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BRAZILIAN JOURNAL OF RADIATION SCIENCES

doi.org/10.15392/2319-0612.2024.2690
2024, 12(4A) | 01-20 | e2690
Submitted: 2024-08-30
Accepted: 2025-05-27

Optimization of PSMA-I&T radiolabeling with ^{177}Lu

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Abstract: Prostate cancer (PCa) is the second most common type of cancer in men and the fifth cause of mortality worldwide. Metastatic prostate cancer is associated with a poor prognosis and decreased life expectancy. Prostate-specific membrane antigen (PSMA) is a type II transmembrane glycoprotein that is anchored in the epithelial prostate cell membrane, overexpressed in prostate cancer, increased in metastatic castration-resistant prostate cancer (mCRPC) patients and with a consensus that its expression level is correlated to the malignancy of the disease. ^{177} Lu-PSMA-I&T stands out as a promissor radiopharmaceutical for therapy of prostate cancer and currently is being described based on this specifically bind to PSMA with the Glu-urea-Lys pharmacophoric group. This present work aimed to determine the most favorable conditions for labeling PSMA I&T with carried-added lutetium-177, evaluating the influence of molar ratio, pH, temperature and reaction time, to obtain the radiopharmaceutical with high radiochemical purity (%RP ≥95%), avoiding the final purification step. The percentage of radiochemical purity was evaluated by High Pressure Liquid Chromatography (HPLC) and Thin Layer Chromatography on silica gel 60 plate (TLC-SG). The results obtained with this work made it possible to define and standardize the best condition for PSMA I&T radiolabeling with carried-added ^{177}Lu.

Keywords: Radiolabeling 1, PSMA I&T 2, Optimization 3, Lutetium-177 4.

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Otimização da radiomarcação do PSMA I&T com ^{177}Lu

Resumo: O câncer de próstata (CaP) é o segundo tipo mais comum de câncer em homens e a quinta causa de mortalidade no mundo. O câncer de próstata metastático está associado a um pior prognóstico e à diminuição da expectativa de vida. O antígeno de membrana específico da próstata (PSMA) é uma glicoproteína transmembrana tipo II que é ancorada na membrana da célula epitelial da próstata, superexpressa no câncer de próstata, aumentada em pacientes com câncer de próstata metastático resistente à castração (mCRPC) e com um consenso de que seu nível de expressão está correlacionado à malignidade da doença. O PSMA-I&T-^{177}Lu se destaca por ser um radiofármaco promissor para terapia do câncer de próstata, com base na ligação específica do grupo farmacosfórico Glu-urea-Lys desse radiofármaco ao PSMA. O presente trabalho teve como objetivo determinar as condições mais favoráveis para marcação de PSMA-I&T com lutécio-177 de baixa atividade específica (c.a), avaliando a influência da razão molar, pH do tampão, temperatura e tempo de reação a fim de obter um radiofármaco com porcentagem de pureza radioquímica alta (%PR ≥ 95%) sem a necessidade da etapa de purificação final. A porcentagem de pureza radioquímica foi avaliada por Cromatografia Líquida de Alta Eficiência (CLAE) e Cromatografia em Camada Delgada com Sílica Gel (CCD-SG). Os resultados obtidos com este trabalho possibilitaram definir e padronizar a melhor condição para radiomarcação de PSMA-I&T com ^{177}Lu de baixa atividade específica.

Palavras-chave: Radiomarcação 1, PSMA I&T 2, Otimização 3, Lutecio-177 4.

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1. INTRODUCTION

Prostate cancer (PCa) is the second most common type of cancer in men, primarily affecting those aged between 45-60 years, the third neoplasm with the most cases and the disease with the highest diagnosis rate among men in the world [1,2]. It is also the fifth leading cause of mortality globally. According to International Agency for Research on Cancer, it is estimated that the incidence will be 1.65 million men affected globally at 2025[1].

Usually, the treatment of choice is generally androgen deprivation therapy (ADT) and taxane-based chemotherapy, however, the problem related to this therapeutic approach is the potentially serious adverse effects. In addition, it is possible that patients develop metastatic castration-resistant prostate cancer (mCRPC), through mechanisms that are not very clear, representing a challenge in the search for new safe and low toxicity therapies, for increasing overall survival [2-5].

Discovered in the early 2000s, Prostate-Specific Membrane Antigen (PSMA) is a type II transmembrane glycoprotein anchored in the epithelial prostate cell membrane. It is overexpressed in prostate cancer [6], particularly in metastatic castration-resistant patients and there is a consensus among authors describing a strong correlation between PSMA expression level and disease malignancy [7-9].

Therefore, some radioligands for diagnosis and therapy of prostate cancer have been described, based on the discovery of PSMA inhibitors, which specifically bind the Glu-urea-Lys pharmacophoric group with emphasis on PSMA-617 and PSMA-I&T for radiolabeling with lutetium-177 [9].

Lutetium-177 is a radioisotope which application for therapy has been intensified, due to its appropriated characteristics like T1/2 of 6.65 days, emission of a β^- (max) radiation of 497 keV (78.5 %) and 230 μm of medium range, making it ideal for the treatment of micro

metastases, such as those that appear in mCRPC and two additional gamma emissions of 208 and 113 keV (11% and 6.4%), respectively [10].

Lutetium-177 can be produced in reactors by two distinct rotes. The first is the direct prodution, through the bombardment of 176-lutetium enriched target and the production of the radioactive isotope of lutetium-177 [^{176}Lu (n,γ) ^{177}Lu]. This route is considered to be carrier added (CA), because there is no 100% radioisotopic conversion [11].

The second way is the indirect production route, by irradiating enriched ytterbium-176 to obtain ytterbium-177 with T1/2 of 1.9 hour which through β^- decay produces non-carried added (NCA) lutetium-177 [12].

Using NCA lutetium-177, it is possible to produce a radiopharmaceutical with greater specific activity than that obtained with CA lutetium-177, which, in principle, constitutes an advantage for a receptor-specific radiopharmaceutical. However, the radionuclide produced by indirect route also has low availability in the international market. Another factor to be considered, is the higher cost of lutetium-177 obtained by the indirect route, which represents an impact on the final price of the radiopharmaceutical. Therefore, it becomes attractive to study the production of the ^{177}Lu-PSMA-I&T using lutetium-177 produced by direct route.

Due to worldwide incidence of prostate cancer, also in the Brazilian male population, and the lack of more effective and targeted treatments for mCRPC, this present work aimed to optimize and standardize the most favorable conditions for labeling PSMA-I&T with carried-added lutetium-177, in order to obtain a radiopharmaceutical with high radiochemical purity, avoiding the final purification step and increasing the yield of the labeling reaction.

2. MATERIALS AND METHODS

2.1. Radiolabeling of ^{177}Lu-PSMA-I&T

The radiolabeling of PSMA-I&T (CMR-Russia) with lutetium trichloride ($^{177}LuCl_3$) (JSC, Russia or Isotopia, Israel) was based on methodology described by Villas Boas [12] and was manually performed. Radiolabeling procedure was performed with 20 μg of PSMA-I&T, and different lutetium-177 activities, due to specific activity (Isotopia > 740 GBq/mg EOB and JSC > 999 GBq/mg), to evaluate the effect of the peptide:lutetium molar ratio (1.5, 2.1, 3.0, 3.5, 3.8 and 4.0). Other labeling conditions were studied including reaction temperature (85, 87, 90 and 95ºC), reaction time (20, 30 and 40 minutes) and the pH of the 0.5 mol. L^{-1} sodium ascorbate buffer (4.4, 4.7 and 5.0).

The ability of potential interfering metal ion impurities, including Al, Ca, Cu, Fe, Pb and Zn, likely present in the $^{177}LuCl_3$ solution, to form thermodynamically and kinetically stable coordination complexes with the radiolabeled peptides is well established [13], so it is of utmost importance to determine their concentration. Both suppliers present the certificate of analysis that attests to a very low concentration of metal impurities.

Several batches of ^{177}Lu-PSMA-I&T were produced, the specific activity of lutetium-177 at the date of labeling was between 321.53 to 1184 GBq/mg.

For the study of each parameter, the others remained unchanged, considering as standard labeling condition 90ºC, 30 minutes, 4.0 molar ratio and pH buffer of 4.7. The first step of labeling procedure was to check the activity and radioactivity concentration of the lutetium-177 chloride solution using an activimeter (Capintec, USA), and an aliquot containing the desired activity was placed in conical tube. The second step was to add sodium ascorbate buffer and, finally 20 μL of PSMA-I&T solution (1mg/mL).

Under the optimized labeling conditions (90°C, 30 minutes, a 4.0 molar ratio, and buffer pH of 4.7), a radiolabeling procedure was scaled up to produce a therapeutic dose

of the radiopharmaceutical (7.4 GBq at calibration time). Additionally, a stability study of the preparation was conducted using both freezing storage and room temperature at a climate chamber.

2.2. Quality Control of ^{177}Lu-PSMA-I&T

The radiochemical purity was determined by High-Performance Liquid Chromatography (HPLC) and Thin Layer Chromatography (TLC) techniques.

HPLC (Shimadzu, Japan) was used composed by automatic injector unit (SIL-AC20), pump (LC-20AT), DGU-20 SR degasser, CBM-20A communication module, UV/VIS detector (SPD-20A), Flow-RAM Radio HPLC Detector (Lablogic, England) gamma radiation flow detector attached to this system with Laura 4.0 software for controlling the HPLC (Lablogic, England).

HPLC analysis was carried out using a C-18 column (Waters model Xterra RP 18 column 4.6 x 250 mm, 5 μm, at 24°C), 100 μL injection volume, 0.6 mL/min flow rate and gradient composed by 0-8.59 min 24% B; 9-18 min 60% B; A= Water/0.1% trifluoroacetic acid, B= acetonitrile/0.1% trifluoroacetic acid [12]. In this system, free lutetium-177 eluted at approximately 4 minutes while the radiolabeled compound ^{177}Lu-PSMA-I&T eluted at approximately 15 minutes. The HPLC analysis was expressed as the percentage of the main peak corresponding to ^{177}Lu-PSMA-I&T).

Thin Layer Chromatography (TLC) was performed using Thin Layer Cromatography Silica Gel 60 (TLC-SG, Merck) aluminum strips (stationary phase) and 0.1 mol. L^{-1} sodium citrate buffer, pH 5.0 (mobile phase). TLC was performed by applying 2 μL of a test solution on to TLC-SG strips. After the run, the strips were cut into 1 cm segments, and the radioactivity was counted (cpm) using a Gamma Counter (Packard, USA). The TLC method was used to determine the percentage of free ^{177}Lu in the labeling preparation.

The percentage of free ^{177}Lu was determined as follows (Equation 1).

$$\% \text{ free Lu} - 177 = \frac{\Sigma \text{ cpm } (9-10 \text{ segments})}{\Sigma \text{ cpm } 1-10 \text{ segments}} x100 \quad (1)$$

In this system radiolabeled compound had an Rf 0.1-0.2 while free lutetium-177 has Rf 0.9-1.0.

The acceptance criteria established were: ≤ 3% of the total activity corresponding to free ^{177}Lu in TLC analysis (Rf 0.9-1.0) and ≥ 95% of the total activity corresponding to the principal peak in HPLC analysis (Rt approximately 15 minutes).

The cold peptide (PSMA-I&T) and free ^{177}Lu was analyses by HPLC showed the retention time was approximately 14:50 minutes (UV detector 254 nm) and approximately 4:10, respectively and TLC-SG where the cold peptide was stained with iodine vapor and had Rf 0.2 and the free lutetium-177 was counted in gamma counter and has Rf 0.9 and 1.0.

2.3. Stability Study of ^{177}Lu-PSMA-I&T

The stability study aimed to determine the shelf life of the radiopharmaceutical. The stability of the preparation was determined based on the percentage of radiochemical purity (%RP) by HPLC and percent of free lutetium by TLC-SG chromatography methodes, evaluation immediately (time 0), 24 and 48 hours of radiolabeling. The preparations were freezed stored (-20 ±5) ºC to prospect the conditions of the transport.

2.4. Statistical analysis

At least three experiments were performed for each experimental condition (N=3).

Statistical analysis was conducted using ANOVA and Tukey's tests (GraphPad Prism® 8.0.2, GraphPad Software, Inc. San Diego, CA, USA). Results were considered statistically significant when P-value was below 0.05.

3. RESULTS AND DISCUSSIONS

The first study carried out evaluated the influence of the PSMA-I&T:Lu molar ratio on the radiochemical purity of PSMA-I&T labeled with lutetium-177. Initial studies with molar ration of 1.5 and 2.1 were not considered because the percentage of main peak was lower than 95 % in HPLC analysis.

The results of TLC and HPLC for molar ratio study, evaluated immediately after labeling (0 h), and 24h and 48h after labeling, are shown in figures 1 and 2, respectively.

Figure 1: Results of Percentage of free ^{177}Lu in ^{177}Lu-PSMA-I&T preparation by TLC-SG: evaluation of the influence of PSMA-I&T:Lu molar ratio.

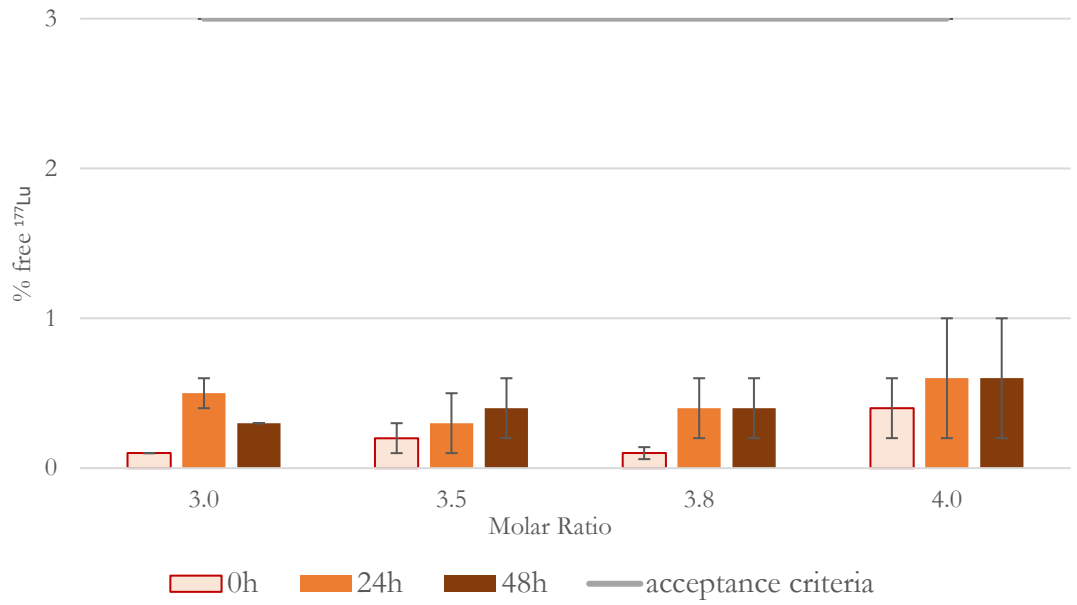
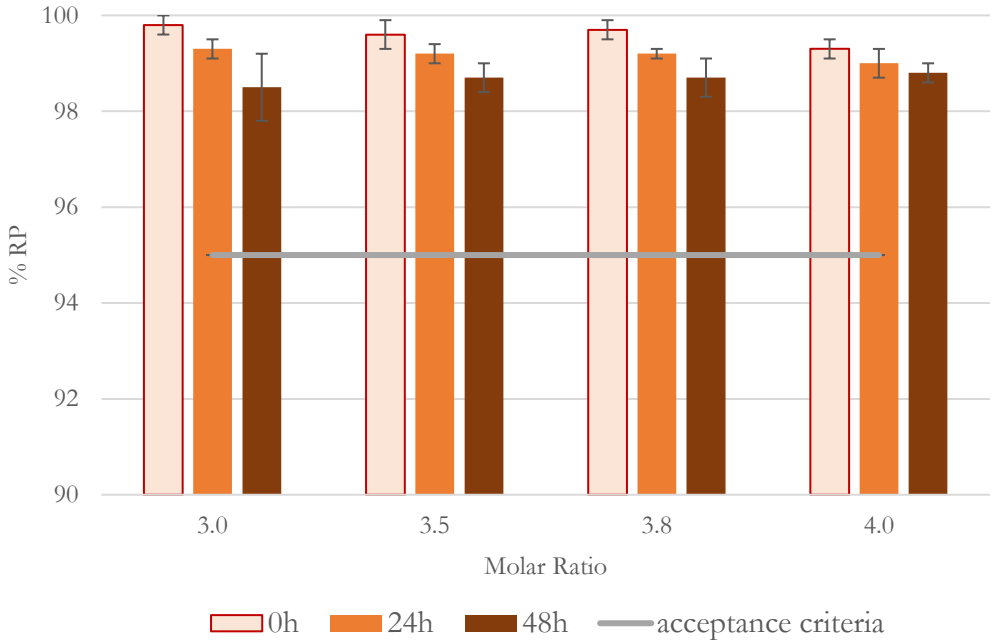


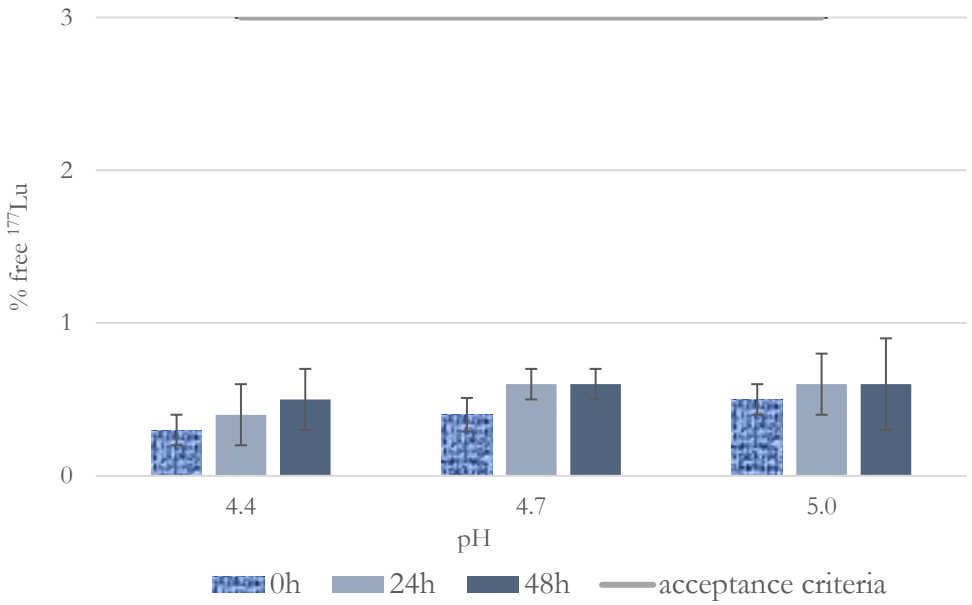
Figure 2: Results of percentage of radiochemical purity (%RP) of ^{177}Lu-PSMA-I&T by HPLC (expressed as % of principal peak): evaluation of the influence of PSMA-I&T:Lu molar ratio.



The radiochemical analysis in both chromatographic systems did not show representative variation between the different peptide:lutetium molar ratios, as demonstrated in ANOVA analysis at 0h (P=0.3060) and 48h (P=0.8312). In the 24h and 48h stability study, the decline in RP was minimal, being due only to the identification of the free lutetium-177 species.

Figures 3 and 4 present the results of HPLC and TLC-SG analysis, respectively for the study of pH buffer variation. No significant difference was observed RP for time zero; however, increasing the pH buffer to 5.0, the RP decreased after 48 hours, despite it is above the acceptance criteria. The ANOVA and Tukey's test applied to HPLC results of pH study at 48 h showed P= 0.4793.

Figure 3: Results of Percentage of free ^{177}Lu in ^{177}Lu-PSMA-I&T preparation by TLC-SG: evaluation of the influence of pH buffer.



The percentage of free lutetium-177 by TLC-SG was lower than 1% in the pH range evaluated.

Figure 4: Results of Percentage of radiochemical purity (%RP) of ^{177}Lu-PSMA-I&T evaluated by HPLC (expressed as % of principal peak): evaluation of the influence of pH buffer.

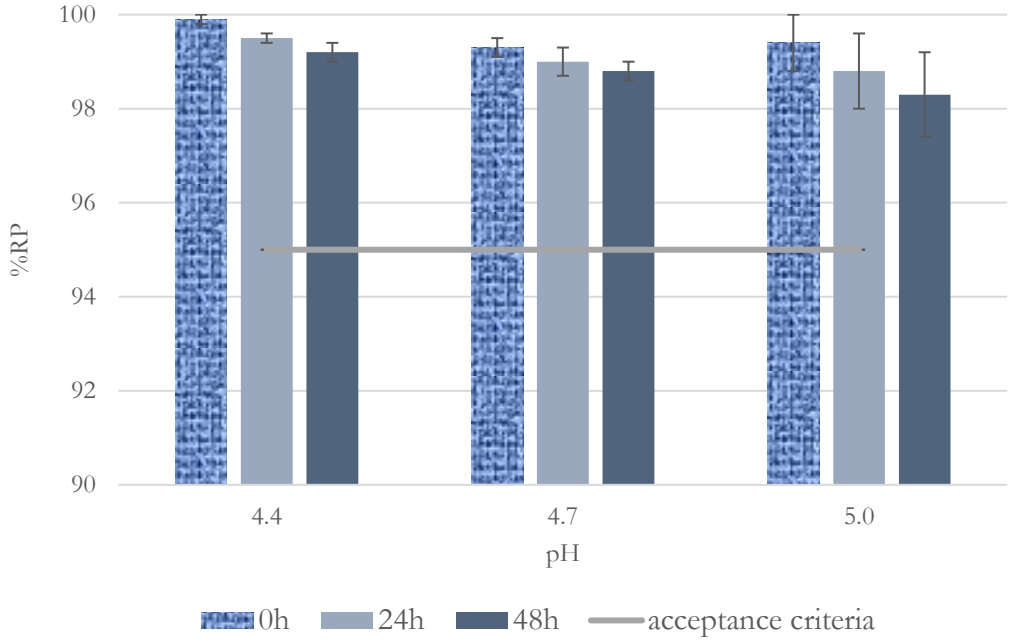


Figure 4 shows that pH variation resulted in percentage of main peak above the acceptance criteria; however, the best labelling condition is in the range between pH 4.4 and 4.7, with P= 0.1270, for 0 h and P= 0.5828 for 48h, by Turkey's analysis. When the percentage of main peak using pH 5.0 at 0 h and 48 h are compared, a decrease was observed, even though the p-value (P=0.4326) does not showed a significant difference.

Once the molar ratio and pH buffer have been defined, the next step studied the influence of temperature in the RP of the preparation. The results are summarized in table 1 and table 2.

Table 1: Results of Percentage of free ^{177}Lu in ^{177}Lu-PSMA-I&T preparation by TLC-SG: evaluation of the influence of reaction temperature.

TEMPERATURE	0 h	24 h	48 h
85 ºC	1.3 ± 1.5	1.1 ± 1.2	1.2 ± 1.1
87 ºC	0.2 ± 0.0	0.3 ± 0.1	0.7 ± 0.4
90 ºC	0.4 ± 0.2	0.6 ± 0.4	0.6 ± 0.4
95 ºC	0.2 ± 0.0	0.2 ± 0.0	0.9 ± 0.6

Table 2: Results of Percentage of ^{177}Lu-PSMA-I&T main peak at HPLC: evaluation of the influence of reaction temperature.

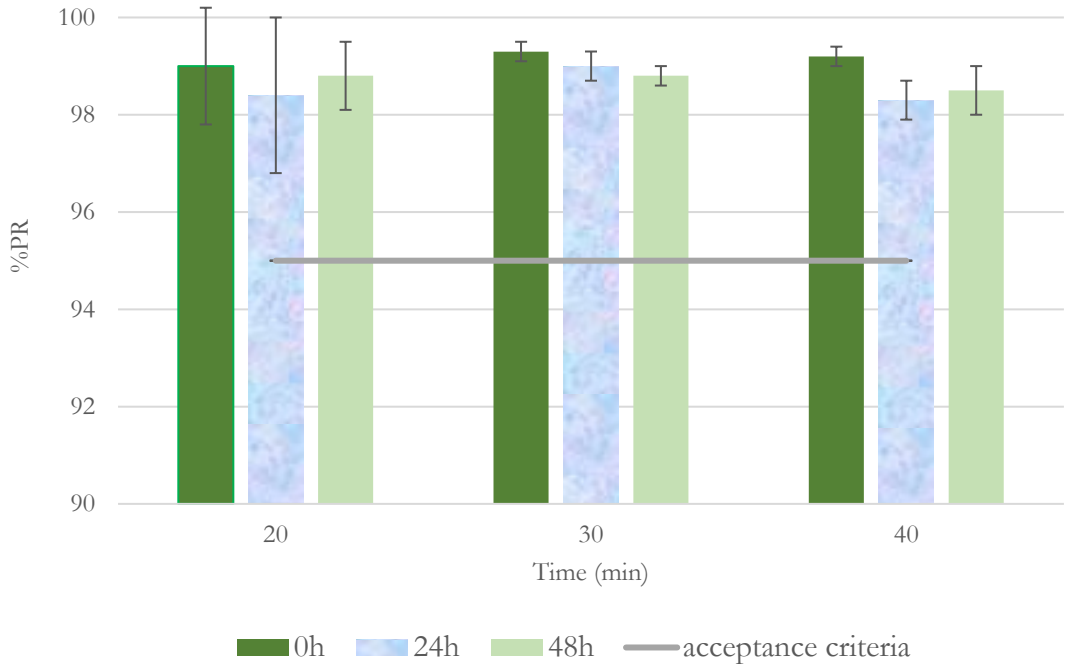
TEMPERATURE	0 h	24 h	48 h
85 ºC	99.1 ±0.7	98.8 ±0.9	98.9 ±0.5
87 ºC	99.8 ±0.2	99.2 ±0.1	99.2 ±0.1
90 ºC	99.3 ±0.2	99.0 ±0.3	98.8 ±0.2
95 ºC	98.1 ±1.7	97.8 ±1.3	97.7 ±1.8

More consistent results and smaller standard deviations were obtained with heating at 90ºC. There were no significant differences in the RP due to reaction temperature up to 48h (ANOVA test, P=0.3767 at 0h and P=0.3719 at 48h).

Regarding to the reaction time, the RP results by HPLC showed no significant differences among 20, 30 and 40 minutes (ANOVA P= 0.8396 at 0h and P=0.8129 at 48h),

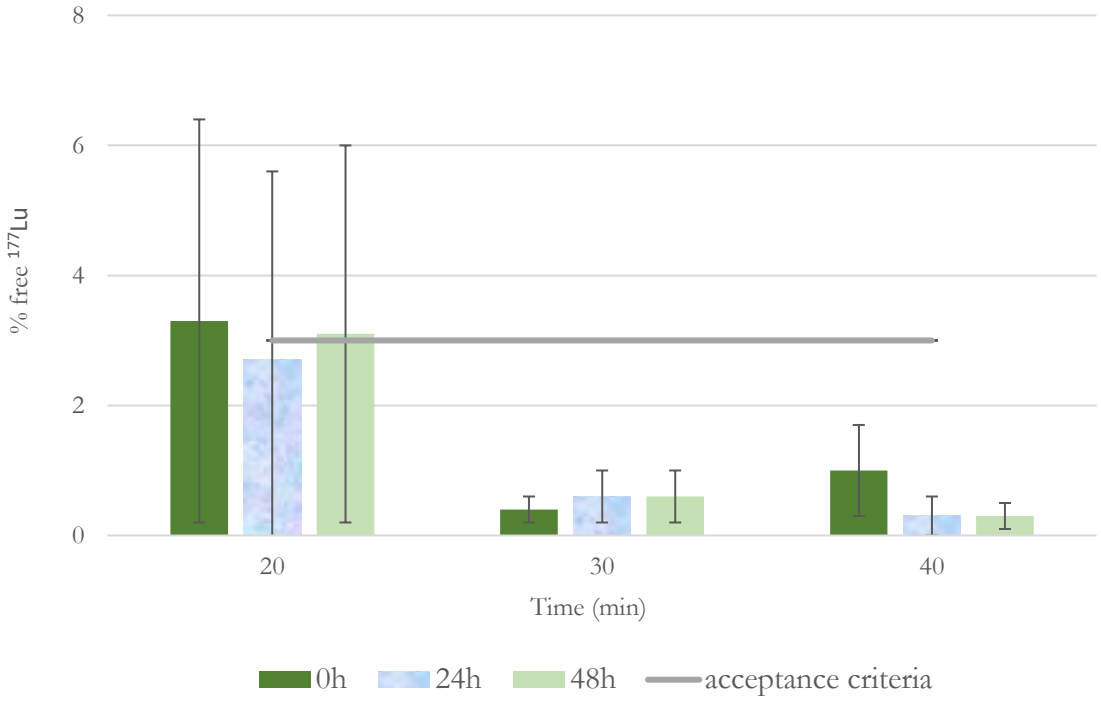
but observed a greater variation between the results at 20 minutes reaction time; 40 minutes slightly impacted the stability of the product at 48h even though all results were above the acceptance criteria of radiochemical purity test (figure 5).

Figure 5: Results of Percentage of radiochemical purity (%RP) of ^{177}Lu-PSMA-I&T evaluated by HPLC (expressed as % of principal peak): evaluation of the reaction time.



The percentage of free ^{177}Lu in TLC-SG analysis for 20 minutes reaction time was higher than the acceptance criterion (≤ 3%) (figure 6).

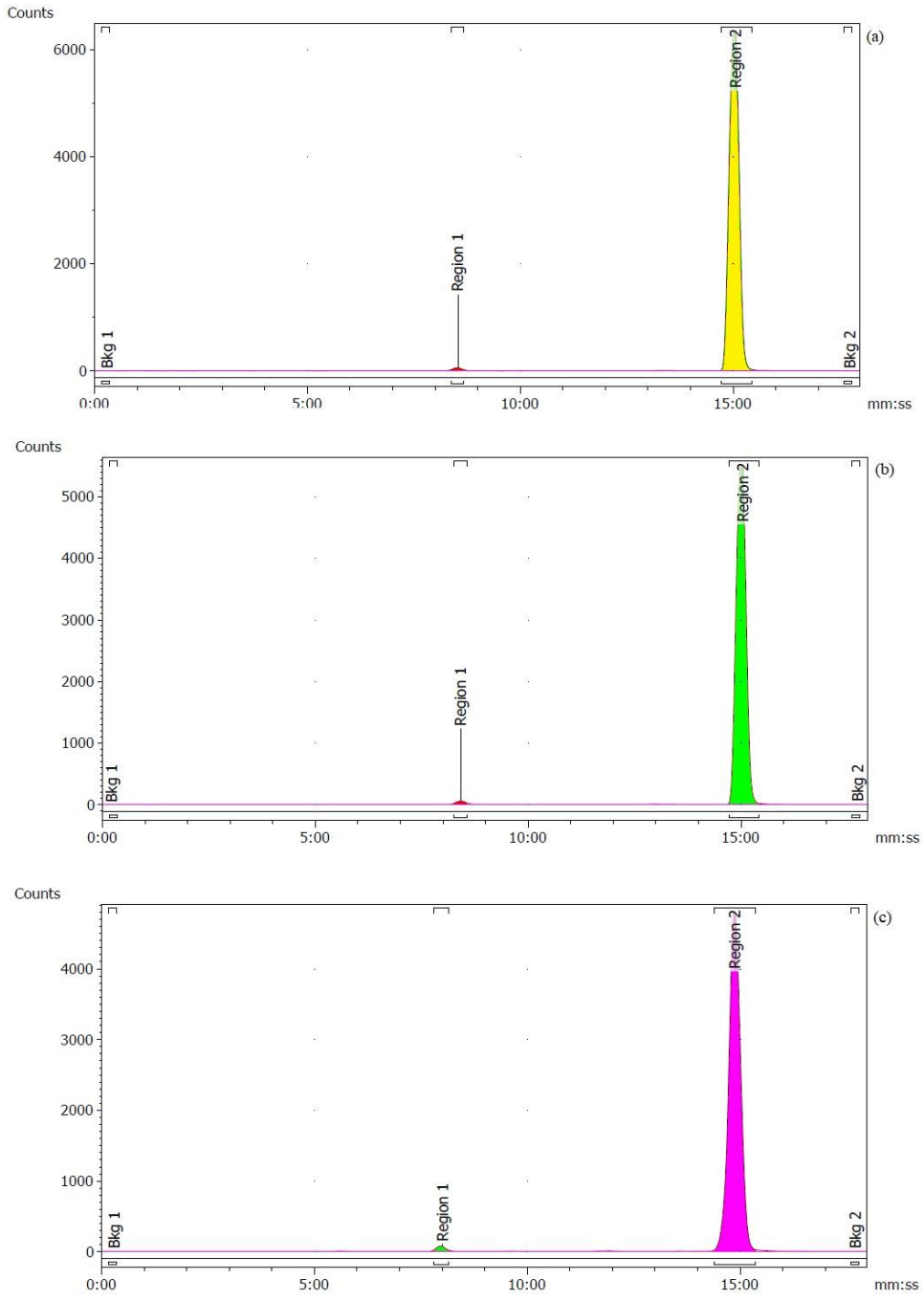
Figure 6: Results of Percentage of free ^{177}Lu in ^{177}Lu-PSMA-I&T preparation by TLC-SG: evaluation of the reaction time of labeling



Considering all studies, the "standard labeling condition" was defined as: PSMA-I&T:Lu molar ratio of 4.0, buffer pH 4.7 buffer, reaction time of 30 minutes and reaction temperature of 90 °C. The %RP results of HPLC and TLC test provided working ranges criterias for the evaluated parameters: pH buffer 4.4 to 4.7; reaction temperature 85°C to 95°C; reaction time 30 to 40 minutes and peptide:Lu molar ratio of 3.8 to 4.0.

Figure 7 shows typical HPLC chromatograms for the standard labeling condition used in the preparation ^{177}Lu-PSMA-I&T at 0, 24 and 48 hours after labeling, demonstrating stability of the preparation.

Figure 7: HPLC profile of standard labeling condition of ^{177}Lu-PSMA-I&T, the radiochromatograms were obtained after labeling and freezed stored: 0 hour (a), 24 hours (b) and 48 hours (c)



After standardization and optimization of PSMA-I&T radiolabeling with carrier-added ^{177}Lu, the same labeling procedure was applied in the preparation of a therapeutic dose.

Considering the patient dose of 7.4 GBq corrected by the ^{177}Lu calibration factor for 48h, the labeling was performed with 9.25 GBq of carried added ^{177}Lu (Specific Activity 706.7 GBq/mg) and 445 μg of PSMA-I&T. After labeling, diethylenetriaminepentaacetic acid (DTPA) was added to the preparation as chelating agent for free ^{177}Lu.

The stability of the therapeutic dose was evaluated by TLC-SG and HPLC to determinate %RP immediately (0h) and after 24 and 48 hours freezed stored (table 3), and after defrosting and keeping 1 to 6 hours and 22 hours in climate chamber at 30ºC and 35 % humidity (table 4).

Table 3: Results of Percentage of radiochemical purity (%PR) of freezed stored therapeutic dose of ^{177}Lu-PSMA-I&T evaluated by HPLC (expressed as % of principal peak) and by TLC-SG (expressed % free ^{177}Lu)

Chromatograms	0h	24h	48h
TLC-SG	0.7	0.4	0.6
HPLC	99.4	98.6	97.2

Table 4: Results of percentage of radiochemical purity (%PR) of therapeutic dose of ^{177}Lu-PSMA-I&T evaluated by HPLC (expressed as % of principal peak) and TLC-SG (expressed as % free ^{177}Lu) after defrosting and kept into the climate chamber.

Chromatograms	1h	2h	3h	4h	5h	6h	22h
TLC-SG	1.1	1.0	1.3	1.2	1.2	1.2	1.8
HPLC	97	97	97	96.5	96.3	96.3	94.0

The therapeutic dose was stable for 48 hours freezed stored ≥ 95% of total radioactivity due to the main peak at HPLC) (figure 8). After defrosting and keeping into a climate chamber, the RP was higher than 95% up to 6 hours at HPLC analyses, despite the additional peaks observed at Rt=4 minutes and Rt=8 minutes, probably related to degradation products due to the radiolysis of the radiopharmaceutical. After 22 hours into the climate chamber, an intense and almost complete degradation of the labeled peptide was observed (figure 9).

Figure 8: HPLC profile of therapeutic dose of ^{177}Lu-PSMA-I&T freezed stored; the radiochromatograms were obtained at 0 hour (a), 24 hours (b) and 48 hours (c).

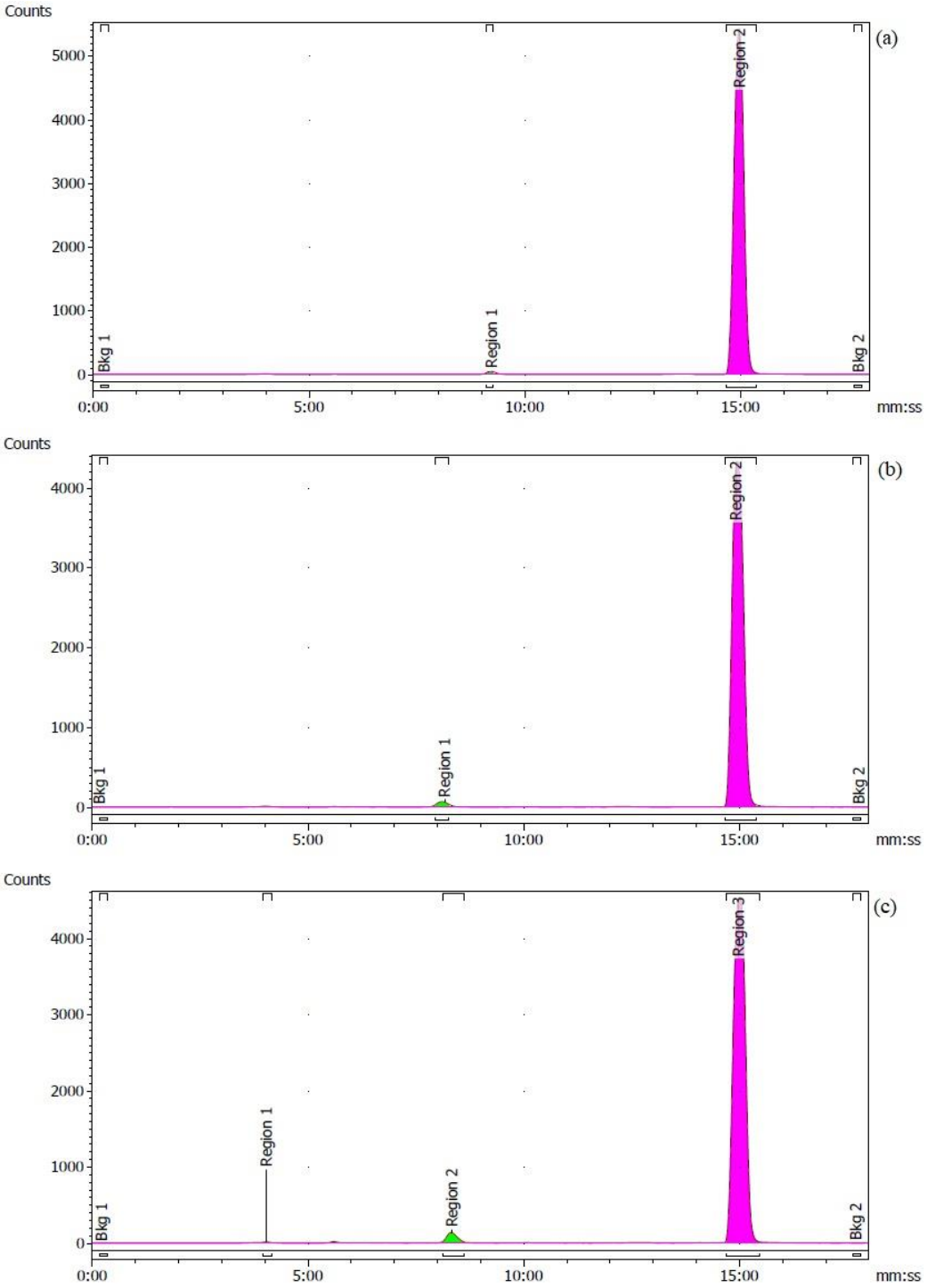
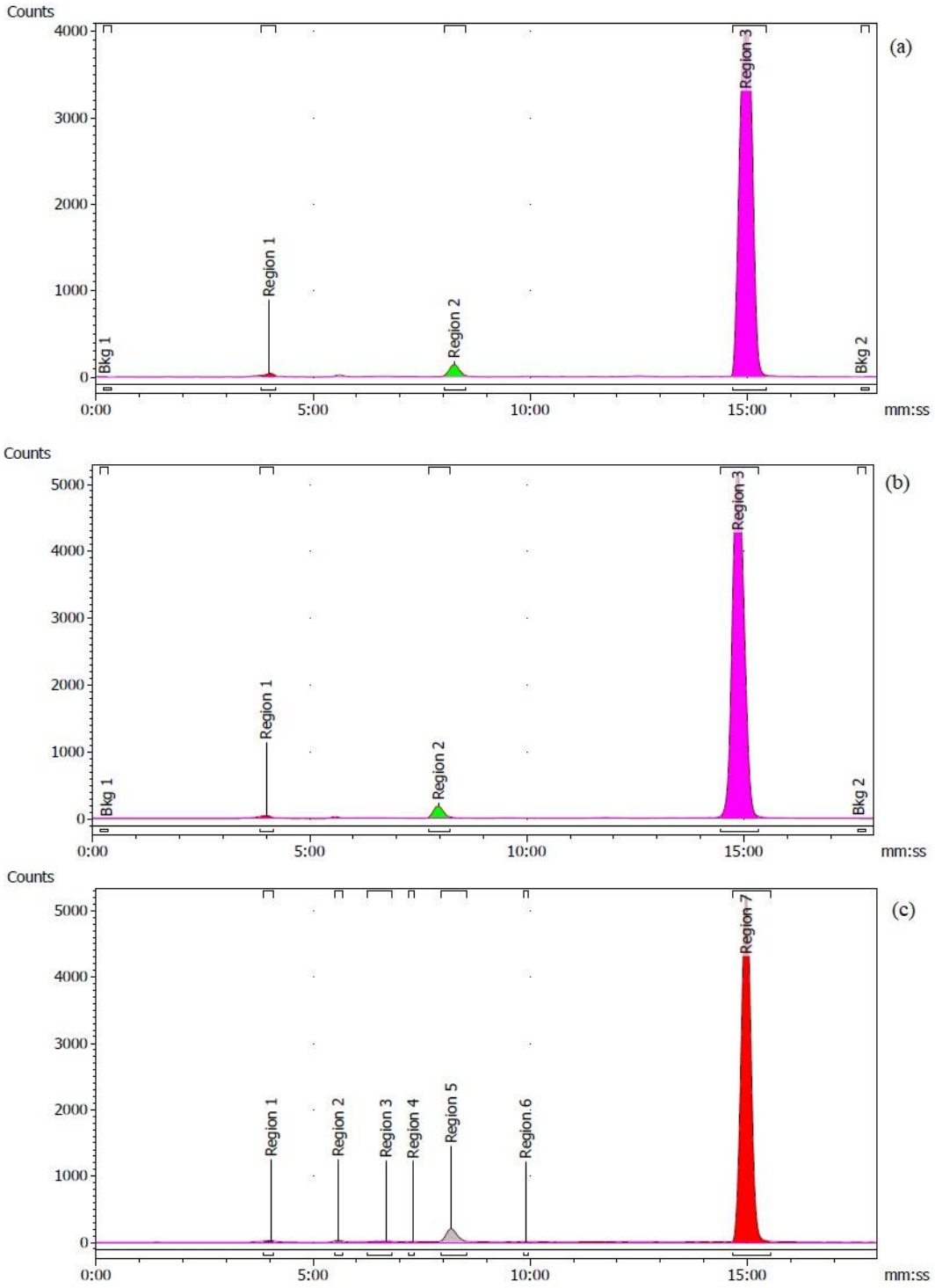


Figure 9: HPLC profile of therapeutic dose of ^{177}Lu-PSMA-I&T after defrosting and keeping into a climate chamber; the radiochromatograms were obtained 1 hour (a), 6 hours (b) and 22 hours (c).



4. CONCLUSIONS

This work described the tests carried out to evaluate the labeling parameters of ^{177}Lu-PSMA-I&T, and it was possible to define the best conditions for radiolabeling PSMA-I&T with carried added ^{177}Lu.

A therapeutic dose was prepared using standard labeling conditions and the stability study of the preparation demostrated that PSMA-I&T labeled with carrier added ^{177}Lu presents stability compatible with the transportation of the frozen product and also after defrosting, mantaining at 30ºC and 35 % humidity, that simulates room temperature, for 6 hours, enabling safe dose management for administration to patients in clinical application.

ACKNOWLEDGMENT

This research was supported by Nuclear and Energy Research Institute IPEN / CNEN, Brazil. The authors express their gratitude to the staff and groups of the Radiopharmacy Center for their valuable contribution, providing insight and expertise that greatly enhanced this research.

FUNDING

This work is part of the professional master's degree title: “Study of the optimization of PSMA I&T peptide labeling processes with lutetium-177 carried added for application in the treatment of metastatic castration-resistant prostate cancer based on a theranostic concept.” IPEN's Institutional Training Program, project number 422164/2023, title: Development of methods and protocols for validation of analytical tests used in quality control of radiopharmaceuticals. It is also part of International Atomic Energy Agency

(IAEA), project number F22078, title: Development of Potential ^{177}Lu Radiopharmaceuticals: Design, Radiolabeling and Nonclinical Evaluation.

Funding Agency: National Nuclear Energy Commission (CNEN) and National Council for Scientific and Technological Development (CNPq).

CONFLICT OF INTEREST

We have no conflicts of interest to disclose.

All authors declare that they have no conflicts of interest.

REFERENCES

[1] GLOBOCAN 2022. Global Cancer Observatory. Disponível em: https://gco.iarc.fr. Acesso em 20 Mar. 2024.)

[2] MORBECK, I. A. P., GADIA, R., CHAVES, N. R., SANTOS, M. Câncer de próstata. Diretrizes Oncológicas. p. 1-24, 2019. Disponível em: https://diretrizesoncologicas.com.br/wpcontent/uploads/2019/10/Diretrizes-oncologicas_separata_Prostata.pdf. Acesso em 20 mar 2024.

[3] CHATALIC, K. LS. *et al.,* Towards Personalized Treatment of Prostate Cancer: PSMA I&T, a Promising Prostate-Specific Membrane Antigen, Targeted Theranostic Agent **Theranostics**, vol. 6, 18387640. p. 849-861, 2016.

[4] BAUM, R.P. *et al.*, ^{177}Lu -Labeled Prostate-Specific Membrane Antigen Radioligand Therapy of Metastatic Castration-Resistant Prostate Cancer: Safety and Efficacy, **Journal of Nuclear Medicine**, vol. 57, p. 1006–1013, 2016.

[5] WEINEISEN, M *et. al.*, 68Ga- and ^{177}Lu -Labeled PSMA I&T: Optimization of a PSMA-Targeted Theranostic Concept and First Proof-of-Concept Human Studies, **Journal of Nuclear Medicine**, vol. 56, p.1169–1176, 2015.

[6] VYAS M., LIM, R., FAGAN, J., CHANDRASHEKCAR, R., Stability matters: Radiochemical Stability of Therapeutic Radiopharmaceutical ^{177}Lu -PSMA I&T., **Journal of Nuclear Medicine Technology**, vol. 50, p. 244-247, 2022.

[7] MALIK, N. *et al.*, Radiofluorination of PSMA-HBED via AI(18)F(2+) Chelation and Biological Evaluations In Vitro. **Molecular Imaging and Biology**, vol.17, p. 777-785, 2015.

[8] RUANGMA A., KIJPRAYOON, S., NGOKPOL, S., PSMA for PET imaging of prostate cancer. **The Bangkok Medical Journal**, vol. 14, p. 95, 2018.

[9] DI LORIO, V. *et al.*, Production and Quality Control of [^{177}Lu] Lu-PSMA-I&T: Development of an Investigational Medicinal Product Dossier for Clinical Trials. **Molecule**s, vol.27, p.4143-4158, 2022.

[10] CHAKRABORTY S, S., *et al.*, Prospects of medium specific activity ^{177}Lu in targeted therapy of prostate cancer using ^{177}Lu -labeled PSMA inhibitor. **Journal of Labelled Componds and Radiopharmaceutical**, vol. 59, p. 364-371, 2016.

[11] ZALUTSKY, M.R. Radionuclide Therapy. *In*: VÉRTES, A.; NAGY, S.; ZOLTÁN, K. **Handbook of Nuclear Chemistry**. Netherlands: Kluwer Academic Publishers, v. 4, p. 315-348, 2003.

[12] BOAS, C. A. W. V., *et al.,* In vitro and in vivo response of PSMA-617 radiolabeled with CA and NCA lutetium-177, **Applied Radiation and Isotopes**, vol. 180, p 1-7, 2022.

[13] DASH, A.; PILLAI, M.R.A.; KNAPP, F.F.JR.; Production of (177) Lu for Targeted Radionuclide Therapy: Available Options. **Nuclear Medicine and Molecular Imaging**, Vol 49, p. 85-107, 2015.

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