3PC-040
ATC V10

RADIOCHEMICAL PURITY DETERMINATION OF ^{177}Lu-PSMA-617: DEVELOPMENT AND VALIDATION OF A HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY ANALYTICAL METHOD

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WHAT WAS DONE

- **[^{177}Lu]Lu-PSMA-617** = treatment of progressive, metastatic, castration-resistant **prostate cancers** expressing PSMA receptors, previously treated with taxane and at least one second-generation hormone therapy.
- [^{177}Lu]Lu-PSMA-617 = **radiopharmaceutical drug** with a marketing authorization, **manufactured industrially** (PLUVICTO®, Novartis).[1]
- It can also be **prepared in-house** (preclinical applications) ⇨ **Quality control procedures** required to determine **radiochemical purity (RCP)**.[2,3]

WHY IT WAS DONE

- A **radio-high-performance liquid chromatography** (HPLC) method was **developed** and **validated** to assess **RCP of [^{177}Lu]Lu-PSMA-617**.

HOW IT WAS DONE

Materials

- Intel i5 computer with GINA 10.x software
- Infinity II 1260 (Shimadzu) automatic chromatograph with multi-wavelength UV detector
- GABI Nova radiodetector, mid-energy probe
- C_{18} ACE® Equivalence™ column (3 x 150 mm, 3 µm)

HPLC analysis

Mobile phase: water + 0.1% TFA/acetonitrile + 0.1% TFA gradient

Acquisition parameters:

- Flow = 0.6 mL/min
- Injection volume = 20 µL
- Energy detection range = 0 – 1100 keV
- Column oven temperature = 30 °C
- Analysis time = 26 min

WHAT WAS ACHIEVED

Three commercial [^{177}Lu]Lu-PSMA-617 batches were used as samples. Parameters considered for method validation were **linearity**, **accuracy**, **precision**, **specificity**, **robustness**, limits of detection (**LOD**) and limits of quantification (**LOQ**).

Radiochemical identity

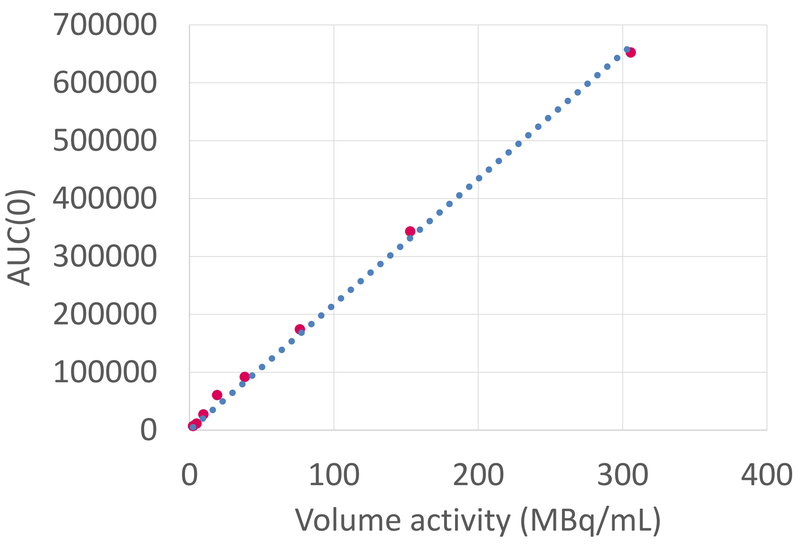
- Each [^{177}Lu]Lu-PSMA-617 commercial batch was measured 10 times and retention times (t_r) were compared.

Batch	1	2	3
t_r (min)	10.07 ± 0.01	10.07	10.13 ± 0.01
%CV	0.11	0	0.005

⇨ **Radiochemical identity confirmed**

Linearity

- 8 range points were measured in sextuplicate and decay-corrected: 300; 150; 75; 37.5; 18.8; 9.4; 4.7 and 2.4 MBq/mL.



- **r = 0.9977 ⇨ Linearity confirmed**

Recovery (part of accuracy)

- 12.2 MBq injected in triplicate;
- 12.87 ± 0.06 MBq recovered at column outlet.

⇨ **Mean recovery = 94.8%**

Accuracy

- Measurement in triplicate of 4 samples contaminated with a known proportion of radio-impurity ([^{177}Lu]Lu-DOTATATE).

%Lu-PSMA	Observed RCP (%)	Theoretic RCP (%)	%CV
100	93.51 ± 0.16	-	100
90	88.85 ± 0.17	87.48	101.57
80	85.64 ± 0.15	82.61	103.67
70	81.74 ± 0.07	78.16	104.59
60	78.93 ± 0.93	74.80	105.52

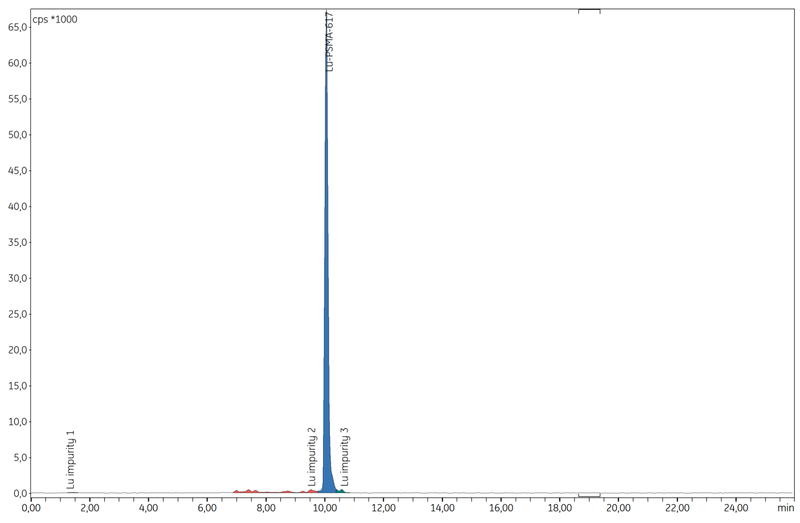
⇨ **Accuracy confirmed** for an amount of impurity ≤ 30% of total radioactivity.

Repeatability (part of precision)

- 12 repeated measurements of a single [^{177}Lu]Lu-PSMA-617 batch.

RCP (%)	%CV	t_r (min)	%CV
93.5 ± 0.1	0.11	10.07 ± 0.01	0.12

⇨ **Repeatability confirmed**



Specificity

- Forced degradation conditions in the presence of acid, base, oxidative stress or heating
  → *In situ* formation of impurities
  → Resolution (Rs) with the [^{177}Lu]Lu-PSMA-617 peak must be >2

Conditions	Mean $w_{0.5}$ (min)	Mean Rs
NaOH 0.1 M	0.09	2.65
HCl 0.1 M	0.083	5.94
H_2O_2 3%	0.087	5.24
Heating 60°C	0.083	2.63

⇨ **Specificity confirmed**

Limit of detection / limit of quantification

- LOQ = 0.68 MBq/mL
- LOD = 0.21 MBq/mL

Robustness

- Conditions 1: flow rate = 0.8 mL/min instead of 0.6 mL/min
- Conditions 2: column oven = 50 °C instead of 30 °C

Conditions	Mean t_r (min)	%CV
1	9.07	9.93
2	9.58 ± 0.08	4.82
Reference	10.07	-

⇨ **Robustness confirmed in conditions 2**

WHAT IS NEXT

A radio-HPLC method for the quality control of [^{177}Lu]Lu-PSMA-617 was validated and can be used for in-house preparations for preclinical purposes of this radioactive drug.[4]

[1] O. Sartor, *et al*. Lutetium-177–PSMA-617 for Metastatic Castration-Resistant Prostate Cancer. *N. Engl. J. Med.* **2021**, *385*, 1091-1103. **[2] P.** Orhon, *et al*. Development and Validation of Analytical Methods for Radiochemical Purity of ^{177}Lu-PSMA-1. *Pharmaceuticals* **2022**, **15**, 522. **[3]** M. Kraihammer, *et al*. Improved quality control of [^{177}Lu]Lu-PSMA I&T. *EJNMMI radiopharm. chem.* **2023**, *8*, 7. **[4]** E. A. M. Ruigrok, *et al*. Extensive preclinical evaluation of lutetium-177-labeled PSMA-specific tracers for prostate cancer radionuclide therapy. *Eur J Nucl Med Mol Imaging* **2021**, *48*, 1339–1350.