The Calculation of Ho Production by indirect Method and Preparation of Polymeric Microsphere for Radioembolisation

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1. Introduction

The reactor-produced radiolanthanides have been essential for development of therapeutic radiopharmaceuticals because they emit proper beta energies to induce tumor necrosis. Some radiolanthanides are very useful in that they have the ability of simultaneous diagnosis and therapeutic effect. This nuclide with both capacities is called as 'theranostic nuclide'. In general, radiolanthanides can be produced by (n,ɣ) and (n,ɣ)β reaction. Of the two reactions, (n,γ)β reaction-product, shows high specific activity which is important things to affect labeling yield, is suitable for preparing the radiophamaceuticals comprising the antibody or peptide.

Especially, Ho-166($t_{1/2}$ = 26.6hr) shows good candidate for theranostic effect because it has proper ɣ-ray energy(80keV) for diagnostics and enough energy ($E_{\beta(av)}$ = 665.7keV) to effect therapy. Ho-166 can also be produced by direct or indirect method.

Direct method :
$^{165}Ho(n, \gamma)^{166}Ho$
Indirect method :
$^{164}Dy(n, \gamma)^{165}Dy(n, \gamma)^{166}Dy \rightarrow {}^{166}Ho + \beta^-$

Generally, most of the applications have been carried out with direct produced Ho-166 using neutron irradiation with stable Ho-165(natural abundance = 100%). This system contains a large amount of inactive holmium atoms.

^{166}Ho-DOTMP(1,4,7,10-tetra-azocyclododedane-1,4, 7,10-teramethylene-phosphonic acid) for bone seeker and ^{166}Ho-FMHA(ferric hydroxide macro aggregate) for synovectomy are applicable to the direct produced ^{166}Ho.

Another application of ^{166}Ho is applicable for radioembolization for liver cancer or radiosynovectomy by using a microsphere. Several reports reveal radioimolization effects in liver cancer. Vente at al showed the preparation of Ho-166 PLLA-MS(microsphere) and performed the *in vivo* study by using large animals. Recently, Ho-166 microspheres have attracted attention as an alternative of Y-90 microspheres because Ho-166 can be visualized in medical imaging technique besides it has similar beta irradiation of Y-90 that eradicate the tumor. In this Ho-166 microsphere system, Ho-166 is mainly produced by direct production process

Dy-166/Ho-166 pair produced indirection process acts as *in vivo* generator that is a kind of isotope generators *in vivo* system. There are few studies to apply Dy/Ho pair to preparation of Ho-166 microsphere.

In this study, we calculate Dy-166/Ho-166 production process to know the contents of mother nuclide(Dy) which may represent a therapeutic effect in microsphere. First attempt to make Dy/Ho microsphere is using an Aesthefill(REGEN Biotech) consists of poly-lactic acid microparticle. We also present here manufacturing process and polymer coating on the surface of miroparticle.

2. Experiments

2.1 Method, reagents and Instruments

The pathway equation and calculation was performed with math lab. All reagents are used ACS grade without metal impurities and purchased from Sigma Aldrich. Microparticle in this experiment was Aesthefill injection which was provided by REGEN Biotech. Radio nuclide analysis was performed using HPGe gamma spectroscopuy(ORTEC Inc. GEM 20P4-70)

2.2 Reaction pathway for Dy-166/Ho-166 production

The detail routs via double (n,γ) reaction can be shown with 5 type pathways and detail processes show Fig 1.

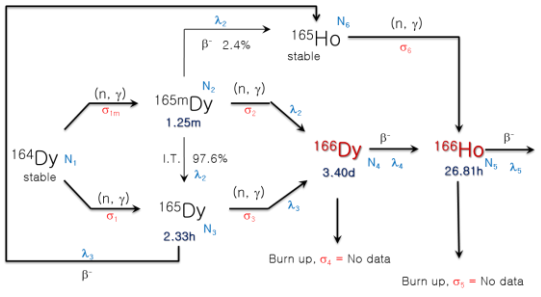

Figure 1 Reaction pathway for production of Dy/Ho-166

The differential equations have been established for each state and calculated with math lab. This equation also can be expressed in 6x6 matrix.

With the condition of thermal neutron flux 5.8E13n/cm^2 at the IP5 irradiation port in HANARO, the maximum production time (^{166}Dy) is when neurons irradiate for 343hrs. The maximum time is depended on the neutron flux. When enriched target(10mg [^{164}Dy]

Dy_2O_3 , 96.7%) is used, the maximum product amount of ^{166}Dy was calculated as 0.21Ci.

2.3 The concept to Dy/Ho Microsphere system

In this experiment, all processes were done with cold nuclide instead of using the radioisotopes. Dy/Ho pair assuming that after neutron irradiation was dissolved with HCl and evaporation was done until eliminating residue HCl. Finally, the volume was adjusted to 1ml with 0.1M HCl. Introducing Dy/Ho pair to the microparticle was performed under reduced pressure. The surface coating on mircrosphere was done by using interfacial reaction between saline and THF saturated with PLA(Poly lactic acid).

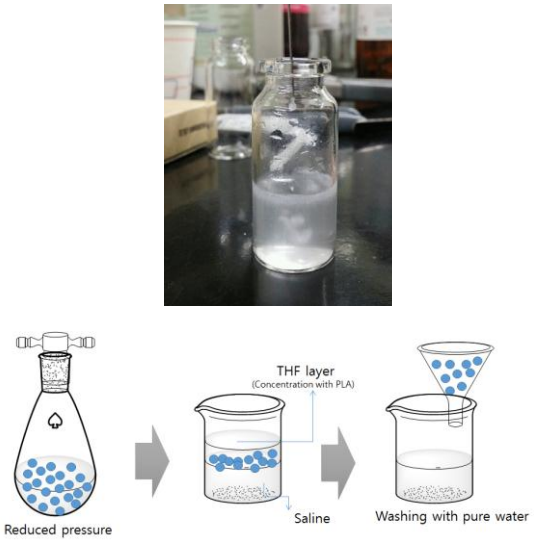

Figure 2. Dy/Ho microsphere

2.4 Pretest using radiolanthanide.

To perform a leak test easier, Lu-177 isotope, instead of Dy/Ho, pair was used for preparing the metal-microparticle. The amount of activity been used was 35 μCi. After washing 5 times with 10 ml, the activity of the residue, metal microparticle, is 1.7μCi. After 24hrs, the water was withdrawn by using 0.2 μm filter from microparticle mixture and checked the activity using HPGe. Little activity was checked.

3. Result and discussion

Some radiolanthanides show the good theranostic effect in that they have proper LET (Linear Energy Transfer) to induce apoptosis for cancer and gamma ray to use as a tracer for cancer diagnosis. Although Ho-166 has been studied for therapeutic purpose since early 1990, production has been limited to direct method. The value of indirect method(double n, γ reaction) is not only it can be obtained with high specific activity holmium, but obtained Dy/Ho pair having the value of *in vivo* generator. In this experiments, the basic calculation of double neutron irradiation process and separation process has already done except doing with hot compounds. To inject Dy/Ho mixture into the microsphere, we first set-up the concepts which are prior metal-administration method and posterior administration method. The latter is shown in this paper. Metal inletting process was done by using alternating between vacuum and pressurization. To prevent the leak of metal ions from metal/microsphere hybrid, surface coating was done by using interfacial reaction between saline and THF contained Poly lactic acid. Surface coating is simply completed just swiveling the vial. All experiments in this study, we just only tested with cold state. Because of interruption of HANARO, we have no choice but to use alternate Lu-177 instead of Dy-166/Ho-166. After HANARO is re-operated, the study of double (n,γ) reaction and preparation of Dy/Ho microsphere will be done.

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