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Application News

GC Nexis™ GC-2030

Quantitation of Residual Solvent in Radiopharmaceuticals

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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 [^{18}F]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 AOC™-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 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.

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

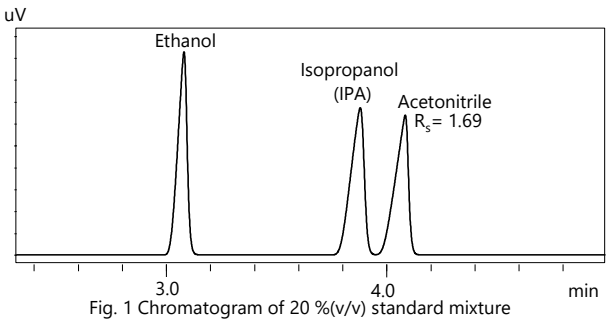

Fig. 1 Chromatogram of 20 %(v/v) standard mixture

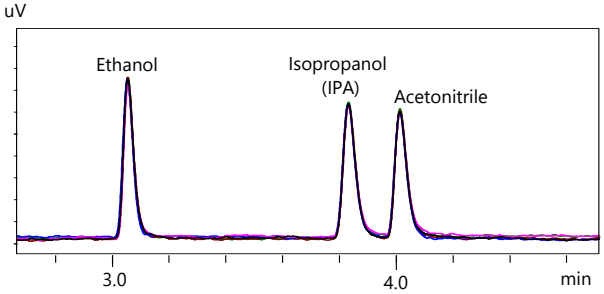

Fig. 2 Overlay of chromatograms (n=5) for 0.005 %(v/v) standard mixtures

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 R^2 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

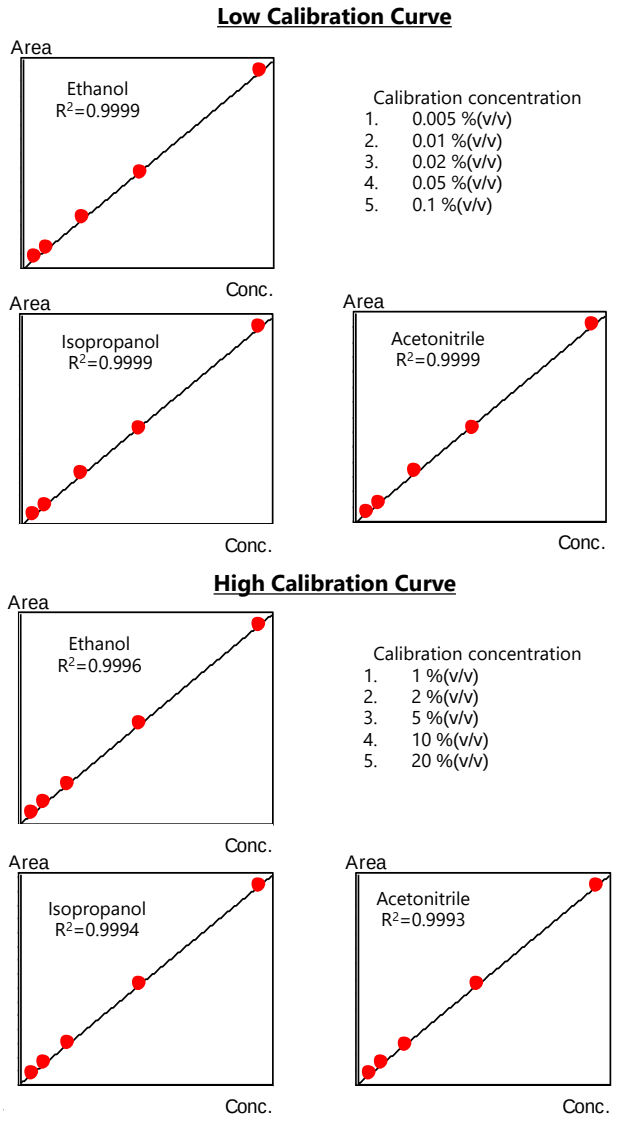

Fig. 3 Calibration curves for all the three standard mixtures

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

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)

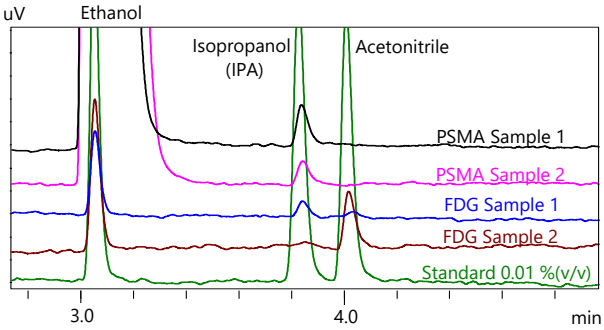

Fig. 4 Overlay of chromatograms for 4 samples and 1 standard 0.01 %(v/v)

■ 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 (R^2=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

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

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