Title

Investigation in Effect of Fourfold Parameters on Preparation of ^{166}Ho Radiopharmaceutical

Authors

Mehdi Mohebali[1*], Hojatolah Salehi[2], Dariush Sardari[1], Masomeh Zoghi[2], Maghsoud Gourani[2] and Hosein Abbasi[2]

1- Islamic Azad University, Science and Research Branch, Tehran, Iran.
2-Nuclear Science Research School, NSTRI, AEOI, Iran.

Abstract

Radiopharmaceuticals are now increasingly used for therapy of cancer, palliation of pain secondary to bone metastasis and for the treatment of rheumatoid arthritis. ^{165}Ho (n,γ) ^{166}Ho is currently used for radiotherapy due to its attractive properties which include emission of high energy β- particles ($E_{\beta-1}$=1855 Kev (51%), $E_{\beta-2}$=1776 Kev (48%) and E_{ave} =666 Kev), an appropriate physical half- life of 26.4 h and decay to stable daughter. In this research holmium oxide (Ho_2O_3, purity > 99.9%) was irradiated in Tehran research reactor (TRR) and four parameters mass, thermal neutron flux (φ), bombarding time (t_b) and cooling time (t_c) were investigated. The best conditions for producing of ^{166}Ho were achieved (m=2 mg, $\varphi=5.7\times10^{13}$ n/cm^2.s, t_b=8 h, t_c=40 h, correction factor 92%).

Key words

Neutron activation; Holmium; Correction factor; Thermal neutron flux.

* Corresponding Author: E. mail: mohebali_2121@yahoo.com

Introduction

Inherent determinants in developing therapeutic radiopharmaceuticals are the choice of radionuclide, local production condition and carrier molecule. The radionuclide should emit sufficient useful destructive radiation and remain in the target site, which depends mainly on the carrier molecule biokinetics.

For therapeutic purpose, the selection of a suitable radioisotope should take into account not only the physicals characteristics (type of energy, range and half-life), but also the specificity of localization and pharmacokinetics [1].

The use of beta particles emitter have a distinct advantage over gamma emitter in that beta particles have a limited penetration in tissue, a highly homogeneous radiation dose and a significantly lower dose delivery beyond target tissue than that induced by gamma rays [2].

The physical properties of ^{166}Ho make this radioisotope attractive for therapeutic applications: high energy beta particles (E_{ave}=666 kev), low intensity and low energy gamma rays (80.5 kev,6%) suitable for imaging, 26.4 h half-life and stable daughter ^{166}Er. In particular, ^{166}Ho can be readily produced using a low or medium flux research reactor because the thermal neutron cross section of this radioisotope is 63.5±3.5 barn [2,3]. This radioisotope is one of the new generation radiopharmaceuticals and because of good characteristics, its use as a therapeutic agent is increased.

Turner et al. (1994) used the 81 kev–gamma emission of ^{166}Ho to determine, by SPECT imaging, the beta dose absorbed by normal liver of pigs administered with ^{166}Ho micro-spheres in intra-hepatic artery [4].

^{166}Ho has different therapeutic applications. For example DTPA is labeled with ^{166}Ho to prevent restenosis in angioplasty balloons. This radioisotope also used for decreasing the pain of bone cancer and treatment of skin cancers [5,6,7].

Generally there are two methods for production of ^{166}Ho:

- Indirect neutron activation: in which the stable nuclide ^{164}Dy with abundance of 25% is used as the target in the reactor (^{164}Dy (n, γ) ^{165}Dy (n, γ) ^{166}Dy (β^-) ^{166}Ho).
- Direct neutron activation: in which the stable nuclide ^{165}Ho with abundance of 100% is used as the target in the reactor (^{165}Ho (n, γ) ^{166}Ho).

Respecting to the low abundance of ^{164}Dy and significant by-product impurities of first method, in this research for the first time in Iran the possibility and improvement of ^{166}Ho production was investigated by direct activation method.

Experimental

Materials and method

Materials: natural holmium powder with 99.9% purity in the form of Ho_2O_3, as a bombardment target, curiemeter Amersham CRC-12, quartz ampoules, aluminum cans.

Method: Ho_2O_3 powder (99.9% purity) was poured into the quartz ampoules and the ampoules were sealed by heating. Then each ampoule placed in aluminum can. In the next step the cans were placed in different positions of Tehran research reactor (TRR). In direct neutron activation method, the theoretical activity can be calculated as follows [8]:

$$A(mCi) = \frac{1}{3.7\times10^{7}} \frac{m\sigma\varphi N_a}{M}(1-e^{-\lambda t_b})e^{-\lambda t_c} \qquad (1)$$

where m is the mass of the holmium powder samples, φ is the neutron flux of the reactor, t_b is the bombarding

time of the samples in the reactor, t_c is the cooling time of the samples, M is atomic weigh of the holmium and N_a is Avogadro number.

To measure the practical activity of the samples after cooling, Amersham CRC-12 curiemeter was used. This curiemeter was daily calibrated with ^{137}Cs standard source, so the measured activity had good precision [9].

In order to obtain the optimum parameters, the effect of four main parameters (flux, mass, bombarding time, cooling time) on the activity of the samples were investigated:

Investigation of flux effect: Five samples of $^{165}Ho_2O_3$ under the same condition (m=1.5 mg, bombarding time (t_b) =2h, cooling time (t_c) =30 h) were placed into the five different positions in Tehran research reactor (TRR).

Investigation of mass: Six samples of $^{165}Ho_2O_3$ with different masses (min=0.5mg, max=3mg incriminate 0.5) were bombarded under the same conditions (t_b=2 h, t_c=40 h, $\varphi=5.7\times10^{13}$ n/cm^2.s).

Investigation of bombarding time: For this purpose four samples of $^{165}Ho_2O_3$ under the same conditions (t_c=50 h, m=1.5 mg, $\varphi=5.7\times10^{13}$ n/cm2.s) were bombarded for 2, 4, 6 and 8 hours.

Investigation of cooling time: Six samples under the same conditions (m=1.5 mg, t_b=2 h, $\varphi=5.7\times10^{13}$ n/cm^2.s) were cooled for 10, 20, 30, 40, 60 and 80 hours.

Results

After applying the above conditions, the activity of the samples for each condition was measured by Amersham CRC-12 curiemeter. The results are shown in Tables 1-4:

Table1- The activity of $^{165}Ho_2O_3$ in different fluxes.

$\varphi\times10^{13}$	2	2.5	3	3.5	5.7	5.94	6.5	8.04	9.5
Activity (mCi)	3.3	6.8	6.4	6.7	10.6	10.68	12.4	14.2	18.5
m=1.5 mg, bombarding time (t_b)=2 h, cooling time (t_c)=30 h									

Table 2- The activity of different amount of $^{165}Ho_2O_3$.

Mass (mg)	0.5	1	1.5	1.9	2	2.5	3.2
Activity (mCi)	2.9	4.46	7.86	11.01	11.87	13.9	17.7
bombarding time (t_b)=2 h, cooling time (t_c)=40 h, $\varphi=5.7\times10^{13}$ n/cm^2.s							

Table 3- The activity of $^{165}Ho_2O_3$ at different bombarding times.

Bombarding time (hour)	2	4.75	6	8
Activity (mCi)	4.1	9.44	10.72	15.9
cooling time (t_c)=50 h, m=1.5 mg, $\varphi=5.7\times10^{13}$ n/cm^2.s				

Table 4- The activity of $^{165}Ho_2O_3$ at different cooling times.

Cooling time (hour)	10	20	30	40	50	60	80
Activity (mCi)	24.91	19.47	13.59	11.87	8.51	5.88	3.5
m=1.5 mg, t_b=2 h, $\varphi=5.7\times10^{13}$ n/cm^2.s							

Discussion

Due to the low purity of ^{164}Dy in indirect neutron activation method for producing ^{166}Ho, the impurity of the product is very high and the purification of ^{166}Ho is costly and time consuming [15]. In comparison with this method, the product of direct neutron activation method, has high purity. This can be shown by performing gamma spectroscopy.

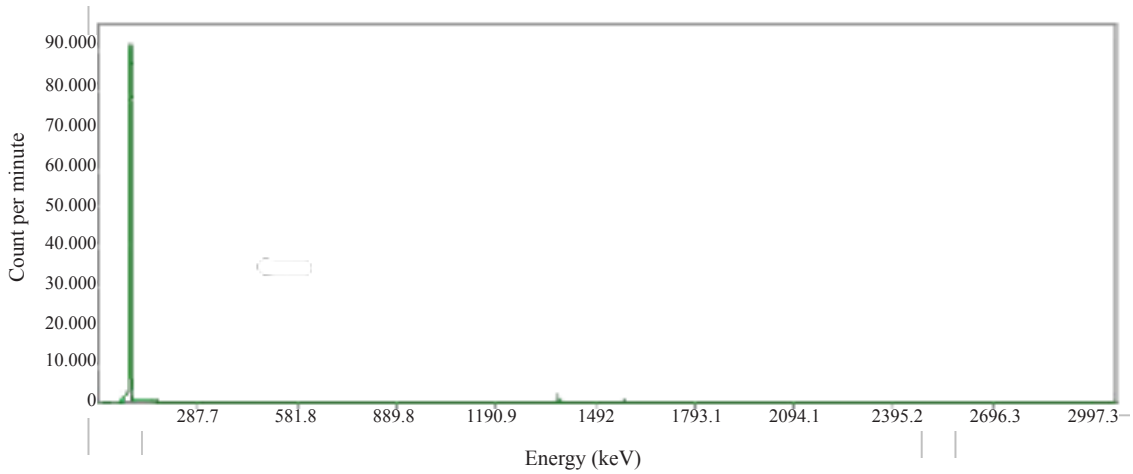

Figure 1- The gamma spectroscopy of ^{166}Ho

As Figure 1 shows the only product of this method which is ^{166}Ho and it is not necessary to perform any purification.

In order to compare the measured activity with that calculated, these two series were plotted in the same coordinate system. Figures 2-5 show such a comparison:

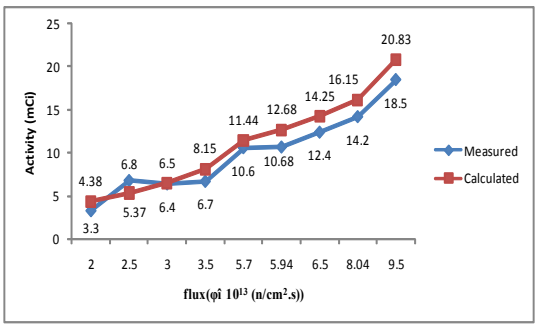

Figure 2- The thermal neutron flux effect in production of ^{166}Ho.

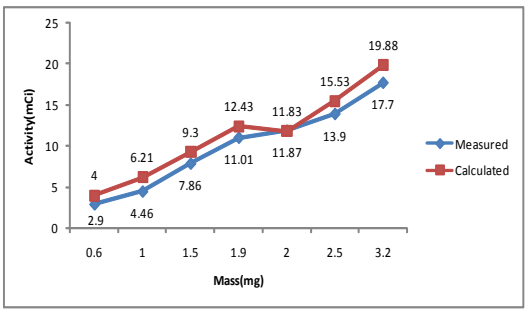

Figure 3- The mass effect in production of ^{166}Ho

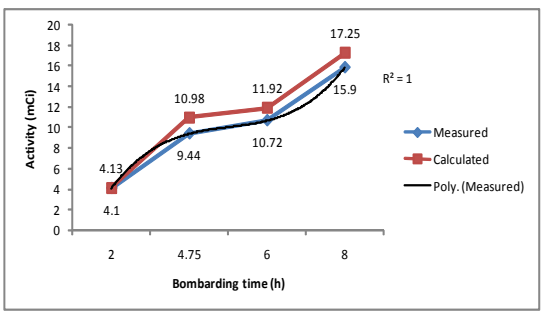

Figure 4- The bombarding time effect in production of ^{166}Ho.

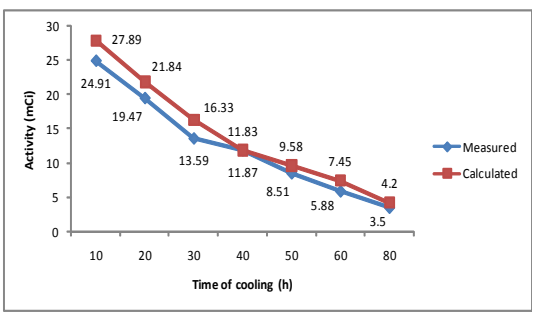

Figure 5- The cooling time effect in production of ^{166}Ho

Flux effect: Figure 2 shows the relationship between the thermal neutron flux and activity of Holmium-166. Comparing the measured and calculated activities one finds a linear relationship between flux and activity, an the other hand, for the flux 5.7×10^{13} n/cm^2.s, minimum difference between

the measured activity and the calculated activity of ^{166}Ho is obtained.

Mass effect: Figure 3 indicates the relationship between the mass of samples with activity of Holmium-166. Comparison of the measured activity and calculated activity indicates a linear relationship between mass and activity. In addition, Minimum difference between measured activity and calculated activity corresponnds to 2 mg of the sample.

Bombarding time effect: The obtained results show the exponential relationship between activity and bombarding time in form of $A \propto (1-e^{-\lambda t_b})$. Using the Mc Lauren form of e^{-x}, this dependency becomes a polynomial in order of 3 and after regression the R-squared value equals one (Figure 3).

Cooling time effect: The results obtained using Equation 1 show the exponential reduction of activity (Figure 4).

As the figures show the activity induced in the target under irradiation will be less than the activity calculated using the above equation, due to several factors, such as:

- Self shielding effect in the target,
- Power variation in the reactor,
- Flux depression due to adjacent samples in the reactor, especially when such samples are high neutron absorbers,
- Burn up of the target material with time, and
- Destruction of the product nucleus due to subsequent neutron capture [10].

Thus a correction factor for neutron activation should be defined as below:

$$KF = \frac{\text{measured activity}}{\text{calculated activity}} \qquad (2)$$

In investigation of each parameter the KF value varies between 84% and 98% which the min value 92% has considered for all of samples. After using this factor for calculated activity the difference between calculated and measured values becomes lower.

Conclusion

According to the obtained results, the best conditions for producing of ^{166}Ho are as follow: m=2 mg, $\varphi=5.7\times10^{13}$ n/cm^2.s, t_b=8 h, t_c=40 h. In this condition, the difference between calculated and measured value become as low as possible and production factors are repeatable.

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