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Freeze-dried multi-dose kits for the fast preparation of ^{177}Lu-Tyr^3-octreotide and ^{177}Lu-PSMA(inhibitor) under GMP conditions

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Abstract ^{177}Lu-Tyr^3-octreotide and ^{177}Lu-PSMA(inhibitor) radiopeptides were obtained with radiochemical purities of 98.7–100%, from lyophilized formulations after reconstitution with sterile solutions of ^{177}LuCl$_3$ (40 GBq/mL) without the need for further purification or sterilization processes. More than 50 radiochemical syntheses were performed with a failure rate of 0% and radiochemical yields of 94–97%. From one lyophilized kit of DOTA-Tyr^3-octreotide or DOTA-iPSMA, it was possible to obtain from 5 (7.4 GBq) to 10 (3.7 GBq) doses suitable for patients. Also, by using a sterile solution of ^{177}LuCl$_3$ approved as a radiopharmaceutical precursor for human use, it is possible to obtain GMP-compliant ^{177}Lu-peptides from sterile freeze-dried formulations without the need of using commercially-available radiochemical synthesizers.

Keywords ^{177}Lu · ^{177}Lu-labeled peptides · ^{177}Lu formulations · PSMA inhibitor · Tyr^3–octreotide · Freeze-dried kit

Introduction

Nowadays, ^{177}Lu is widely used as a therapeutic radionuclide for targeted radiotherapy because of its excellent nuclear properties (half-life of 6.647 d, β-max emission of 0.497 MeV and γ radiation of 0.208 MeV, useful for diagnostic imaging), coordination to different chelator-biomolecules and commercial availability [1, 2].

Of particular concern are the ^{177}Lu-Tyr^3-octreotide (^{177}Lu-DOTA-Tyr^3-octreotide; DOTA = 1,4,7,10-tetraazacyclododecane-N,N′,N″,N‴-tetraacetic acid) and ^{177}Lu-iPSMA (iPSMA = prostate-specific membrane antigen inhibitor, e.g., DOTA-PSMA-617) radiopharmaceuticals, which have successfully been used in the treatment of patients with neuroendocrine tumors and advanced metastatic prostate cancer, respectively [3–5].

Nevertheless, the current challenge in the routine production of ^{177}Lu radiopharmaceuticals is the development of quick and efficient processes that comply with the requirements established by regulatory authorities regarding Good Manufacturing Practices (GMP). One approach is the use of commercially-available radiochemical synthesizers connected or adjacent to ISO Class 5 areas, from which the automated procedure allows to perform and record critical steps during the batch production such as the filter membrane integrity test, as well as to carry out the dosing process under clean air conditions. However, the radiochemical yield using synthesizers ranges from 74 to 90%, and the number of therapeutic doses obtained by batch is usually limited to or less than three [6–8]. Furthermore, the acquisition of commercial disposable cassettes and specific reagent kits for each produced batch is mandatory, significantly increasing production costs.

It has also been previously reported that various lyophilized formulations for the one-step preparation of ^{177}Lu-DOTA-Tyr^3-octreotate (^{177}Lu-DOTA-TATE) and ^{177}Lu-DOTA-Tyr^3-octreotide (^{177}Lu-DOTA-TOC), with excellent results utilizing ^{177}Lu prepared by neutron irradiation of ^{176}Lu (carrier added) or ^{176}Yb (non-carrier added) [9–12]. Nonetheless, said formulations are reported as kits for the preparation of mono-doses (up to

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7.4 GBq, one dose for one patient), which are reconstituted with solutions of $^{177}LuCl_3$ sterilized through a 0.22 μm membrane, for which its certification as a GMP product authorized for use in humans, is not clear.

The non-carrier added $^{177}LuCl_3$, prepared as a sterilized solution with a content of bacterial endotoxin equal to or below 20 EU/mL and a radioactive concentration of 40 GBq/mL (EndolucinBeta, ITG, Germany), was approved in 2016 by the European Medicines Agency (EMA) as a radiopharmaceutical precursor for human use. Since the specific activity and the radioactive concentration of $^{177}LuCl_3$ are routinely reproducible, it is possible to design freeze-dried sterile formulations to obtain ^{177}Lu-peptides by simple reconstitution of a lyophilized powder with the sterile solution of $LuCl_3$, followed by heating of the vial for a complete ^{177}Lu-conjugate formation under sterile conditions.

The aim of this study was to develop freeze-dried, multidose formulations for the preparation of ^{177}Lu-Tyr^3-octreotide and ^{177}Lu-iPSMA (up to 37 GBq/vial) in high radiochemical yields without the need for further purification or sterilization processes under GMP conditions.

Experimental

Design of the freeze-dried formulations

Lutetium (^{177}Lu) chloride was obtained from ITG, Germany (EndolucinBeta 40 GBq/mL, in aqueous 0.04 M HCl solution, > 3 TBq/mg). DOTA-iPSMA (1,4,7,10-tetraazacyclododecane-N,N′,N″,N‴-tetraacetic acid -hydrazinonicotinyl-lysine-urea-glutamate derivative) and DOTA-Tyr^3-octreotide (GMP grade) were supplied by Ontores Biotechnologies (China) and ABX (Germany), with certified chemical purities of > 98%. Sodium acetate, ascorbic acid, and mannitol were purchased as pharmaceutical-grade reagents from Sigma-Aldrich (USA).

Freeze-dried kits were preformulated by using different amounts of DOTA-Tyr^3-octreotide and DOTA-iPSMA peptides (ng/MBq), to evaluate the effect of the variations on the ^{177}Lu-peptide radiochemical purity. The amount of each component in the formulation was designed for the labeling of one lyophilized vial with 40 GBq of $^{177}LuCl_3$, applying a factorial experimental design (Table 1). The analysis of variance (ANOVA) was performed with the GraphPad Prism software.

Manufacturing process of freeze-dried kits (3 validation runs)

Preparation of the lyophilized formulations was done in aseptic conditions under GMPs. DOTA-iPSMA (12 mg) or DOTA-Tyr^3-octreotide (16 mg) were dissolved in 20 mL of injectable-grade water (stirring and incubation at 70 °C). Posteriorly, 1 g of mannitol and 2 g of ascorbic acid were also dissolved, with stirring, in 20 mL of injectable-grade water. The peptide and mannitol/ascorbic acid solutions were then mixed (pH = 2.5–3.5). Finally, the formulation was sterilized by filtration (Millipore, 0.22 μm) and 2 mL were dosed in 20 previously-depyrogenized ampoule vials to then be lyophilized for 19 h (freezing at −40 °C/1 h, primary drying for 6 h and secondary drying at 0 °C/4 h, 25 °C/4 h and 29 °C/4 h). After freeze-drying the formulation, the kit was stored at 2–8 °C.

Additionally, 30 mL of 1 M sodium acetate buffer solution pH 5.0 was prepared, which was filtered through a 0.22 μm membrane, and 1.5 mL were dosed in 20 sterile ampoule vials.

For each one of the precursors, a manufacturing process validation was done, which consisted in the fabrication of three consecutive batches with a batch size of 20 vials each. The same manufacturing conditions were maintained to guarantee reproducibility. Process controls were established, such as solution pH, determination of dose volume through weight ($n = 3$), filter integrity (bubble point test, Millipore, BP > 56 psi), as well as the environmental monitoring of viable and non-viable particles for ISO-5 and ISO-6 areas, in accordance with the guidelines established by the official Mexican regulation (NOM-241-SSA1-2012).

Quality control and stability tests of freeze-dried kits

For the quality control of the lyophilized formulations, parameters such as color, appearance, pH, sterility,

Table 1 Factorial experimental design applied in the development of the freeze-dried kit formulations

Variable	Levels	Values
Amount of ascorbic acid (mg)	3	50, 100, 150
Volume of acetate buffer (pH 5.0, 0.2 M) plus $^{177}LuCl_3$ added for lyophilized powder reconstitution (mL)	3	2.0, 2.5, 3.0
Time (h), stability	1	72

Dependent variable Radiochemical purity

bacterial endotoxins and radiochemical purity (reversed phase HPLC, with a 3.9 mm × 30 cm μBondapak™ C18 column, using a gradient system), were evaluated in accordance with the Mexican Pharmacopeia [13], in its section referring to "General Methods of Analysis" (MGA). The retention time of the radiolabeled peptide (^{177}Lu-DOTA-Tyr^3-octreotide or ^{177}Lu-DOTA-iPSMA) was 15.0 ± 2.0 min, while the retention time of $^{177}LuCl_3$ was 3.0 ± 1.0 min. All batches were subjected to stability tests for 12 months after their manufacturing dates.

Production process: Radiochemical synthesis

^{177}Lu-DOTA-iPSMA and ^{177}Lu-DOTA-TOC were prepared in a shielded cell (Comecer, Italy) which has a main compartment, waste compartment, and material entry/exit compartments. All compartments contain shielding made up of lead ingots (98% purity, with 2% Sb). The main chamber was equipped with a dose calibrator operated through specialized software and controlled through a touchscreen. It is also equipped with a UV lamp and a laminar flow system with HEPA terminal filters (99.997% efficiency), which was programmed with a vertical laminar flow of 0.3 m/s, granting an ISO Class 5 degree of cleanliness. For the incubation step, a Cole Palmer dry bath was placed within the shielded cell.

For the radiochemical synthesis, the $^{177}LuCl_3$ original vial (40 GBq/mL) was vented with a needle, and then 1.0–1.5 mL of the 1 M acetate buffer pH 5.0 was added. The total volume was withdrawn using a sterile syringe and was afterward employed for the reconstitution of the DOTA-iPSMA or DOTA-Tyr^3-octreotide lyophilized kit. The reconstituted vial was heated in the dry bath at 95 °C for 30 min. After cooling to room temperature, the vial was vented with a needle, and the volume was taken up to 10 mL with injectable-grade water (Pisa, Mexico) through using a sterile syringe. The dosing step was carried out directly in delivery syringes using leaded glass shielding or using a dosing module (Timo-2, Comecer, Italy).

Quality control and stability testing for finished radiopharmaceuticals

For the quality control of the radiopharmaceuticals, a sample was taken for pH, sterility, bacterial endotoxins and radiochemical purity (reversed-phase HPLC/gradient system) tests in accordance with the Mexican Pharmacopeia [13], in its section referring to MGAs [13]. Stability of the radiolabeled products was evaluated at 72 h post-production by reversed-phase HPLC.

In vivo studies

LNCaP (PSMA-positive) human prostate cancer cells and AR42 J (somatostatin receptor-positive) rat pancreatic cancer cells were acquired from the ATCC (USA). Biodistribution and tumor uptake studies in mice were carried out in agreement with the Mexican regulation (NOM-062-ZOO-1999).

LNCaP or AR42 J tumors were induced using a subcutaneous injection of cancer cells suspended in 0.1 mL phosphate-buffered saline (1×10^6 cells), into the upper back region of 8-week-old nude mice. ^{177}Lu-octreotide or ^{177}Lu-iPSMA obtained from lyophilized kits (3.7 MBq in 0.05 mL) was injected into the tail vein of the mice. The mice ($n = 5$) were sacrificed at 1, 4, 48 and 96 h post-injection. Tumor, lung, liver, spleen, kidney, intestine and blood were dissected. The activity was determined in a NaI(Tl) detector, along with 0.5 mL aliquots of the diluted standard representing 100% of the injected activity. The activities were used to determine the percentage of injected dose per gram of tissue (% ID/g).

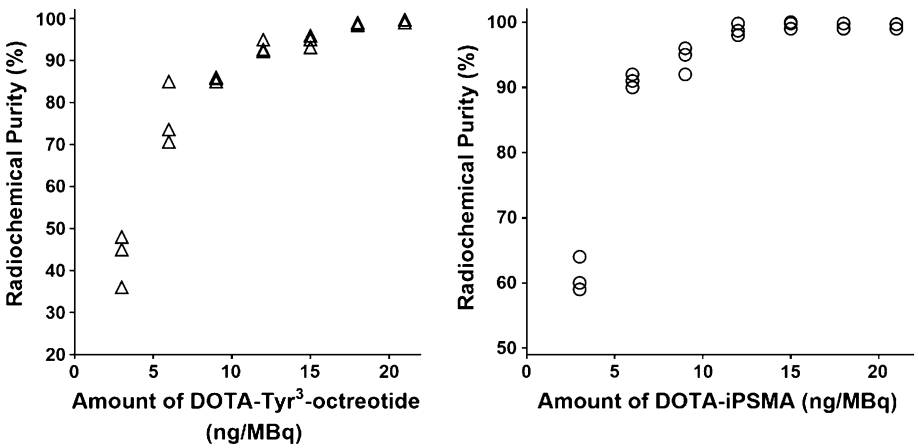

Fig. 1 Effect of the DOTA-Tyr^3-octreotide and DOTA-iPSMA mass per added activity (MBq) on ^{177}Lu-peptide radiochemical purity

Results and discussion

Freeze-dried formulation design

As shown in Fig. 1, the mass per MBq necessary to obtain radiochemical purities (RP) of > 98% was different between peptides, but the number of DOTA moles required to achieve RP over 98% was the same in both peptides

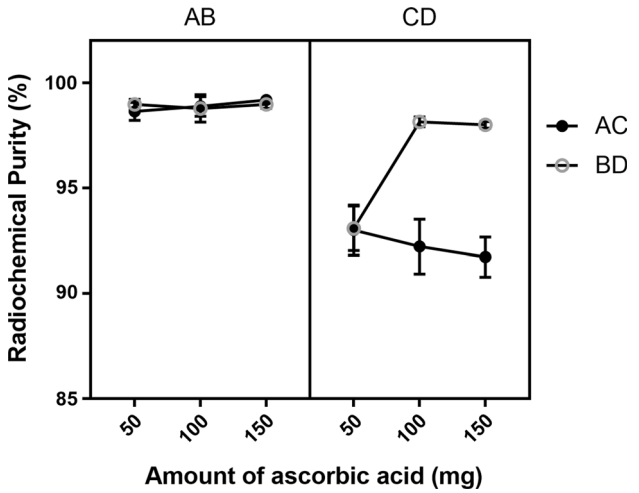

Fig. 2 ANOVA results. Volume of acetate buffer (pH 5.0, 1.0 M) plus $^{177}LuCl_3$ added for lyophilized powder reconstitution: **a** 2.0, **b** 2.5 and **c** 3.0 mL **d** stability at 72 h after radiochemical synthesis

(~ 0.015 nmol/MBq). Therefore, differences between the spatial conformation of peptides with different steric hindrance are not factors which affect the radiochemical reaction yield, contrary to what occurs with other peptides [14]. These results correlate to those reported by Iori et al. [6], where amounts from 11 to 40 ng/MBq were found suitable to obtain RP over 98% for ^{177}Lu-peptides. Based on the pre-formulation study (Fig. 1), the selected amount of peptide per vial to obtain 37–40 GBq of ^{177}Lu-Tyr^3-octreotide and ^{177}Lu-iPSMA was 0.8 mg (571 nmol) and 0.6 mg (597 nmol), respectively.

The ANOVA results indicated that all components have a significant effect ($p < 0.01$) on the RP and present significant interaction amongst themselves ($p < 0.01$) (Fig. 2). When 1.0–1.5 mL of the acetate buffer was added to the $^{177}LuCl_3$ vial (1 mL) for reconstitution of the lyophilized powder (total volume of 2.0 or 2.5 mL), the RP was over 98% at all levels of ascorbic acid mass, but after 72 h an amount of 50 mg of ascorbic acid was not enough to maintain the RP over 95%, which presented the same behavior when a reconstitution volume of 3 mL was used. Therefore, the selected kit composition was: (1) one lyophilized vial containing 0.8 mg (DOTA-Tyr^3-octreotide) or 0.6 mg (DOTA-iPSMA) of the peptide, 100 mg of ascorbic acid and 50 mg of mannitol as a diluent, and (2) a second vial containing 1.5 mL of 1.0 M acetate buffer pH 5.0.

Table 2 Production process controls and environmental monitoring for the lyophilized peptide formulations

Parameters	Specification	Average of three production batches	
		DOTA-iPSMA	DOTA-Try^3-octreotide
pH of the final mixture	2.5–3.5	2.59	2.67
Acetate buffer (pH)	4.5–5.0	4.97	4.97
Volume (determined by weight) (g)	2.0	2.003–2.010	1.996–2.004
Acetate buffer volume (determined by weight) (g)	1.5	1.502–1.511	1.500–1.510
Filter integrity (bubble point test)	> 56 psi	79.25 ± 0.33	79.19 ± 0.19
Environmental monitoring			
ISO-5			
Viable particles (CFU)	Sedimentation ≤ 1 m^3	0	0
	Contact ≤ 1 per plate	0	0
	Air ≤ 5 per plate	0	0
Total particles/m^3	0.5 μm ≤ 3520	0	0
	5.0 μm ≤ 29	0	0
ISO-6			
Viable particles (CFU)	Sedimentation ≤ 10 m^3	0	1
	Contact ≤ 5 per plate	2	2
	Air ≤ 5 per plate	3	1
Total particles/m^3	0.5 μm ≤ 35200	526	752
	5.0 μm ≤ 293	23	15

Manufacturing process

The results of all three lyophilized batches for DOTA-iPSMA and DOTA-Tyr^3-octreotide production confirmed that control processes and environmental conditions complied with the specifications established by the regulatory authorities (GMP-grade formulations) (Table 2). Thus, the quality control tests performed to all three validation batches were also compliant with the specifications established in the Mexican Pharmacopeia as preparations suitable for human use. In general, limpid, colorless and sterile solutions were obtained after reconstitution, with bacterial endotoxins of < 20 EU/V, pH 5.0 and average radiochemical purities over 97% (Fig. 3) [13].

As can be seen in Fig. 4, DOTA-iPSMA and DOTA-Tyr3-octreotide lyophilized formulations were stable, since the three validation batches consistently produced ^{177}Lu-radiopharmaceuticals with radiochemical purities in agreement with the established specification ($> 97\%$) [13] over a period of 12 months after preparation.

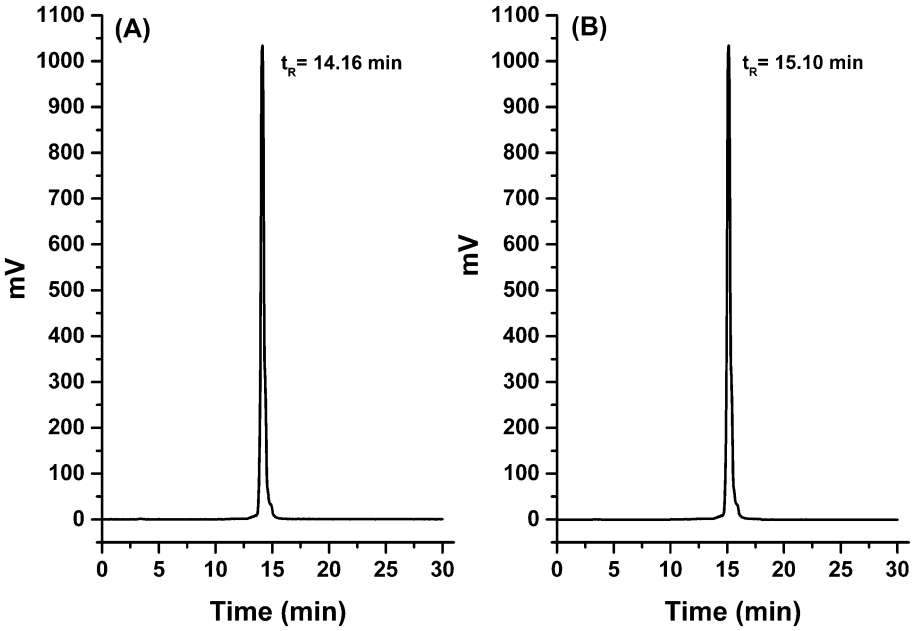

Fig. 3 Reversed-phase radio-HPLC chromatograms of **a** ^{177}Lu-iPSMA and **b** ^{177}Lu-Tyr^3-octreotide radiopharmaceuticals

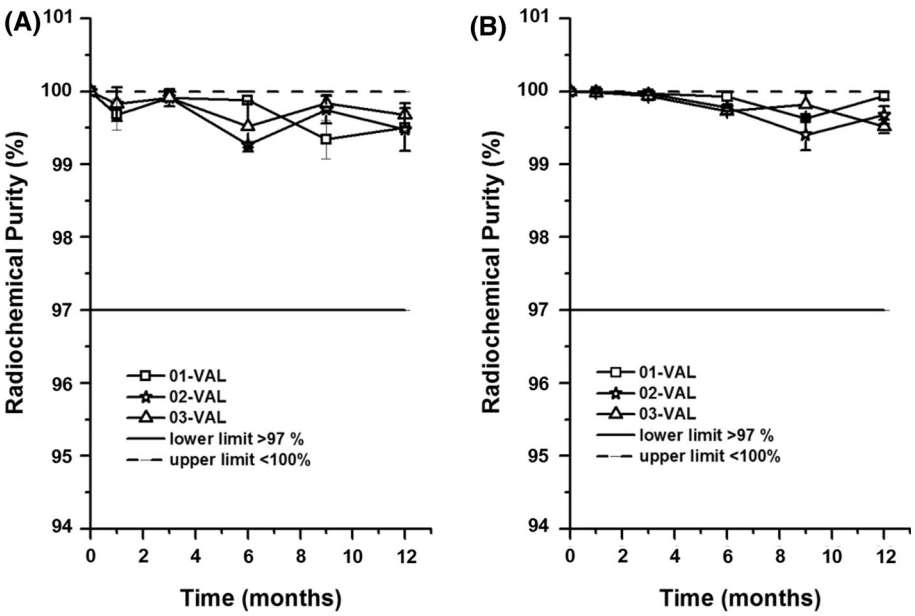

Fig. 4 Stability of three validation batches (01-, 02- and 03-VAL) of **a** DOTA-iPSMA and **b** DOTA-Tyr^3-octreotide lyophilized formulations over a 12-month period, as determined by radiochemical purity after ^{177}Lu labeling

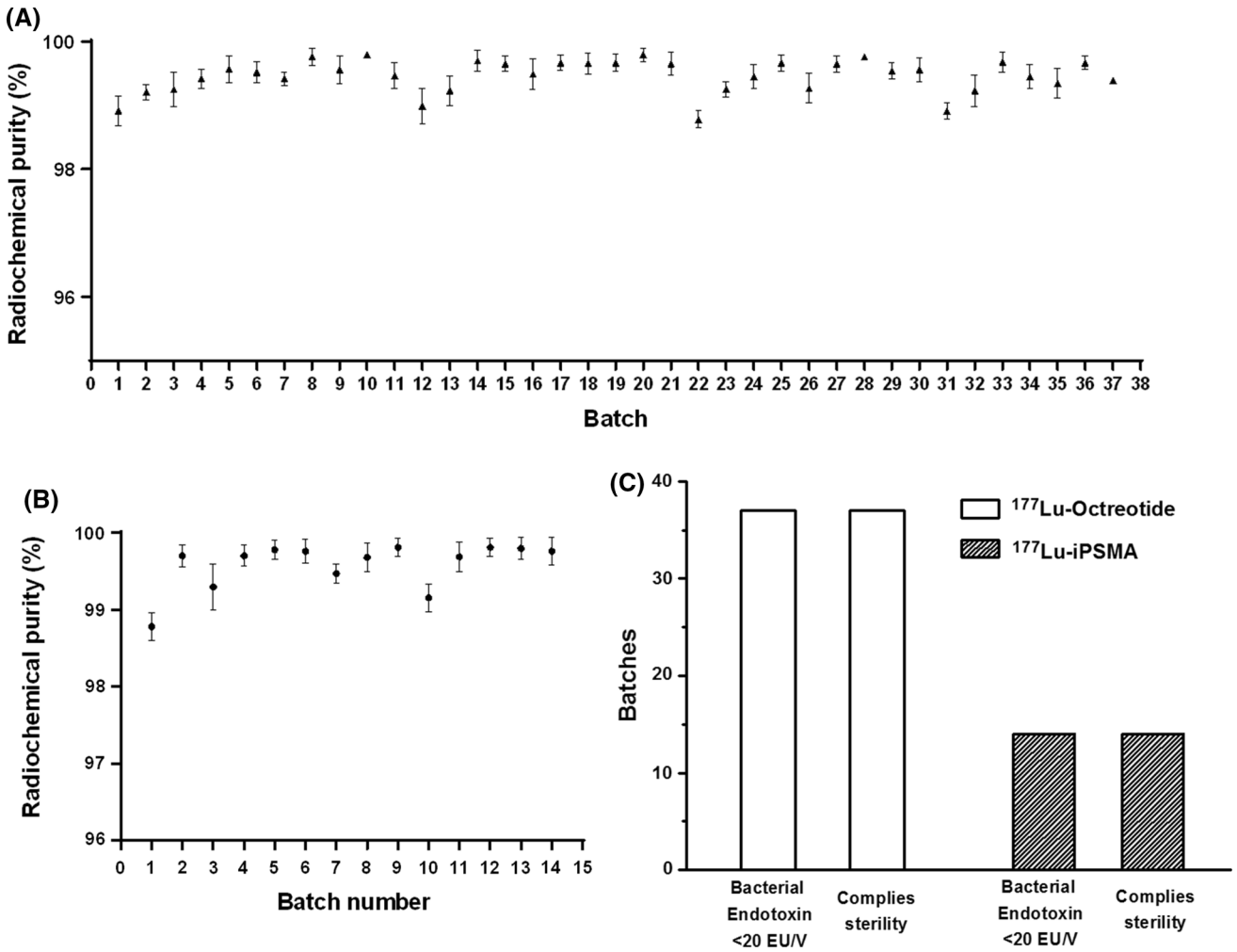

Fig. 5 Stability of **a** ^{177}Lu-Tyr^3-octreotide and **b** ^{177}Lu-iPSMA, and **c** sterility and level of bacterial endotoxin at 72 h post-production

Table 3 Biodistribution in mice with induced tumors after i.v. administration of ^{177}Lu–Tyr^3-octreotide or ^{177}Lu-iPSMA prepared from lyophilized kits (% ID/g)(n = 3)

TISSUE	^{177}Lu-Tyr^3-octreotide (AR42 J-induced tumors)				^{177}Lu-iPSMA (LNCaP-induced tumors)			
	1 h	4 h	48 h	96 h	1 h	4 h	48 h	96 h
Blood	1.64 ± 0.07	0.47 ± 0.02	0.01 ± 0.03	0.00 ± 0.00	1.07 ± 0.02	0.25 ± 0.03	0.00 ± 0.00	0.00 ± 0.00
Lung	2.60 ± 0.19	1.40 ± 0.08	0.12 ± 0.06	0.00 ± 0.00	1.45 ± 0.09	0.74 ± 0.04	0.01 ± 0.00	0.00 ± 0.00
Liver	9.16 ± 0.80	7.47 ± 0.40	1.92 ± 0.42	0.19 ± 0.07	5.58 ± 0.56	3.40 ± 0.31	0.27 ± 0.06	0.08 ± 0.02
Spleen	8.48 ± 0.65	4.39 ± 1.14	0.98 ± 0.27	0.26 ± 0.08	2.09 ± 0.17	1.38 ± 0.24	0.11 ± 0.04	0.00 ± 0.00
Kidneys	21.47 ± 1.96	15.95 ± 1.28	3.26 ± 0.22	0.83 ± 0.42	19.20 ± 1.78	11.92 ± 1.01	0.88 ± 0.04	0.15 ± 0.09
Intestine	4.16 ± 1.24	5.72 ± 0.29	0.93 ± 0.33	0.03 ± 0.02	3.16 ± 0.09	3.04 ± 0.16	0.38 ± 0.13	0.04 ± 0.03
Tumor	12.20 ± 1.19	9.66 ± 0.92	4.39 ± 1.02	3.26 ± 0.62	9.03 ± 1.98	8.93 ± 0.84	5.59 ± 1.07	3.42 ± 0.74

Radiochemical synthesis

A total of 51 radiochemical syntheses (51 batches) were performed by using one lyophilized vial for each batch. Thirty-seven corresponded to ^{177}Lu-Tyr^3-octreotide and fourteen to ^{177}Lu-iPSMA. The radiochemical yield in all cases ranged from 94.0 to 97.0% (to obtain 37.5–38.8 GBq of the ^{177}Lu-peptide), with the main loss of activity in the $^{177}LuCl_3$ original vial. This yield is higher than those previously reported (from 70 to 90%), in which

radiochemical synthesizers were used [6–8]. The radiochemical purity for all batches was 98.7–100% and remained stable after 72 h (Fig. 5). This radiochemical purity was slightly higher than the mean value reported by Iori et al. [6]. Although the general formulation was designed for the preparation of 37.5–38.8 GBq ^{177}Lu-peptides, some batches with 20–37 GBq were also successfully prepared with radiochemical purities of 100% by using 0.5–1.0 mL of $^{177}LuCl_3$ (40 GBq/mL) plus 1–1.5 mL of 1 M acetate buffer pH 5.0 for reconstitution of the lyophilized powder. From each batch, it was possible to obtain from 5 (7.4 GBq, 5.55 GBq or 3.7 GBq) to 10 (3.7 GBq) doses, suitable for patients. Quality control tests also confirmed that no post-production sterilization is required since the ^{177}Lu–iPSMA and ^{177}Lu-Tyr^3-octreotide radiopharmaceutical solutions maintained their sterility and level of bacterial endotoxin after the radiosynthesis procedure (Fig. 5).

Maus et al. [7] evaluated the effect of final volumes (5, 20 and 100 mL) on the quenching effect of ascorbic acid. They found that at 5 mL final volume, re-addition of ascorbic acid with a concentration of 100 mM after purification resulted in radiochemical purity $\geq$ 95% at 72 h post-labeling, whereas no re-addition of ascorbic acid resulted in a radiochemical purity of 92% at 72 h post-labeling. In the case of this study, no such re-addition was necessary, since purification after radiolabeling was not necessary and the removal of ascorbic acid does not occur. It is also worth noting that in the formulations reported in this study, a concentration of 57 mM ascorbic acid was used, and was still capable of producing a sufficient stabilizing effect.

It is important to note that the multi-dose kits for the preparation of ^{177}Lu-iPSMA and ^{177}Lu-octreotide, here developed, are limited to the exclusive use of non-carrier added ^{177}Lu (40 GBq/mL, GMP-grade), with the finality of preparing 5 (5 doses of 7.4 GBq) or 10 (10 doses of 3.7 GBq) doses of radiopeptide with clinical usefulness from only one vial.

In Table 3, results of the biodistribution and biokinetic studies are shown. Establishing whether ^{177}Lu-Tyr^3-octreotide prepared from the multi-dose kit has a different biodistribution pattern concerning that previously reported for other somatostatin analog radiopeptides such as ^{177}Lu-DOTA-TATE is difficult, since studies were not carried out under the same experimental conditions. However, one piece of data that may be valuable for comparison under different experimental conditions is the tumor-to-organ ratio, rather than the absolute value of % ID/g in the tumor. In this study, the average tumor-to-blood ratio was 20.6 at 4 h for ^{177}Lu-Tyr^3-octreotide, which is in agreement with previously reported preclinical results for ^{177}Lu-DOTA-TATE [15].

Conclusions

The production of radiochemical precursors ($^{177}LuCl_3$) and lyophilized ligand formulations as sterilized and GMP-grade products, allows fast and routine preparation of ^{177}Lu therapeutic radiopharmaceuticals with a quality suitable for clinical use. This procedure lacks the need for the use of an automated synthesizer and thus reduces production costs.

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