Stability Matters: Radiochemical Stability of Therapeutic Radiopharmaceutical ^{177}Lu-PSMA I&T

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Labeling radiopharmaceuticals and testing the quality of the labeled product before injecting it into patients are standard operating procedures in the nuclear medicine department. There is a different shelf life for each labeled product, which determines how long a product can maintain in vitro stability before it needs to be discarded. ^{177}Lu is a radioactive isotope that is increasingly being accepted into the treatment paradigm for palliation of advanced-stage tumors, including metastatic castration-resistant prostate cancer (mCRPC) and neuroendocrine tumors (NETs). In our institution, synthesis of ^{177}Lu with prostate-specific membrane antigen imaging and therapy (PSMA I&T) for palliation of mCRPC is performed on an automated synthesis system. **Methods:** After each synthesis, the final product quality was evaluated by high-performance liquid chromatography (HPLC) and instant thin-layer chromatography (ITLC) at 3 different time points: 0, 24, and 48 h. Between February 2020 and October 2020, the quality of 35 batches of ^{177}Lu-PSMA I&T was evaluated. **Results:** The average radiochemical purity of ITLC-silica gel was found to be greater than 99% (99.70% ± 0.05%), and HPLC was greater than 98% (98.60% ± 0.05%). **Conclusion:** Our findings demonstrate that synthesis of ^{177}Lu-PSMA I&T with an automated synthesis system can remain stable for 48 h after labeling.

Key Words: quality assurance; radiochemistry; radionuclide therapy; high-performance liquid chromatography (HPLC); instant thin-layer chromatography (ITLC); lutetium-177 (Lu177); prostate-specific membrane antigen image and therapy (PSMA)

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Patients with metastatic castration-resistant prostate cancer have disease progression despite using maximum androgen blockade, as evidenced by a low testosterone level (*1*). It is therefore an advanced, and usually end-stage, form of prostate cancer. Prostate-specific membrane antigen (PSMA) is a type II transmembrane glycoprotein with enzymatic properties that is anchored in the cell membrane of prostate epithelial cells and is overexpressed by prostate cancer cells (*2*). As a result, PSMA can be used as a biomarker for prostate cancer. For peptide receptor radionuclide therapy, PSMA peptides can be radiolabeled with the β-emitter radioisotopes ^{90}Y and ^{177}Lu (PRRT). PSMA I&T, PSMA-617, and J591 are 3 analogs frequently used in therapy (*2*). Because of its favorable physical characteristics (half-life [t1/2] = 6.73 d; mean energy of β-particle [Emax] = 0.497 MeV), ^{177}Lu has been identified as one of the most promising radionuclides for therapeutic applications (*3*). The β-particle emitted by ^{177}Lu has a short pathlength of 1.5 mm, allowing it to deliver effective tumor radiation while causing minimal damage to surrounding normal tissues. The use of the 2 primary γ-energies of 113 and 208 keV, respectively, allows for the use of SPECT imaging after treatment (*4*). The aim of this work was to evaluate the stability of ^{177}Lu-PSMA I&T using the high-performance liquid chromatography (HPLC) and instant thin-layer chromatography (ITLC) methods. This evaluation will assist in the understanding of the shelf life of the labeled product, which might be helpful for logistic purposes.

MATERIALS AND METHODS

The labeling of lutetium trichloride ($177LuCl_3$) and peptide (PSMA I&T; 40 mg of ascorbic acid and 10 mg of sodium hydroxide) was prepared with a fully automated radiopharmaceutical synthesis device using Modular-Lab Pharm Tracer (Eckert & Ziegler). PSMA I&T was labeled with ^{177}Lu using good manufacturing practice–grade disposable cassettes and reagent kits supplied by ABX Advanced Biochemical Compounds (Fig. 1). Labeling of ^{177}Lu-PSMA I&T was performed per the ABX and Eckert & Ziegler synthesis instructions, with the help of a pressure-based cassette (Eckert & Ziegler). The non–carrier-added $177Lucl_3$ was supplied by ANSTO and ITG (Isotope Technologies Garching GmbH). Radiation quantity was procured on the basis of the number of patients treated per cycle. The required dose for 1 patient was usually 7 GBq, based on the estimated synthesis yield of 80%. ABX supplied the accessory chemical, including sodium hydroxide–ascorbic acid and 50 mL of sodium chloride (saline) along with 0.55 μmol filters, long needles, and vent needles. PSMA I&T was supplied by Huwai Chem in a 1-mg vial, which was fractionated into 200 μg and stored in the freezer. The required amount of PSMA I&T (200 μg/5 GBq) was reconstituted with 1.5 mL of sodium ascorbate (0.57 M) to adjust the pH to 4.5 ± 0.1. Labeling was performed using a computer-based automated system (Modular-Lab Eazy; Eckert & Ziegler). All production cassettes were supplied by vendors and were made for a single use only.

The shelf life of prepared ^{177}Lu-PSMA I&T was established on the basis of the evaluation of radiochemical purity (RCP) by HPLC and ITLC-silica gel (ITLC-SG) (*5*).

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FIGURE 1. Modular-Lab Pharm cassettes supplied by Eckert and Ziegler.

HPLC was used for radiochemical analyses and purification of the ^{177}Lu-labeled PSMA I&T conjugates. A dual-pump HPLC unit with a C18 reversed-phase column (25 × 0.46 cm) (Knauer) purified the labeled conjugates. Mixtures of 1% trifluoroacetic acid, Ultrapure (Sigma-Aldrich) water (solvent A) and and 0.1% trifluoroacetic acid and acetonitrile (solvent B) were used as the mobile phase (*6*). The following gradient elution technique was adopted for the separation: 0–3 min—A, 100% and B, 0%; 3–10 min—A, 50% and B, 50%; 10–15 min—A, 0% and B, 100%. HPLC analysis showed that the fast eluting compound was hydrophilic ^{177}Lu cation (1.0 min), whereas ^{177}Lu-PSMA I&T with a high molecular weight was eluted after

TABLE 1
HPLC Results at Various Times

Batch no.	HPLC purity result at 0 h	HPLC purity result at 24 h	HPLC purity result at 48 h
1	99.78	99.7	99.7
2	99.75	99.87	99.75
3	99.56	99.5	99.65
4	99.89	99.8	99.89
5	99.91	99.91	99.95
6	99.92	99.92	99.92
7	99.98	99.98	99.98
8	99.87	99.87	99.87
9	99.76	99.76	99.76
10	99.56	99.56	99.56
11	99.6	99.6	99.75
12	99.76	99.76	99.76
13	99.8	99.8	99.8
14	99.45	99.45	99.45
15	99.13	99.13	99.13
16	99.35	99.35	99.35
17	99.56	99.56	99.56
18	99.87	99.87	99.87
19	99.74	99.74	99.74
20	99.15	99.15	99.15
21	99.3	99.3	99.3
22	98.9	98.9	98.9
23	99.56	99.56	99.56
24	99.45	99.45	99.45
25	99.57	99.57	99.6
26	99.45	99.45	99.55
27	99.87	99.87	99.77
28	99.67	99.7	99.67
29	99.78	99.78	99.78
30	99.55	99.55	99.55
31	99.65	99.65	99.75
32	99.15	99.2	99.15
33	99.45	99.45	99.45
34	99.5	99.65	99.5
35	99.75	99.75	99.7

TABLE 2
ITLC-SG Results at Various Times

Batch no.	TLC purity result at 0 h	TLLC purity result at 24 h	TLC purity result at 48 h
1	99.70	99.7	99.7
2	99.65	99.87	99.75
3	99.76	99.5	99.65
4	99.95	99.8	99.89
5	99.97	99.91	99.95
6	99.95	99.92	99.92
7	99.98	99.98	99.98
8	99.97	99.87	99.87
9	99.98	99.76	99.76
10	99.66	99.56	99.56
11	99.60	99.6	99.75
12	99.76	99.76	99.76
13	99.80	99.8	99.8
14	98.67	99.45	99.45
15	98.76	99.13	99.13
16	99.76	99.35	99.35
17	99.56	99.56	99.56
18	99.87	99.87	99.87
19	99.65	99.74	99.74
20	99.15	99.15	99.15
21	99.35	99.3	99.3
22	98.91	98.9	98.9
23	99.65	99.56	99.56
24	99.45	99.45	99.45
25	99.57	99.57	99.6
26	99.45	99.45	99.55
27	99.77	99.87	99.77
28	99.67	99.7	99.67
29	99.78	99.78	99.77
30	99.55	99.55	99.55
31	99.65	99.65	99.75
32	99.25	99.2	99.45
33	99.45	99.45	99.45
34	99.65	99.65	99.55
35	99.75	99.75	99.67

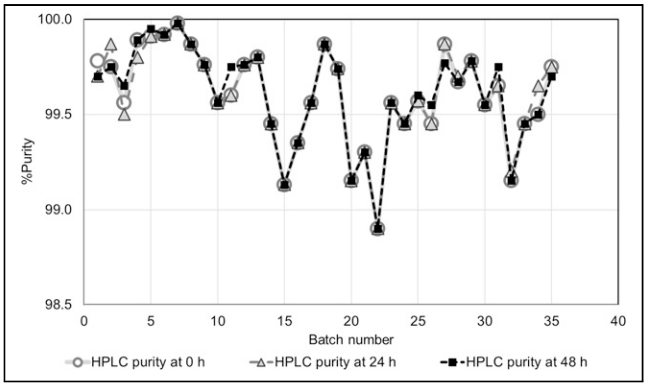

FIGURE 2. A line graph showing HPLC quality control result comparison at 0, 24, and 48 h.

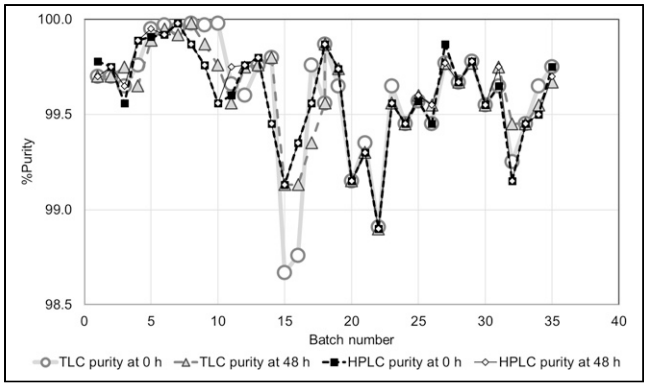

FIGURE 4. A line graph showing result of HPLC and ITLC-SG at 0 and 48 h.

8 min. The typical retention time of radiolabeled PSMA under the above conditions is approximately 500 s (8–10 min).

The ITLC-SG method was applied to check the RCP of the radiolabeled complex. The principle of the ITLC-SG analytic method is that a mobile phase moves along a stationary phase due to capillary forces. Therefore, depending on the distribution of components between the stationary and mobile phase, a radioactive sample spotted in the adsorbent will migrate with different velocities, and thus impurities are separated. The study was performed using a 10-cm-long Whatman 3MM chromatography paper's stationary phase. For this study, 5 μL of the test solution was spotted at 1.5 cm from the lower end of the paper strips, developed in 10% ammonium acetate in methanol as mobile phases (30:70 vol/vol). After each synthesis, the given amount of radiolabeled complex (∼10 MBq) was kept at room temperature for 48 h while being checked by HPLC and ITLC-SG at specified time intervals of 0, 24, and 48 h after preparation (Tables 1 and 2).

RESULTS

Thirty-five batches of ^{177}Lu-labeled PSMA I&T were completed between February 2020 and October 2020. The average RCP of ITLC-SG was greater than 99 percent (99.70 ± 0.05 percent), and HPLC was greater than 98% (98.60% ± 0.05%) at room temperature at both 24 and 48 h after synthesis, which was consistent with the various concentrations of the ^{177}Lu-PSMA I&T (Supplemental Table 1 [available at http://jnm.snmjournals.org]; Figs. 2–4).

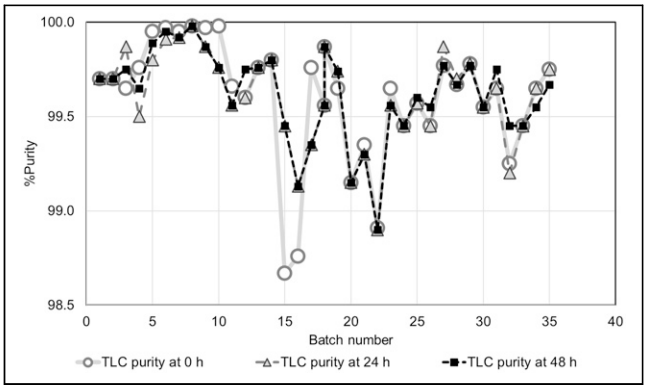

FIGURE 3. A line graph showing ITLC-SG quality control result comparison at 0, 24, and 48 h.

DISCUSSION

Radiopharmaceuticals used for diagnosis and therapeutic purposes are required to have an RCP of greater than 95%, and the length of time a radiopharmaceutical remains at this RCP demonstrates the shelf life of the product. Longer stability allows the radiopharmaceutical to be transportable to distant places, especially in the current COVID-19 environment where traveling is a complex procedure for the patients. The current study found that labeled ^{177}Lu-PSMA I&T stays stable for up to 48 h, which justifies the manufactured product and the influential role of applied quenchers. Both HPLC and ITLC-SG were found to agree with final product stability. In our formulation, we applied sodium ascorbate as a quencher with a concentration of 2 mg/mL. All the results have been evaluated following the suggested methods by Eckert & Ziegler Eurotope's Modular-Lab Pharm Tracer.

CONCLUSION

Our study demonstrates that ^{177}Lu-PSMA I&T, using the automated synthesis of Eckert & Ziegler Eurotope's Modular-Lab Pharm Tracer, can remain stable for 48 h. This longer stability suggests it is feasible for prelabeled ^{177}Lu-PSMA I&T to be supplied from a source location to distant satellite clinics, potentially improving access to PSMA-directed radioligand therapy for palliation treatment metastatic castration-resistant prostate cancer.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

KEY POINTS

QUESTION: Is the ^{177}Lu-PSMA I&T stable enough to allow it to be transported?

PERTINENT FINDINGS: ^{177}Lu labeled with PSMA I&T was found to be stable for up to 48 h in our study. This finding is encouraging because it suggests that labeled products can be transported from one location to another.

IMPLICATIONS FOR PATIENT CARE: The current finding is encouraging because it suggests that the ^{177}Lu-PSMA I&T has a long enough shelf life. In addition, it opens the door to the possibility of patients receiving treatment without having to travel away from their home locations.

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