed. The initial oven temperature was set to 60°C and maintained for 4 min, followed by a temperature ramp of 30°C/min to 200°C, which was held for 3 min. This temperature program enabled efficient elution and adequate separation of all analytes. The oven temperature was subsequently increased to 260°C to promote elution of any remaining high-boiling compounds and to minimize potential carryover.

The FID temperature was set to 300°C to accommodate analytes with relatively high boiling points, while the inlet temperature was maintained at 250°C to ensure efficient vaporization and transfer of the analytes onto the column. An injection volume of 1 µL was used in split mode. Initial experiments were performed using a split ratio of 1:3. Under these conditions, satisfactory separation of the target analytes was achieved using a J&W DB-624 GC column (30 m × 0.53 mm i.d., 3.00 µm film thickness), with resolution values ranging from 2.5 to 10.0. The lowest resolution ($R_s \approx 2.5$) was observed for MeCN, which also exhibited slight peak broadening compared with the other solvents.

To improve the chromatographic performance of MeCN, split ratios of 1:5, 1:10, and 1:15 were evaluated. Increasing the split ratio resulted in a modest improvement in resolution, with a maximum R_s of approximately 3.0. No substantial improvement was observed at split ratios above 1:10. A split ratio of 1:10 was therefore selected as a compromise between improved peak shape and adequate sensitivity. The improvement in peak shape with increased split ratio is consistent with the lower sample load introduced onto the column, which may reduce peak broadening and improve peak symmetry.

FID gas flows were set to 400 mL/min for air, 35 mL/min for hydrogen, and 25 mL/min for helium as make-up gas. The total chromatographic run time was 11 min 40 s. Under the optimized conditions, all validated analytes achieved baseline separation within a single chromatographic program, supporting the use of a common analytical platform for multiple radiopharmaceutical products. The optimized chromatographic conditions summarized in Table 1 were used for all subsequent analyses.

Table 1
Comparison of GC-01 and GC-02 chromatographic conditions.

Components	GC-01	GC-02
System	6850	7890B
Inlet	Split mode Heater 250°C Split ratio 1:80 Pressure 2.76 psi	Split mode Heater 250°C Split ratio 1:10 Split flow 50 mL/min Total flow 58 mL/min Pressure 4.04 psi
Oven and gradient	Hold at 35°C for 3.5-4 min. Ramp 70–80°C/min to 100–240°C and hold for 0.5-3 min. Ramp 70–80°C/min to 220°C and hold for 0.5 min. Max temp: 250°C.	Hold at 60°C for 4 min. Ramp 30°C/min to 200°C and hold for 3 min. Max temp: 260°C.
Detector	Temperature: 250°C Air flow: 250 mL/min Hydrogen flow: 25 mL/min He flows: 30 mL/min Makeup mode: Constant makeup flow Flame: ON	Temperature: 300°C Air flow: 400 mL/min Hydrogen flow: 35 mL/min He flows: 25 mL/min Makeup mode: Constant makeup flow and fuel flow Flame: ON
Column	Res-Solv, 30m x 0.53mm id x 1 µm film	DB-624, 30m x 0.53mm id x 3.00µm film
Run time	7–9 min	11min 40 sec
Injection volume	2 µL	1 µL
Method	Product-specific	Single harmonized

Range and Linearity

The concentration range for each solvent was established based on the expected analyte concentrations encountered during routine quality control (QC) and was designed to encompass the applicable acceptance

limits. For the radiopharmaceuticals listed in Table 2, with the exception of [^{18}F]FDG, system suitability test (SST) reference solutions are routinely prepared at concentrations of 80.00 mg/mL for EtOH, 5.00 mg/mL for acetone, 0.27 mg/mL for MeCN, 0.36 mg/mL for THF, and 3.30 mg/mL for DMSO. In routine QC, the acceptance criterion specifies that the concentration of each residual solvent in the sample must not exceed 110% of the corresponding SST reference concentration.

Table 2
Formulation composition of investigated radiopharmaceutical products.

Radiopharmaceutical	Component 1	Component 2	Component 3	Component 4	Component 5
[^{18}F]FDG	EtOH	Di-sodium hydrogen citrate	Sodium citrate	0.9% NaCl	Sterile water
[^{18}F]FE-PE2I	EtOH	Sodium ascorbate	-	0.9% NaCl	Sterile water
[^{11}C]Methionine	EtOH	Potassium phosphate monobasic	Potassium phosphate dibasic trihydrate	0.9% NaCl	Sterile water
[^{68}Ga]FAPI-46	EtOH	Sodium ascorbate	Sodium acetate trihydrate	0.9% NaCl	Sterile water
[^{68}Ga]ATH001	EtOH	Sodium ascorbate	Sodium acetate trihydrate	0.9% NaCl	Sterile water
[^{177}Lu]ABY-271	EtOH	Sodium ascorbate	Sodium acetate trihydrate	-	Sterile water

Accordingly, the following calibration ranges were selected: 5.00–100.00 mg/mL for EtOH, 0.42–8.33 mg/mL for acetone, 0.05–1.09 mg/mL for MeCN, 0.03–0.60 mg/mL for THF, and 0.21–4.22 mg/mL for DMSO. Linearity was evaluated at seven concentration levels within each range. Linear regression analysis demonstrated excellent linearity for all analytes, with coefficients of determination (r^2) ranging from 0.998 to 0.999.

For application to [^{18}F]FDG, lower concentration ranges were investigated for EtOH and MeCN because the QC sample is diluted during routine analysis, resulting in lower residual solvent concentrations. Reference solutions for SST were prepared at 0.80 mg/mL for EtOH and 0.066 mg/mL for MeCN, and the same acceptance criterion was applied. Accordingly, calibration ranges of 0.10–1.20 mg/mL for EtOH and 0.02–0.24 mg/mL for MeCN were selected. Linearity was assessed at five concentration levels and yielded r^2 values > 0.999.

The coefficients of determination of 0.998–0.999 across the general calibration ranges indicate a highly consistent linear response for all five target solvents. Importantly, these ranges encompassed the concentrations used for routine SST and QC analysis, supporting their use as a common calibration framework. For [¹⁸F]FDG, the additional low-concentration ranges produced r^2 values > 0.999, demonstrating that the same chromatographic platform could also provide a suitable linear response after the dilution of high-activity QC samples.

Limits of Detection and Quantification

The sensitivity of the developed GC–FID method was evaluated by determining the limit of detection (LOD) and limit of quantification (LOQ) for each analyte. LOD and LOQ were calculated from the standard deviation of the response (σ) and the slope of the calibration curve (S), using the following equations in accordance with ICH Q2(R2):

$$\text{LOD} = (3.3 \times \sigma) / S$$

$$\text{LOQ} = (10 \times \sigma) / S$$

where σ is the standard deviation of the response and S is the slope of the calibration curve.

For the general method, the LOQ values were 11.09 mg/mL for EtOH, 0.54 mg/mL for acetone, 0.09 mg/mL for MeCN, 0.037 mg/mL for THF, and 0.43 mg/mL for DMSO. The corresponding LOD values were 3.66, 0.179, 0.031, 0.012, and 0.142 mg/mL, respectively.

For application to [¹⁸F]FDG, substantially lower LOQ values were obtained for EtOH and MeCN, at 0.135 and 0.022 mg/mL, respectively. The corresponding LOD values were 0.045 and 0.0073 mg/mL. The substantially lower LOQ values obtained for the [¹⁸F]FDG-specific concentration range demonstrate the importance of matching the validated calibration range to the concentrations encountered after routine sample dilution. Thus, rather than requiring a separate chromatographic method for diluted FDG samples, the low-concentration range extended the applicability of the same GC–FID platform to this specific QC scenario.

Precision and Accuracy

The precision and accuracy of the developed GC–FID method were evaluated in accordance with ICH guidelines. Precision was assessed in terms of repeatability (intra-day precision) and intermediate precision (inter-day precision), while accuracy was evaluated based on recovery according to the following equation:

$$\text{Recovery (\%)} = (\text{measured concentration} / \text{nominal concentration}) \times 100$$

The results for precision and accuracy are summarized in Table 3.

Table 3
Precision and Accuracy results.

Solvent	Conc. (mg/mL)	Intra-day RSD (%)	Inter-day RSD (%)	Recovery Range (%)
EtOH	5.00	0.4	2.4	98–105
	40.00	0.2	3.0	97–104
	100.00	3.3	3.9	93–108
Acetone	0.42	0.6	1.6	94–99
	3.33	0.3	1.6	95–100
	8.33	0.4	1.6	95–105
MeCN	0.05	0.5	1.7	104–108
	0.44	0.1	1.9	94–100
	1.09	0.3	1.9	95–105
THF	0.03	0.9	1.5	90–95
	0.24	0.5	1.2	90–93
	0.60	0.4	1.3	93–98
DMSO	0.21	0.6	8.6	90–110
	1.69	0.9	4.3	94–105
	4.22	0.8	3.7	97–109

Repeatability was evaluated at three concentration levels within the established range for each analyte, while intermediate precision was assessed over three consecutive days using the same concentration levels. For the general method, all investigated solvents (EtOH, acetone, MeCN, THF, and DMSO) demonstrated satisfactory repeatability, with intra-day RSD values ranging from 0.1% to 3.3%. Intermediate precision showed slightly greater variability, with inter-day RSD values ranging from 1.2% to 8.6%. The highest variability was observed for DMSO at the lowest concentration level (0.21 mg/mL), whereas all other analytes exhibited

inter-day RSD values below 4.0%. The higher variability observed for DMSO at the lowest concentration is consistent with the increased relative variability generally observed as analyte response approaches the lower end of a calibration range. The relatively high boiling point of DMSO may also contribute to greater sensitivity to chromatographic conditions.

For application to [^{18}F]FDG, repeatability was additionally evaluated at lower concentration levels for EtOH and MeCN, yielding RSD values of 2.5–3.0%. These results confirmed acceptable precision at the lower concentration range.

Accuracy was evaluated at three concentration levels using triplicate measurements, resulting in at least nine determinations per analyte. Independent standard preparations were used to minimize potential

preparation bias. EtOH, acetone, and MeCN showed recoveries close to 100%, typically ranging from 95% to 105%, whereas THF and DMSO demonstrated mean recoveries of approximately 92–96% and 100–103%, respectively. Slightly broader recovery ranges were observed at the lower concentration levels; however, the results remained within generally accepted limits for quantitative chromatographic analysis.

Overall, the method showed acceptable repeatability, intermediate precision, and accuracy across the validated concentration ranges. These findings support the suitability of the method for reliable residual solvent quantification in routine GMP QC.

Applicability to Additional Residual Solvents

To further evaluate the applicability of the developed method, a reference standard containing additional residual solvents commonly encountered in radiopharmaceutical manufacturing was analyzed alongside the solvents included in the validation study. Despite the presence of compounds with relatively similar boiling points, adequate chromatographic separation was maintained, with all analytes achieving a minimum resolution of 2.2. A representative SST chromatogram is shown in Fig. 1.

These findings indicate that the developed chromatographic conditions may accommodate a broader range of residual solvents than those formally included in the validation study. However, these additional solvents were not included in the formal validation and therefore require appropriate product- and analyte-specific validation or verification before quantitative routine application.

Applicability Across Radiopharmaceutical Formulation Matrices

Table 2 lists the investigated radiopharmaceutical products and their respective formulation compositions. The theoretical concentrations in the aqueous reference standard were 60.00 mg/mL for EtOH, 5.00 mg/mL for acetone, 0.23 mg/mL for MeCN, 0.30 mg/mL for THF, and 3.00 mg/mL for DMSO. Across the investigated matrices, measured residual solvent concentrations and chromatographic resolution were in close agreement with those obtained using Milli-Q water, with maximum deviations of 4.17% and 2.17%, respectively (Table 4). The limited variation between the aqueous reference standards and formulation matrices indicates that the investigated formulation components did not substantially affect residual solvent quantification or chromatographic separation. This is particularly relevant to the proposed harmonized approach because the evaluated products contained different formulation compositions.

Table 4
Effect of Formulation Matrices on Residual Solvent Analysis

Solvents	Methionine Concentration Variance (%)	Methionine Resolution Variance (%)	FAPI Concentration Variance (%)	FAPI Resolution Variance (%)	FDG Concentration Variance (%)	FDG Resolution Variance (%)
EtOH	1.84	N/A*	0.46	N/A	1.21	N/A
Acetone	1.70	1.95	0.38	1.08	0.76	2.17
MeCN	4.17	1.52	< 0.01	1.04	< 0.01	0.64
THF	3.03	0.89	< 0.01	0.97	< 0.01	0.97
DMSO	1.38	1.15	1.38	0.03	0.69	< 0.01
*Not applicable						

Calibration standards were prepared in Milli-Q water and in the methionine, FAPI-46, and FDG formulation matrices for comparison. Chromatographic performance remained consistent across the investigated matrices, with no evidence of significant co-eluting interferences or changes in chromatographic separation.

These results indicate that the developed method was not substantially affected by the investigated matrix effects. The close agreement with the aqueous reference standards supports the suitability of the method for routine QC analysis of radiopharmaceuticals with diverse formulation compositions.

Application to Routine Radiopharmaceutical QC Samples

Representative chromatograms of radiopharmaceutical products manufactured at our site using the newly developed method are presented in Fig. 2. EtOH was the predominant residual solvent detected in the investigated formulations. Additional unidentified peaks observed below the LOQ were considered likely to originate from formulation components or trace impurities. Because these signals were below the LOQ, they were not considered to have a significant impact on the residual solvent assessment.

Prior to sample analysis, all SST acceptance criteria were met, confirming adequate system performance for routine use. For [^{18}F]FDG, the acceptance ranges for EtOH and MeCN were 0–0.80 mg/mL and 0–0.034 mg/mL, respectively. For [^{18}F]FE-PE2I, the corresponding acceptance ranges were 0–80 mg/mL for EtOH and 0–0.27 mg/mL for MeCN. DMSO in [^{18}F]FE-PE2I was evaluated using a limit test, with the sample response required to remain below that of the corresponding SST reference solution. For L-[^{11}C]methionine, [^{68}Ga]FAPI-46, and [^{177}Lu]ABY-271, the acceptance range for EtOH was 0–80 mg/mL, whereas acetone in L-[^{11}C]methionine was evaluated using a limit test.

As summarized in Table 5, all measured residual solvent concentrations complied with their respective acceptance criteria. The application of the method to both PET and therapeutic radiopharmaceuticals demonstrates its applicability across different product classes. Together with the validation and matrix-

effect results, these findings support the use of the method as a common platform for routine residual solvent QC.

Table 5
Residual Solvent Content in Radiopharmaceutical Samples in mg/mL.

Radiopharmaceutical	Acceptance criteria (mg/mL)	EtOH (mg/mL)	Acetone	MeCN (mg/mL)	DMSO
[¹⁸ F]FDG	EtOH ≤ 0.80 MeCN ≤ 0.034	0.48	--*	LLQ	--
[¹⁸ F]FE-PE2I	EtOH ≤ 80 MeCN ≤ 0.27 DMSO: Limit test	60.58	--	LLQ	LLQ
[¹¹ C]Methionine	EtOH ≤ 80 Acetone: Limit test	33.60	LLQ	--	--
[⁶⁸ Ga]FAPI-46	EtOH ≤ 80	47.60	--	--	--
[⁶⁸ Ga]ATH001	EtOH ≤ 80	48.90	--	--	--
[¹⁷⁷ Lu]ABY-271	EtOH ≤ 80	31.87	--	--	--
*--: indicates that the solvent is not present in the product matrices.					

Method Comparison Between GC Systems

In GC-01, baseline instability was observed around the DMSO peak, necessitating the use of a peak-area limit rather than quantitative determination, and the method showed poor linearity for DMSO. In contrast, the GC-02 method showed improved baseline stability, enabling reliable peak integration and the construction of a calibration curve with acceptable linearity.

For comparison, a reference solution was analyzed using both systems, and representative chromatograms are shown in Fig. 3. Although GC-02 employs a generalized analytical method, its SST reference solution contains all residual solvents included in the method. In contrast, GC-01 uses product-specific methods, and the corresponding SST reference solution contains only the residual solvents relevant to the respective radiopharmaceutical.

Despite these differences, the SST reference solutions for both GC systems were routinely prepared at the same concentrations: 80.00 mg/mL for EtOH, 5.00 mg/mL for acetone, 0.27 mg/mL for MeCN, 0.36 mg/mL for THF, and 3.30 mg/mL for DMSO. For [¹⁸F]FDG, the SST reference solution was prepared at 0.80 mg/mL for EtOH and 0.066 mg/mL for MeCN. The results obtained using both systems are summarized in Table 6. Values below the lower limit of quantification are reported as LLQ.

Table 6
Residual Solvent Content by GC-01 and GC-02 (mg/mL)

Radiopharmaceutical	Solvent	GC-01	GC-02	Variance (%)
[¹⁸ F]FDG	EtOH	0.50	0.49	2.86
	MeCN	LLQ	LLQ	–
[¹⁸ F]FE-PE2I	EtOH	56.78	60.58	6.48
	MeCN	LLQ	LLQ	–
	DMSO	LLQ	LLQ	–
[¹¹ C]Methionine	EtOH	33.71	33.60	0.32
	Acetone	LLQ	LLQ	–
[⁶⁸ Ga]FAPI-46	EtOH	50.00	47.60	4.92
[¹⁷⁷ Lu]ABY-271	EtOH	35.17	31.87	9.84
[⁶⁸ Ga]ATH001	EtOH	48.31	48.90	1.21

Comparison of routine sample results provided an additional assessment of method performance in complex formulation matrices beyond the formal validation. The comparable performance of the two GC systems also supports their potential use as complementary or backup systems in a GMP setting, subject to appropriate product-specific verification and applicable laboratory procedures, thereby improving operational flexibility and continuity during instrument downtime.

Across the investigated radiopharmaceuticals, GC-02 produced results that were comparable to those obtained using GC-01, with deviations below 10% for all quantitatively determined analytes. Across the samples investigated, no consistent directional bias between the two analytical setups was apparent. The agreement between the two systems is notable because the comparison was made despite differences in chromatographic conditions, column configuration, and method design. These findings suggest that the developed harmonized method produced results comparable to those obtained using an established product-specific GMP approach under the investigated conditions.

This support the feasibility of using a common GC method for residual solvent QC across multiple radiopharmaceutical products. By demonstrating comparable results between the two GC systems under the investigated conditions, the developed method may reduce the need for separate chromatographic approaches across selected products, subject to product-specific verification and applicable laboratory procedures.

Conclusions

This study demonstrates the feasibility of a generalized single-column GC–FID platform for residual solvent analysis in multiple diagnostic and therapeutic radiopharmaceuticals. The method provided baseline separation of EtOH, acetone, MeCN, THF, and DMSO within 11 min 40 s using a DB-624 column and

demonstrated satisfactory linearity, sensitivity, precision, and accuracy across the investigated concentration ranges. An additional low-concentration calibration range for EtOH and MeCN was validated for diluted [^{18}F]FDG samples, extending the applicability of the same chromatographic platform to a specific analytical challenge associated with routine QC of high-activity products.

The principal contribution of this work is the validation of a harmonized GC-FID platform across multiple radiopharmaceutical classes, formulation matrices, and routine GMP applications. The method was evaluated using three representative formulation matrices and applied to routine QC samples from [^{18}F]FDG, [^{18}F]FE-PE2I, L-[^{11}C]methionine, [^{68}Ga]FAPI-46, [^{68}Ga]ATH001, and [^{177}Lu]ABY-271. These applications covered both PET and therapeutic radiopharmaceuticals and represented ^{11}C -, ^{18}F -, ^{68}Ga -, and ^{177}Lu -labeled products. The agreement between the developed method and an established product-specific GMP GC-FID procedure further supported its practical applicability under the investigated conditions.

The consistent performance across different formulation matrices and radiopharmaceutical classes indicates that a common chromatographic platform can support multiple routine residual solvent QC applications without requiring a separate method for each investigated product. The primary benefit of this approach is therefore not necessarily superior analytical sensitivity or precision compared with every product-specific method, but rather the combination of adequate analytical performance, broad applicability, and reduced method-specific complexity. This may facilitate more consistent approaches to method maintenance, analyst training, documentation, and instrument utilization in GMP radiopharmacy laboratories.

The chromatographic conditions also enabled separation of additional solvents, including MeOH, DCM, and DMF. However, these solvents were not included in the formal validation and require appropriate analyte- and product-specific validation or verification before quantitative routine application. Similarly, implementation for new radiopharmaceutical products or substantially different formulation matrices should be supported by product-specific verification or additional validation, as required by applicable GMP procedures and regulatory expectations.

These results support the use of the developed method as a common platform for residual solvent testing across the investigated radiopharmaceutical products. The approach has the potential to reduce reliance on multiple product-specific methods while maintaining the analytical performance required for routine QC.

Declarations

Sample availability

Not available.

CRedit authorship contribution statement

Sarko Jabari: Validation, Writing – original draft, Methodology, Conceptualization. Noemi Molina: Writing – review & editing. Jenny Gröhn: Visualization. Thuy Tran: Writing – review & editing, Supervision. Mohammad Mahdi Moein: Conceptualization, Supervision, Writing – review & editing.

Informed consent statement

Not applicable.

Funding

This research received no external funding.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

References

1. Grodowska K, Parczewski A (2010) Organic solvents in the pharmaceutical industry. *Acta Pol Pharm* 67:3–12
2. World Health Organization Study Group (1981) Recommended health-based limits in occupational exposure to selected organic solvents. WHO Technical Report Series No. 664. World Health Organization, Geneva
3. United States Pharmacopeial Convention (2023) 467 Residual solvents. In: USP–NF. United States Pharmacopeial Convention, Rockville, MD. DOI 10.31003/USPNF_M99226_09_01
4. European Directorate for the Quality of Medicines & HealthCare (EDQM) (2025) European Pharmacopoeia, 12th edn. Council of Europe, Strasbourg
5. International Council for Harmonisation (ICH) (2021) ICH Harmonised Guideline Q3C(R8): Impurities—Guideline for residual solvents. International Council for Harmonisation, Geneva
6. Saha GB (2018) Fundamentals of nuclear pharmacy, 7th edn. Springer International Publishing, Cham. 10.1007/978-3-319-57580-3
7. International Atomic Energy Agency (IAEA) (2018) Quality control in the production of radiopharmaceuticals. IAEA-TECDOC-1856. International Atomic Energy Agency, Vienna
8. Kılçar AY (2023) Quality assurance and quality control methods in radiopharmacy. *Nucl Med Semin* 9:76–83. 10.4274/nts.galenos.2023.0010
9. Chhabra A, Tanwar KS (2025) Quality considerations in radiopharmaceuticals. In: Srivastava V, Vatsa R (eds) Targeted radiopharmaceuticals and imaging: development challenges and opportunities, vol 5. Royal Society of Chemistry, Cambridge, pp 435–452. DOI 10.1039/9781837677139-00435
10. Mercado R, Lagos S, Velásquez E (2023) Radiochemical purity and identity in radiopharmaceuticals: design and improvement of quality control methods by HPLC. *Advances in dosimetry and new trends in radiopharmaceuticals*. IntechOpen, London. DOI 10.5772/intechopen.112355
11. Faivre-Chauvet A, Bourdeau C, Bourgeois M (2022) Radiopharmaceutical good practices: regulation between hospital and industry. *Front Nucl Med* 2:990330. 10.3389/fnume.2022.990330

12. Ekinci M, Santos-Oliveira R, İlem-Özdemir D (2022) Quality assurance and quality control of radiopharmaceuticals: an overview. *J Fac Pharm Ankara* 46:1044–1063. 10.33483/jfpau.1109583
13. Kresnik D, Bajor B, Steuer C (2026) Ease of analysis through unification: one gas chromatographic method for the chemical profiling of essential oils. *J Pharm Biomed Anal* 272:117350–117359. 10.1016/j.jpba.2026.117350
14. Meng DS, Li GJ, Sun SG, Ma CX, Zhu TQ, Liu Y (2025) GC and HPLC-RID method development and validation for the determination of twelve related substances, including several novel compounds in tetrabenazine. *J Pharm Biomed Anal* 260:116814. 10.1016/j.jpba.2025.116814
15. Claude A, Kalalian C, Boissard C, Gros V, Leymarie J, Puga-Freitas R (2026) A portable fast gas chromatography-mass spectrometry workflow for quantification of biogenic volatile organic compounds with humidity-dependent sensitivity correction. *MethodsX* 16:103939. 10.1016/j.mex.2026.103939
16. Sadat Miri M, Badakhshan D, Akhgari M, Ghadipasha M (2025) Chemical components analysis of handmade alcoholic beverages with special focus on psychoactive drugs as adulterants. *MethodsX* 14:103230. 10.1016/j.mex.2025.103230
17. Lourenço KS, Suleiman AKA, Pijl A, Dimitrov MR, Cantarella H, Kuramae EE (2024) Mix-method toolbox for monitoring greenhouse gas production and microbiome responses to soil amendments. *MethodsX* 12:102699. 10.1016/j.mex.2024.102699
18. Matmour D (2023) Analysis of residual solvents-impurities by HS-GC-FID: case of seven samples of ciprofloxacin API. *Hacettepe Univ J Fac Pharm* 43:32–42. 10.52794/hujpharm.1098619
19. Liu Y, Hu CQ (2006) Establishment of a knowledge base for identification of residual solvents in pharmaceuticals. *Anal Chim Acta* 575:246–254. 10.1016/j.aca.2006.05.098
20. Cheng C, Liu S, Mueller BJ, Yan Z (2010) A generic static headspace gas chromatography method for determination of residual solvents in drug substance. *J Chromatogr A* 1217:6413–6421. 10.1016/j.chroma.2010.08.016
21. Teglia CM, Montemurro M, De Zan MM, Cámara MS (2015) Multiple responses optimization in the development of a headspace gas chromatography method for the determination of residual solvents in pharmaceuticals. *J Pharm Anal* 5:296–306. 10.1016/j.jpha.2015.02.004
22. Kolb B, Ettre LS (2006) *Static headspace-gas chromatography: theory and practice*, 2nd edn. Wiley, Hoboken, NJ. 10.1002/0471914584
23. Klok RP, Windhorst AD (2006) Residual solvent analysis by gas chromatography in radiopharmaceutical formulations containing up to 12% ethanol. *Nucl Med Biol* 33:935–938. 10.1016/j.nucmedbio.2006.07.003
24. Costa FM, dos Santos Costa CL, Silva JB, Ferreira SMZM (2019) Validation of new gas chromatography–flame ionization detection procedure for quantitation of residual solvents in [¹⁸F]FDG. *Braz J Radiat Sci* 7(2A):e642. 10.15392/bjrs.v7i2A.642
25. Mihon M, Tuță CS, Ion AC, Niculae D, Lavric V (2017) Fast method for the determination of residual solvents in radiopharmaceutical products. *Rev Chim (Bucharest)* 68:666–670. 10.37358/RC.17.4.5526
26. Hassan H, Othman MF, Zakaria ZA, Saad FFA, Abdul Razak HRA (2021) Analytical GC-FID method for the determination of organic solvents in radiopharmaceuticals. *Curr Radiopharm* 14:131–144.

27. Józai I, Vékei N, Bajnai D, Kertész I, Trencsényi G (2022) A generic gas chromatography method for determination of residual solvents in PET radiopharmaceuticals. J Pharm Biomed Anal 207:114425. 10.1016/j.jpba.2021.114425
28. A'Keen CV, Mroz J, Joseph SK, Baquero J, Cantorias MV, Carberry P (2023) OMNI: gas chromatograph captures seven common PET radiotracer analytes in under 5 minutes. Pharmaceuticals 16:1623. 10.3390/ph16111623

Figures

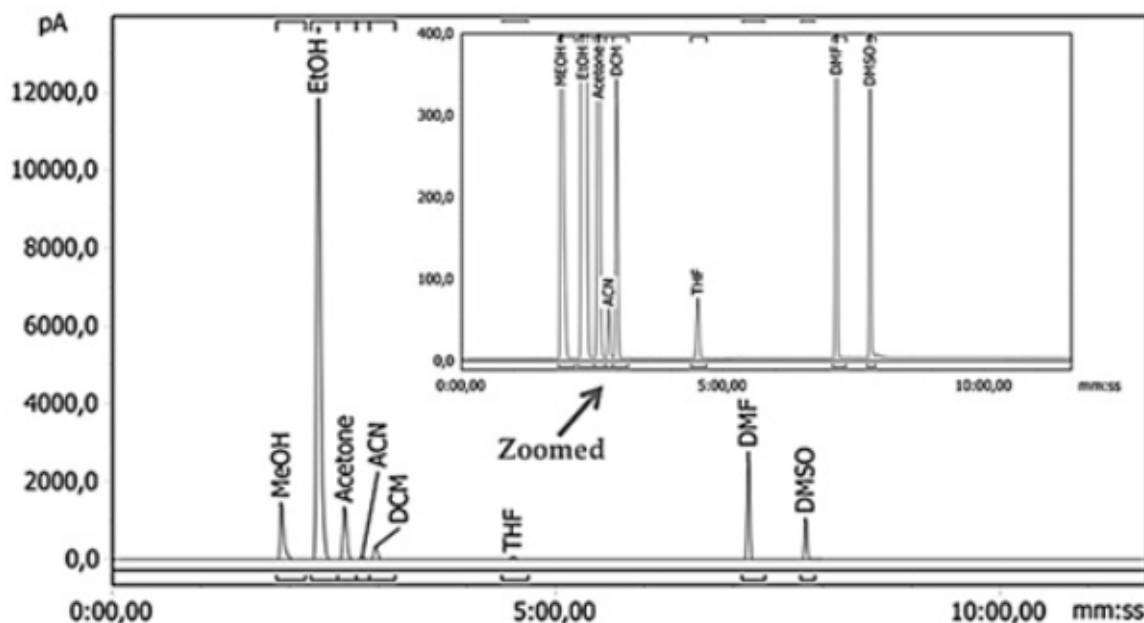


Figure 1

Typical SST chromatogram of commonly used residual solvents in radiopharmacy using the validated method.

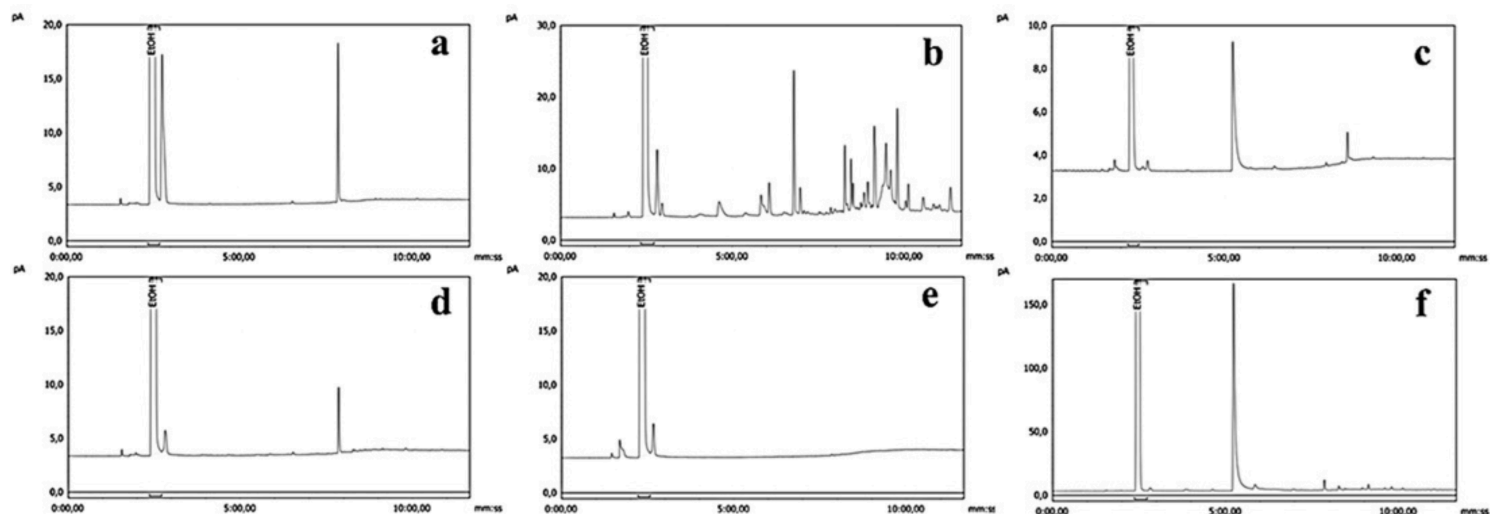


Figure 2

Representative zoomed chromatograms for [^{11}C]Methionine (a), [^{18}F]FE-PE2I (b), [^{18}F]FDG (c), [^{68}Ga]FAPi-46 (d), [^{68}Ga]ATH001(e) and [^{177}Lu]ABY-271 (f) using the validated method. Unidentified peaks originating from product matrices or trace impurities were below the LOQ.

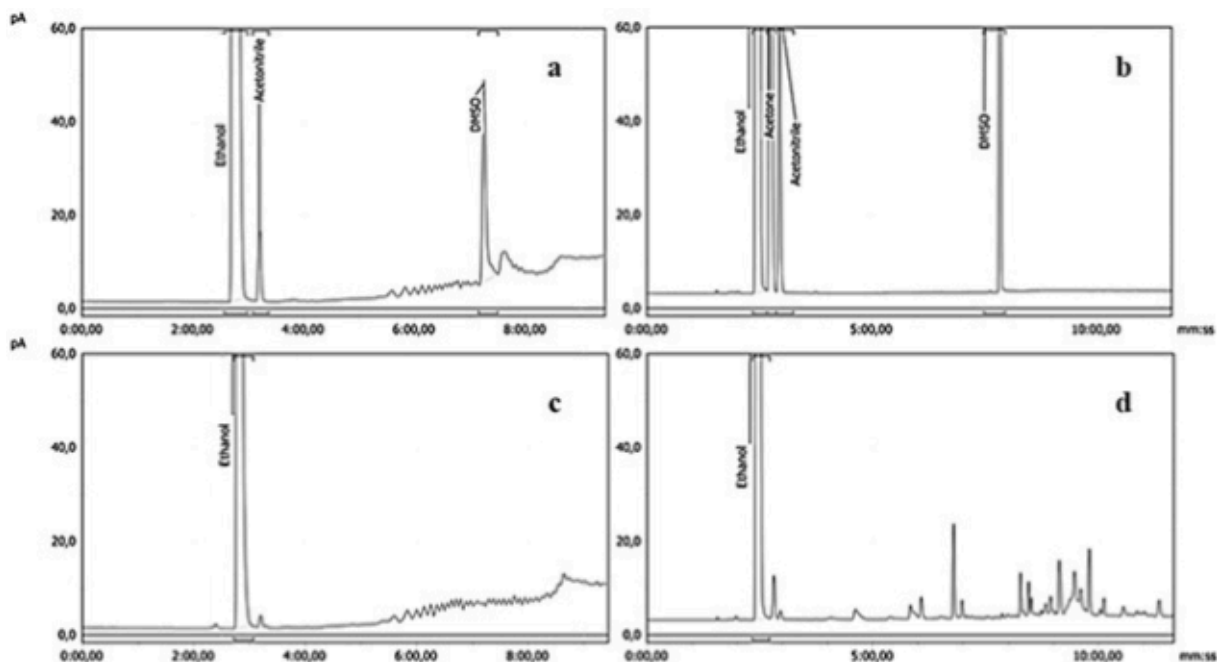


Figure 3

Representative zoomed chromatograms of the SST reference solution (a, b; top) and the FE-PE2I product sample (c, d; bottom) acquired using GC01 and GC02, respectively.