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Production and Quality Control of ^{18}F-PSMA for imaging of Prostate Cancer

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Abstract

We report an automatic radiosynthesis of fluorine-18-labelled prostate-specific membrane antigen (PSMA) -ligand [^{18}F]PSMA-1007 as the next generation radiofluorinated for routine production in large scale. A synthera V2 module with in-house prepared materials and method were optimized to produce and purify of ^{18}F-PSMA radiopharmaceutical. PSMA-1007 was synthesis in Kimia Pazhooh Dorsa company and after characterization tests is used for labeling with ^{18}F. Phosphate buffered saline and sodium L-ascorbate were used for pH adjustment and stability of final product. Quality control tests were done base on European Pharmacopoeia (EP) Reference Standard. The purity of final product was more than 98% and stabitlty test was done for 6 hours after production and shows a good stability during these duration.

Keywords: Prostate Cancer, [^{18}F]PSMA-1007 Radiopharmaceutical

Introduction

The most commonly diagnosed cancer in men is prostate cancer, which can be localized or metastatic at diagnosis time or in follow-up of the patients. The localized disease can be controlled by some methods such as active surveillance, radical prostatectomy, external beam radiotherapy and brachytherapy. In metastatic disease, only systemic therapy should be performed. PSMA- based PET radiopharmaceuticals with high sensitivity and selectivity can be used for detection of metastasis in hormone naïve and patients with castration-resistant metastatic prostate cancer [1].

^{18}F-PSMA-1007 as a novel prostate-specific membrane antigen (PSMA)-based radiopharmaceutical has be considered for imaging prostate cancer (PCa)which because of low clearance via the urinary tract (1.2 percentage of injected dose over 2 h) is favorable for primary and local relapse tumors [2]. Also F-18 with half-life 110 min, suitable positron energy (which improves the resolution of images), the possibility of producing in large scale and centralized and distribution is cost benefit [3].

Experimental

Preparation of the materials

All materials in this work, was prepared by in-house methods. The most important ingredient, PSMA-1007 was synthesized by Kimia Pazhooh Dorsa company and was characterized by Pars Isotope Company. After passed all test, a Synthera V2 module and other materials were used for an automatic synthesis. ^{18}F-PSMA synthesis takes about 40 minutes and has column purification instead of HPLC. Sodium ascorbate and phosphate buffer saline were used to produce a product that will be stable during transfer, injection and PET imaging.

Results and discussion

There are three important steps in ^{18}F-PSMA-1007 radiopharmaceutical synthesis. The first is, prepare a chemical active F-18 that produced after Cyclotron bombardment. A tetrabutylammonium solution that has potassium carbonate for removing of F-18 from quaternary methyl ammonium (QMA) column, was used for this step. After removing of F-18, it transferred to a reaction vial for drying and preparing to next step. During this step the temrature of reaction vial set on 110^{o}C.

The Second is labeling step. In this step, PSMA-1007 that was solved in 1.5 ml of dimethyl sulfoxide (DMSO) is added to reaction vial in 100 ^{o}C. Labeling time can be variable due to starting activity of F-18. If the starting activity was less than 100 gigabecquerels, it can take about 7 minutes and if more than 150 gigabecquerels it can be reduced to 5 minutes. High starting activity cause radiolysis of the product, so low starting activity are preferred. In end of labeling, all contents of the reaction vial were transferd on C18ec column for doing purification.

The third step is purification step. It was done by 27 ml of 5% ethanol solution and takes about 9 minutes. During the purification process, it is tried to remove the impurities as much as possible by trapping the final product on a column. washing the column with 5% ethanol solution removes the impurities while the product remains on the column. For separation of final product, a 6ml of 25% ehanol solution was used. The

product was transferred to a vial containing 400 mg of sodium ascorbate in 15 ml of phosphate buffer saline solution. All of this steps was shown in Fig. 1.

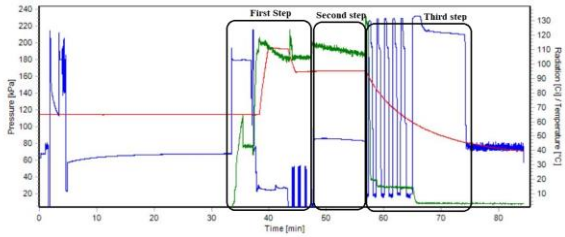

Figure 1. Three important steps of ^{18}FPSMA production

Quality Control tests

Any drug to be injected into the human body must pass quality control tests. There is a European Pharmacoupe (EP) Monography that define all specifications for ^{18}F-PSMA-1007. Parameters and acceptance criteria was shown in below picture.

Parameter	Method	Acceptance Criteria
Appearance	Visual	Clear and colourless
Identity	HPLC	$R_t \pm 0.5$ min of reference standard
Radiochemical purity	HPLC	≥95%
	TLC	≥95%
Radionuclidic purity	Half life	110 ± 5 min
	Gamma spectroscopy	511 keV ≥ 99.9% (post-release)
Chemical purity #	HPLC	PSMA-1007: ≤0.1 mg/V_{max}
		Any other impurity *: ≤0.1 mg/V_{max}
		Sum of all impurities *: ≤0.5 mg/V_{max}
	TLC	TBA: ≤2.6 mg/V_{max}
	GC	Acetonitrile: ≤4.1 mg/V_{max}
		DMSO: ≤50 mg/V_{max}
		EtOH: ≤10% V/V
		Acetone: ≤50 mg/V_{max}
pH	Potentiometric or strip indicator	4.5–7.5
Endotoxins	LAL test	≤175 IU/V_{max}
Filter integrity	Bubble point test	≥3.5 bar (Cathivex-GV 0.22 µm)
Sterility	Post-release	Sterile (post-release)

Figure 2. recommended tests for quality control of ^{18}F-PSMA-1007

The purity of final product in our hot production test was 98% that shows a good purity for PET imaging. For determination of the purity used a High-performance liquid chromatography (HPLC) instrument and a Radio Thin Layer Chromatography (RTLC) scanner with EP configurations and solution. Gamma and UV detector were used in HPLC configuration. A retention time of 3.3 and a single peak detection for both detectors indicate the high purity of the product.

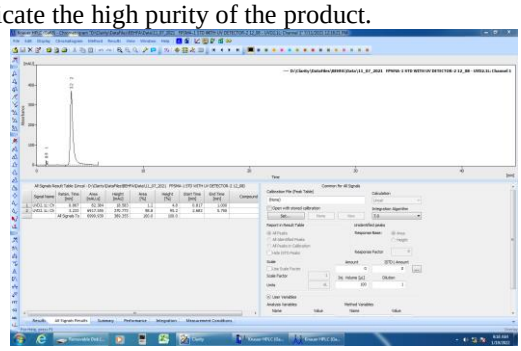

Figure 2. The outlet of UV detector in HPLC

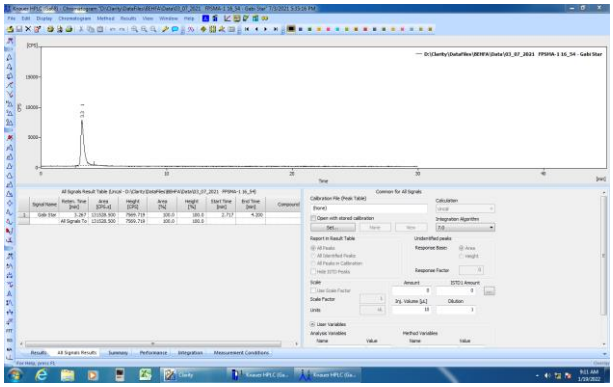

Figure 4. The outlet of gamma detector in HPLC.

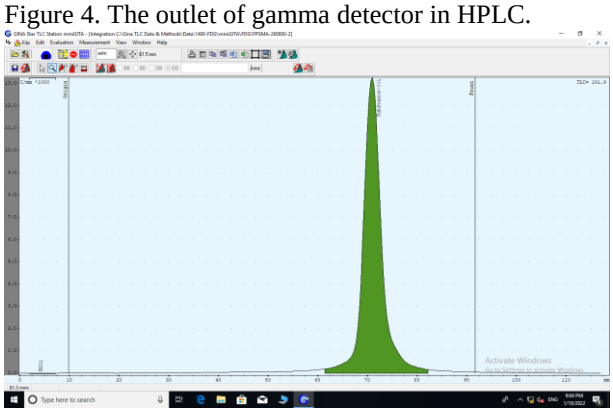

Figure 5. The outlet of RTLC scanner

Conclusions

Synthesis of ^{18}F-PSMA-1007 by in-house preparation materials and method was done and the final product checked with EP monography for quality control tests. The yield of synthesis was 35% with high purity (more than 98%) and stability for PET imaging of Prostate Cancer.

Acknowledgments

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