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Radiopharmaceutical production of 68Ga-PSMA at the National Cancer Institute. Bogotá-Colombia.

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Background
68Ga-prostate-specific membrane antigen (PSMA) radioligand diagnostic is a novel diagnostic option in patients with metastatic prostate cancer. The aim of this work was to standardize an efficient automated synthesis method for radiolabeling radiopharmaceutical-grade 68Ga-PSMA for PET/CT diagnosis of prostate cancer.
Methods:

We employed PSMA-HBED-CC (PSMAHBED) peptide manufactured according to GMP requirements (purity >96%) obtained from ABX (Advanced Biochemical Compounds) and 1850 MBq ITG 68Ge/68Ga generator consisting of organic-matrix column metal free. Sodium acetate, ascorbic acid, NaCl, HCl Ultrapur and EtOH was obtained from Merck

Automated synthesis module "Taddeo"from COMECER was installed in a shielded Hot cell and used for radiolabeling. The 68Ga solution was eluted from the generator with 7mL of 0.1M HCl at a flow rate of 2.5mL/min and transferred to a PS-H+ column and eluted with 5M NaCl (1.8mL) . The total 68Ga activity (1400MBq) were transferred directly into the reaction vessel containing 5µg PSMA-HBED-CC peptide, dissolved in 1mL of Acetate buffer 1.0M with pH 4 and Ascorbic acid 10µL, heated to 92oC per 8 min. To process the radiolabeling product Strata-X-tubes pre-conditioned (Phenomenex) were used. The 68Ga-PSMA-HBED-CC was retained and unreacted 68Ga passed through into a waste vial. The Strata-X-tubes were then washed with 5mL of pure water and the 68Ga-PSMA HBED-CC was recovered with 1.2mL EtOH/Water (1:1) followed by 10 mL of 0.9% saline. Finally the product was sterile-filtered under aseptic conditions through 0.22µm membrane filter (Milex-GV, Millipore) and the activity was measured in a Capintec-CRC-15R dose calibrator.

The radiochemical purity and identity of the 68Ga-68Ga-PSMA solution was assessed by RP-HPLC equipped with a UV and ɤ detector. A Lichospher-100 column C-18 (25mm x 4.6mm, 5µm) , was used as stationary phase. The mobile phase was as follows: 0-0.5min: 95%B; 0.5-10min: a linear gradint 80% A, flow rate 2ml/min (6). Retention times were 1.5- 2.0 min for free 68Ga (III) and 4.9- 5.1 the themodynamically more stable diastereomer (RR), 5.2- 5.4 the thermodynamically less stable.

An indicator strip was used for the pH analysis of the 68Ga-PSMA dose and the Bacterial endotoxin content was analyzed using an Endosafe R system (LAL test), the values limit were <175/IU/ml. The sterile filter integrity test of the 68Ga-PSMA solution was performed with a limit value >50psi
68Ge-contamination was detected and quantified using a gamma counter (at full open window and at a 1min measurement time) retaining the preparation for at least 48h to allow 68Ga to decay to a level allowing the detection of the impurities. The total radioactivity due to 68Ge must not be >0.001% referred to the original activity.
Radionuclidic identity and purity tests were performed by gamma-ray spectrometry and the principal gamma peaks analyzed, energies of 511Kev and 1077Kev were only allowed. The physical half-life was measured 3 times using a Capintec-CRC-15R Radioisotope Dose Calibrator. The half-life must be 62-74min.
Sterility test was performed by an external laboratory, according to the current US-pharmacopoeia.
Results:
The synthesis of 68Ga -PSMA-HBED-CC parameters were optimized as described previously with 75% +/- 5% decay corrected radiochemical yield . The production of 68Ga- PSMA-HBED-CC was within 28 min+/-1. Over the study period we made 52 synthesis of 68Ga- PSMA-HBED-CC. The radiochemical purity was >99.7% as two diastereomers, with pH range 5.5-7.0. The 68Ge impurities was found to be <0.0010% in the radiolabelled compounds. All samples passed the bacterial endotoxin test at values <10IU/mL and the sterility test. The residual solvent of the final product was ethanol in less than 10%. Up date we have injected 45 patients.
Conclusion: We have shown that it is possible to perform an automated sinthesis to 68Ga- PSMA-HBED-CC using an Automated synthesis module "Taddeo"from COMECER ensuring a quality and high radiochemical yields and radiochemical purity > 99.7%.

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