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Production of Sn-117m in the BR2 high-flux reactor

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ABSTRACT

The BR2 reactor is a 100 MW_{th} high-flux 'materials testing reactor', which produces a wide range of radioisotopes for various applications in nuclear medicine and industry. Tin-117m (^{117m}Sn), a promising radionuclide for therapeutic applications, and its production have been validated in the BR2 reactor. In contrast to therapeutic beta emitters, ^{117m}Sn decays via isomeric transition with the emission of monoenergetic conversion electrons which are effective for metastatic bone pain palliation and radiosynovectomy with lesser damage to the bone marrow and the healthy tissues. Furthermore, the emitted gamma photons are ideal for imaging and dosimetry.

1. Introduction

Tin-117m ($T_{1/2}$ 13.6 d; γ 159 keV, 86%) is a promising radionuclide for therapeutic applications. In contrast to beta emitters, ^{117m}Sn emits low-energy conversion electrons that deposit their intense energy (127, 129, 152 keV) within a short range (0.22–0.29 mm) and which can destroy tumors with lesser damage to the bone marrow and other healthy tissues. Furthermore, the 159 keV emitted gamma photons allow imaging for targeting and dosimetric purposes. The main goal of the present work was to demonstrate that the production of ^{117m}Sn in the BR2 high-flux reactor (Mol, Belgium) could supply Brookhaven National Laboratory (BNL, Upton, NY-USA) with sufficiently high specific activity to establish a production strategy together with the HFIR high-flux reactor (Oak Ridge National Laboratory, ORNL, TN-USA) as already demonstrated in the past for the production of Tungsten-188 (Ponsard et al., 2003).

2. Tin-117m production routes

^{117m}Sn can be reactor produced by two routes involving either the ^{116}Sn (n_{th}, γ) ^{117m}Sn radiative neutron capture reaction on enriched ^{116}Sn targets or the ^{117}Sn (n_{fast}, n' γ) ^{117m}Sn neutron inelastic scattering reaction on enriched ^{117}Sn targets. The first reaction involves thermal neutrons and is characterized by a cross-section of about 6 ± 2 mb. The second reaction involves fast neutrons with an energy threshold of 318 keV and is characterized by a cross-section of 222 ± 16 mb (Mirzadeh et al., 1997). It has also been reported (Mirzadeh et al., 1997) that the neutron inelastic scattering on enriched ^{117}Sn targets is the most attractive reaction to produce ^{117m}Sn in high-flux reactors as the gain in cross-section compensates significantly for the loss in neutron flux (fast neutron flux with an energy above 100 keV versus thermal neutron flux).

3. Therapeutic applications of Tin-117m

Therapeutic applications of ^{117m}Sn have been developed; they are characterized by selective delivery of radiation doses to target tissues and by limited toxicity and few long-term effects.

Therapeutic radiopharmaceuticals which are currently most widely used rely on the effects of the beta emissions by particular radionuclides, some of which may also emit imaging photons. Among the objectives of radionuclide therapy are the achievement of effective reduction of the pain caused by bone metastases and the significative improvement of the patients' quality of life. Requirements for an optimal therapeutic radionuclide agent for the palliation of painful bone metastases are based upon the desired physical half-life, the energy of the emitted particles, the abundance of these emissions, the extent of metastatic disease, the size of the lesions in relation to the range of the radionuclide, the bone marrow reserve and the availability and cost of the radiopharmaceutical. For instance, patients with a limited number of painful skeletal metastases and good bone marrow reserve and manageable pain may be treated with ^{89}Sr or ^{32}P. On the other hand, in patients with extensive skeletal metastases, limited bone marrow reserve, and/or in whom early response is mandatory, the use of ^{186}Re or ^{153}Sm is more appropriate (IAEA, 2007).

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The chemical composition of the therapeutic radionuclide agent primarily determines its biological behavior such as residence time, excretion and its avidity to concentrate in bone metastases. Emitted gamma photons with an energy in the range of 100–200 keV and a reasonable abundance (>10%) allow in vivo dosimetric monitoring. Table 1 lists the radionuclides which are currently used or being investigated for bone pain palliation and their nuclear and physical characteristics (^{89}Sr, ^{32}P, ^{153}Sm, ^{186}Re, ^{188}Re, ^{177}Lu, ^{166}Ho, ^{169}Er, ^{223}Ra, ^{90}Y, ^{117m}Sn). The same radionuclides also have properties that make them useful for radiosynovectomy, an attractive alternative to chemical or surgical synovectomy for the treatment of inflammatory synovial disease, including rheumatoid arthritis (Srivastava, 2004).

In contrast to beta emitters, ^{117m}Sn emits low-energy monoenergetic conversion electrons that deposit their intense energy (127, 129, 152 keV) within a short range (0.22–0.29 mm) and which can destroy tumors with less damage to the bone marrow and other healthy tissues. The accompanying 159 keV (86%) gamma photons emitted are very useful for monitoring the distribution of the radiopharmaceutical in the patient.

4. The BR2 high-flux reactor

The BR2 reactor is a 100 MW_{th} high-flux 'materials testing reactor' (Ponsard, 2007) which has been refurbished in 1995–1997 after more than 30 years utilization to provide a lifetime extension of more than 20 years. The availability of high thermal neutron fluxes up to 10^{15} n cm^{-2} s^{-1} allows an important opportunity for routine production of radioisotopes for medical (^{99}Mo/^{99m}Tc, ^{192}Ir, ^{153}Sm, ^{186}Re, ^{177}Lu, ^{188}W/^{188}Re, ^{32}P, ^{125}I, ^{90}Y, ^{89}Sr, etc.) and industrial applications (^{192}Ir, ^{203}Hg, etc.). Serious efforts have been made to perform all the commercial activities (production of 'radioisotopes' and 'neutron transmutation doped silicon') in accordance with a 'Quality Management System' that has been certified to the requirements of the 'EN ISO 9001: 2000' (December 28, 2006).

Currently, a standard irradiation cycle consists of 3–4 weeks operation at an operating power between 50 and 70 MW_{th}. The present operating regime consists of five irradiation cycles per year. The BR2 reactor uses 93% ^{235}U enriched uranium as fuel and is moderated by light water and beryllium. The core is composed of beryllium hexagons with central irradiation channels of 200, 84, 50 or 33 mm diameter. The cooling water is pressurized at 12 bars and has a temperature of 40–45 °C.

The aluminum pressure vessel (Fig. 1) is located in a pool filled with demineralized water.

The actual core configuration (Fig. 2) is characterized by 32 fuel elements, seven control rods and a regulating rod. These are arranged around the central beryllium plug H1 in order to provide thermal neutron fluxes up to 10^{15} n cm^{-2} s^{-1} in its seven irradiation channels for the production of radioisotopes of high specific activities. Other irradiation positions are located in

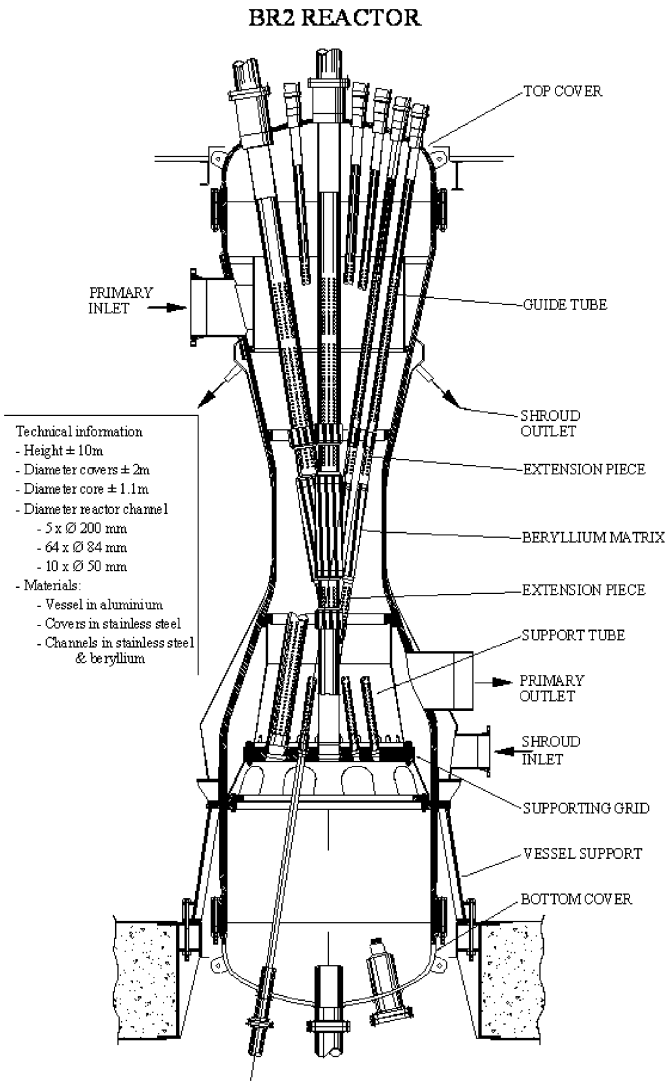

Fig. 1. BR2 high-flux reactor.

Table 1
Characteristics of radionuclides for bone pain palliation.

Radionuclides	Half-life $T_{1/2}$ (days)	Maximum β^- energy (MeV)	Average β^- energy (MeV)	Average penetration in soft tissues (mm)	Gamma photons (abundance) (keV)
Erbium-169	9.40	0.34	0.10	0.30	–
Holmium-166	1.12	1.84	0.67	3.30	81 (6%)
Lutetium-177	6.71	0.50	0.14	0.35	208 (11%)
Phosphorus-32	14.26	1.71	0.70	3.00	–
Rhenium-186	3.78	1.08	0.35	1.05	137 (9%)
Rhenium-188	0.71	2.12	0.64	3.8	155 (15%)
Samarium-153	1.95	0.81	0.22	0.55	103 (29%)
Strontium-89	50.53	1.46	0.58	2.4	–
Yttrium-90	2.67	2.28	0.94	3.6	–
Tin-117m	13.60	0.15 CE	conversion e$^-$	0.22–0.29	159 (86%)
Radium-223	11.43	5.75α	α particle	<0.01	154 (6%)

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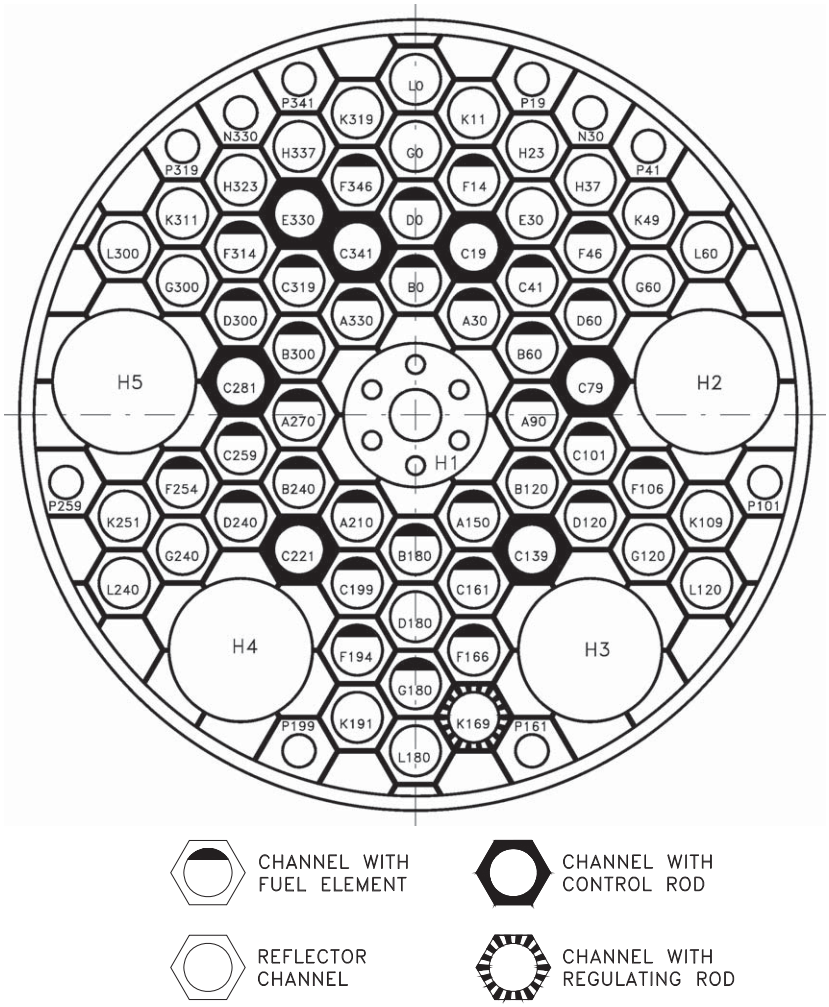

Fig. 2. BR2 core configuration.

peripheral reflector channels (peak thermal neutron fluxes from 1 to 3.5×10^{14} n cm^{-2} s^{-1}).

5. Calculated and measured ^{117m}Sn specific activities in the BR2 reactor

Since fast neutron fluxes are required for the production of ^{117m}Sn from irradiation of ^{117}Sn targets, several potential irradiation positions inside standard BR2 fuel elements have been identified to maximize the production yield of ^{117m}Sn within a single full reactor cycle of 21 or 28 days at a reactor operating power of about 58 MW$_{th}$. Each standard BR2 fuel element consists of an assembly of six concentric plates which offers a central irradiation channel; up to six aluminum irradiation cans (90 mm in length × 15 mm diameter) can be loaded inside this type of fuel element. The 12 fuel irradiation channels A and B (Fig. 2) surrounding the central beryllium plug H1 provide peak neutron fluxes ($E_n > 100$ keV) up to 5×10^{14} n cm^{-2} s^{-1}, depending on the burnup of the fuel element.

Calculations of ^{117m}Sn yields and specific activities were performed using 'LAURA' (Mirzadeh and Walsh, 1998), a two-group nuclear transmutation and decay code. These calculations were carried out for the irradiation of 200 mg tin metal target with an enrichment of 92.23% ^{117}Sn and 7.54% ^{116}Sn in a type A fuel irradiation channel of the actual core configuration (Fig. 2).

Table 2
BR2 neutron flux data (n cm^{-2} s^{-1}).

Neutron energies	BR2 (A/B)	BR2 (H1)
Thermal	2.5×10^{14}	4.2×10^{14}
Epithermal	3.7×10^{13}	4.0×10^{13}
Fast > 100 keV	5.0×10^{14}	6.0×10^{14}

The same calculations have been performed in an upgraded core configuration including the loading of a standard BR2 fuel element in the central position of the H1 beryllium plug characterized by a peak neutron flux ($E_n > 100$ keV) up to 6×10^{14} n cm^{-2} s^{-1}. Neutron flux data used in these calculations are summarized in Table 2. Thermal neutron cross-sections and resonance integrals were obtained from the literature (Mughabghab, 2006). Effective cross-sections for the inelastic scattering reaction ^{117}Sn (n_{fast}, n' γ) ^{117m}Sn were calculated using the measured neutron fluxes and the reported cross-section of 222 mb (Mirzadeh et al., 1997). The inelastic scattering reaction has a threshold of 318 keV and as such, the appropriate flux to use for ^{117m}Sn production is the total flux above 318 keV. This neutron flux was taken to be the average of the fluxes above 100 keV and above 1 MeV. 'LAURA' computes reaction rates using the thermal neutron flux and an effective cross-section calculated from the

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Table 3
Tin neutron cross-section data (all values in b) in BR2.

Reactions	σ_0	I_γ
^{116}Sn (n,γ) ^{117}Sn	0.124	11.41
^{116}Sn (n,γ) ^{117m}Sn	0.006	0.49
^{117}Sn (n,γ) ^{118}Sn	1.07	15.7
^{117m}Sn (n,γ) ^{118}Sn	1[a]	1[a]
^{117}Sn ($n,n'\gamma$) ^{117m}Sn	BR2 A/B	0.336
	BR2 H1	0.240

[a] Assumed.

Table 4
Calculated ^{117m}Sn specific activities (Ci g^{-1}) in BR2.

Irradiation positions	21 Days	28 Days
BR2 (A/B)	7.1	8.2
BR2 (H1)	8.6	9.9

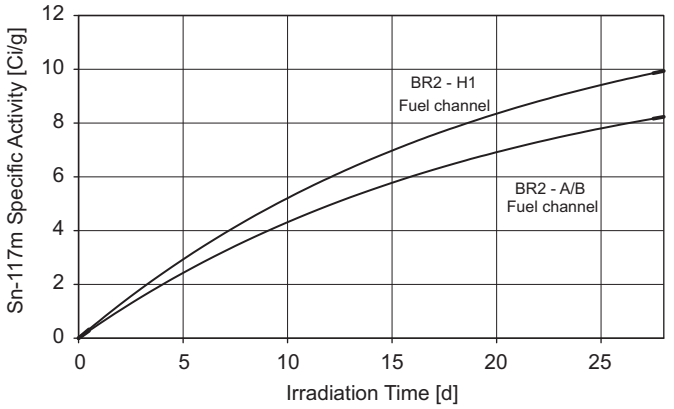

Fig. 3. ^{117m}Sn yield for 200 mg 92% ^{117}Sn enriched targets in the BR2 high-flux reactor.

equation

$$\sigma_{eff} = \sigma_0 + \frac{1}{r} I_\gamma$$

where σ_0 is the 2200 m s^{-1} thermal neutron cross-section, I_γ is the resonance integral, and r is the ratio of the thermal neutron flux to the epithermal neutron flux per unit lethargy. Effective cross-sections values for the neutron inelastic scattering reaction were calculated by multiplying 222 mb by the ratio of the neutron flux above 318 keV to the thermal neutron flux. Cross-sections used in the calculations are given in Table 3.

It can be seen from Table 4 and Fig. 3 that high ^{117m}Sn specific activities are achieved in the BR2 high-flux reactor within a single full reactor cycle of 21 or 28 days. The results of the calculations have been validated by a 21 day 'test' irradiation inside a standard BR2 fuel element loaded in a type A fuel irradiation channel. The measured ^{117m}Sn specific activity reached at the end of the irradiation 'EOI' (6.1 Ci g^{-1}) was found about 15% lower than the theoretically predicted value (7.1 Ci g^{-1}).

6. Conclusions

The measured ^{117m}Sn specific activity achieved by the neutron inelastic scattering reaction ^{117}Sn (n_{fast}, n' γ) ^{117m}Sn on 92% ^{117}Sn enriched metal targets inside standard BR2 fuel elements is in good agreement with the calculated value. The detailed Ge spectral analysis for radionuclidic contaminants and the Inductively Coupled Plasma Mass Spectrometry (ICPMS) analysis for radiometallic impurities performed by BNL demonstrated that no radiometals or other normal metallic impurities were observed relative to ^{117m}Sn and ^{117}Sn.

The 6–10 Ci g^{-1} ^{117m}Sn specific activity range reached at 'EOI' after irradiation at the routine operating reactor power of 58 MW$_{th}$ is suitable for the palliative treatment of bone metastases (Srivastava et al., 1998). This level is high enough to minimize the concentration of tin in the patient body and to limit its chemical toxicity.

The present work has validated the BR2 reactor for the production of ^{117m}Sn and showed that effective collaboration between the BR2 reactor, ORNL and BNL can be envisaged to secure the availability of this promising therapeutic radioisotope.

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