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Production logistics of ^{177}Lu for radionuclide therapy

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Abstract

Owing to its favourable decay characteristics ^{177}Lu [$T_{1/2} = 6.71$ d, $E_\beta(\max) = 497$ keV] is an attractive radionuclide for various therapeutic applications. Production of ^{177}Lu using [^{176}Lu $(n,\gamma)^{177}$Lu] reaction by thermal neutron bombardment on natural as well as enriched lutetium oxide target is described. In all, ~4 TBq/g (108 Ci/g) of ^{177}Lu was obtained using natural Lu target after 7 d irradiation at 3×10^{13} n/cm^2/s thermal neutron flux while it was ~110 TBq/g (3000 Ci/g) of ^{177}Lu when 60.6% enriched ^{176}Lu target was used. In both the cases, radionuclidic purity was ~100%, only insignificant quantity of ^{177m}Lu [$T_{1/2} = 160.5$ d, $E_\beta(\max) = 200$ keV] could be detected as the radionuclidic impurity. Production logistics using different routes of production is compared. Possible therapeutic applications of ^{177}Lu are discussed and its merits highlighted by comparison with other therapeutic radionuclides.

Keywords: Radionuclide therapy; ^{177}Lu; ^{177m}Lu; Radionuclidic purity; Specific activity; Targeted therapy

1. Introduction

Radionuclide therapy (RNT) employing open sources of radiotherapeutic agents is fast emerging as an important part of nuclear medicine, primarily due to the development of sophisticated molecular carriers (Volkert et al., 1991; Volkert and Hoffman, 1999; Srivastava and Dadachova, 2001; Ercan and Caglar, 2000; Jhu et al., 1998; Meredith et al., 1996; Delaloye and Delaloye, 1995). In order to develop effective radiopharmaceuticals for therapy, it is essential to carefully consider the choice of appropriate radionuclides as well as the carrier moiety with suitable pharmacokinetic properties that could result in good in vivo localization and desired excretion (Volkert et al., 1991; Wessels and Rogus, 1984; Fritzberg et al., 1995). The major criteria for the choice of a radionuclide for radiotherapy are suitable decay characteristics, ease of production and amenable chemistry. As regards the decay characteristics, physical half-life of the radionuclide should match with the biological half-life of the radiopharmaceutical. The energy of the particulate emission should be compatible to the volume of lesion to be irradiated and at the same time should result in minimal dose delivery to the tissues surrounding the site of localization. Also, the ratio of non-penetrating to penetrating radiation should be high (Volkert and Hoffman, 1999; Srivastava and Dadachova, 2001; Qaim, 2001; Ehrhardt et al., 1998; Mausner et al., 1998). Other practical considerations in selecting a radionuclide for targeted therapy are availability in high radionuclidic purity as well as high specific activity and production logistics.

In recent years there is considerable interest in the standardization of easy and economically viable production methods for promising therapeutic radioisotopes such as ^{188}Re, ^{186}Re, ^{90}Y, ^{153}Sm and ^{166}Ho. The radionuclidic characteristics and methods of production of these radionuclides are shown in Table 1. These radionuclides in the form of labelled compounds or conjugates of suitable biomolecules have already been

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Table 1
Decay characteristics and production routes of some important radionuclides for therapy

Radionuclide	$T_{1/2}$	$E_{\beta,\max}$(MeV)	E_γ (keV) (%)	Method of production		
				Nuclear reaction	% Natural abundance	σ_{th} (barns)
^{188}Re	16.9 h	2.12	155 (15)	^{188}W(69.4 d)–^{188}Re generator	—	—
				^{187}Re (n,γ)	62.6	73
^{186}Re	90.6 h	1.07	137 (9)	^{185}Re (n,γ)	37.4	106
^{90}Y	64.1 h	2.27	—	^{90}Sr(28.3 d)–^{90}Y generator	—	—
				^{89}Y (n,γ)	100	1.3
^{153}Sm	46.3 h	0.81	103 (28)	^{152}Sm (n,γ)	26.7	206
^{166}Ho	26.9 h	1.85	81 (6.4)	^{165}Ho (n,γ)	100	66
^{89}Sr	50.5 d	1.49	—	^{88}Sr(n,γ)	82.6	0.0058
^{117m}Sn	13.6 d	0.13, 0.15	159 (86)	^{116}Sn(n,γ)	14.4	0.006
				^{117}Sn(n,n',γ)	7.7	—

widely investigated (Das et al., 2000; De Jong et al., 1998; Goeckeler et al., 1987; Ma et al., 1996; Mausner and Srivastava, 1993; Mumper et al., 1992). ^{177}Lu is a radioisotope having very good potential for use in in vivo therapy, because of its favourable decay characteristics. ^{177}Lu decays with a half-life of 6.71 d by emission of β^- particles with E_{max} of 497 keV (78.6%), 384 keV (9.1%) and 176 keV (12.2%) to stable ^{177}Hf. It also emits γ photons of 113 keV (6.4%) and 208 keV (11%) (Firestone, 1996), which are ideally suited for imaging the in vivo localization with a gamma camera. The physical half-life of ^{177}Lu is comparable to that of ^{131}I, one of the most commonly used radioisotopes for radionuclide therapy. The long half-life of ^{177}Lu provides logistic advantage for facilitating supply to places far away from the reactors.

^{177}Lu can be produced by two different routes, namely, by irradiation of natural Lu_2O_3 target (^{176}Lu, 2.6%) or enriched (in ^{176}Lu) Lu_2O_3 target, as also by irradiation of Yb target (Yb_2O_3) followed by radiochemical separation of ^{177}Lu from Yb isotopes. The above two production routes lead to the product having different specific activities. Although the specific activity obtained in (n,γ) activation is usually low, owing to the high thermal neutron capture cross-section of ^{176}Lu (σ= 2100 b) direct (n,γ) activation of even natural Lu_2O_3 powder results in reasonably high specific activity of ^{177}Lu. Table 2 lists the isotopic abundance of natural Lu and all possible (n,γ) activation products. The specific activity could be further enhanced considerably by using Lu target enriched in ^{176}Lu, by carrying out irradiation in a high flux reactor, as well as optimizing the duration of irradiation. On the other hand, activation of ^{176}Yb and subsequent β^- decay gives no carrier added (NCA) ^{177}Lu. However, in this technique, radiochemical separation of ^{177}Lu activity from irradiated Yb_2O_3 target is very crucial because of the radionuclidic purity requirement.

Table 2
Isotopic abundance of natural Lu and activation products

Isotope	% Natural abundance	σ (barns) for (n,γ) reaction	Product RN and its characteristics
^{175}Lu	97.4	7	^{176}Lu (stable)
		16.4	^{176m}Lu (β^-, 3.7 h)[a] ^{176}Hf (stable)
^{176}Lu	2.6	2100	^{177}Lu (β^-, 6.71 d) ^{177}Hf (stable)
		7	^{177m}Lu (β^-, 160.5 d)[b] ^{177}Hf (stable)

[a] E_β = 1.2 MeV, E_γ = 88 keV.
[b] E_β= 0.2 MeV, E_γ= 128, 153, 228, 378, 414, 418 keV.

In the present paper, we describe the production of ^{177}Lu by (n,γ) activation using natural as well as enriched Lu_2O_3 target and its possible uses in various radiotherapeutic applications. Also, a comparison between the two above-mentioned routes for production of ^{177}Lu has been drawn and the merits of (n,γ) activation as a simple and viable production route of ^{177}Lu are highlighted.

2. Materials and methods

Natural Lu_2O_3 powder (spectroscopic grade, >99.99% pure) was obtained from Johnson Matthey & Co. Ltd., UK. A weighed amount (typically 6 mg) of natural Lu_2O_3 powder was irradiated in Dhruva reactor for 3–7 days at a thermal neutron flux of $\sim 3\times10^{13}$ n/cm^2/s. The irradiated target was dissolved in 1 M HCl by gentle warming inside a lead-shielded plant. The resultant solution was evaporated to near dryness and reconstituted in double distilled water. A known aliquot

was drawn for assessment of radioactivity content and radionuclidic purity evaluation.

For production of high specific activity ^{177}Lu, isotopically enriched Lu_2O_3 (60.6% ^{176}Lu) (Isoflex, USA) was irradiated. A stock solution of enriched target was prepared by dissolving enriched Lu_2O_3 powder in 0.1 M HCl (1 mg ml^{-1} concentration). A known aliquot of this solution was taken in a quartz ampoule and carefully evaporated to dryness. The ampoule was subsequently flame sealed and irradiated after placing inside an aluminium can. The can was irradiated at a thermal neutron flux of 3×10^{13} n/cm^2/s for 3–7 days. The chemical processing of the irradiated target was carried out as described above for the natural Lu_2O_3 target.

Radioactivity assay was carried out by measuring the ionization current obtained when an aliquot of the batch was placed inside a pre-calibrated well-type ion-chamber (the calibration factor for the ion chamber for ^{177}Lu was arrived at 1.143×10^{-14} A MBq^{-1}). Radionuclidic purity was determined by recording γ-ray spectrum of the appropriately diluted solution of the irradiated target using an HPGe detector (EGG Ortec/Canberra detector) connected to a 4 K multichannel analyser (MCA) system. A ^{152}Eu reference source (Amersham Inc.) was used for both energy and efficiency calibration. All the nuclear data used were taken from the *Table of isotopes* (Firestone, 1996). Several spectra were recorded for each batch at regular time intervals. Samples measured initially for the assay of ^{177}Lu were preserved for complete decay of ^{177}Lu (over 10–15 $T_{1/2}$ of ^{177}Lu, i.e. for a period of 2–3 months) and re-assayed to determine the activity of long-lived ^{177m}Lu ($T_{1/2}$= 160.5 d). Appropriately diluted sample solutions were counted for 1 h.

3. Results and discussion

The typical yields of ^{177}Lu from natural as well as enriched targets for different durations of irradiation in Dhruva reactor (3×10^{13} n/cm^2/s) are shown in Table 3. These values are in excess of theoretically calculated values, which are also given alongside in Table 3. This could perhaps be attributed to the contribution from epithermal neutrons (resonance integral = 1087 b), which is not accounted in theoretical calculations (Knapp et al., 1995; Ramamoorthy et al., 2002). The variations in the yield of ^{177}Lu between different batches are mostly due to fluctuations in the irradiation conditions such as the exact duration, intervening shutdown and variation of neutron flux due to the power level of reactor operation.

The radionuclidic purity of ^{177}Lu produced from either natural or enriched target was ~100% as estimated by analysing the γ-ray spectrum. In a typical γ-ray spectrum of the irradiated target after chemical processing (Fig. 1), the major γ peaks observed were 72, 113, 208, 250 and 321 keV, all of which correspond to the photopeaks of ^{177}Lu (Firestone, 1996). This was further confirmed from the decay as followed by monitoring peak area cps values at those peaks according to the half-life of ^{177}Lu. It is worthwhile to mention that there is a possibility of formation of ^{177m}Lu ($T_{1/2}$ = 160.5 d) on thermal neutron bombardment of Lu_2O_3 target (Knapp et al., 1995; Neves et al., 2002). However, γ-ray spectrum of the irradiated Lu target after chemical processing did not show any significant peak corresponding to the photopeaks of ^{177m}Lu (128, 153, 228, 378, 414, 418 keV) (Firestone, 1996). This is expected as the radioactivity due to ^{177m}Lu produced will be insignificant and below the detectable limit on a 7 d irradiation owing to its long half-life and comparatively low cross-section (σ = 7 barns) for its formation. Attempt to assay any trace level of ^{177m}Lu activity by recording γ-ray spectrum of a sample aliquot, initially having high radioactive concentration, after complete decay of ^{177}Lu activity showed the presence of trace level of ^{177m}Lu. The average level of radionuclidic impurity burden in ^{177}Lu due to ^{177m}Lu was found to be 5.5 kBq of ^{177m}Lu/37 MBq of ^{177}Lu (150 nCi/1 mCi) at EOB.

Table 3
Specific activities of ^{177}Lu produced from natural and enriched Lu_2O_3 target due to thermal neutron bombardment at a flux of ~3×10^{13} n/cm^2/s

Target	Duration of irradiation (d)	Specific activity (at EOB) (TBq/g)	
		Theoretical	Experimental
Natural Lu	3	1.50	2.5±0.3
	5	2.27	3.3±0.2
	7	2.90	4.0±0.3
Enriched Lu (60.6% ^{176}Lu)	3	34.96	72±5
	5	52.91	92±3
	7	67.59	110±5

3.1. Production logistics—yield and specific activity

Owing to its suitable decay characteristics, the usefulness of ^{177}Lu in radionuclide therapy (RNT) has already been pointed out (Volkert et al., 1991; Srivastava and Dadachova, 2001; Liu et al., 2001; Ma et al., 1996; Stein et al., 2001, Sola et al., 2001). Although, natural Lu target contains only 2.6% of ^{176}Lu, the specific activity of ^{177}Lu obtained by (n,γ) activation of natural Lu_2O_3 target is reasonably high because of the very high thermal neutron capture cross-section. In fact the cross-section (2100 barns) is the highest encountered among all (n,γ) produced radionuclides presently used for therapy. The high

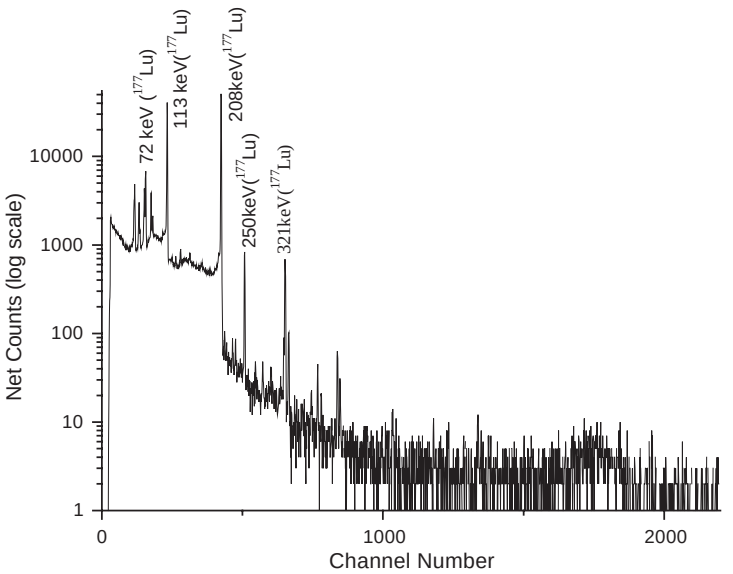

Fig. 1. γ-ray spectrum of ^{177}Lu.

cross-section also ensures that there will be no constraints with respect to large-scale production of the isotope. It is feasible to produce ^{177}Lu with high specific activity suitable for developing agents for targeted radiotherapy, taking the advantage of high flux reactor and target enriched in ^{176}Lu.

However, a careful optimization of the time of irradiation will have to be carried out in order to obtain the highest specific activity. In high flux reactors the target burn up will be considerably high due to the high thermal neutron capture cross-section of ^{176}Lu and hence, the usual assumption that the number of target atoms remain constant during the period of irradiation will not be valid in this case. Considering the number of target atoms is a function of irradiation time, the commonly used differential equation,

$$dN_2/dt = N_1\sigma\phi - N_2\lambda$$

can be modified as,

$$dN_2/dt = N^0 e^{-\sigma\phi t}\sigma\phi - N_2\lambda,$$

where, N^0 is the number of ^{176}Lu atoms used as target (at $t = 0$), N_1 the number of ^{176}Lu atoms at any time t, N_2 the number of ^{177}Lu atoms at any time t, λ the decay constant of ^{177}Lu, σ the thermal neutron capture cross-section of ^{176}Lu, ϕ the thermal neutron flux of the reactor and t the time of irradiation. ^{177}Lu activity produced at the end of bombardment can be calculated by the following equation, which is obtainable by solving the modified differential equation mentioned above

$$A = \frac{N^0\lambda\sigma\phi}{\lambda - \sigma\phi}\left[e^{-\sigma\phi t} - e^{-\lambda t}\right].$$

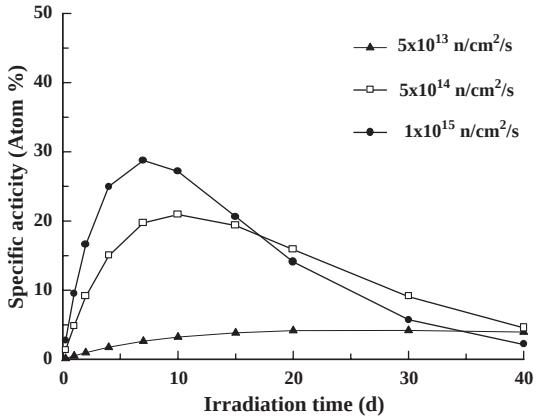

Fig. 2. Variation of ^{177}Lu activity with respect to duration of irradiation at different thermal neutron fluxes.

The ^{177}Lu activity produced at the end of bombardment as a function of irradiation time at three different thermal neutron fluxes has been calculated on the basis of above equation and the results are shown in Fig. 2. It is evident from the figure, that depending on neutron flux the activity of ^{177}Lu produced will be maximum after a certain duration of irradiation, beyond which the activity will decrease owing to the high target burn up. Higher the thermal neutron flux of the reactor, shorter will be the time of irradiation for attaining maximum activity. Therefore, in order to obtain maximum specific activity using enriched ^{176}Lu target, the time of irradiation must be judiciously decided as per the neutron flux available.

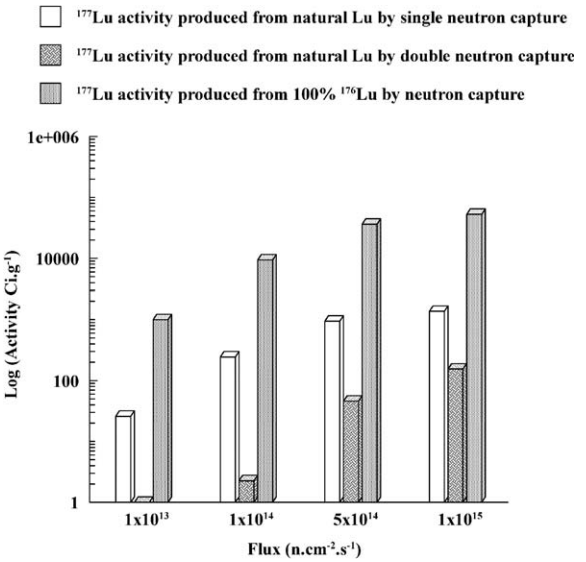

Fig. 3. ^{177}Lu activity produced from ^{175}Lu and ^{176}Lu in natural Lu target along with ^{177}Lu activity obtainable from 100% enriched ^{176}Lu target for 7 d irradiation at various thermal neutron fluxes.

It is also pertinent to point out that ^{175}Lu present in the natural Lu target (97.4%) will also contribute to ^{177}Lu activity produced by undergoing successive neutron capture. Fig. 3 shows the ^{177}Lu activity produced from ^{175}Lu and ^{176}Lu in natural Lu target along with ^{177}Lu activity obtainable from 100% enriched ^{176}Lu target for 7 d irradiation at various thermal neutron fluxes. Although, the ^{177}Lu activity produced by double neutron capture of ^{175}Lu is insignificant at relatively low neutron flux, the contribution from this route becomes quite significant with the increase of neutron flux. This is because of the activity of a radionuclide produced by a successive neutron capture process being proportional to the square of the neutron flux. It is evident from Fig. 3 that at a flux of 1×10^{15} n/cm^2/s, ^{175}Lu$(n,\gamma)^{176}$Lu$(n,\gamma)^{177}$Lu is a significant contributor to ^{177}Lu activity produced. Therefore, the specific activity of ^{177}Lu obtainable from high flux reactor using natural Lu target will be higher than that expected from ^{176}Lu$(n,\gamma)^{177}$Lu only.

3.2. Potential for use in metastatic bone pain palliation

Some promising forms of RNT do not require high specific activity radionuclides for the formulation of the radiotherapy agents. An important class of such radiotherapy agents has been widely used in palliative treatment of skeletal metastases. ^{153}Sm-EDTMP and ^{186}Re-HEDP, the two agents used most extensively in this purpose employ (n,γ) produced carrier added radioisotopes (Mausner et al., 1998; Ketring, 1987). Although, enriched ^{152}Sm is normally used as the target for the preparation of ^{153}Sm-EDTMP, it was demonstrated that ^{153}Sm produced from even natural Sm target can be effectively utilized in making patient dose of ^{153}Sm-EDTMP (Ramamoorthy et al., 2002). However, the radionuclide will have to be used within 3–4 d, in view of the presence of radionuclidic impurities of ^{154}Eu ($T_{1/2}$= 8.8 y) and ^{155}Eu ($T_{1/2}$= 4.96 y). The utility of ^{153}Sm ($T_{1/2}$= 46.3 h) is also limited in places not well connected with reactor site and in countries having poor transport logistics. Due to the 46.3 h half-life, substantial quantities of the isotope produced at EOB is lost by decay during chemical processing, preparation and quality control of radiopharmaceuticals and subsequent transportation. Hence, the activity to be produced in case of ^{153}Sm at EOB will have to be several times higher than that used for actual administration. This necessitates the handling of large quantum of activity while making ^{153}Sm products. Similarly logistics problems affect the merit of ^{186}Re ($T_{1/2}$= 90.6 h) also. One has to either use highly enriched ^{185}Re target for irradiation or avail of prolonged cooling periods of $\sim$120 h ($\sim 5T_{1/2}$ of ^{188}Re) to let ^{188}Re decay to acceptable level while using natural Re targets. Long-lived isotopes such as ^{89}Sr is also very effectively used for bone pain palliation. The major advantage with ^{89}Sr is that due to the long half-life (50.5 d) the activity administrable can be significantly lower, say 4–5 mCi, to give the required cumulative dose. The long half-life of ^{89}Sr also helps in transportation of the radiopharmaceutical across the world. However, the production of ^{89}Sr in adequate quantities is expensive due to the low cross-section of ^{88}Sr (5.8 mb) for thermal neutron capture and hence the need to have very high neutron flux for irradiation and preferably also enriched target. Again, ^{89}Sr is also expected to give high bone marrow dose due to the emission of high energy β^- particles ($E_{\beta(\max)}$ = 1.49 MeV). Due to the above reasons, despite being an efficacious radiopharmaceutical, utility of $^{89}SrCl_2$ has remained limited. Considering that 50–70 mCi is the patient dose for ^{153}Sm, 35–40 mCi for ^{186}Re and about 4–5 mCi for ^{89}Sr for the same application, the dose requirement for ^{177}Lu is expected to be considerably lower, say $\sim$15–20 mCi, than that of ^{153}Sm and ^{186}Re to give the same cumulative dose. Taking into consideration the comparatively lesser decay loss as well the lower per patient dose, it will be possible to treat at least 10 times more patients with the same amount of activity at EOB with ^{177}Lu as compared to ^{153}Sm. In the present study, we have found that neutron activation of natural Lu target at a moderate thermal neutron flux of 3×10^{13} n/cm^2/s for 7 d ($\sim$half saturation value) produces 4 TBq/g (108 Ci/g) of ^{177}Lu. Hence, irradiation of 100 mg of natural Lu target at 3×10^{13} n/cm^2/s can yield $\sim$10 Ci of ^{177}Lu sufficient for treating 300–500 patients. The most significant advantage of ^{177}Lu will hence be

the easy and economical production of large quantities of the radioisotope in relatively low flux reactor available in several places around the world. Also, enriched target will not be essential for making therapeutic radiopharmaceuticals for bone pain palliation. In relatively high flux reactors (say, 5×10^{14} n/cm^2/s) the specific activity could be increased to $\sim$35 TBq/g (950 Ci/g) as obtained from theoretical calculations. ^{177}Lu labelled linear as well as cyclic polyaminophosphonic acid ligands have been prepared with high yield at low [ligand]:[metal] ratio and evaluated in animal models as potential agents for palliation of pain due to bone metastasis (Chakraborty et al., 2002; Das et al., 2002). Some of these agents have shown excellent properties as bone seeking radiophamaceuticals.

^{117m}Sn(IV)-DTPA was proposed as an efficacious bone pain palliation agent by Atkins et al. (1995); Srivastava et al. (1998). ^{117m}Sn derives its therapeutic strength from the copious Auger electron emission following electron capture (EC) decay ($T_{1/2}$= 13.6 d). The accompanying 156 keV (86%) gamma photon emission is not exactly preferred for RNT applications. Nonetheless, thanks to 0.2–0.3 mm tissue range of the Auger electron of ^{117m}Sn, very effective dose deposition on bone surface as well as very high bone-to-bone marrow ratio has been demonstrated while using ^{117m}Sn(IV)-DTPA (Bishayee et al., 2000). ^{117m}Sn is however, difficult to produce economically in large quantities and hence the utility has remained limited. The excellent matching of tissue range of ^{177}Lu (0.5–0.6 mm) for similar dose deposition can be inferred from the above results reported with the use of ^{117m}Sn-DTPA. The adequacy of $E_{\beta^-} \sim 0.5$ MeV of ^{177}Lu for effective bone pain palliation can hence be advocated as major attractive feature in addition to the convenient half-life and production logistics enumerated earlier. The mylotoxicity of ^{177}Lu complex will be slightly higher than that of the Auger electron of ^{117m}Sn, but the 86% abundant 156 keV gamma emission of ^{117m}Sn places additional burden of absorbed dose to far off tissues/organs.

3.3. Potential for other therapeutic applications

Besides, radiolabelled particulates or microspheres for therapy of hepatic tumour also require only low specific activity radionuclides and ^{177}Lu could be used for development of these agents. ^{177}Lu could be very effective in radiation synovectomy of medium size joints and could be a good replacement for the difficult to produce ^{169}Er which is used in small joint radiation synovectomy (Deutsch et al., 1993). It has already been reported that, for medium size joints dose requirement for ^{153}Sm labelled hydroxy apatite (HA) is $\sim$74 MBq ($\sim$2 mCi). For ^{177}Lu-HA, the activity requirement is expected to be even lower, due to the long half-life and higher cumulative dose per mCi activity. Hence, ^{177}Lu could be an attractive candidate for the preparation of radiopharmaceuticals for radiation synovectomy.

In the case of applicability of larger lesions, ^{177}Lu would suffer due to lower E_{β^-}. Thus for the current approaches, such as, hepatocellular carcinoma, ^{177}Lu would be unattractive now. Advances in diagnostic techniques continuously helping early pick up of smaller lesions could bring further a demand for medium β^- energy products too in future. In fact, "patient tailored RNT" has been reported as a distinct possibility in future. Potential of ^{177}Lu applicability is thus far reaching.

In targeted radiotherapy using peptides and other receptor based carrier molecules, the use of high specific activity (preferably no carrier added) radionuclide in formulating the radiopharmaceutical is essential in order to deliver sufficient number of radionuclides to the target site without saturating the target (Volkert et al., 1991; Mausner and Srivastava, 1993). The use of high specific activity ^{177}Lu in targeted therapy (conjugated to receptor specific peptides or monoclonal antibodies) has already been proposed (Ehrhardt et al., 1998; Srivastava and Dadachova, 2001; Meredith et al., 1996; Mausner and Srivastava, 1993; Liu et al., 2001; Stein et al., 2001).

3.4. Specific activity aspects

No carrier added ^{177}Lu can be produced by irradiation of enriched ^{176}Yb target. The nuclear reaction leading to the formation of no carrier added ^{177}Lu is

$$^{176}\underset{\sigma=2.4\ b}{\mathrm{Yb}}(n,\gamma)\,^{177}\mathrm{Yb}\xrightarrow[T_{1/2}=1.9\ \mathrm{h}]{\beta^-}{}^{177}\mathrm{Lu}\xrightarrow[T_{1/2}=6.71\ \mathrm{d}]{\beta^-}{}^{177}\mathrm{Hf\ (stable)}$$

From theoretical calculations employing the appropriately modified form of the Bateman equation, it can be shown that irradiation of 1 mg of 99% enriched $^{176}Yb_2O_3$ target at a reasonably high thermal neutron flux of 5×10^{14} n/cm^2/s will produce $\sim$5.55 GBq ($\sim$150 mCi) of ^{177}Lu which is carrier free having a theoretical specific activity of 1.09×10^5 Ci/g. However, radiochemical separation of ^{177}Lu activity from irradiated Yb_2O_3 target is a difficult task owing to the similarity in the chemistry of the two adjacent members of the lanthanide series. Presence of Yb will reduce the effective specific activity of the product. Since Yb^{+3} is an equally good complexing ion, it would interfere during the preparation of radiopharmaceuticals. This is one of the major impediment in the ready production of no carrier added ^{177}Lu via ^{176}Yb (n,γ, β^-) ^{177}Lu route. Moreover, use of enriched targets with low activation cross-section is not economical for isotope production, as a significant part of the target will be wasted. Though, theoretically in the present case recovery of the target is feasible, there will be practical problems.

We have produced ^{177}Lu having specific activity of $\sim$110 TBq/g (3×10^3 Ci/g) by irradiation of commercially available enriched Lu_2O_3 powder at a flux of 3×10^{13} n/cm^2/s for 7 d (Table 3). From theoretical calculations, the specific activity of ^{177}Lu will be 800 TBq/g (2.17×10^4 Ci/g) in a relatively high flux reactor (say, 5×10^{14} n/cm^2/s) under the same irradiation conditions. In other words, it translates to a specific activity of $\sim$0.20 atoms of ^{177}Lu per atom of all lutetium nuclides, resulting in 20% of the maximum achievable theoretical specific activity. This is expected to be sufficient for the preparation of targeted therapy agents involving minimum number of carrier molecules capable of delivering required dose to the target (Volkert et al., 1991; Mausner and Srivastava, 1993). As for example, in the formulation of ^{177}Lu labelled peptide for targeted tumour therapy, 10 μg of peptide (say, $\sim$1000 D molecular weight) could incorporate >1 μg of Lu. With a specific activity of 2.17×10^4 Ci/g, even 1 μg corresponds to 21.7 mCi of ^{177}Lu activity. Similarly, in radioimmunotherapy (RIT), assuming the conjugation of an average of one lutetium atom per monoclonal antibody (Mab) molecule, 1 mg Mab preparation could hold >1 μg of ^{177}Lu corresponding to an activity of >20 mCi sufficient to deliver the required therapeutic dose (Volkert et al., 1991; Wessels and Rogus, 1984; Mausner and Srivastava, 1993). The major advantage of the present method of production is that a simple and quick post irradiation chemical processing gives radionuclidically as well as radiochemically pure product.

3.5. Comparison with other therapeutic radionuclides

The use of no carrier added (NCA) β^- emitting radionuclides in radioimmunotherapy (RIT) and other forms of targeted therapy is a very popular practice (Volkert et al., 1991; Srivastava and Dadachova, 2001; Mausner and Srivastava, 1993). Most of the NCA radionuclides are produced in the reactors either via indirect reactions or obtained from generator systems where the longer-lived parent radionuclide may be obtained by direct neutron activation. Table 4 gives a list of most widely used radionuclides in NCA levels in targeted therapy. ^{188}Re and ^{90}Y are the two most attractive generator-produced radionuclides for RNT applications. ^{188}Re is available in the NCA form from a ^{188}W–^{188}Re generator installed at hospital radiopharmacy (Kamioski et al., 1994). However, the availability of ^{188}W, the parent radionuclide, in adequate quantity and specific activity is restricted, since it is produced by a double neutron capture reaction. Only very few reactors in the world having thermal neutron flux of the order of $>5\times10^{14}$ n/cm^2/s (such as, HFIR of ORNL, USA, MIR.M1 and SM reactor of Russian fedaration, BR-2 reactor of Belgium) are capable of producing reasonable quantities of ^{188}W for the preparation of ^{188}W–^{188}Re generator. ^{90}Sr–^{90}Y generator system is now being used to provide NCA ^{90}Y for targeted therapy (Venkatesh et al., 2001). However, the possible radionuclidic contaminant ^{90}Sr ($T_{1/2}=28.3$ y, a natural bone seeker) and other trace metals in the eluted ^{90}Y is a very crucial factor. ^{105}Rh is another isotope having suitable decay properties for therapeutic applications and can be made available in NCA form through ^{104}Ru (n,γ,β^-) ^{105}Rh route. However, production of ^{105}Rh with high radiochemical and radionuclidic purity involves multi-step chemical preparations and purification that prohibit its widespread application (Volkert et al., 1991; Grazman and Troutner, 1988; Unni and Pillai, 2002). Moreover, due to poor activation cross-section, large quantities of the target need to be handled during irradiation and chemical processing. ^{67}Cu is also very convenient for RIT and several bifunctional chelating agents have been developed for its conjugation to monoclonal antibodies and other biomolecules (Rogers et al., 1996). However, the cross-section for (n,p) production of ^{67}Cu ($\sigma=0.0012$ b) is too small to enthuse reactor production in sufficient quantities for widespread therapeutic applications (O'Brien, 1969).

Even though many β^- emitting radionuclides show considerable promise for therapy, ^{131}I ($T_{1/2}=8.03$ d, $E_{\beta(\max)}=0.81$ MeV) continues to play a significant role

Table 4
Radionuclides (produced in NCA form) most widely used in targeted therapy

Radionuclide	$T_{1/2}$(h)	E_β(max) (MeV)	E_γ (keV)	Source
^{67}Cu	62	0.57	184 (48%) 92 (23%)	^{67}Zn (n,p) ^{67}Cu, $\sigma=0.0012$ b
^{105}Rh	35.5	0.57	319 (19%) 306 (5%)	^{104}Ru (n,γ,β^-) ^{105}Rh, $\sigma=0.5$ b
^{90}Y	64.1	2.27	—	^{235}U (n,f) ^{90}Sr→ ^{90}Sr(28.3y)– ^{90}Y generator
^{188}Re	16.9	2.12	155 (15%)	^{186}W (n,γ) ^{187}W (n,γ) ^{188}W→ ^{188}W(69.4 d)–^{188}Re generator
^{47}Sc	80.2	0.60	159 (68%)	^{46}Ca (n,γ,β^-) ^{47}Sc, $\sigma=0.7$ b ^{47}Ti (n,p) ^{47}Sc ($E_n>1$ MeV)

Table 5
Theoretical specific activities of potential therapeutic radionuclides produced by neutron bombardment at a flux of 5×10^{14} n/cm^2/s for 7 d or from radionuclide generator

Isotope	Source (enrichment)	Cross-section (barns)	Specific activity	
			Ci/g	Atom%
^{188}Re	^{188}W/^{188}Re generator	—	9.80×10^5	100
^{188}Re	^{187}Re (n,γ) ^{188}Re (99%)	73	3.14×10^3	0.32
^{186}Re	^{185}Re (n,γ) ^{186}Re (99%)	106	3.35×10^3	1.76
^{90}Y	^{90}Sr/^{90}Y generator		5.44×10^5	100
^{153}Sm	^{152}Sm (n,γ) ^{153}Sm (98%)	206	8.60×10^3	2.21
^{166}Ho	^{165}Ho (n,γ) ^{166}Ho (100%)	66	3.16×10^3	0.45
^{177}Lu	^{176}Lu (n,γ) ^{177}Lu (60.6%)	2100	2.17×10^4	19.74

for RNT (Volkert et al., 1991). Though ^{131}I has a tissue penetration range which is well suited for the treatment of small tumours, the accompanying 364 keV γ emission with high abundance (81%) is a major drawback for its use in therapeutic purposes. ^{177}Lu can be considered as a viable alternative of ^{131}I for the therapy of non-thyroid small sized tumours. Relatively low energy major γ emission (208 keV) with low abundance (11%) is a distinct advantage in favour of ^{177}Lu. ^{177}Lu will also give much lower external dose emanating from the patient thereby enabling early discharge of the patient from the isolation ward, which could save money as well as making such isolation wards available for other patient use. One of the advantages cited for the routine use of ^{131}I is its availability with relatively high specific activity ($\sim$17 atom%) (Volkert et al., 1991) from commercial sources. However, our theoretical calculations show that, ^{177}Lu also can be produced with comparable specific activity ($\sim$20 atom%) from a moderately high flux reactor ($\sim 5 \times 10^{14}$ n/cm^2/s) by 7 days irradiation of commercially available 60.6% enriched ^{176}Lu target. It may also be possible to get ^{176}Lu with higher enrichment. The production of ^{131}I needs more elaborate chemical separation and consequent waste disposal measures, as it is produced either by irradiation of natural tellurium target or from fission of ^{235}U.

^{177}Lu, produced via neutron activation of enriched ^{176}Lu target is an attractive candidate for targeted therapy applications, since it satisfies specific activity as well as radionuclidic purity requirements and can be made available in large quantities very easily in the desired chemical form. A comparison of specific activities of a few potential therapeutic radionuclides produced by neutron activation or from radionuclide generators is given in Table 5. Though atom% of generator produced isotopes is theoretically 100%, in actual practice the decay product of the radionuclide though inactive will interfere in complexation thereby reducing the effective specific activity.

4. Conclusions

^{177}Lu has got very good potential as a therapeutic radionuclide especially in developing countries with limited facilities of reactor irradiation and for indigenous production capability of radiopharmaceuticals. The high thermal neutron cross-section of ^{176}Lu$(n,\gamma)^{177}$Lu reaction facilitates large-scale production, while relatively longer half-life provides logistic advantage for production, radiochemical processing and transportation of finished radiopharmaceuticals. The present studies show $\sim$4 TBq/g (108 Ci/g) and $\sim$110 TBq/g (3000 Ci/g) of ^{177}Lu activity could be produced by thermal neutron bombardment at a flux of 3×10^{13} n/cm^2/s for a period of 7 days using natural and enriched (60.6% ^{176}Lu) Lu_2O_3 targets, respectively. ^{177}Lu produced by neutron irradiation of natural Lu_2O_3 target in medium to high flux reactor could be used in the development of bone pain palliation and radiation synovectomy agents for small and medium size joints, wherein the specific activity requirement is low. On the other hand, ^{177}Lu produced with enriched target will have adequate specific activity for labelling peptides, antibodies etc. for targeted radiotherapy, such that NCA ^{177}Lu production through tedious radiochemical separation from irradiated Yb target can be avoided.

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