ABSTRACT HAS BEEN MOVED TO A POSTER PRESENTATION AT THE REQUEST OF THE AUTHORS

ACCESS TO REMOTELY CONTROLLED PRODUCTION OF ^{86}Y USING AQUEOUS TARGET MATRICES AS ALTERNATIVE TO SOLID STATE TARGETRY

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Aim

In the recent years other – mostly metallic – radionuclides for PET gained more and more interest. However, for production of these alternative positron emitters the vast majority of them affords solid targets in form of metal foils, oxide or salt pellets [1, 2] which can not be operated by an automated processing. The disadvantages are: 1st, manual cyclotron intervention is practically unsuited for daily routine radionuclide production and 2nd the operating staff receives high radiation doses from the activated target. An alternative could be the irradiation of aqueous salts of target isotopes, allowing automated target operation. The major requirements are: I.) thermal stability of the dissolved compound, II.) avoidance of counter ions containing nuclides which produce long-lived radionuclides under irradiation and III.) high solubility of the salt in the aqueous matrix. Here we report the possibility of this alternative radionuclide production concept by production of ^{86}Y (cf. [3, 4]), generated by irradiation of strontium nitrate dissolved in water.

Method

A "Nitrogen-13 target" liquid target was filled with a $Sr(NO_3)_2$ solution (natural isotopic composition, 81 % of maximum solubility) and irradiated with 16 MeV protons for 60 minutes at 6 µA. After end of bombardment (EOB) the target content was delivered to a 25 mL glass vial containing phosphate buffer pH 7. Then, the target was flushed 5 times by a 25 mM HNO_3 solution collected in the same vial resulting in a total final volume of about 16 mL. Two aliquots (10 and 100 µL) were taken and measured several times applying gamma spectrometry (HPGe detector). Nuclear decay and emission data were taken from Ref. [5].

Results

Produced activities of Y isotopes at EOB were: ^{88}Y (1.2 MBq), ^{87}Y (4.5 MBq), ^{87m}Y (16.8 MBq), ^{86}Y (21.6 MBq), ^{86m}Y (46.7 MBq), ^{85}Y (<3.2 MBq), ^{85m}Y (not detectable), ^{84m}Y (<7.8 MBq). In case the beam upscaling for the described target system would work without physico-chemical complications, PET nuclide ^{86}Y would be produced in activities of more than 4 GBq by proton irradiation of aqueous dissolved $^{86}Sr(NO_3)_2$ applying the parameters: 96.3 % isotopic enrichment of ^{86}Sr, 16 MeV protons, 30 µA beam current, 5 h irradiation time. Radioisotopic activity fraction (among Y radionuclides) will rise from 52 % (EOB) to 88 % (3 h later). Formed ^{13}N, ^{18}F, ^{11}C as well as Sr and Rb radionuclides can be chemically removed during workup of the irradiated target solution for ^{86}Y purification and ^{86}Sr recovery [4]. Since the used target was not tight enough regarding cooling water, we recommend to use the "high yield F-18 target" from GE-MS instead with differently designed loading.

Thus, demonstrated by the reported experiment, an opportunity is opened to produce radionuclides, which in the past were only accessible by solid target production technology.

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Keywords: Targetry, Y-86-Production, Gamma Spectrometry

A SERIES OF HYDRATED HEXAGONAL TUNGSTEN BRONZE SORBENTS FOR USE IN THE SEPARATION OF RADIOMETAL IONS

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There is growing interest in the potential of novel inorganic ion exchangers for radioisotope separation. Hydrated hexagonal tungsten bronze oxides show potential as ion exchangers and for treatment of radioactive waste.[1-3] A series of hydrated molybdenum doped hexagonal tungsten bronze (HTB, Mo_{10}-HTB, Mo_{20}-HTB) were synthesized and characterized by X-ray (XRD) and neutron (NPD) powder diffraction. The mechanism of metal ion binding was investigated under various conditions to probe their potential for radioisotope separation.

The sorbents were synthesized using hydrothermal methods. XRD patterns were collected using a 0.02° step size in the 2*q* range 10° - 80° using a Scintag II diffractometer. NPD patterns were collected on the medium-resolution powder diffractometer (MRPD) at HIFAR (High-Flux Australian Reactor) over 2*q* range 4° - 140° with a step size of 0.1° .[5] The binding affinity (K_d [mL/g]) of the sorbents for a range of radiometal ions (e.g. $^{201}Tl^{+}$, $^{201}Pb^{2+}$, $^{194}Gd^{3+}$, $^{57}Co^{2+}$, $^{141}Ce^{3+}$, $^{141}Ce^{4+}$) was determined under various acid and electrolyte conditions (e.g. 0.1 – 8.0 M HCl, H_2SO_4, HNO_3, 0.1 – 1.0 M, NaCl, $MgCl_2$, $BaCl_2$, KCl, KNO_3, $KHSO_4$). Figure 1 illustrates refine HTB structure.

For all radiotracers the optimum binding was achieved between 0.1 M to 1.0 M acid concentrations, and binding affinity generally decreased as acid concentrations increased. As electrolyte concentration increased, binding of radiotracer ion decreased significantly. Figure 2 illustrates selected data from these studies. Binding of Co^{2+} and Ce^{3+} in the presence of electrolyte varies significantly with type of cation and anion for all sorbents. However there appears to be no systematic relationship between Mo doping of HTB and metal ion binding. All radiotracers showed negligible binding to all sorbents in the presence of $KHSO_4$ and $BaCl_2$, suggesting these electrolytes could be employed for eluting the radiotracer. Collectively XRD, NPD and solution studies suggest that metal ion binding of the sorbents involves both cation exchange and/or redox mechanisms and the choice of anion may also play a significant role. We expect this knowledge will assist in the development of new strategies in sorbent design and synthesis.

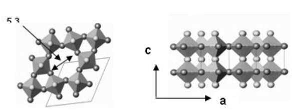

Figure 1. The HTB possesses a rigid tungsten-oxygen framework built up of layers containing corner-shared WO_6 octahedra that are arranged in six membered rings.

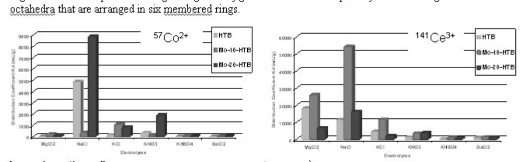

Figure. 2. Effect of electrolyte (0.1 M) on binding of Co^{2+} and Ce^{3+} to HTB, Mo_{10}-HTB and Mo_{20}-HTB.

Keywords: Separation, Inorganic Sorbents,Generator Materials

EXPERIENCE WITH DOUBLE-GRID NIOBIUM [^{18}O]H_2O TARGET FOR HIGH YIELD OF [^{18}F]FLUORIDE PRODUCTION WITH CYCLONE-30

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The 30 MeV cyclotron of Cyclone-30 was installed and in operation at KIRAMS in 2002 from IBA. Since installation, we have routinely produced F-18 on a daily basis and Tl-201, Ga-67 and I-123 on a weekly basis. Recently, we renovated the F-18 targetry system with double-grid target sealed with synthetic plastic (LDPE or HDPE) to increase beam current on target. In this study, we would like to describe the F-18 production yield increasing and pressure development depending on beam current.

The target was fabricated as shown in Fig. 1. The target body material used was titanium and foils were niobium. The total volume of cavity was 1.1 mL. Both open sides of cavity are blocked with 50 μm niobium foils without welding and PE was used for sealing material other than conventional O-ring. Two aluminium grids are placed out side of each foil. Both sides of target were cooled directly by water flow. Grids were adapted to cool foils and prevent their thermal expansion under high pressure during bombardment. The bombarding energy on target was 15 MeV calculated using SRIM 2003 code. Approximately 80% of the incident beam current was bombarded on the target due to aluminium grid screening.

The beam current was increased to 45 μA starting from 5 μA. The pressure developed was plotted in Fig. 2. As shown in Fig. 2., the pressure was gradually developed and no burst until 45 μA. F-18 production yield were 4.0±0.2 Ci (n=10) after 120 min irradiation. This results show that the cooling performance of double-grid niobium target is better compare to conventional foil welded target and this target can be used for routine production of [^{18}F]fluoride in high yield.

Keywords: Fluorine-18, Niobium, Grid Target

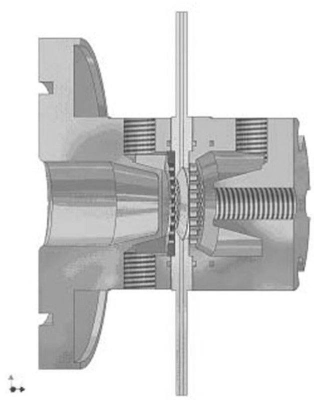

Figure 1. 3D drawing of target assembly(cross section)

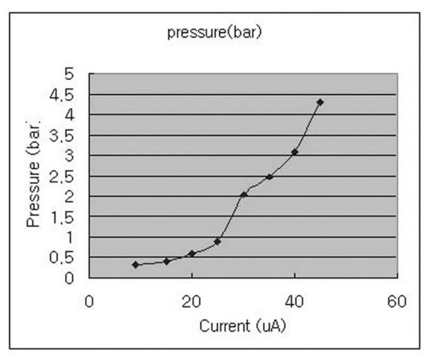

Figure 2. Target pressure development depending on beam current.

PREPARATION OF CYCLOTRON Re-186 AND COMPARISON WITH REACTOR Re-186 AND GENERATOR Re-188 FOR THE LABELING OF BOMBESIN

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The radioisotopes Re-186 and Re-188 have been extensively investigated for various forms of radiotherapy due to their useful and high abundance beta particle emissions, low abundance and imageable gamma rays, and chemical resemblance to technetium. In addition, Re-188 is available in NCA (no carrier added) form from long lived W-188 generators, while Re-186 can produced in large quantities from reactors, albeit not in NCA form. However, NCA Re-186 can be produced by (p,n) reactions on W-186. The purpose of this study was to compare labeling of the peptide bombesin with these various forms of rhenium isotopes.

Cyclotron produced, NCA ^{186}Re was separated radiochemically using high quality methyl ethyl ketone (MEK). The resulting ^{186}Re-MEK was then loaded into a small alumina column in order to purify the resulting ^{186}Re from any remaining ^{186}W. The yield of the separated ^{186}Re was 98%, while the radiochemical purity was found to be >99%. The experimental levels of impurities associated with ^{186}Re at the end of the separation process were found to be 5.7 x 10^{-6} Ci ^{182}Re (0.57%, $t_{1/2}$ = 12.7 h) and 1.283 x 10^{-5} Ci ^{182m}Re (1.28%, $t_{1/2}$ = 2.67 d). The identities of the radionuclides were further confirmed from their decay half-lives using the decay equation. The radionuclidic purity of the separated ^{186}Re was found to be 99.6%. The chemical identity of the product ^{186}Re was determined by performing thin layer chromatography in both saline and acetone; both were found to be >99%. The radiochemical purity was further confirmed by HPLC, showing a peak at 2.85 min corresponding to perrhenate ($^{186}ReO_4^-$). The scale up to the production of multi-curie quantities of NCA ^{186}Re seems feasible due to the rapidity, simplicity, efficiency, and ease of operation, as well as radionuclidic purity, radiochemical purity and recovery of the isolated NCA ^{186}Re as a moderate energy b-particle emitting radionuclide with therapeutic potential.

^{186,188}Re- N_3S-5Ava-BBN(7-14) NH_2 conjugates provide flexibility for designing ^{186,188}Re - labeled conjugates that retain high *in vitro* and *in vivo* specificity targeting of GRP receptor expressing cells. This study showed that the N_3S-5Ava-BBN(7-14) NH_2 could be labeled with ^{186,188}Re following the preconjugation, post-metalation approach. The $^{186,188}Re^{V}O$-N_3S-5Ava-BBN(7-14) NH_2 complexes were found to form stable complexes by the reduction of perrhenate ($Re^{VII}O_4^-$) with stannous chloride at room temperature, as verified by HPLC and stability studies. The radiolabeling yield was found to be >99%. The HPLC chromatograms of ^{186,188}Re-N_3S-BFC complexes revealed two peaks for each conjugate, reflecting the presence of *syn*-and *anti*-isomers, which were not resolvable by the HPLC elution method used. The biodistribution studies showed that the compounds were excreted through the renal and hepatobiliary systems, and demonstrated an average pancreas uptake of 8.15% ID/g. Administration of cold BBN effectively blocked pancreatic uptake and further reflects the high specificity this conjugate has for the GRP receptors.

At low radioactivity levels the effect of radiolysis was not detected. However, scale up may or may not elicit this effect. The pancreatic uptake of the Re-conjugate was found to be 7.6 ± 1.8, 8.3 ± 2.2 and 8.5 ± 1.0 %ID/g for the NCA ^{188}Re-conjugate, carrier-added and NCA ^{186}Re conjugate, respectively, at 1 hour post-injection. The biodistribution studies demonstrated that the CA and NCA ^{186,188}Re-conjugates behaved similarly.

Keywords: Rhenium-186, Bombesin, Radiotherapy

IMPROVEMENT AND QUALITY CONTROL OF $^{62}Zn/^{62}Cu$ GENERATOR BASED ON CATION EXCHANGE METHODS

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Introduction: The generator nuclide ^{62}Cu ($T_{1/2}$ = 9.7 min) is a suitable positron emitter for repeated PET study without a cyclotron. A $^{62}Zn/^{62}Cu$ generator, which employs an anion exchange resin as a generator column [1], has been widely used as a ^{62}Cu source for the synthesis of useful ^{62}Cu-labeled radiopharmaceuticals, such as ^{62}Cu-PTSM [2, 3]. However, this generator had some disadvantages such as high osmotic pressure, low pH. Another type of $^{62}Zn/^{62}Cu$ generator, which uses a strong cation exchange resin as a generator column and glycine (Gly) solution for the elution of ^{62}Cu, has been developed by Fujibayashi et al. [4]. This generator yields ^{62}Cu solutions with high elution efficiency under physiological conditions. However, the ^{62}Cu solution was contaminated by relatively large amount of ^{62}Zn (~2.2%). We found that the ^{62}Cu elution efficiency and ^{62}Zn leakage level were highly improved using the Sep Pak CM cartridge, which is a silica based weak anion exchanger. Therefore, we applied this cartridge to the $^{62}Zn/^{62}Cu$ generator to establish a generator column. We report here the improved $^{62}Zn/^{62}Cu$ generator and its performance.

Methods: ^{62}Zn was produced using natural Cu as the target via the ^{nat}Cu(p, xn) reaction. Irradiation was carried out with 30 MeV proton beam at a beam current of 10 µA for 1 hr. The irradiated Cu foil (2 g) was dissolved in c-HNO_3 (5 mL) then diluted with c-HCl (5mL) and pure H_2O (10 mL). The mixture was passed through an anion exchange column to separate ^{62}Zn from Cu. The column was washed with 2N HCl (20 mL), then 99.5% EtOH (20 mL) to remove Cu and HCl. ^{62}Zn was eluted from the column with H_2O. A $^{62}Zn/^{62}Cu$ generator was prepared by passing the ^{62}Zn solution through a Sep-Pak Plus Accell CM cartridge. The cartridge was washed with pure H_2O (10 mL) and 200 mM Gly (10 mL) to remove trace Cu.

Results and Discussion: The isolated ^{62}Zn solution was charged onto a Sep-Pak Plus CM cartridge with more than 99% efficiency. The generator performance was evaluated with various Gly concentrations. ^{62}Cu was obtained with >96% efficiency using a small volume (1.5 mL) of 200 mM Gly solution. The maximal leakage of ^{62}Zn was observed in the first fraction (ca 0.1%), however, ^{62}Zn breakthrough decreased to less than 0.01% with repeated elution. The breakthrough level of ^{62}Zn was followed up to 50 elutions, however, ^{62}Zn breakthrough was retained at the same level. Radionuclidic purity of the ^{62}Cu solution was greater than 99.9%. Carrier Cu contamination level was less than 1 ppm and other metal contaminants of Zn^{2+}, Co^{2+}, Ni^{2+} were under detection level (<0.05 ppm) on radio ion chromatogram. ^{62}Cu-ATSM was prepared with more than 95% radiochemical purity and specific activity of 480 GBq/µmol using the obtained ^{62}Cu solutions.

Conclusion: The present study showed that the $^{62}Zn/^{62}Cu$ generator using a weak anion exchanger of Sep-Pak CM cartridge had a superior performance compared to that of the previous methods.

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Keywords: 62Zinc-62/Copper-62 Generator, Weak Cation Exchanger, Generator

ACHIEVEING HIGH (APPARENT) SPECIFIC ACTIVITY FORMULATIONS USING FLUOROUS-PHASE CHEMISTRY

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Modern radiotracers are often designed in such a manner that the parent ligand and the radiolabeled compound have similar affinities for the biological target. In many cases it is necessary to remove the large excess of unlabeled ligand that is present after labeling so that it will not interfere with ability of the tracer to bind to the target. Furthermore, for animal imaging studies, residual ligand can have serious consequences in terms of the health of the subject.

The removal of unlabeled ligand for research studies is traditionally done using HPLC. More recently a raft of solid-phase labeling techniques were developed in which a substrate is bound to an insoluble support in such a manner that upon reaction with the radioisotope only the desired compound is released into solution. We have developed a new radiolabeling strategy in which the unlabeled ligand can be easily removed without requiring the use of HPLC or polymer-supported substrates. This new solution phase approach avoids the numerous limitations associated with using solid-supports.

The new strategy, which unlike solid-phase methods allows for purification of all precursors, is based on the use of soluble fluorous-phase supports.[1] Aryl-stannanes containing perfluorooctyl chains were synthesized, iodinated and purified using simple solid-phase extraction procedures. The solid-phase material is designed to retain the starting material and other highly fluorous substrates, while allowing the desired products to be eluted selectively.

The feasibility of the fluorous labeling system was examined using derivatives of benzoic acid that were labeled with ^{125}I. The precursors were synthesized using standard synthetic strategies, purified by preparative HPLC and characterized by normal spectroscopic techniques. A series of oxidants were examined and Iodogen was found to give the highest yields of the desired products.[2] Radiochemical yields of 3- and 4-iodobenzoic acid, for example, were greater than 96% with purity greater than 99%. The range of substrates tagged using the fluorous labeling methodology and its utility in the radiopharmaceutical discovery process will be presented.

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Keywords: Fluorous, Iodine-125, Radiopharmaceutical Production