

Application News

GC NexisTM GC-2030

Quantitation of Residual Solvent in Radiopharmaceuticals

Elgin Ting ¹, Cynthia Lahey ¹ 1 Shimadzu (Asia Pacific) Pte Ltd.

User Benefits

- Direct injection of samples without sample preparation
- Sensitive and reproducible at 0.005 %(v/v)

■ Introduction

Radiopharmaceuticals are a group of biological active drugs which consist of radioactive isotope compounds to aid in therapy and diagnostic imaging, such as positron emission tomography (PET) [1]. Solvents are used during the manufacturing of radiopharmaceuticals and may not be completely removed. As solvents could be harmful to human health, it is critical to control and regulate residual solvents amount in radiopharmaceuticals.

In this study, GC-FID is utilized to quantitate acetonitrile, ethanol and isopropanol (IPA) residual solvents in radiopharmaceuticals, i.e. cold [18F]fluoro-deoxy-D-glucose (FDG) and cold prostate-specific membrane antigen (PSMA). The radioactive labelled compounds were left to fully decay (cold) at an appropriate facility before conducting experiment on it. According to United States Pharmacopeia, USP <467>, acetonitrile maximum daily dosage is 4.1 mg/day which is equivalent to a concentration of 400 ppm [2]. Ethanol and IPA are recommended to be less than 50 mg/day (5000 ppm), but higher amount is still acceptable if they can be justified [2].

■ Measurement Conditions and Samples

Nexis GC-2030 gas chromatograph and AOCTM-20i Plus liquid injection autosampler (both from Shimadzu Corporation, Japan) were used in this work. The analytical conditions used for the separation and detection of acetonitrile, ethanol and IPA are shown in Table 1.

Acetonitrile, ethanol and IPA were purchased from Kanto Chemical Co, Inc. Deionized water was used to dilute all the three standards into 1 mixture solution. Two different sets of calibration standard mixtures (low calibration curve standards and high calibration curve standards) were prepared. For the low calibration curve standards, the concentration prepared were 0.005, 0.01, 0.02, 0.05 and 0.1 %(v/v). For the high calibration curve standards, the concentration prepared were 1, 2, 5, 10 and 20 %(v/v).

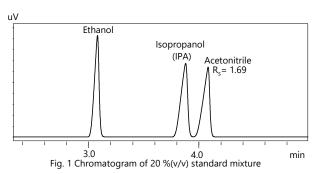
■ Results

GC-FID method was optimized to separate all the three compounds at 20 %(v/v) (Figure 1). A baseline resolution was achieved between IPA and acetonitrile with resolution greater than 1.5.

A repeatability test (n=5) using 0.005 %(v/v) was done to check the stability and sensitivity of the method. The %RSD (n=5) of peak area was less than 2.5 and the average signal

Table 1 GC-FID analytical conditions for residual solvent analysis of radiopharmaceuticals

Instruments and Column information				
GC-FID	Nexis GC-2030			
Auto Injector	AOC-20i Plus			
Column	SH-BAC Plus 1			
	30 m x 0.32 mm ID x 1.80 μm df			
Detector	FID-2030 Flame Ionization Detector			
GC-FID parameter				
Injection Temperature	250°C			
Injection Mode	Split mode			
	Split ratio 30			
Injection Volume	0.2 μL injection with a 0.5-μL syringe			
Carrier Gas	Helium			
Gas Flow Condition	Constant linear velocity mode			
	Linear velocity 25 cm/s			
Oven Temperature Programming	35 °C (4.5 min) →20 °C/min to 220 °C (5 min)			
Detector Temperature	240°C			
Hydrogen Flow	32 mL/min			
Synthetic Air Flow	200 mL/min			
Make-up Gas Flow	24 mL/min			



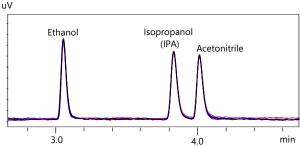


Fig. 2 Overlay of chromatograms (n=5) for 0.005 %(v/v) standard mixtures

to noise (S/N) ratio was more than 35 for all the compounds (Table 2). An overlay chromatogram (n=5) of 0.005 %(v/v) is shown in Figure 2.

Both the repeatability and S/N ratio results demonstrated that 0.005 %(v/v) can be set as limit of quantitation (LOQ). Good linearity with R² value greater than 0.999 was achieved for all the calibration curves (Figure 3). These results indicated that the GC-FID method from Table 1 had been fully optimized for these 3 compounds for concentration ranging from 0.005 %(v/v) to 20 %(v/v).

Table 2 Targeted compound peak area %RSD (n=5) and average S/N ratio (n=5)

Compounds	Peak area %RSD (n=5)	Average S/N ratio (n=5)
Ethanol	2.4	45.3
Isopropanol	2.4	38.6
Acetonitrile	2.3	36.2

Low Calibration Curve A<u>rea</u> Ethanol Calibration concentration $R^2 = 0.9999$ 0.005 %(v/v) 0.01 %(v/v) 3. 0.02 %(v/v) 4. 0.05 %(v/v) 0.1%(v/v)Conc Acetonitrile Isopropanol R²=0.9999 $R^2 = 0.9999$ Conc. **High Calibration Curve** Ethanol Calibration concentration $R^2 = 0.9996$ 1 %(v/v) 2 %(v/v) 5 %(v/v) 10 %(v/v) 20 %(v/v) Conc. Area Acetonitrile Isopropanol $R^2 = 0.9993$ $R^2=0.9994$

Fig. 3 Calibration curves for all the three standard mixtures

The average concentration (n=2) of the compounds in each sample is tabulated in Table 3. An overlay chromatogram of all the 4 cold samples together with a 0.01%(v/v) standard is shown in Figure 4.

Four cold radiopharmaceuticals samples, i.e. two FDG samples and two PSMA samples, were analyzed. The samples were collected from Advanced Medical Imaging (AMI). They were left to fully decay before collection and analysis.

Table 3 Concentrations of residual solvents in samples

	Tuble 5 Confectitutions of residual solvents in samples				
Sample Name	Ethanol Concentration %(v/v)	Isopropanol Concentration %(v/v)	Acetonitrile Concentration %(v/v)		
PSMA Sample 1	4.948	Below LOQ (<0.005)	Not detected		
PSMA Sample 2	5.180	Below LOQ (<0.005)	Not detected		
FDG Sample 1	Below LOQ (<0.005)	Below LOQ (<0.005)	Below LOQ (<0.005)		
FDG Sample 2	0.005	Not detected	Below LOQ (<0.005)		

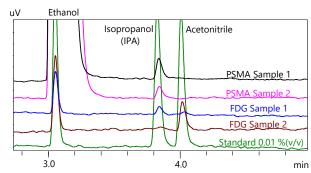


Fig. 4 Overlay of chromatograms for 4 samples and 1 standard 0.01 %(v/v)

■ Conclusion

A GC-FID method has been successfully performed to determine residual solvents ranging from 0.005 %(v/v) to 20 %(v/v) for cold FDG and PSMA samples with excellent linearity of the calibration curves (R2=0.9993 or above). Good sensitivity and repeatability were achieved for all the three types residual solvents (acetonitrile, ethanol, IPA) at 0.005 %(v/v).

■ References

- M. Elisa Crestoni, Radiopharmaceuticals for Diagnosis and Therapy, Reference Module in Chemistry, Molecular Sciences and Chemical Engineering, Elsevier, 2018,
- The United States Pharmacopeia, USP <467> RESIDUAL SOLVENTS.

■ Acknowledgement

We would like to acknowledge Advanced Medicine Imaging (Singapore) for providing samples for this experiment.

Nexis and AOC are trademarks of Shimadzu Corporation or its affiliated companies in Japan and/or other countries



Shimadzu Corporation www.shimadzu.com/an/

SHIMADZU (Asia Pacific) Pte. Ltd, www.shimadzu.com.sg

For Research Use Only. Not for use in diagnostic procedure.

This publication may contain references to products that are not available in your country. Please contact us to check the availability of these products in your country

The content of this publication shall not be reproduced, altered or sold for any commercial purpose without the written approval of

See http://www.shimadzu.com/about/trademarks/index.html for details

See http://www.shimadzu.com/about/trademarks/index.html for details. Third party trademarks and trade names may be used in this publication to refer to either the entities or their products/services, whether or not they are used with trademark symbol "TM" or "6". The information contained herein is provided to you "as is" without warranty of any kind including without limitation warranties as to its accuracy or completeness. Shimadzu does not assume any responsibility or liability for any damage, whether direct or indirect, relating to the use of this publication. This publication is based upon the information available to Shimadzu on or before the date of publication, and subject to change without notice

04-AD-0249-EN

First Edition: Oct. 2021