JOINT INSTITUTE FOR NUCLEAR RESEARCH
Flerov Laboratory of Nuclear Reactions
Chemistry of Transactinides

FINAL REPORT ON THE SUMMER STUDENT PROGRAM

"Target preparation for platinum isotopes production with higher specific activity at microtron MT-25"

Supervisor:
Dr. Nikolay V. Aksenov

Student:
Đorđe Cvjetinović, Serbia
University of Belgrade

Participation period:
July 24 – September 17

Dubna, 2017

Abstract

Radiopharmaceuticals that specifically bind to tumor cells are seen as the future in the cancer treatment. In order to create such radiopharmaceuticals, one needs high specific activities of corresponding radionuclides. One of the most promising radionuclides is ^{195m}Pt, thanks to its high Auger electron yield. Many different pathways for ^{195m}Pt production have been proposed, and in this work photonuclear production of ^{195m}Pt using Microtron MT-25 has been reviewed. Targets for irradiation were prepared in such a way that they allow acquisition of high activity using the Szilard-Chalmers effect coupled with specific binding of ^{195m}Pt to manganese(II)-oxide.

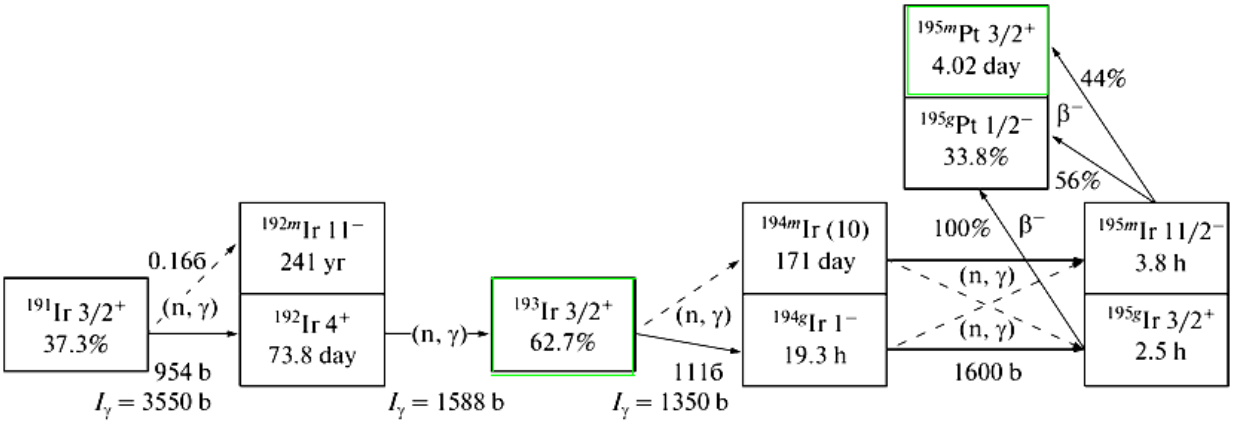
Outline

Introduction

Radiopharmaceuticals are radioactive agents that are used in nuclear medicine for either medical diagnosis or therapeutic purposes[1]. Depending on their type they can be administered in various ways, but mainly intravenously. Radiopharmaceuticals used in diagnosis use low gamma or positron emitting radionuclides while those used for therapy utilize beta, alpha or Auger emitting radionuclides. Radioactive particles with smaller LET are preferred for therapeutic use, because they do not produce long range damage of healthy tissue but rather only local damage. For example this means that the administered dose of radiation can be applied only on tumor cells.

Platinum-195m

Platinum is considered to be a noble metal, due to its relatively high chemical inertness. It is one of the rarest metals on the planet, yet one with a wide array of applications in science and industry[2]. Natural occurring platinum is constituted out of six stable isotopes ^{192}Pt, ^{194}Pt, ^{195}Pt, ^{196}Pt, ^{198}Pt and one long lived radioisotope ^{190}Pt. Isotope with the highest natural abundance is isotope ^{195}Pt which makes out 33.8 % of natural occurring platinum. This isotope is off great interest because it can be artificially transformed to the ^{195m}Pt nuclear isomer, which undergoes internal conversion process, and as a result of this emits high number of Auger electrons[3]. There are many different nuclear reactions and pathways that can be used to make ^{195m}Pt[4]. Scheme 1 represents a possibility that has been investigated for ^{195m}Pt production.



Scheme 1. Double neutron capture production of ^{195m}Pt

Other possibility for making radiopharmaceutical grade quality ^{195m}Pt is using the brehmsstralung radiation[5]. Basic concept behind this idea is to excite the nuclei of ^{195}Pt atoms using photons of high enough energy. Main goal of this work was production of the platinum targets that will be irradiated by brehmsstralung radiation, in order to give high radiochemical yield of ^{195m}Pt. Irradiation process was accomplished using the MT-25 microtron in JINR, Dubna, while the experimental part of target production is given further in the text, along with the results. Figure 1 shows the basic concept of achieving brehmsstralung radiation.

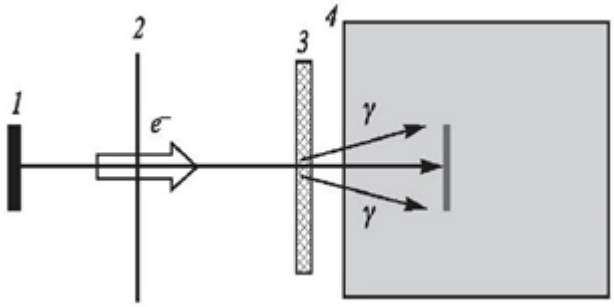


Figure 1. Simple geometry of target irradiation by bremsstrahlung. 1-electron source; 2-exit foil (≈ 0.1-0.3 mm thick Ti); 3-converter (W plate ≈ 2.5 mm thick); 4-target

The MT-25 microtron that was used can accelerate electrons up to 25 MeV of energy, with beam current up to 20 μA and beam powers of 0.57 kW. In our study electrons were accelerated up to 23.5 MeV and to beam powers of 15 μA. Figure 2 shows the outlook of the MT-25 microtron.

Figure 2. Outlook of the MT-25 microtron in JINR, Dubna

Szilard-Chalmers effect

In 1934 L. Szilard and T. A. Chalmers discovered that bond breaking could occur for atoms following nuclear reaction or radioactive decay even though the recoil energy in the initial process is not sufficient to overcome the bonding energy[6]. In the case of thermal neutron capture the processes involved in the emission of the -y-ray, which removes the nuclear excitation energy, impart recoil energy to the atom to break most chemical bonds (n,y-recoil). If, after rupture of the bonds, the product atoms exist in a chemical state different and separable from that of the target atoms, the former may be isolated from the large mass of inactive target. This provides a means of obtaining high specific activities in reactions where target and product are isotopic.

This process is known as the Szilard-Chalmers reaction and was discovered when, following the irradiation of ethyl iodide with thermal neutrons, it was found that radioactive iodide could be extracted from the ethyl iodide with water. Moreover, when iodide carrier and silver ions were added to this aqueous phase, the radioactive iodide precipitated as silver iodide. The obvious interpretation of these results is that the neutron irradiation of the ethyl iodide, which caused the formation of ^{128}I, ruptured the bonding of this atom to the ethyl group. The bond energy of iodine to carbon in C_2H_5I is about 2 eV. Since this exceeds the recoil energies of neutron capture, the bond breakage must have resulted from the γ-emission which followed neutron capture and not the capture process itself.

The ^{128}I loses its kinetic energy and is stabilized as an iodine atom or iodide ion; it can also be recaptured by the C_2H_5 radical (retention of activity in C_2H_5I). In addition to the necessity that the recoiling species have sufficient energy to rupture the bond, it is also necessary for a successful enrichment of specific activity by the Szilard-Chalmers process that there is no rapid exchange at thermal energies between the active and inactive iodine atoms in ethyl iodide. Result is the retention of the activity within the organic molecule. Retention is decreased by diluting the ethyl iodide with alcohol which reduces the probability of collision and exchange with C_2H_5I molecules as the hot atoms of ^{128}I are being slowed.

Isomeric transitions which proceed by emission of γ-rays may not provide sufficient recoil energy to break covalent bonds. However, in these cases or very low energy isomeric transitions, the extent of internal conversion is large. This results in vacancies in the inner electron orbitals. When electrons in outer orbitals move to fill the vacancies, the difference in electron binding energies is sufficient to cause some ionization, resulting in relatively high charge states for the atom, leading to bond rupture.

Experimental part

Platinum radioisotopes have been produced by irradiation of cisplatin at the MT-25 microtron according to the following reactions: $^{196}Pt(\gamma,n)^{195m}Pt$, $^{195}Pt(\gamma,\gamma')^{195m}Pt$, $^{194}(\gamma,n)^{193m}Pt$, $^{192}Pt(\gamma,n)^{191}Pt$.

In order to increase the specific activities of platinum radionuclides one should use Szilard-Chalmers effect. For this purpose in our experiments neutral complex cisplatin cis-$[Pt(NH_3)_2Cl_2]$ was homogeneously mixed with cryptomelane $K_2(Mn^{4+},Mn^{2+})_8(O,OH)_{16}$ to collect recoil nuclei during irradiation in presumably most stable hexachloroplatinate form $[PtCl_6]^{2-}$. Cryptomelane shows high ion exchange selectivity towards ions with effective ionic radius of 1.3-1.5 Å. Cryptomelane was synthesized by mixing of the solutions of 0.5 M $KMnO_4$ in 1 M H_2SO_4 and 1 M $MnSO_4$ in 1 M H_2SO_4 at 60 ˚C[7]. After cooling, the precipitate was filtered out from the solution.

Under irradiation platinum nuclei in cisplatin acquire kinetic energy by releasing neutron, fly off the compound and are captured by cryptomelane. Thus, having cryptomelane and cisplatin separated radioactive platinum isotopes with high specific activity can then be separated from the manganese matrix by means of extraction chromatography.

To prepare targets for the experiments, first three samples of cisplatin and cryptomelane mixture in the ratio of 1:2; 1:4 and 1:6 correspondingly were prepared. To do it, amount of cryptomelane required was transferred onto the bottom of a glass and poured with hot solution of calculated amount of cisplatin. After that substances in the glasses were evaporated to dryness and separately transferred to aluminum foils. Next 16.32 mg of cisplatin as a reference point and a tracer for recoil chemistry investigation were wrapped inside an aluminum foil. These foils were placed in a plastic round holder and have been irradiated for 2 days. This was done in set of 3 probes, and the results are given as average values.

After irradiation samples were consequently measured at the HPGe y-detector for 600s, in order to estimate activity and quantity. Same measurements were performed after the separation process. Results are given in table 1.

Table 1. Activity after separation*

Target	A [%]		
	^{191}Pt	^{195m}Pt	^{197}Pt
1	51.0	56.3	45.2
2	51.5	61.1	39.8
3	52.6	70.2	34.3

*Activity after separation is normalized to activity measured at the end of bombardment

Conclusion

A method for simultaneous production of medically relevant ^{191,193m,195m}Pt isotopes with high specific activity was presented. Depending on the target preparation radiochemical yield was found to be between 56% and 70% for ^{195m}Pt. This could mean a potential breakthrough in medical scale ^{195m}Pt production.

Acknowledgment

I would like to thank my supervisor and mentor Nikolay Aksenov for the opportunity to come to FLNR laboratory in JINR, Dubna as well as for the professional guidance and advice. I would also like to thank Alexander Madumarov for the time he has spent helping me and guiding me with the project.

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