"Gheorghe Asachi" Technical University of Iasi, Romania

AN IMPROVED METHODOLOGY FOR DETERMINATION OF RADIOCHEMICAL AND CHEMICAL IMPURITIES IN THE SYNTHESIS PROCESS OF ^{18}F-FDG (2-[^{18}F] FLUORO-2-DEOXY-D-GLUCOSE)

**Mirela Mihon[1,2], Catalin Tuta[2], Radu Leonte[2,3],
Alina Catrinel Ion[1], Vasile Lavric[1], Dana Niculae[2]***

[1]University Politehnica of Bucharest, Faculty of Applied Chemistry and Materials Science,
1-7 Polizu Str., 011061 Bucharest, Romania
[2]National Institute for Physics and Nuclear Engineering "Horia Hulubei", 30 Reactorului Str., 077125 Magurele Ilfov, Romania
[3]University Politehnica of Bucharest, Faculty of Applied Sciences, 313 Splaiul Independenţei, 060042 Bucharest, Romania

Abstract

^{18}F-FDG is a glucose analog in which the hydroxyl group on the second carbon is substituted with ^{18}F, being used as an indicator of glucose uptake and cell viability.

The aim of this work was to synthesize the ^{18}F-FDG and to validate the methodology for the assessment of its both radiochemical and chemical purities, according to the European Pharmacopoeia. The proposed methodology encompasses three chromatographic methods: radio-HPLC, radio-TLC and HS/GC.

Radiochemical impurities may originate from radionuclide production, incomplete purification and radiolysis after synthesis. Chromatographic methods should effectively separate these species, as radioactive impurities can affect the clinical outcome of positron emission tomography imaging studies because of nonspecific uptake. Chemical impurities, on the other hand, can affect nucleophilic substitution mechanism. Keeping these contaminants at as low concentrations as possible is the key of a successful synthesis. Therefore, the determination of both type of impurities in short time is an essential step in characterizing of each batch, due to the rapid decay of ^{18}F (109.8 min half-life).

By optimizing the operating conditions, both chemical and radiochemical impurities analysis can be done within 12 min. The optimized methodology shows good performance: linearity, specificity, precision, limit of quantification, limit of detection and reproducibility, thus it could be successfully applied in the quality control tests of radiopharmaceuticals according to the European Pharmacopoeia.

Key words: 18F-FDG, chemical impurities, gas chromatography, quality control, radio-HPLC, radio-TLC

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1. Introduction

Positron Emission Tomography (PET) is a technology aimed to obtain *in vivo* biological information quantitatively and noninvasively using radiopharmaceuticals administered intravenously. Chemical and radiochemical impurities may interfere with PET measurements and may cause adverse reactions in the body (Vallabhajosula, 2009).

European Pharmacopoeia (Eur.Ph.) is the official reference source of quality specifications for a pharmaceutical product**.** The analytical methods predominantly used to asses them are: high performance liquid chromatography (HPLC), thin layer chromatography (TLC), and gas chromatography (GC). For the ^{18}F-FDG radiopharmaceutical, certain quality criteria are required to pass the quality control. For this purpose, the following parameters are to be tested:

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* Author to whom all correspondence should be addressed: e-mail: dana.niculae@nipne.ro; Phone: +40 21 404 5033; Fax +40 21 457 4945

radiochemical and chemical purities, endotoxin content, pH, appearance, osmolality, sterility. Analytical methods need to be fast, very accurate and consistent with the usual quality standards of pharmaceuticals, while the detection limit should be as low as *ppm*, due to the short lifetime, and the radiation protection of the operator (special conditions for handling radioactive substances); the latter necessitates a very small amount of chemical compound. The methods should be comparable with the half-life of the radioisotope; in the case of ^{18}F, all tests except the sterility should be performed within 30 minutes post production – a longer analysis time means a loss of radiopharmaceutical's activity (IAEA, 2012).

The radiochemical purity is the ratio, expressed as a percentage, of the radioactivity of the nuclide of interest in the specified chemical form and the radionuclide's total radioactivity in the radiopharmaceutical preparation, respectively (Saha, 2004). A pure radiopharmaceutical compound must not contain other radioactive species. For ^{18}F-FDG, the radiochemical impurities are other species labeled with ^{18}F, such as ^{18}F-fluoride or ^{18}F-acetylglucose (intermediaries). The radiochemical identity can be confirmed by HPLC or TLC. The simplest chromatographic method useful for determination of radiochemical purity is the TLC (Koziorowski, 2010).

The chemical identity and purity address non-radioactive materials in radiopharmaceuticals, including raw materials, solvents and other compounds used in the preparation process (stabilizers, additives etc.). Some examples of non-radioactive core components that require testing in ^{18}F-FDG preparation are: 2-fluoro-2-deoxy-D-glucose (FDG) and 2-chloro-2-deoxy-D-glucose (ClDG), residual solvents (acetonitrile, acetone and ethanol), and Kryptofix 2.2.2 (aminopolyether). Depending on the hydrolysis type in the synthesis path (acidic or alkaline), ClDG impurity could be produced or not (Mosdzianowski et al., 2002).

The aim of this work is the development and validation of faster methods, comparing with those recommended by the Eur.Ph., to determine both radiochemical and chemical purities of ^{18}F-FDG and which can be used in quality control.

The analysis of residual solvents by GC has been widely described concerning some injection techniques, columns and temperature profiles. Apart from different Pharmacopoeia, several methods of analysis have been described (Channing et al., 2001; Fliszar et al., 2004; Klick and Skold, 2004; Qin et al., 2004; Raghani, 2002). A new head-space/gas chromatography (HS/GC) method is presented and validated for the determination of residual solvents (ethanol, acetone and acetonitrile) in this radiopharmaceutical product. Both chemical and radiochemical purities were also validated using a HPLC equipped with electrochemical and radioactive detectors, in accordance with the monograph in Eur.Ph. (EDQM, 2014).

Up to date, several detectors such as UV/VIS, refractive index and pulsed amperometric detector (PAD) coupled with HPLC system were tested for carbohydrates analysis, but each of them has several advantages and disadvantages. For example, the detection of carbohydrates by HPLC with UV/VIS detector is difficult due to the low molar absorbance in the UV/VIS region. Several precolumn or postcolumn derivatizations (i.e., 2-cyanoacetamide and 1-phenyl-3-methyl-5-pyrazolone) of FDG and ClDG have been reported (Nakao et al., 2005, 2008), but derivatizations are not suitable for routine quality control of the ^{18}F-FDG preparations due to the long labeling time, the short half-life of ^{18}F and the radiation exposure of the operator (Nakao et al., 2008).

The refractive index detector can be used only for high concentration of carbohydrates. PAD, working with a gold electrode, could be used if the concentrations of carbohydrates are very low (Jensen et al., 1997; LaCourse et al., 1993). HPLC/PAD has been reported to be a sensitive method, without derivatization, and has been advocated in the Eur.Ph. as the recommended technique.

2. Experimental

2.1. Materials

All solvents were purchased from Merck and used without purification. Ultrapure water was prepared using the Millipore MilliQ Direct 8/16 water purification system. Standards (reference chemicals) were obtained from ABX (Germany).

^{18}F-Fluoride was produced at National Institute for Physics and Nuclear Engineering "Horia Hulubei", Radiopharmaceuticals Research Centre (Ursu et al., 2013), in the Cyclotron TR19 (ACSI).

The synthesis of ^{18}F-FDG was performed according to the nucleophilic substitution method (Hamacher et al., 1986), followed by alkaline hydrolysis of the intermediary product [^{18}F]fluoro-1,3,4,6-tetra-O-acetyl-D-glucose (FTAG) (Fig. 1), on the synthesis module FASTlab (GE Healthcare, USA). The leaving group, triflate is converted to trifluorosulfonic acid (CF_3SO_2OH), which is removed at a later stage in the purification process.

2.2. High performance liquid chromatography

HPLC was performed with an Agilent Bio-inert 1260 Series equipped with electrochemical (Decade II, Antec – USA) and radioactive (Gabi, Raytest – Germany) detectors. A Carbopac PA1 column (Dionex) 250x4.5 mm with 1.0 μm internal diameter was used for separation of chemical impurities of FDG by isocratic elution with 0.1 M sodium hydroxide (NaOH) as mobile phase; flow rate 1.2 mL/min, temperature of the column and electrochemical cell 35 ^{0}C.
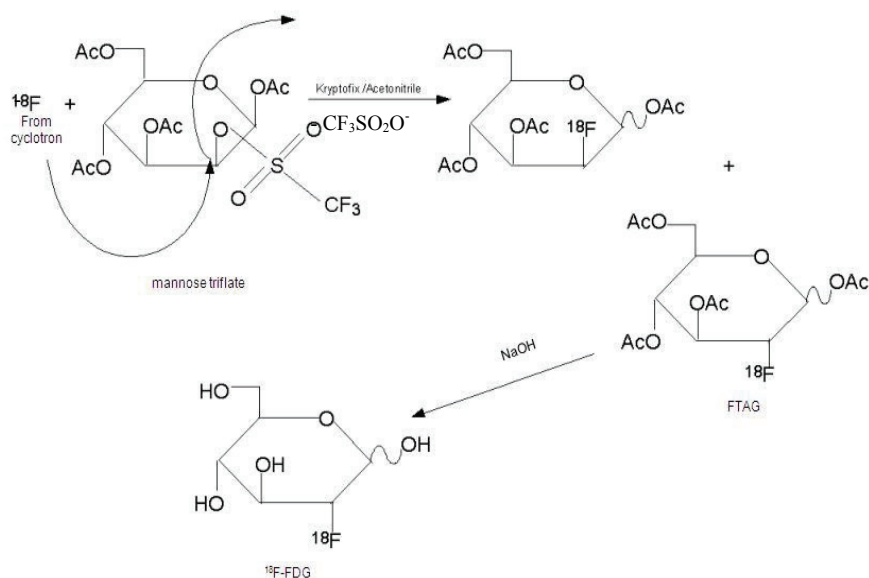
Fig. 1. Synthesis of ^{18}F-FDG by nucleophilic substitution followed by alkaline hydrolysis (Yu, 2006)

Electrochemical detection was performed in pulsed mode used an Au cell with Ag/AgCl reference electrode. Radioactive samples were analyzed using a gamma radioactive detector with NaI cell.

2.3. Gas Chromatography

An Agilent 6890A GC equipped with an FID and a 7694 HS sampler was used for the experiments. The HS/GC system was controlled using Agilent Chem32 software. The GC column was a J&W DB – 624 (6% cyanopropylphenyl / 94% dimethylpolysiloxane) fused silica capillary column, having 30 m length, 0.53 mm internal diameter, 3 μm film thickness.

2.4. Thin Layer Chromatography

The TLC Chromatographic method was applied only to determine the radiochemical purity, as alternative method. A VCS 201 System - Veenstra Instruments Holland was used. The data acquisition was obtained with the VCS 203 software.

2.5. Method validation

The validation of the analytical method was carried out according to ICH Q2 (R1) guidelines (ICH, 2005). The parameters of the validation were: system suitability, specificity, precision, accuracy, linearity, limit of detection (LoD) and limit of quantification (LoQ) (Burlacu et al., 2009; ICH, 2005). The system suitability was evaluated by injecting the blank solution (duplicate) and standard test solution (six injections) using the optimized method.

The chromatograms were recorded, evaluated and the relative standard deviations were computed. The resolution between two successive peaks was measured. The specificity of the method was performed by injecting standard solutions of each residual solvent and a mixture of standard solutions for these compounds and comparing the retention time of each standard. The precision was performed by injecting six standard test solutions (100%), measuring the response for each solvent peak and calculating its relative standard deviation (%).

The method's accuracy was validated through recovery experiments by spiking with known amount of each solvent at 80%, 100% and 120%. Each concentration was prepared in triplicate and the percent recovery was calculated.

The linearity of the method was investigated using six concentration levels ranging from 100 to 1,000 ppm for ethanol and acetone and 10 to 100 ppm for acetonitrile. The correlation coefficient of determination (R^2) was calculated for each solvent.

The sensitivity of the method was presented as the LoQ with a signal to noise ratio of 10:1 and the LoD with a signal to noise ratio of 3:1. Both LoQ and LoD have been established on the basis of S/N ratio by six injections at LoD level and six injections at LoQ level.

2.6. Standard preparation

For GC determinations, a standard stock solution of solvents was prepared from 2.5 g ethanol, 2.5 g acetone and 0.25 g acetonitrile, accurately weighted and diluted with water in a 10 mL volumetric flask. Working standard solutions were prepared by diluting the standard stock solution with water. Test solutions were obtained by diluting 200 μL of sample to 1.0 mL with water.

For HPLC determinations, 2 mg of FDG standard was weighted and transferred accurately into 10 mL volumetric flask and dissolved in water to obtain the standard stock solution. Working standard

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solutions were obtained by serial dilution of standard stock solution. The test sample was directly injected in the chromatographic system.

3. Results and discussion

3.1. Development of the method assessing Residual Solvents using HS/GC

Based on the methods described in Eur.Ph. regarding the analysis of residual solvents in pharmaceutical products, a new and faster method was developed to determine three residual solvents, namely ethanol, acetone and acetonitrile, which may be found in ^{18}F-FDG radiopharmaceutical product.

The proposed method has significant changes in comparison with the method described in Eur.Ph. We varied a number of parameters in the HS system: temperature (oven, transfer line and loop), time (vial equilibration and injection) and pressure. The equilibration temperature was increased from 90 °C to 105 °C. The equilibration time in headspace module was decreased from 45 to 2 minutes. The GC cycle was optimized at 10 min. A number of GC parameters were evaluated during the development of

this method: the oven temperature gradient, the flow rate of the carrier gas and the sample split ratio. The ramp temperature was optimized in the 40–100 °C interval.

All the solutions (standards and samples) were diluted with water. The parameters of the improved HS/GC method are listed in Table 1. In this method the maximal used temperature was 100 °C because all the residual solvents have been eluted before this value. The specificity is the ability of the method to confirm the analyte identity from other interferences. The specificity of the method was confirmed by the resolution between two consecutive peaks, both in sample and in standard solutions.

No interference from the blank at each retention time of analyte peaks was observed. A chromatogram obtained from the standard solution is shown in Fig. 2. The data obtained for standard solutions are presented in Table 2; the resolution between two successive eluting peaks was higher than 2.0, which meets the acceptance criteria. The method has been shown to be linear by a plot of six points in the range 100–1,000 ppm for ethanol and acetone.

Table 1. Chromatographic parameters for HS/GC optimized method

| Headspace Parameter	Settings	
	Eur.Ph. method	*Optimised method*
Equilibration temperature	90 ^{0}C	105 ^{0}C
Transfer line temperature	105 ^{0}C	110 ^{0}C
Loop temperature	110 ^{0}C	
Vial equilibration time	45 min	2 min
Injection Duration	0.2 min	0.2 min
GC Cycle	30 min	10 min
Volume Injection	1 μL	
GC Parameter		
Inlet temperature	150 ^{0}C	
Carrier (He) flow rate	36 mL/min	82.1 mL/min
Pressure	2.3 psi	3.65 psi
Inlet split ratio	10:1	15:1
Oven temperature gradient	40 ^{0}C–240 ^{0}C	40 ^{0}C–100 ^{0}C
Ramping to	30 ^{0}C / min	15 ^{0}C / min.
FID temperature	250 ^{0}C	
Detector gas flow	30 mL/min.	
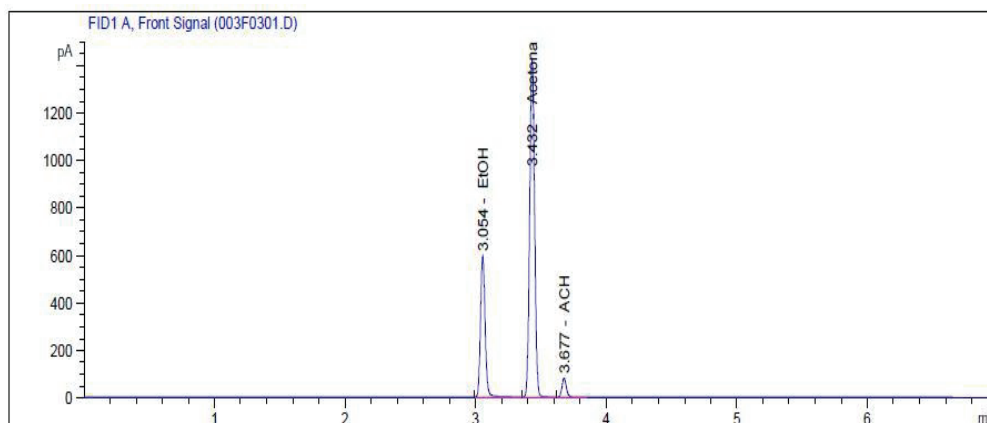
Fig. 2. The chromatogram of the standard residual solvents

The linearity range was determined in between 10–100 ppm for acetonitrile. Good linearity was achieved for all solvents (see Fig. 3). The correlation coefficient (R^2) for each residual solvent had value higher than 0.998.

Table 2. Specificity of the method

Solvent	Retention Time (min)	Relative Retention Time	Resolution
Ethanol	3.05	1.0	-
Acetone	3.43	1.14	5.6
Acetonitrile	3.67	1.22	3.1

a)

b)

c)
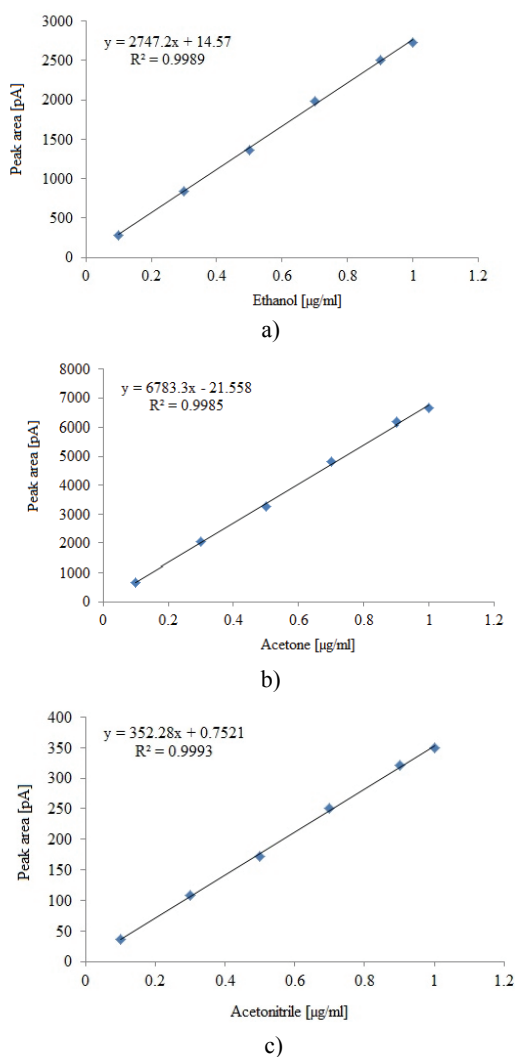
Fig. 3. Calibration curves for residual solvents: a. ethanol; b. acetone; c. acetonitrile

The precision of this method was expressed as relative standard deviation (RSD) data and was performed by injecting six standard test solutions. Both the standard deviation (SD) and RSD were calculated for each solvent. The RSD was found out to be less than 15%. All values are listed in Table 3.

The limits of both LoD and LoQ were calculated following the formulas: LoD = 3.3 σ/S, and LoQ = 10 σ/S, respectively, where σ is the SD of

the response and S is the slope of the calibration curve of the solvent. The results are shown in Table 4.

Table 3. The precision of the method

Number of injection	Area		
	Ethanol	Acetone	Acetonitrile
1	1454.6	3562.4	184.5
2	1417.6	3481.8	181.5
3	1446.7	3427.9	180.8
4	1483.2	3421.3	182.8
5	1386	3297.1	174.7
6	1342	3350	174.1
Average	1421.7	3423.4	179.7
SD	43.3	79.4	3.6
% RSD	3.1	2.3	2.0

Table 4. The values of the LoD and the LoQ for the residual solvents

Solvent	Limit of detection [µg/mL]	Limit of quantitation [µg/mL]
Ethanol	0.52	1.57
Acetone	0.39	1.18
Acetonitrile	0.04	0.11

The system suitability has been demonstrated by analyzing the standard solutions during the validation study. The system performance was checked by the resolution, % RSD and asymmetry. The results obtained for the system suitability of this method are presented in Table 5.

3.2. Development of the method for assessing chemical purity using HPLC

The adopted synthesis route of ^{18}F-FDG product involves a nucleophilic substitution mechanism and a basic hydrolysis. In this case, the 2-chloro-2-deoxy-D-glucose impurity is absent. The limit of FDG standard is 0.5 mg/V, with V being the maximum recommended dose in milliliters. The HPLC analysis's parameters are listed in Table 6.

The detection of FDG was completed in less than 12 minutes (Fig. 4).The range of linearity was determined between 2–200 µg/mL for FDG standard. The calibration line is shown in Fig. 5.

The parameters of the validation process such as precision, accuracy, linearity, LoD and LoQ were determined in conformity with the ICH standard requirements. The results are present in Table 7.

3.3. Complementary TLC method used to identity and to assess the radiochemical purity

The radiochemical purity was evaluated by TLC scanner. TLC mobile phase is a mixture of acetonitrile and water (95:5 v/v). It should be noted that the results of TLC may vary due to different companies producing the paper chromatography and the operating conditions (EDQM, 2014).

Table 5. The system suitability's parameters for the improved HS/GC method

Number	System Suitability Parameters	Value			Specification
		Ethanol	Acetone	Acetonitrile	
1.	Resolution	-	5.6	3.1	>2
2.	% RSD	3.1	2.3	2.0	<15
3.	Asymmetry	0.84–0.94	0.87–0.97	0.85–0.95	0.8–1.2

Table 6. The chromatographic parameters for HPLC/ EC (PAD) method

Chromatographic parameters	Settings
Flow	Isocratic at 1,2 mL/min
Column	Thermo Scientific Dionex Carbopac: PA1, 4x250 mm,1.0 µm i.d.
Temperature	35 ^{0}C
Injection volume	5 µL loop
Mobile phase	0.1M Sodium hydroxide (NaOH)
EC parameters (PAD)	Working potential +200 mV vs. Ag/AgCl reference electrode
Range	50 µA
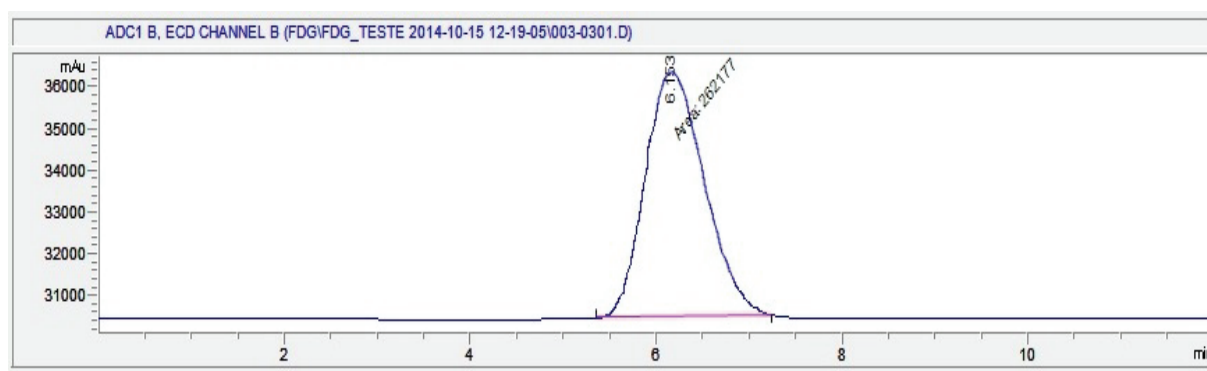
Fig. 4. The HPLC report for the FDG Standard
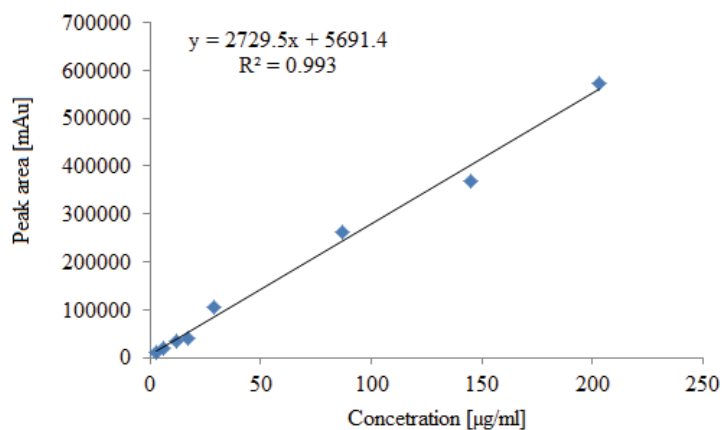
Fig. 5. The calibration line for the FDG standard

Therefore, it is important to use the same type of paper, and also to TLC freshly prepared mobile phase. The size of the spot should be 5 µL. After separation in 95:5 acetonitrile/water mixture, the paper chromatography was dried. Radiochemical purity is defined as the percentage of the radioactivity present in the nuclide of the specified chemical form of interest from the total radioactivity of the radionuclide present in R_f preparation, respectively. In the case of ^{18}F-FDG synthesis, the radiochemical impurities are other species marked with ^{18}F, ^{18}F such as F or radio-labeled intermediaries.

The radiochemical impurities are separated due to their differing affinities to the mobile phase. The chromatographic paper was dried after separation of the spot in 95:5 acetonitrile/water mixture. The front ratio (R_f) values for ^{18}F-FDG, free ^{18}F and acetylated ^{18}F-FDG are 0.65; 0.00 and, respectively 0.80 to 0.95 (Table 8).

The product migration profile was determined by scanning the chromatogram plate with a suitable collimated radiation detector. The radiochemical purity of the preparation is acceptable if the percent of the area peak of the ^{18}F-FDG is higher than 95%. The radiochemical purity of the synthesized product, i.e. ^{18}F-FDG, was 100% and the radiochromatogram is presented in Fig. 6.

4. Conclusions

The most important aspect of working with ^{18}F-FDG is the short time which can be spent on quality control in the laboratory, which now is about 30 minutes. The critical factors are the speed, the simplicity and the reliability of the new developed analytical method.

An improved and fast HS-GC method for the quality control of ^{18}F-FDG has been developed and validated, meeting all the acceptance criteria in terms of linearity, specificity, precision, accuracy, as well as LoD and LoQ. The HS-GC method is characterized by the high correlation coefficients and the short time of analysis (10 min), comparing to the 30 min corresponding to the method outlined in the Eur.Ph..

Table 7. The results of HPLC/EC (PAD) validated method

Validation Parameter	
Linearity: The correlation coefficient (R^2) should be > 0.99	
Regression Equation	y = 2729.5x + 5691.4
Correlation coefficient (R^2)	0.993
Range (µg/mL)	2–200
Precision: %RSD, should be < 5%	
Repeatability	3.47
Intra-day precision	
80%	2.31
100%	1.00
120%	2.43
LoD (µg/mL)	1.22
LoQ (µg/mL)	3.71
Accuracy: %Recovery should be within 80-120%	
Concentration (%)	Recovery (%)
80	96.32
100	99.13
120	97.88

Table 8. Informative R_f values

$R_F \sim 0$	Free [^{18}F] fluorine ions – $^{18}F^-$
$R_F \sim 0.65$	2-[^{18}F] fluoro -2-deoxy-D-glucose – [^{18}F]FDG
$R_F \sim 0.9$	Incompletely hydrolyzed sugar derivations – Ac-[^{18}F]FDG
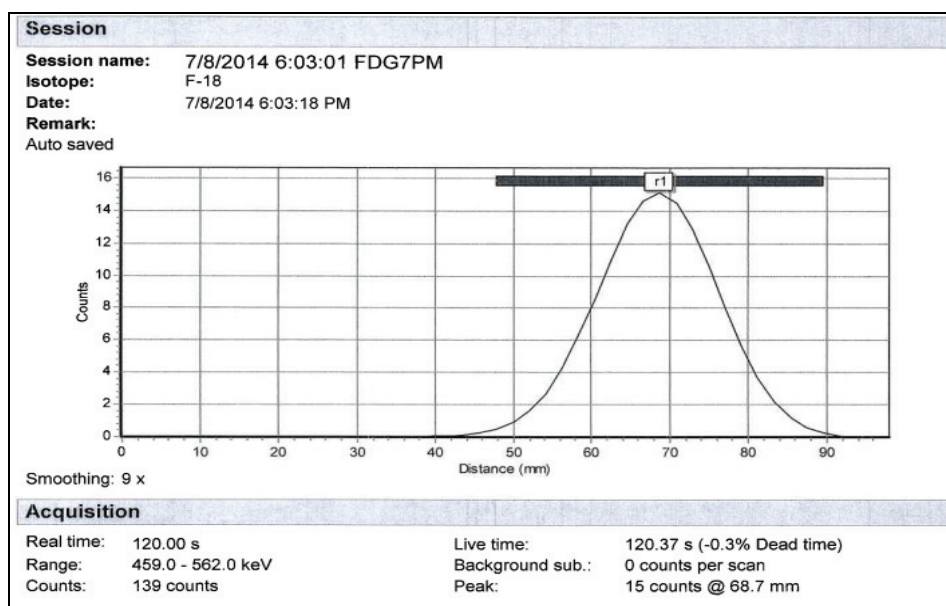
Fig. 6. The TLC report for the synthesized ^{18}F-FDG

The HPLC method for determination of 2-fluoro-2-deoxy-D-glucose (FDG) is specific, precise, accurate, linear and robust. The analysis time is short, just 12 minutes to complete. Also, the determination of the radiochemical purity using TLC is reliable and fast.

These methods are selective and thus can also be used in quality control of other radiopharmaceutical compounds.

Acknowledgements

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