PRODUCTION OF TIN-117m AND ITS APPLICATIONS IN NUCLEAR MEDICINE

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ABSTRACT

Due to its physical properties ^{117m}Sn is proposed as a potentially very useful therapeutic radionuclide. DTPA (IV) labeled with ^{117m}Sn is suggested to be an effective agent for the palliation of pain from bony metastases. This radionuclide can be obtained in large activities only in high flux nuclear reactors. The major drawback is, however, low specific activity thus limiting its use in bone pain palliation and synovectomy. Therefore, attempts are made to develop the production of high specific activity ^{117m}Sn in cyclotrons.

Key words: tin-117m, nuclear medicine, therapy, radiopharmaceuticals

1. Introduction

For many years the emphasis in nuclear medicine was on diagnostic procedures. The major exceptions were the uses of ^{131}I in the therapy of benign and malignant thyroid disease and ^{32}P in the treatment of certain hematological diseases. However, in the last decade targeted radionuclide therapy became a rapidly developing field [1-3]. Several new radioactive drugs (radionuclides and radiopharmaceuticals) are proposed and discussed and some of them achieved already the clinical application. The criteria regarding the necessary physical properties are established. The supreme radioactive drug should have particulate emission (β^-, Auger, conversion electron, α). The half-life up to 14 days was found to be optimal. The presence of the accompanying gamma photon in reasonable abundance and in the energy span of 100-300 keV is advantageous. It can be used for dosimetry, for monitoring of the accumulation and follow-up of the effects of the therapy. The principles of a large scale and economical production are known. The relations between the type and the location of the disease and the curability for therapy with a certain radioactive drug are investigated extensively. A lot of investigations was devoted also to the development and clinical application of therapeutic radiopharmaceuticals. This includes the ease of preparation, *in vivo* and *in vitro* stability, shelf life and costs.

The most important radionuclides used in therapy are ^{32}P, ^{89}Sr, ^{90}Y and ^{131}I. Several others, like ^{153}Sm and the radioactive isotopes of rhenium (^{186}Re, ^{188}Re) are considered [4,5]. One of the candidates is ^{117m}Sn. The basic difference regarding the other therapeutic radioisotopes is its mode of decay. Tin-117m emitts conversion electrons of discrete energies and range. The half life of 14 days is adequate and the decay is accompanied by the emission of gamma photon of 159 keV. Although this radionuclide is not yet in routine clinical exploitation, the use of some agents, such as stanic-DTPA-^{117m}Sn for bone pain palliation, seems to be very promising. However, further investigations and patient trials are needed. The vital contribution to the wide use of this attractive radionuclide would be the transfer of its production from nuclear reactors to cyclotrons where the product of high specific

activity is expected. This paper reveals some aspects of the production, labeling and use of ^{117m}Sn and ^{117m}Sn-radiopharmaceuticals.

2. Production of tin-117m in nuclear reactor

At present ^{117m}Sn is produced in nuclear reactors by using two nuclear reactions [6,7]:

$$^{116}Sn(n,\gamma)^{117m}Sn,\ \sigma = 6\pm2\ (10^{-24}\ m^2)$$
$$^{117}Sn(n,n'\gamma)^{117m}Sn$$

The first involves neutron capture in the target consisting of enriched ^{116}Sn and the second the neutron inelastic reaction on enriched ^{117}Sn. The latter is more atractive at least for the use in higher flux reactors as it enables the production of ^{117m}Sn with the specific activity about two times higher than that which could be achieved by the first reaction.
The main physical characteristics of tin-117m are shown in Table 1.

Table 1. The main characteristics of ^{117m}Sn, adapted from refs. [6, 7]

$T_{1/2}$	*Energy of conversion electrons (MeV)*	*Range (mm)*	E_γ, MeV *(Yield, %)*
14 d	0.13 (64.9%) 0.15 (26.2%)	0.22 0.29	0.159 (86.4%)

By irradiation of up to 100 mg of tin metal (enriched in ^{117}Sn 84%) in high flux reactor for 3-4 weeks the achieved specific activity of ^{117m}Sn is 74-296 MBq/mg [8].

3. Chemical processing procedures

For the radiochemical treatment of the irradiated target several procedures can be applied. The choice depends on the subsequent chemical requirements. For the preparation of organometallic compounds of ^{117m}Sn the irradiated metallic tin is converted to tin tetrachloride by reaction with gaseous chlorine. The obtained ^{117m}Sn-tetrachloride is an useful starting compound for the conversion to a variety of alkyl tin chlorides. They can be readily converted, e.g., to some lithium salts, such as lithium trimethyl tin-117m, via lithiation with metallic lithium metal.
One of the most tested ligands is DTPA (diethylenetriamine pentaacetic acid). Although DTPA has wide use in the measurement of glomerular filtration rate, in tin(IV)-DTPA-^{117m}Sn complex form this radiopharmaceutical can be used for bone pain palliation. For its production the target is also metallic tin. After irradiation it is in oxygen-free conditions dissolved in concentrated HCl under heating and the acid salt of DTPA is added in excess. Afterwards, pH is adjusted by NaOH to 6 and heated until the complexation is completed. Then hydrogen peroxide and $CaCl_2.2H_2O$ are added. The preparation is sterile filtered or autoclaved. Finally, the radiochemical purity is determined by chromatography and the sterility and pyrogenicity are checked by the standard methods [8].
Several other ligands were also considered. They include chloride, PyP (pyrophosphate), EHDP (ethylidenehydroxy disodiumphosphonate) and MDP (methylene diphosphonate).
For the chemical processing of the irradiated target an appropriate lead-shielded hot cell should be constructed.

4. Production of tin-117m in cyclotron

At present, specific activity of ^{117m}Sn which can be achieved in nuclear reactor is about 300 MBq/mg. This is sufficient for the preparations for bone pain palliation but not high enough for the development of labeled monoclonal antibodies or peptides. Generally, one of the important advantages of nuclear reactions in cyclotrons is high specific activity of the product. For the production of ^{117m}Sn in no carrier-added form the nuclear reaction on antimony target in natural abundance ^{nat}Sb(p,αn/α3n) can

be used. The use of the reaction ^{nat}Sb(p,2pxn) is also reported. The projectiles are protons with energy of 70 MeV [9].
The high energy nuclear reactions for the production of ^{117m}Sn and some other promising radioisotopes, can be performed in a limited number of installations in the world. The main are BLIP (Brookhaven Linac Isotope Producer) in BNL (Broohaven National Laboratory, USA), LAMPF (Los Alamos Meson Physics Facility, USA), TRIUMPF (Tri-University Meson Facility, Canada), PSI Switzerland (Paul Scherrer Institute Switzerland), NAC (National Accelerator Center, South Africa) and IPPE (Institute of Physics and Power Engineering, Russian Federation).
However, these installations are mainly dedicated for research purposes in physics. The production of radionuclides can be performed only occasionally depending on the decision of the owner. For the routine use therapeutic radionuclide should be available regularly and on an affordable price. Such high-energy machines rarely operate all year round and the costs to build and operate such an installation are very high, thus restricting the use of a given radioisotope. Therefore, to ensure a regular supply of radioisotopes the construction of a dedicated machine is necessary. It should operate regularly all year round and have the possibility of the production of several radionuclides at moderate prices. In the case of ^{117m}Sn such a device would use (p,n) reaction for the production of no-carrier added product.

5. Properties of tin-117m for the application in therapeutic nuclear medicine

The indications for the possible applications of ^{117m}Sn in therapy are shown in Table 2.

Table 2. Examples of the indications for the use of ^{117m}Sn in therapy

Indications for the use of ^{117m}Sn	Route of administration
Oncology	
Solid tumors: Micrometastases	iv
Leukemias, lymphomas	iv
Pain palliation: Metastatic bone pain	iv
Non-oncology	
Synovectomy	Regional
Marrow ablation	iv
Receptor-binding tracers and cellular (nuclear) antigens	iv

Low specific activity of ^{117m}Sn which can be achieved in nuclear reactors is sufficient only for the radiopharmaceuticals for the use in oncology for bone pain palliation and synovectomy.
The use of ^{117m}Sn bone seekers is based on the assumption that low-energy conversion electrons and their restricted range should result in relative sparing of the bone marrow while delivering high radiation doses to the sites of bony metastatic disease. This means that higher activities could be applied, i.e., higher doses could be accumulated in the target tissue or organs without an elevated irradiation of the surrounding healthy tissue.
Both tin (IV) and tin(II) are excellent bone seekers with the affinity for bone much higher than that of strontium and diphosphonates. However, due to their tendency to hydrolyze, they should be administered in the presence of a suitable chelating agent. Various ligands were tested (MDP, HEDP, DTPA) but ^{117m}Sn(IV)-DTPA gave the best results [4,8,11,12].
The comparison of radiation doses of several bone agents is shown in Table 3. It can be seen that for ^{117m}Sn(IV)-DTPA the absorbed dose to the marrow is considerably lower, giving the best bone/marrow ratio [10].

Table 3. Radiation doses (nGy/Bq) of ^{117m}Sn(IV)-DTPA for bone surface and red marrow as well as the ratio bone/marrow in comparison with other bone seeking agents [10]

Radioisotope (chemical)	Bone surfaces (nGy/Bq)	Red marrow (nGy/Bq)	Bone/marrow dose ratio
^{117m}Sn(IV)-DTPA	17.6	2.6	6.6
$^{89}SrCl_2$	17.0	11.0	1.5
^{153}Sm-EDTMP	4.2	0.8	5.2
^{186}Re-HEDP	1.9	0.8	2.3

DTPA- diethylenetriamine pentaacetic acid; EDTMP-ethylnediaminetetramethylene phosphate; HEDP- 1-hydroxyethane diphosphonate

If in the future ^{117m}Sn will be available in no carried-added form its use in the form of labeled antibodies or peptides may turn out to be very advantageous.

4. Conclusion

Tin-117m is a very suitable tracer for studying of the biological behavior of tin compounds and the development of radiopharmaceuticals. In contradistinction to other therapeutic radioisotopes it is not a beta emitter. It decays primarily by isomeric transition with the emission of conversion electrons of discrete energies and range. These properties are also the premise for its use. The potent lethality of high-LET (Linear Energy Transfer) of conversion electrons, particularly when the emitter is located inside the cell, on or near nucleus, is well known. At present, the specific activity of reactor-produced ^{117m}Sn is about 300 MBq/mg. This is sufficient for the production of the agents for bone palliation, such as ^{117m}Sn(IV)-DTPA. However, the use this radioisotope for labeling of monoclonal antibodies, peptides or receptor-binding tracers will be possible only when a method of the production of no-carrier-added ^{117m}Sn will be developed.

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5. References

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