Journal of Labelled Compounds and Radiopharmaceuticals
J Label Compd Radiopharm 2007; **50**: 480–482.
Published online in Wiley InterScience
(www.interscience.wiley.com). DOI: 10.1002/jlcr.1210

JLCR

Short Research Article

Photonuclear production of ^{193m,195m}Pt and synthesis of radioactive cisplatin†

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Received 13 August 2006; Revised 24 November 2006; accepted 25 November 2006

Keywords: cisplatin; nuclear reaction; cell; platinum; isotope; bremsstrahlung

Introduction

Radiopharmaceuticals labelled with low-energy electron emitters will be used as radiotherapeutic agents in near future. Deceleration of emitted electrons leads to the energy release in an extremely small volume around the decay site and, as a result, the local dose is 10^4–10^7 Gy. In this case the radiotoxicity of Auger electrons is caused mainly (90%) by an indirect mechanisms.[1,2] Practically all the antineoplastic pharmaceuticals used in the oncology have a strong toxicity. The combined influence of bystander effect,[3] a high density of deceleration losses, cytotoxic effect and apoptosis can be reached by application of radioactive cisplatin. It will allow considerable reduction of cisplatin dose and, consequently, reduction of the toxic cisplatin influence in the course of medical treatment.

Results and discussion

The samples of cisplatin solution produced by the Mili Healthcare Limited Company (UK) and crystal Sigma Aldrich, Pt (USA) were placed in the polyethylene ampoules within an aluminium container, and were irradiated by bremsstrahlung from the electron accelerators with the energies of 26 and 34 MeV, respectively. The following nuclear reactions ^{196}Pt(γ,n)^{195m}Pt, ^{195}Pt(γ,γ')^{195m}Pt, ^{194}Pt(γ,n)^{193m}Pt, ^{192}Pt(γ,n)^{191}Pt, ^{198}Pt(γ,n)^{197}Pt on the platinum isotopes were realized. The energy of platinum isotope recoil is several keV which leads to the atom escaping from the cisplatin compound and to the formation of $PtCl_4^{2-}$ and $PtCl_6^{2-}$ molecules. We have therefore developed an alternative method for the preparation of radioactive cisplatin by chemical synthesis. The ^{195m}Pt yield in the ^{196}Pt(γ,n)^{195m}Pt reaction was calculated with the help of the program complex PENELOPE. The maximum specific activity for different platinum targets is given in Figure 1.

More important is the use of the nuclear reaction ^{197}Au(γ,np)^{195m}Pt. Samples of gold were irradiated by bremsstrahlung from the electron accelerator with energy 34 MeV. The ^{195m}Pt has been isolated chemically after separation of gold. In this case the specific radioactivity of synthesized cisplatin is a factor of 6 larger than specific radioactivity of directly irradiated cisplatin.

Measurement of radioactivity was performed by means of a Ge(Li)-detector. The activity of cisplatin was from 250 to 11 000 Bk/ml. The radiation dose in the process of irradiation of cisplatin was from 1.5 to 5 MGy.

The methods of crystal optics and infrared spectroscopy were used to investigate untreated and radioactive cisplatin. The samples in the form of a drop were placed between the windows made of RRS-5 (TlBr–Tl). Only minor changes were observed in the IR spectra of untreated and radioactive cisplatin. The absorption band, corresponding to 1420 cm^{-1} for untreated cisplatin, was more distinct than for radioactive cisplatin. The doublet of lines, corresponding to absorption bands 1190, 1170 cm^{-1} for radioactive cisplatin was more distinct than that in the untreated

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Contract/grant sponsor: STCU; contract/grant number: 1768
†Proceedings of the Ninth International Symposium on the Synthesis and Applications of Isotopically Labelled Compounds, Edinburgh, 16–20 July 2006.

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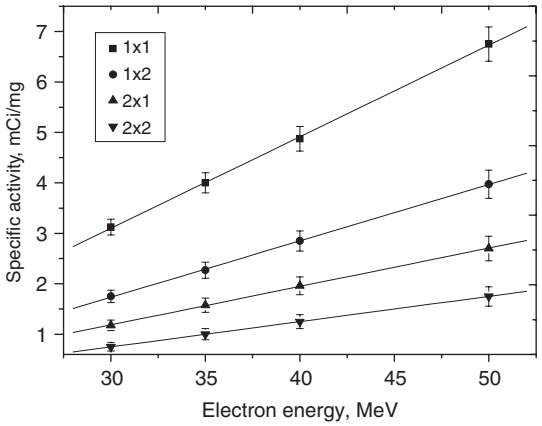

Figure 1 Specific activity at saturation of different targets as a function of electron energy (beam current 200 μA, enriched ^{196}Pt, diameter of beam 5 mm). Symbols–cylindrical targets (diameter × height, cm).

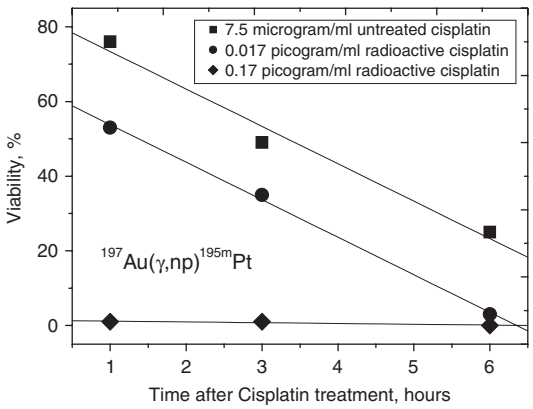

Figure 2 Viability of Ehrlich adenocarcinoma cells after action of untreated and radioactive cisplatin.

one. It has been found that synthesized cisplatin is similar to the untreated one.

As experimental model, Ehrlich's adenocarcinoma was chosen. The suspension of the cells (2×10^6 cells/ml, 0.5 ml) with 1.5 ml of physiological solution and 0.03 ml of untreated or radioactive cisplatin (cisplatin dose was from 0.5 to 15 μg/ml) were placed in the thermostat at 37°C for the incubation. The morphology of untreated cisplatin-sensitive Ehrlich's adenocarcinoma cells in dynamics is characterized by the cell membrane injury that is evident in the cell shape deformation. Sometimes giant cells are observed.

The morphology of radioactive cisplatin-sensitive Ehrlich's adenocarcinoma cells is characterized by the formation of cell conglomerates. These cells became smaller due to the shrinkage.

The cell size measured by means of a polarization microscope (x600) was 0.015 mm before incubation. After 12–hour incubation the size of Ehrlich adenocarcinoma cells with the untreated cisplatin was 0.010–0.015 mm and with radioactive cisplatin it was 0.005–0.007 mm.

We observed the presence of apoptotic cells after 8–12 hours of incubation of Ehrlich adenocarcinoma with radioactive cisplatin. A distinctive feature of apoptotic cells is their reduced size, strictly round shape and the absence of colour after dye action (trypan blue).

It should be noted that the influence of ^{195m}Pt is possible in the various forms (transplatin, bisplatinum complex and other platinum compounds) for translocation of this isotope to the cell nucleus.

The observed states of apoptosis and necrosis in the tumour cell with radioactive cisplatin, probably indicate different mechanisms of cell death. The dose dependence of untreated and radioactive cisplatin effect on the viability of Ehrlich adenocarcinoma cells was studied (Figure 2).

The radioactive cisplatin was obtained by the reaction ^{197}Au(γ,np)^{195m}Pt. The ^{196}Pt content (reaction

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DOI: 10.1002.jlcr

$^{197}Au(\gamma,n)^{196}Au \rightarrow {}^{196}Pt$) was 1.7 ng/ml. The content of apoptosis cells was 8% for untreated cisplatin and 10% for radioactive cisplatin (0.017 pg/ml) after treatment over 6 hours.

Acknowledgements

This work was supported by STCU, project #1768.

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