ISOLPHARM 111Ag Production and Separation at L.E.N.A.

NENE
International Conference
Nuclear Energy for New Europe

ISOLPHARM 111Ag Production and Separation at L.E.N.A.

Alfinito Federico
LENA, University of Pavia
Via Aselli, 41
27100, Pavia, Italy
federico.alfinito@unipv.it

Morselli, Luca[3]; Donzella, Antonietta[5]; Arzenton, Alberto[8]; Asti, Mattia[9]; Bortolussi, Silva[6]; Corradetti, Stefano[3]; D'Agostino, Giancarlo[7]; Di Luzio, Marco[7]; Ferrari, Matteo[10]; Gandini, Andrea[1]; Tosato, Marianna[2]; Di Marco, Valerio[2]; Lunardon, Marcello[4]; Villa, Valerio[5]; Salvini, Andrea[1]; Zangrando, Lisa[4]; Zenoni, Aldo[5]; Andrighetto, Alberto[3]
Organization(s):
1: Laboratorio per l'Energia Nucleare Applicata, via G. Aselli 41, 27100 Pavia, Italy;
2: UNIPD - Dipartimento di Scienza Chimiche, Via Marzollo 1, 35122 Padova, Italy;
3: INFN, Laboratori Nazionali di Legnaro, Viale dell'Università 2, 35020 Legnaro, Padova, Italy;
4: INFN, Sezione di Padova, Via F. Marzolo 8, 35131 Padova, Italy;
5: Dipartimento di Ingegneria Meccanica e Industriale, Università degli Studi di Brescia, Via Branze 38, 25123 Brescia, Italy;
6: Dipartimento di Fisica, Università degli Studi di Pavia, Via A. Bassi 6, 27100 Pavia, Italy;
7: Istituto Nazionale di Ricerca Metrologica, Dipartimento di Chimica Generale, Università degli Studi di Pavia, Viale T. Taramelli 12, 27100 Pavia, Italy;
8: Dipartimento di Scienze Fisiche della Terra e dell'Ambiente, Università degli Studi di Siena, Via Roma 56, 53100 Siena, Italy;
9: Radiopharmaceutical Chemistry Section, Nuclear Medicine Unit, AUSL-IRCCS di Reggio Emilia, Viale Risorgimento 80, 42122 Reggio Emilia, Italy;
10: Laboratoire Hubert Curien, CNRS, UMR 5516, Université Jean Monnet, F-42000, Saint-Etienne, France

ABSTRACT

The ISOLPHARM project was created with the idea of producing and testing new radionuclides for cancer treatment and diagnosis. The idea is to exploit the isotope separation on-line (ISOL) technique to produce unconventional radionuclides that are difficult to obtain with standard production techniques. Among different radionuclides of interest particularly promising for therapy is ^{111}Ag, being a beta emitter with a range of about 1.8mm, an average lifetime of 7.45 days.

Until the SPES cyclotron is completed at the Legnaro laboratories, production of ^{111}Ag is possible through the Neutron Activation process of both natural and enriched ^{110}Pd. Within this context is the experimentation at L.E.N.A. Not only the activation of ^{110}Pd but also the radiochemical separation of Silver from the remaining Palladium is of crucial importance. Radiochemistry experiments focused on the dissolution of the irradiated target where ^{111}Ag is obtained are required to optimize the radioisotopic purification. In Addition, considering the high enrichment costs of ^{110}Pd even a possible reuse of the irradiated samples was considered during the purification process.

1 INTRODUCTION

1.1 The LENA research reactor

LENA is an interdepartmental centre of the University of Pavia, and it is part of the Cravino Nuclear Pole, which includes the radiochemistry area, the sub-critical SM1 complex and the environmental monitoring laboratory.

The TRIGA Mark II nuclear research reactor operating in Pavia is a 250 kW pool-type research reactor powered by up to 20% enriched ^{235}U, cooled and partially conditioned by demineralized light water.
The reactor core is made up of ninety slots containing the fuel elements, a neutron source, and three control rods arranged in five concentric rings around a central channel, known as the Central Thimble (CT). The total neutron flux in CT is about 1.7×10^{13} n/(cm^{2}s) at maximum power. [1]

1.2 The ISOLPHARM project

The aim of the ISOLPHARM project at INFN-LNL (Istituto Nazionale di Fisica Nucleare-Laboratori Nazionali di Legnaro) is to produce high purity radionuclides for nuclear medicine applications. The Isotope Separation On-Line (ISOL) technique will produce both traditional and innovative radionuclides with high specific activities, exceeding the current state of the art of radiopharmaceutical research. To achieve this goal, the ISOLPHARM project intends to utilise the recently developed Radioactive Ion Beams (RIBs) facility called SPES (Selective Production of Exotic Species) at LNL-INFN, which is under construction. The ISOLPHARM project will undertake preclinical experimentation of innovative radiopharmaceuticals based on ^{111}Ag. This will be carried out using ^{111}Ag that is produced through the $^{110}Pd(n,\gamma)^{111}Pd \rightarrow ^{111}Ag$ reaction at the TRIGA Mark II nuclear research reactor located in the LENA laboratory of the University of Pavia. [2]

2 CHOICE OF THE RADIONUCLIDE

Among the possible radionuclides producible by the SPES-ISOLPHARM facility, Scandium is an excellent element for radiotheranostics. This is because $^{43/44}Sc$ are PET radionuclides, whilst ^{47}Sc is a beta emitter with the appropriate decay characteristics for therapy. ^{43}Sc, ^{44}Sc, ^{47}Sc could potentially be produced using titanium-based targets, such as Titanium Carbide (TiC). ^{64}Cu is a radionuclide ideal for PET, whereas ^{67}Cu has excellent decay properties for therapy, but is very challenging to produce using current techniques.

Although these nuclides are very interesting, among the producible ones ^{111}Ag appears to be one of the most promising for cancer therapy due to its favourable decay properties: it is a β-emitter with a medium half-life (7.45 days), a convenient energy (360 keV) corresponding to a medium tissue penetration (1.8 mm). The decay of ^{111}Ag results in the emission of low-energy gamma rays (245 keV (1.24%) and 342 keV (6.7%)), enabling single-photon emission computed tomography (SPECT) imaging. This allows for simultaneous therapy and in vivo monitoring of the delivered dose. The ISOLPHARM-Ag collaboration project aims to assess the viability of producing a radiopharmaceutical based on ^{111}Ag using the ISOLPHARM approach. The production of ^{111}Ag using conventional neutron irradiation methods leads to carrier-added ^{111}Ag. To obtain no-carrier-added ^{111}Ag, enriched ^{110}Pd must be used instead of natural palladium. By contrast, the ISOL technique can easily provide quantities of ^{111}Ag not only of very high purity, but also at high production rates corresponding to the estimated in-target production. [3]

3 THE METHOD

^{111}Ag can be obtained by thermal neutron irradiation of a palladium target via the ^{110}Pd(n, γ)^{111}Pd nuclear reaction and by the subsequent decay of the intermediate nuclide (^{111}Pd, $t_{1/2}$ = 23.4 min) to ^{111}Ag. Natural palladium could be used for this approach, but in this case several additional radionuclides are produced simultaneously with ^{111}Ag due to the parallel parasitic reactions occurring on the other isotopes of the natural element. Therefore, ^{111}Ag generated as a result of neutron irradiation of natural palladium targets is consistently a negligible product of the reaction and is contaminated with several stable and radioactive nuclides, including silver isotopes themselves. The use of ^{110}Pd-enriched targets is thus recommended to improve ^{111}Ag yield and circumvent the parasitic reactions *(Figure 1)*.

Unfortunately, even though the occurrence of silver stable isotopes is mostly avoided, the utilization of an enriched target does not eliminate the necessity for chemical purification after irradiation in order to remove the metal impurities generated in the process and to recover the target material. Due to the high cost of the material used, it is crucial to establish highly effective recycling approaches to recover the ^{110}Pd for future irradiations. [4]

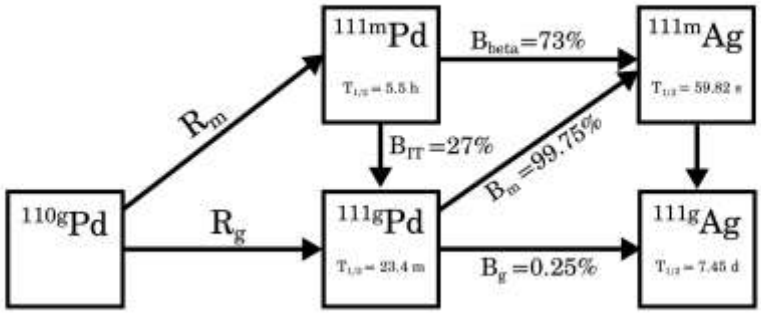

Figure 1: ^{111}Ag Production process

3.1 Separation Protocol

Separation is a key step for the good performance of a radiopharmaceutical. The amount of impurities must be kept to a minimum both to prevent other materials from competing with the radionuclide during labelling and to prevent other radionuclides from giving an undesired dose to the tissue.

Among the various options developed in recent years, the most suitable method for separation was found to be using a cationic resin.

A protocol has been developed to carry out the separation, which consists of three steps:

-dissolution

-conditioning of the column and loading

-elution

The irradiated Palladium sample is dissolved in aqua regia and subsequently evaporated. The process is repeated four times on the residue using 12 M HCl.

A final dissolution is carried out using 0.005M HCl to which NaCl is added.

LN resin (Triskem) was used for separation, namely 800 mg packed on a polypropylene chromatographic column.

Conditioning of the resin is performed by loading 0.005M HCl using a peristaltic pump at a flow rate of 1.0 - 1.5 ml/min.

At the end of the process, the dissolved sample containing both Ag and Pd is loaded onto the column using a dedicated peristaltic pump at a flow rate of 1.0 ml/min.

The obtained fraction from the column is set aside for the recovery of Pd.

All activities involving the irradiated sample are conducted in a dedicated fume-hood.

Once all the sample has been loaded into the column, the palladium is extracted.

Subsequently, 0.005M HCl solution is pumped into the column at a flow rate of 1ml/min using a peristaltic pump.

The fractions generated are collected in 10ml vials.

To confirm complete removal of palladium from the column the colour change of the resin, from light brown to white, can be observed.

Once the palladium has been removed entirely, silver can be eluted by pumping 1M HCl solution through the column, also at a flow rate of 1ml/min.

The resulting fractions are collected in test vials.

At this stage, the ^{111}Ag is dissolved in a 1M HCl solution. This condition is not consistent with the labelling conditions of the radiopharmaceutical. Two solutions are

feasible:

- undergoing a direct evaporation, to minimize volumes and increase the pH of the solution
- proceed with a second separation utilizing a TK200 resin, and then elute the silver in water

3.2 Recycling Protocol

As previously mentioned, in order to prevent the production of species that would compete with ^{111}Ag and to improve the production yield, an enriched palladium target should be used instead of natural palladium. However, due to the high cost of enriched palladium, the development of a protocol for the recovery of irradiated palladium for subsequent production is crucial. [5]

After separation of Ag-Pd through LN resin, the fractions containing Pd are merged and then transferred into a flask of 100 mL.

The solvent obtained after separation is then evaporated on a heated plate.

To the resultant solid, a solution of 0.1 M HCl and a 20% NaBH4 solution are added.

The solution is left to stir for an hour and then transferred into a centrifuge flask of 50 mL.

Overnight addition of concentrated HCl leads to the precipitation of palladium. Centrifugation is then carried out to eliminate the supernatant. This process is performed three times with the addition of distilled water to remove any residue.

The remaining solid is then washed with ethanol and repeated three times.

A last series of three washes with diethyl ether is then carried out, followed by centrifugation and removal of the supernatant.

The resulting solid is placed in a vial and left to dry overnight.

4 IRRADIATION AND SEPARATION

Once the separation protocol is established, the first tests were carried out on irradiated material.

The material initially selected is natural Palladium, even if the production of ^{111}Ag is limited at this stage what is of interest is to verify the quality of the method. Using natural Palladium also means that the activity produced is lower and therefore more manageable from a radiation protection point of view.

For this experiment, a 50 mg sample of natural palladium was irradiated. The sample was activated by being placed inside the central channel of LENA's TRIGA MARK II reactor for 1 hour. To ensure maximum exposure to the neutron flux, the selected position was on the equatorial line of the reactor core.

4.1 First Experiment

Upon analysis of the irradiated sample, it was found that the produced activity was:

- $1.41 * 10^8$ Bq of ^{109}Pd
- $2.72 * 10^5$ Bq of ^{111}Ag

Following the previously described method, the sample was dissolved using 4ml of aqua regia.

After being placed on a plate heated to 80 degrees for 30 min the process was repeated three times using 3ml of 12M HCl.

The last dissolution required the use of 4ml of 0.005M HCl with the addition of 7.5mg NaCl.

The LN resin is conditioned with 0.005M HCl and the sample is loaded using the peristaltic pump.

The last step (elution) is divided into two stages, a first one in which ^{109}Pd is collected using 0.005M HCl and a second one in which ^{111}Ag is recovered using 1M HCl.

Specifically, 15 samples were collected in 10ml tubes.

The sample masses collected and their activity are shown in the *table 1*.

							End of Irradiation			
		Mass Fraction [g]	Activity [Bq]		Recovery [%]		Activity [Bq]		Recovery [%]	
			Pd	Ag	Pd	Ag	Pd	Ag	Pd	Ag
	A_0		8,95E+06	2,21E+05			1,40E+08	2,71E+05		
HCl 0.005 M	1	9,4140	5,37E+06	0,00E+00	60,06	0,00	9,21E+07	0,00E+00	65,96	-
	2	12,42	7,03E+05	0,00E+00	7,85	0,00	1,21E+07	0,00E+00	8,68	-
	3	13,1613	1,38E+04	0,00E+00	0,15	0,00	2,40E+05	0,00E+00	0,17	-
	4	11,0302	4,32E+03	0,00E+00	0,05	0,00	7,06E+04	0,00E+00	0,05	-
	5	10,9963	4,34E+03	0,00E+00	0,05	0,00	6,89E+04	0,00E+00	0,05	-
HCl 1 M	6	4,1941	6,76E+03	0,00E+00	0,08	0,00	1,09E+05	0,00E+00	0,08	-
	7	3,6079	1,39E+04	2,53E+03	0,16	1,15	1,81E+05	3,08E+03	0,13	1,14
	8	4,0945	4,69E+03	3,82E+03	0,05	1,73	6,14E+04	4,64E+03	0,04	1,72

	9	3,6950	1,59E+03	4,77E+04	0,02	21,62	2,11E+04	5,80E+04	0,02	21,45
	10	7,4979	9,92E+02	6,48E+04	0,01	29,39	1,32E+04	7,90E+04	0,01	29,18
	11	6,3820	3,93E+02	2,50E+04	0,00	11,33	5,31E+03	3,05E+04	0	11,25
	12	8,2652	1,58E+03	1,49E+04	0,02	6,74	2,15E+04	1,81E+04	0,02	6,7
	13	6,2547	5,37E+02	7,53E+03	0,01	3,41	7,42E+03	9,20E+03	0,01	3,4
	14	9,9370	1,47E+02	4,95E+03	0,00	2,24	2,07E+03	6,05E+03	0	2,23
	15	43,4811	0,00E+00	2,84E+04	0,00	12,90	0,00E+00	3,82E+04	0	14,11
					Tot	**Tot**			**Tot**	**Tot**
					68,50	90,52			75,22	91,18

Table 1: Results of the first separation experiment

The results demonstrate good separation of palladium from silver, with over 90% of ^{111}Ag being collected.

Looking at the separation pattern, it is evident that almost all of the Pd is collected in the first two vials and becomes almost negligible in the subsequent ones. Consequently, the number of samples collected prior to the actual silver collection can be reasonably reduced. Silver, on the other hand, has a more constant elution over time and therefore requires a greater number of runs to obtain good results.

The results obtained are even more evident if we consider the graph in *Figure 2*, where we can also see the prompt elution of silver when the HCl concentration is increased.

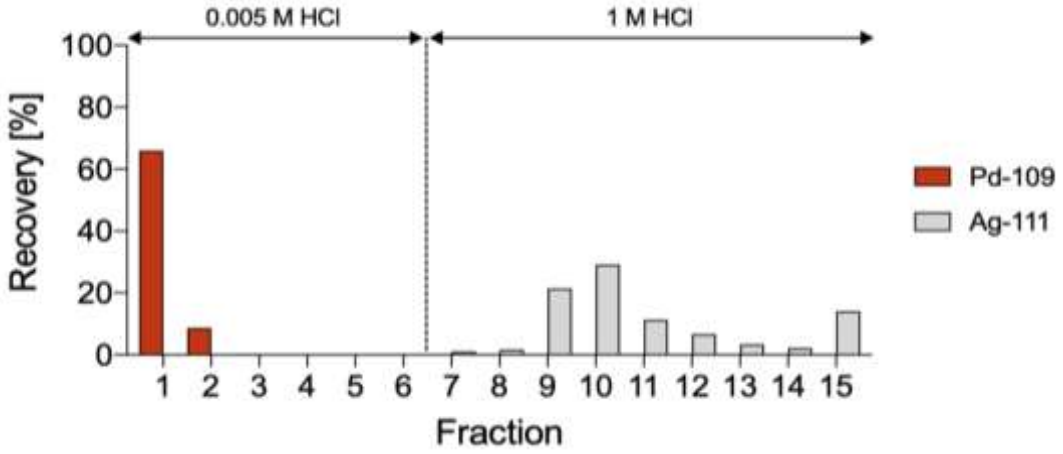

Figure 2: elution of Pd and Ag in the different fractions

4.2 Second Experiment

To verify the performance of the separation method, a second experiment was carried out. The activity produced in this test was:

- $3{,}10 * 10^7$ Bq of ^{109}Pd
- $6{,}59 + 10^4$ Bq of ^{111}Ag

Although the method used remained the same, the fractions collected were optimised.

A further step carried out in this experiment was to attempt to elute the silver in water after the separation had taken place.

This resulted in two separate stages, firstly the ^{111}Ag was separated from the palladium target and secondly the silver was transferred from a 1M HCl solution to an aqueous solution using a TK200 column.

The results of the second test are shown in *table 2 and figure 3.*

			End of Irradiation			
First Separation		Mass Fraction [g]	Activity [Bq]		Recovery [%]	
	A_0		Pd	Ag	Pd	Ag
HCl 0.005 M	1	58,1950	2,22E+07	0,00E+00	71,62	0
HCl 1 M	2	12,5200	0,00E+00	4,82E+04	0	73,1
	3	16,8218	0,00E+00	1,04E+04	0	15,8
	4	14,3474	0,00E+00	3,33E+03	0	5,06
	5	16,7200	0,00E+00	0,00E+00	0	0
					Tot	**Tot**
					71,62	**93,96**
Second Separation						
H_2O on TK200 column	1	2,5971	0,00E+00	0,00E+00	0	0
	2	2,4877	0,00E+00	0,00E+00	0	0
	3	5,1755	0,00E+00	0,00E+00	0	0
	4	5,2900	0,00E+00	4,47E+04	0	68
	5	5,2639	0,00E+00	3,50E+03	0	5
					Tot	**Tot**
					0	**73**

Table 2: Elution result of the second experiment and concentration test

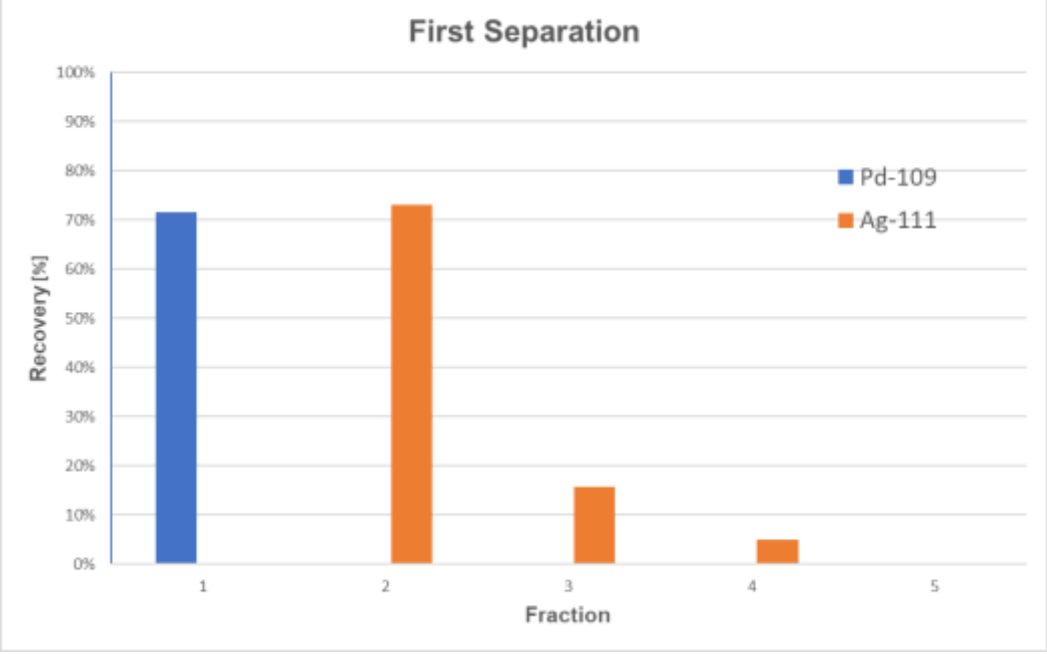

Figure 3: trend of the elution during second experiment

4.2.1 Recycling

At the conclusion of the separation tests of the second experiment, the recycling protocol for Pd was also tested.

Following the method described above, 40mg of Pd was obtained from an initial irradiated target of 48.8mg.

This method recovered 82% of the Palladium. This outcome facilitates the use of an enriched Palladium target instead of natural Palladium for testing purposes to optimize material and cost.

5 OBSERVATIONS AND FURTHER DEVELOPMENT

While the construction of the SPES facility is complete, the ISOLPHARM project has focused on the production and separation of ^{111}Ag using traditional techniques. A novel silver separation protocol has been developed and tested in collaboration with the various institutions and facilities involved in the project. The tests carried out so far in the LENA laboratories of the University of Pavia have yielded good results and will be continued in order to further optimise the various stages of the separation, concentration and recycling process.

In particular, initial tests are planned with an enriched palladium target and further tests on the concentration of ^{111}Ag, including testing alternative methods to elution through the TK200 column. All this preliminary work is crucial to foster and stimulate research on radiopharmaceuticals relying on ^{111}Ag, a radioisotope of great unexplored potential.

The upcoming stage of the ISOLPHARM project will concentrate on examining markers and agents for silver separated from other substances. This will allow for preliminary in-vitro and in-vivo experiments to further validate the potential of ^{111}Ag-based radiopharmaceuticals.

ACKNOWLEDGEMENTS

The authors would like to thank all the institutes and researchers whose participation makes the project possible.

REFERENCES

[1] Prata, M., Alloni, D., De Felice, P., Palomba, M., Pietropaolo, A., Pillon, M., Quintieri, L., Santagata, A., Valente, P., 2014. Italian neutron sources. Eur. Phys. J. Plus 129 (11), 1–15.

[2] L. Morselli, A. Donzella, A. Arzenton, M. Asti, S. Bortolussi, S. Corradetti, G. D'Agostino, M. Di Luzio, M. Ferrari, A. Gandini, M. Lunardon, V. Villa, A. Salvini, L. Zangrando, A. Zenoni, A. Andrighetto. Production and characterization of 111Ag radioisotope for medical use in a TRIGA Mark II nuclear research reactor.

[3] Andrighetto, A., Tosato, M., Ballan, M., Corradetti, S., Borgna, F., Di Marco, V., Marzaro, G., Realdon, N., 2019. The ISOLPHARM project: ISOL-based production of radionuclides for medical applications. J. Radioanal. Nucl. Chem. 322 (1), 73–77.

[4] Tosato M. , Asti M. Lights and Shadows on the Sourcing of Silver Radioisotopes for Targeted Imaging and Therapy of Cancer: Production Routes and Separation Methods. Pharmaceuticals 2023, 16,929.

[5] Ohya *et al.* Separation of radiosilver from a cyclotron-irradiated palladium target, *Radiochimica Acta*, 108, 8, 2020, 641-648.