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Chelation reaction *vs.* isotope exchange for production of effective receptor-targeted radiopharmaceuticals

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Peptide-based pharmaceuticals have applications in both diagnostic imaging and targeted therapy. Various prostate-specific membrane antigens (PSMA) are of considerable interest in the development of specific markers for the diagnosis and treatment of prostate cancer (PCa).

The aim of the present study was to compare the methods for the production of two diagnostic radiopharmaceuticals based on PSMA – [^{68}Ga]PSMA-11 and [^{18}F]SiPSMA-14. The syntheses of the indicated products differ in the modification of the starting peptide precursor, the duration and the mechanism of the process. Two methods for radiochemical synthesis were applied – chelation reaction and isotope exchange reaction. The peptide precursor PSMA was labelled with two different positron-emitting radionuclides ^{68}Ga and ^{18}F, obtained from a ^{68}Ge/^{68}Ga generator and a cyclotron, respectively. An automated synthesis procedure was applied to ensure safe and efficient production of the radiopharmaceuticals. The radiochemical yield, chemical and radiochemical purity, and radionuclide identity of both radiopharmaceuticals were determined according to the requirements of the European Pharmacopoeia.

In conclusion, [^{18}F]SiPSMA-14 is a new PET radiotracer for radiopharmaceutical science, recently introduced into clinical practice for the evaluation of PCa patients. The isotope exchange reaction was adapted and used for the first time in Bulgaria. The production of [^{18}F]SiPSMA-14 is a faster process and occurs under milder reaction conditions compared to the production of [^{68}Ga]PSMA-11. The high yield of [^{18}F]SiPSMA-14 and the better nuclear characteristics of ^{18}F are essential. An additional advantage of the production of [^{18}F]SiPSMA-14 is the availability of an in-house cyclotron in the clinic.

Keywords: radiopharmaceuticals, PSMA, ^{68}Ga, ^{18}F, prostate cancer

Abbreviations:

[^{68}Ga]PSMA-11 – Prostate-specific membrane antigen labelled with ^{68}Ga
[^{18}F]SiPSMA-14 – Prostate-specific membrane antigen labelled with ^{18}F
PCa – Prostate cancer
PET – Positron emission tomography
CT – Computed tomography
SPECT – Single-photon emission computed tomography
HBED-CC – Hydroxy-5-(carboxyethyl)benzyl ethylenediamine diacetic acid
NOTA – Triazacyclononane-triacetic acid (bifunctional chelator)
HEPES – Hydroxyethyl piperazineethanesulfonic acid
HPLC – High performance liquid chromatography
TLC – Thin-layer chromatography
TFA – Trifluoroacetic acid
SPE – Solid phase extraction
QMA cartridge - Quaternary methyl ammonium
HLB cartridge - Hydrophilic-lipophilic balanced sorbent

INTRODUCTION

Prostate cancer is one of the most common malignancies in men. With the development of molecular imaging diagnostics, PSMA (prostate-specific membrane antigen) has become established as a key marker for the detection, monitoring and targeted therapy of the disease due to its high tumor expression [1-3]. PSMA is found on the surface of prostate cancer cells at all stages of the disease. Therefore, this protein is considered the best target antigen [4, 5], although its low expression is also found in the salivary glands, kidneys and in the endothelium of most solid tumors [6]. Initially, PSMA antibodies [7] or their fragments were used as radionuclide carriers in nuclear medicine for the treatment of prostate cancer [8, 9]. In recent years, various new radiopharmaceuticals based on PSMA ligands have been introduced into clinical practice

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for PET or SPECT imaging and therapy [3, 10, 11]. ^{68}Ga and ^{18}F-labelled PSMA ligands are commonly used for PET diagnostics [12], as they provide high image contrast [13].

The radionuclide ^{18}F is a positron emitter with a half-life of 109 min. It is mainly produced in a cyclotron by proton bombardment of ^{18}O-enriched water. The rapid initiation of the ^{18}O(p,n)^{18}F reaction permits the production of large quantities of ^{18}F using cyclotrons with average energies up to 20 MeV. A major advantage of this method of production is the lack of competing nuclear reactions [14]. The radionuclide ^{68}Ga is also a positron emitter with a half-life of 68 min. It can be produced in a cyclotron by proton bombardment of a liquid target containing a solution of [^{68}Zn]Zn$(NO_3)_2$ [15]. However, for the purpose of routine radiopharmaceutical synthesis of ^{68}Ga-labelled radiopharmaceuticals, a ^{68}Ge/^{68}Ga generator system is primarily used. The ^{68}Ga radionuclide is obtained by a standard hydrochloric acid elution method. The availability of a ^{68}Ge/^{68}Ga generator facilitates the on-site production of ^{68}Ga-labelled radiopharmaceuticals [16].

Some PSMA PET agents are labelled by chelating with ^{68}Ga, while others are directly labelled with ^{18}F [17]. The most commonly developed PSMA radiotracers are labelled with gallium-68, e.g., [^{68}Ga]PSMA-11 and [^{68}Ga]PSMA-617 [18]. One advantage of Ga-labelled compounds is that they include a chelate that can also be used to bind isotopes such as ^{177}Lu or ^{225}Ac in the production of therapeutics, thus constituting a true theragnostic agent [17, 19]. Although the most commonly used PSMA PET radioligands are currently labelled with ^{68}Ga, this is associated with a number of disadvantages compared with fluorine-18 labelled ones. The short half-life and relatively low available radioactivity of gallium-68 limits both the transport of ^{68}Ga-labelled PET compounds to other PET centers and delays imaging [18]. Furthermore, ^{68}Ge/^{68}Ga generators are associated with logistical limitations such as long delivery duration due to shortage of commercially available approved generators; moreover, high activity yields cannot be obtained due to capacity limitations of available generators [20]. Gallium-68 produced by a generator is readily available for radiolabelling using lyophilized precursor formulations, but production capacity is limited to 2–4 patient doses depending on the lifetime of the generator. A significant disadvantage of using ^{68}Ga-radiolabelled PSMA synthetic peptides is the reduced number of patients that can be imaged with PET/CT at one time. Such a limitation is due to the relatively low amount of ^{68}Ga available after each elution and the decrease in generator activity over time [21, 22]. On the other hand, cyclotron-produced fluorine-18 can be obtained with significantly higher activity, allowing for more doses to patients and a higher dose activity [18, 23, 24]. The longer half-life of ^{18}F allows for the delivery of final radiopharmaceuticals to off-site PET centers that are no more than 4 hours away from the cyclotron-equipped manufacturing facility [25]. This has led to a rapid and significant increase in the development of ^{18}F-labelled PSMA ligands [18]. Several ^{18}F-labelled PSMA targeting radiotracers have been introduced and increasingly used in clinical practice [21, 22].

One of the ^{18}F-labelled radiopharmaceuticals used is [^{18}F]PSMA-1007, the initial synthesis of which consists of the production of an activated ^{18}F-labelled prosthetic group, which is subsequently coupled to the unprotected precursor, followed by HPLC-purification of the product (total 1.5%-6.0% decay-corrected yield, 45 min) [26, 27]. The implementation of multi-step and time-consuming radiofluorination procedures is particularly detrimental for the radiolabelling of large biomolecules, which require mild conditions and a one-step labelling procedure [18, 28]. A one-step procedure was later presented that can produce [^{18}F]PSMA-1007 with improved radiochemical yield (25%-80%) in less than 55 min [29]. Other alternative ^{18}F-labelling strategies were developed. A new technique for introducing fluorine-18 to a biomolecule is through metal-based radiochemistry. Ga^{3+} and Al^{3+} are trivalent metals with similar ionic radii, and the fluoride-aluminum (AlF^{2+}) complex is associated with strong bond formation and high *in vivo* stability. This suggests that AlF^{2+} can form stable complexes with hexadentate ligands such as NOTA or HBED-CC [18, 30]. This radiofluorination method is efficient, simple, rapid, and can be performed in aqueous media, eliminating the need for azeotropic drying [31].

To avoid the complex multi-step process of C – F bond formation, the labelling can be performed by another efficient radiofluorination method based on isotope exchange using a silicon fluoride (SiFA) acceptor building block. This reaction proceeds rapidly with high yield and high molar activity and is resistant to hydrolysis due to the surrounding sterically demanding substituents [5, 18, 32]. Kinetic analysis of the isoenergetic substitution of ^{19}F with the positron isotope ^{18}F in the SiFA moiety revealed a low energy barrier of only 15.7 kcal/mol [33]. This explains the rapid isotopic exchange reaction from ^{19}F to ^{18}F at room temperature within 5 min, giving [^{18}F]SiFA-conjugated compounds with high yields

(40%) and high molar activity. Furthermore, the lack of by-products allows for simple cartridge-based purification, resulting in a total synthesis time of 30 min [34-36]. The introduction of radiohybrid ligands containing both a SiFA building block and a chelator allows labelling of the biomolecule with both a diagnostic (e.g., fluorine-18 or gallium-68) and a therapeutic (e.g., lutetium-177) radioisotope [32, 37].

The aim of the present study was to compare the methods for the production of two diagnostic radiopharmaceuticals based on PSMA – [^{68}Ga]PSMA-11 and [^{18}F]SiPSMA-14. The presented synthesis methods were not developed in our clinic, but were introduced as standardized procedures for the production of the indicated radiopharmaceuticals. Syntheses were performed according to the manufacturer's synthesis instructions (Scintomics, Fürstenfeldbruck, Germany). The novelty is the application of the isotope exchange reaction as a convenient method for labelling the PSMA molecule with ^{18}F in one step, without the risk of destroying the peptide structure. In addition, the aim was to point out the advantages not only of this production method, but also of the radionuclide ^{18}F itself. In the presence of an in-house cyclotron, it is more convenient and preferable to produce the ^{18}F-labelled radiopharmaceutical [^{18}F]SiPSMA-14.

EXPERIMENTAL

Materials and equipment

For the production of both radiopharmaceuticals [^{68}Ga]PSMA-11 and [^{18}F]SiPSMA-14, standardized automated synthesis procedures with a Scintomics GRP radiochemical synthesis module were applied. Disposable synthesis cards for synthesis of [^{68}Ga]PSMA-11, appropriate peptides and reagent kits supplied by ABX Advanced Biochemical Compounds (Radeberg, Germany) were used. All solvents and reagents (ethanol 70%, ethanol/water 1/1, water for injections, 1.5 M hydroxyethyl-piperazineethanesulfonic acid (HEPES) buffer, 5 M NaCl, phosphate buffered saline (PBS) (pH=7.4) were sterile and ultrapure. In addition to the above reagents, lyophilized peptide precursor PSMA-11 (10 µg) was used for the synthesis, and 4 ml of 0.05 M HCl was used for elution of ^{68}Ga from the ^{68}Ge/^{68}Ga generator.

The kit for the production of [^{18}F]SiPSMA-14 included: 10 ml of anhydrous acetonitrile (>99.9%), 250 µl of dimethyl sulfoxide anhydrous (DMSO, >99.9%), 3 ml of ethanol/water 1/1, 2 ml of anhydrous acetonitrile (for dissolving the eluent, >99.9%), 38 ml of 0.1 M citrate buffer (pH=5.0), lyophilized eluent cocktail, 100 µl of 1M oxalic acid and lyophilized peptide precursor SiPSMA-14 (150 nmol/vial). All solvents and reagents for synthesis of [^{18}F]SiPSMA-14 were sterile and ultrapure or HPLC grade from Huayi isotopes, China.

- *Production of [^{68}Ga]PSMA-11*

The synthesis of this radiopharmaceutical was based on the chelation reaction between ^{68}Ga and the peptide precursor PSMA-11. The complexation of the radionuclide gallium-68 was achieved by the bifunctional acyclic chelator HBED-CC, which is a hexadentate chelator. For the production of [^{68}Ga]PSMA-11, the radionuclide ^{68}Ga was obtained *via* a ^{68}Ge/^{68}Ga generator (1850 MBq, ITM Isotope Technologies Munich SE, Germany) by elution with 0.05M HCl, as a part of the automated procedure.

After elution of ^{68}Ga from the ^{68}Ge/^{68}Ga generator in the form of [^{68}Ga]Cl_3, it entered the synthesis cassette, then was captured in a PSH cartridge**.** NaCl solution was used for elution of $^{68}Ga^{3+}$. The radiolabelling was carried out at a temperature of 95°C followed by purification of the product on a C18 cartridge. Subsequently, the product was eluted with 3 ml of ethanol/water in a sterile vial and diluted with PBS (pH 7.4). The entire synthesis procedure lasted 30 min. The procedure for preparing the radiopharmaceutical [^{68}Ga]PSMA-11 is standard and adapted from literature data [16, 40]. The structure of the ^{68}Ga-labelled radiopharmaceutical is presented in Figure 1.

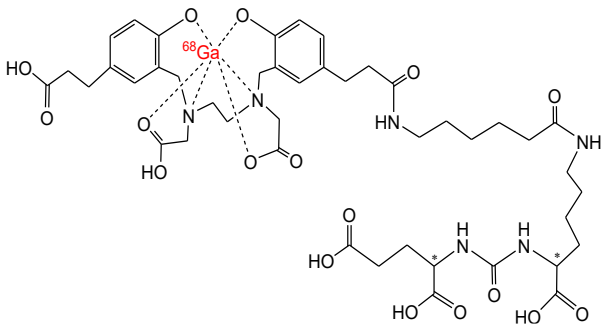

Figure 1. Structure of [^{68}Ga]PSMA-11

Automated production of [^{68}Ga]PSMA-11 using a synthesis module reduces radiation exposure to operators, allows for high reproducibility, and compliance with local health requirements, regulatory standards, and good manufacturing practice (GMP) standards [15, 38, 39].

- *Production of [^{18}F]SiPSMA-14*

The synthesis of [^{18}F]SiPSMA-14 was based on the ^{19}F/^{18}F isotope exchange reaction, without modifying the drug molecule itself. For this purpose, the radionuclide ^{18}F was produced in a liquid target using a medical cyclotron with a proton energy of 7.5 MeV (ABT Molecular Imaging BG-75) by

irradiating a standard volume of 280 μL of ^{18}O-enriched water, [^{18}O]H_2O (≥98% purity; Taiyo-Nippon Sanso Corporation, Japan). Two consecutive bombardment cycles of 45 min each were carried out at an average target current of 4 μA, after which the resulting ^{18}F was transferred to the automated radiosynthesis module. After ^{18}F entered the synthesis card, the production of [^{18}F]SiPSMA-14 included the following steps: fluoride fixation; drying of the quaternary methyl ammonium (QMA) cartridge with CH_3CN anhydride; elution of the QMA with an eluent cocktail (K222/KOH in CH_3CN anhydride); labelling of the peptide; dilution of the reaction mixture with citrate buffer; solid phase extraction (SPE) of the product in the HLB cartridge; SPE purge; SPE elution; sterile filtration of the product using a sterile 0.2 μm filter; dilution of the product with citrate buffer (pH = 5.0) [41]. The labelling reaction was carried out at room temperature for 17 min. There was no need for HPLC purification as in direct ^{18}F labelling of substrates. The synthesis was performed according to the manufacturer's synthesis instructions (Scintomics, Fürstenfeldbruck, Germany). The structure of the ^{18}F-labelled radiopharmaceutical is presented in Figure 2.

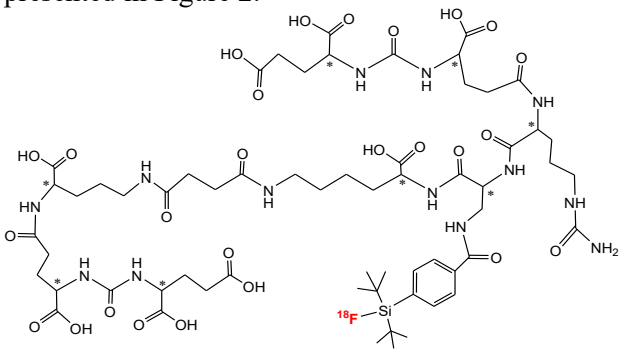

Figure 2. Structure of [^{18}F]SiPSMA-14

Quality control of [^{68}Ga]PSMA-11 and [^{18}F]SiPSMA-14 products

To release both radiopharmaceuticals for clinical use, appropriate quality control measures were taken, according to the European Pharmacopoeia (Ph. Eur.) [42-44].

The radionuclides ^{18}F and ^{68}Ga were identified by determining the physical half-life ($t_{1/2}$) of each radionuclide, measuring five activity values over a 15-min interval using an ISOMED 2010 dose calibrator. A Digital Spectrum Analyzer DSA-1000 gamma spectrometer with a germanium detector was used to determine the radionuclide purity. The physicochemical characterization of the two final products was performed by radiochemical identification and determination of radiochemical purity, chemical purity, pH measurement and analysis of solvent residues. In addition, a test for endotoxin determination was performed using the Endosafe PTS Charles River apparatus.

Routinely, radiochemical purity is determined by radio-TLC, which is a fast and cheap method (Scan–Ram PET/SPECT radio TLC-scanner, using Laura software, version V5.0.974.SP6). Paper chromatography plates (iTLC-SG, Agilent Technologies) were used as stationary phase, and a mixture of methanol and 0.1 M ammonium acetate in a ratio of 1/1 was used as mobile phase. The radiochemical purity was confirmed by radio-HPLC (HPLC–system SCI8100 Plus, software YL-Clarity, version 8.7), using a Meteoric Core C18 BIO chromatographic column (100 mm × 3.0 mm). The mobile phase used included the following two components: phase A (0.1 % TFA in water) and phase B (0.1 % TFA in acetonitrile). The analysis was performed using a gradient method with the following parameters: 0–0.5 min: 95% phase A and 5% phase B; 0.5–10 min: phase A 95% → 60% and phase B 5% → 40%; 10–11 min phase A 60% → 95% and phase B 40% → 5%; 11–16 min phase A 95% and phase B 5%. The mobile phase flow rate was 0.6 ml/min. The radio-HPLC system was equipped with a UV/VIS detector SCI8120 (YL9120) and a radioactivity detector SN:6967 operating at a wavelength of 280 nm.

RESULTS AND DISCUSSION

For clinical purposes, [^{68}Ga]PSMA-11 and [^{18}F]SiPSMA-14 were successfully prepared with good radiochemical yield and high radiochemical purity. Both products were qualitatively characterized and met the requirements of the European Pharmacopoeia. The two procedures differed in the modification of the precursor used, the type of reaction, the duration of the process and the reaction conditions. For the analysis of the results, a sample of 24 syntheses was taken for each of the produced radiopharmaceuticals, on the basis of which the average radioactivity of the final product obtained and the average radiochemical yield were calculated. A summary of the data is presented in Table 1.

The data from the [^{68}Ga]PSMA-11 syntheses were taken from the initial stage of the ^{68}Ge/^{68}Ga generator operation, when its activity and production capacity were at their highest. The theoretically expected initial activity of the eluted ^{68}Ga at that time was between 1620 – 1680 MBq.

Table 1. Comparative data for [^{68}Ga]PSMA-11 and [^{18}F]SiPSMA-14

Indicator	[^{68}Ga]PSMA-11 (sample of 24 syntheses)	[^{18}F]SiPSMA-14 (sample of 24 syntheses)
Average activity of the final product	855.9 ± 12.6 MBq	1821.6 ± 17.3 MBq
Specific activity of the final product	50.4 ± 5.6 MBq/mL	107.2 ± 7.9 MBq/mL
Average radiochemical yield	52.2 ± 11.3%	68.6 ± 12.4%
Labelling temperature [°C]	95°C	22°C
Labelling time [min]	30	17
Purification	SPE – PS-H$^+$, C18	SPE – QMA, HLB
Radiochemical purity	> 98%	> 99%
Number of patients injected	72	100

The synthesis of [^{68}Ga]PSMA-11 was performed in 30 min and resulted in a product volume of 17-18 ml, an average radiochemical yield of 52.2 ±11.3% (non-decay corrected), specific activity of 50.4 ± 5.6 MBq/mL and radiochemical purity greater than 98%. During the study period, the ^{68}Ga-labelled radiopharmaceutical was obtained with an activity ranging between 680.6 and 916.4 MBq, the mean activity value being 855.9 ± 12.6 MBq. After successful quality control tests, the product was distributed to three patients.

Regarding the other product, the initial activity of ^{18}F produced after two consecutive bombardment cycles was in the range between 2000 and 2950 MBq, depending on the state of the ion source and the target in the cyclotron. The synthesis of [^{18}F]SiPSMA-14 was performed in 17 min and resulted in a product volume of 17-18 ml, average radiochemical yield of 68.6 ± 12.4% (non-decay corrected), specific activity of 107.2 ± 7.9 MBq/ml and radiochemical purity greater than 99%. The resulting activity of the final product [^{18}F]SiPSMA-14 varied between 1100 and 2353 MBq, with a mean value of 1821.6 ± 17.3 MBq. The activity of the ^{18}F-labelled radiopharmaceutical produced was sufficient to perform imaging studies on up to five patients, allowed for a longer injection interval between patients, and enabled later scanning.

CONCLUSIONS

In the activities of the Clinic of Nuclear Medicine, Varna since 2019, the radiopharmaceutical [^{68}Ga]PSMA-11 has been used for the diagnosis of prostate cancer, and in 2023 [^{18}F]SiPSMA-14 was introduced as an alternative radiopharmaceutical. For the first time, the isotope exchange reaction was used as a convenient method for labelling the PSMA molecule with ^{18}F. [^{18}F]SiPSMA-14 has great advantages compared to [^{68}Ga]PSMA-11 in terms of both the radionuclide ^{18}F and the synthesis method. The radionuclide ^{18}F was produced on site in the clinic with the in-house cyclotron with a significantly higher initial activity compared to that of ^{68}Ga obtained from a ^{68}Ge/^{68}Ga generator. ^{18}F has a longer half-life and lower average positron energy, which allows for PET images with higher resolution and longer scanning time to be obtained. The process of obtaining [^{18}F]SiPSMA-14 by isotope exchange has the following advantages: (1) it leads to the formation of an *in-vivo* stable ^{18}F-Si bond; (2) it proceeds faster at room temperature, which is gentler to the peptide molecule PSMA; (3) no by-products are expected, so there is no need for additional purification. [^{18}F]SiPSMA-14 is obtained with a higher radiochemical yield, higher molar activity and better selectivity compared to [^{68}Ga]PSMA-11. The synthesis also allows the obtained product to be administered to more patients. When an in-house cyclotron is available, it is more expedient and preferable to produce and use the ^{18}F-labelled radiopharmaceutical [^{18}F]SiPSMA-14. This approach provides an opportunity to overcome the difficulties associated with the production, high cost and logistic issues related to the use of ^{68}Ge/^{68}Ga generators.

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