RADIOANALYTICAL STUDIES ON ORGANICALLY BOUND CADMIUM WITH SPECIAL REFERENCE TO ITS CHEMICAL SPECIATION AND PLANT ACCUMULATION

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Agricultural plants represent an important pathway for the movement of potentially toxic trace elements from soils to human beings. Not only elevated concentrations of metals, but even low level of metals which enter the food chain via plant uptake from soil, constitute potential health hazards in the long term. Among various toxic metals, cadmium is considered an important toxic metal. Significant efforts have been expended during past years to evaluate the transfer of this element from source to plant. In recent years, it is emphasized that consideration of total metal concentration does not provide the real picture of bioaccumulation, since only a fraction of the total metal concentration is available for uptake. It needs information regarding various physical and chemical interactions, which they undergo in natural system. The mobility, bioavailability and toxicity of trace metals depend on their physico-chemical forms. Soil rhizosphere interactions particularly, of low molecular weight organic acids (LMWOAs) released as root exudates, play prominent role in the element acquisition by the plant and highlight metal-Organic acid interactions in soil plant system an area of sustained research.

In continuation of our work on Metal-Organic acid interactions in soil-plant system, the present paper reviews our work on the effect of various organic acids on the uptake and translocation of root absorbed cadmium by maize (*Zea mays*), tomato (*Lycopersicum esculantum*), soybean (*Glycine max*) and wheat (*Triticum vulgare*) plants grown in hydroponic, sand and soil culture. The comparison of uptake pattern of the plants grown in hydroponic, soil and quartz sand (inert matrix) are expected to point out the existence of Metal-Organic acid interactions, modifying the chemical nature of cadmium (chemical speciation) and its subsequent uptake by plants (Plant availability). An increase in Cd uptake from various Cd treatments with increasing supplementation of organic acids may be ascribed to the tendency of Cd to interact with organic ligands resulting into the formation of organically bound Cd, which is soluble, mobile and therefore becomes plant available.

Based on the inherent capability of the combination of techniques like Radiotracer, electrophoresis and ion exchangers (Dowex-50, Dowex-1 and XAD-2), experiments have been conducted to demonstrate the electrochemical nature of organically bound Cd and its quantitative estimation.

THE SOLID PHASE SYNTHESIS OF PEPTIDE RADIOPHARMACEUTICALS

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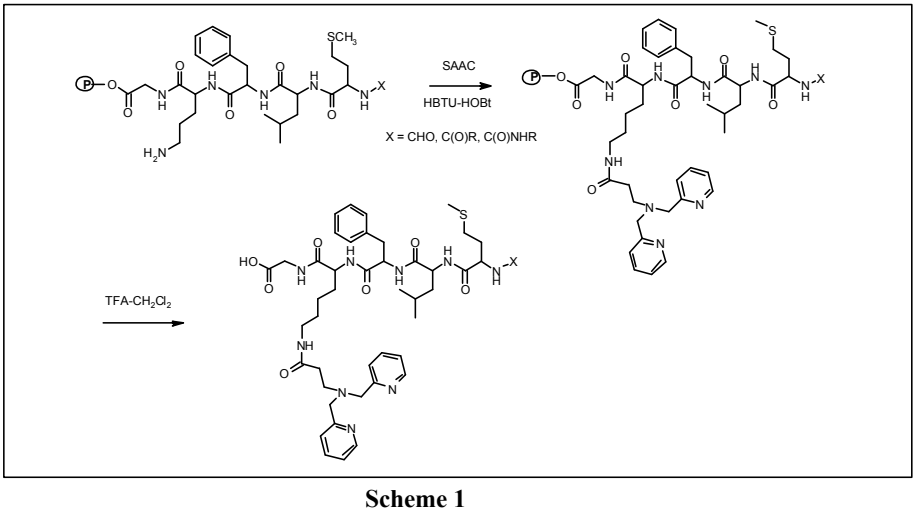
Keywords: Keywords: Drug Discovery, Peptides, Radiopharmaceuticals, Technetium.

Methodologies for developing new radiopharmaceuticals have traditionally followed linear drug discovery techniques. There are only a limited number of examples of where modern drug discovery and screening strategies have been developed to rapidly prepare and identify novel radioimaging and/or radiotherapeutic agents.

We have developed a strategy to prepare parallel arrays of peptide-chelate conjugates. As a model system a library of X-MLFKG conjugates were synthesized on a solid support in such a manner that the nature of the X group, the chelate attached to the epsilon amine of lysine and the length of the spacer groups, among other factors, were readily varied. A particular emphasis was placed on using variants of the recently described single amino acid chelates (SAAC), (bis-2-pyridylmethyl)-aminoalkylcarboxylic acid (**Scheme 1**) and their metal complexes. Their stability and the characteristic IR absorptions make the SAAC-metal complexes ideal synthons for solid phase synthesis.

The products of the library, which were characterized by HPLC and mass spectrometry, were subsequently screened for receptor binding using human leukocytes. The bacterial peptide formyl-MLF was used as a structural lead and positive control ligand. The utility and power of the strategy for developing a model library of chemotactic peptide derived conjugates was demonstrated through the identification of two candidates having high affinity (10-50 nM) for the FPR receptor. These high affinity peptides containing the $Re(CO)_3$ core, appear to be imaging candidates given the B_{max} for this target receptor. The synthetic methodology, characterization data and results of the biological studies will be presented.



Scheme 1

BEAM-LINE ACCESSORIES AND ENHANCEMENTS FOR THE RDS-112 CYCLOTRON

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Keywords: Cyclotron; Target; Beam-line

The RDS-112, manufactured by CTI Cyclotron Systems[1] of Knoxville, TN, USA, is an 11 MeV, self-shielded (H-) cyclotron. These systems were designed for production of PET isotopes at University hospitals and research laboratories, and for radio-pharmaceutical production and distribution by commercial companies. While this particular accelerator has been supplanted by a newer model -- the RDS-111 – there are approximately 40 of the RDS-112's still in use world-wide. The '112 has four independent beam extractors, each of which is associated with a single target position. Three of the targets are mounted on 30 cm long beam-pipe extensions. A fourth target is mounted directly on the wall of the main vacuum tank. Thus, four targets can be maintained in a 'ready' state inside the cyclotron shield and selected for bombardment remotely, without manual intervention. Additional targets can be utilized, but doing so requires opening the cyclotron shield, physically removing a target, and installing a new one.

We have developed a two-position target-switching apparatus which is compatible with standard RDS-112 targets and fits within the space constraints imposed by the cyclotron shield. The switcher allows the user to maintain more than the standard compliment of targets in a ready state without manual intervention. The target-switcher bolts to the main vacuum tank, taking the place of a beam-pipe extension. One switcher allows the user to maintain 5 targets in a ready-to-bombard state; adding a second switcher (replacing a second beam-pipe) would support a total of 6 targets, etc.

As an adjunct to the above, we have also introduced two additional beam-line components which can be installed on a standard RDS-112 to improve overall system utility and reliability:

1) An auxiliary passive focusing magnetic channel which is clamped onto a beam-pipe. The new channel is excited by the external fringe field of the cyclotron magnet, and augments the standard (already-present) internal focusing channel to produce a focusing doublet, providing a tighter beam and thus higher transmission efficiency. Results to date indicate that with the addition of the new magnetic channel element the beam transmission through the 1 cm diameter target entrance (the ratio of beam on target to total extracted beam) improves from the low 60's to approximately 75% for the particular beam-line which, among the four standard beam-lines, normally has the largest beam spot-size.

2) An improved 4-jaw collimator which fits in the standard RDS-112 target collimator frame assembly. Compared with the original 'stock' design, this new collimator provides significantly enhanced power-handling capacity through greater thermal mass, plus improved heat conduction to the water-cooled frame. The new collimator also has a substantially longer bore which, in turn, helps to insure that the beam trajectory is positioned for optimum centering on the target entrance.

[1] Now known as CTI Molecular Imaging, Inc.

STANDARDIZED HIGH SOLID Tl-203, Zn-68 AND Te-124 TARGETS FOR CYCLOTRON PRODUCTION OF DIAGNOSTIC RADIONUCLIDES

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Keywords: Electroplating, Radionuclides, Thallium-203, Zinc-67, Tellurium-124

Cyclotron produced radionuclides are being increasingly utilized in nuclear medicine for both research and routine clinical diagnosis of an extensive variety of diseases. Iodine-123, Thallium-201 and Gallium-67 are enjoying spectacular use as Single Photon Emission Computerized Tomography (SPECT) radionuclides. Iodine-124, which can be used for Positron Emission Tomography (PET) studies as well as radiotherapy, is another radioisotopes, which shows great promise.

The old solid state targets in general were mainly prepared by constant voltage electrolysis from rather intricated plating solutions, which mostly results in dendrite formation and non-uniformed plates due to gases evolution making mechanical rolling (smoothing) post electroplating a general requirement. Such rolling produces non-homogeneous layers. As a result, crater formation and peeling-off of such layers when bombarded with high beam current. This will result in loosing of very expensive enriched materials inside the cyclotron and more importantly, decrease the radionuclide yield, which become major obstacle in meeting the needs of nuclear medicine demands.

Utilizing new electroplating technology in collaboration with the International Atomic Energy Agency taking in consideration composition of plating solution, stirring and the current density range has enable us to produce simultaneously four targets within short period of time, which through microscopic inspection appear to be dense, smooth and homogeneous. In addition, the high quality electroplated Tl-203, Zn-68 and Te-124 targets did not require any post electroplating mechanical smoothing.

The new Tl-203, Zn-68 and Te-124 targets has allowed increasing the proton beam current to 50-100% without damaging or burning the targets. These high currents have led to the increased in radionuclidic yield to nearly acceptable level. Moreover, the new electroplating technique has shown superiority by recovering more than 99.9 % of the enriched material from the depleted solution in a simple manner when compare with the laborious old methods.

THE DESIGN AND CONSTRUCTION OF A NEW PET RADIOPHARMACY

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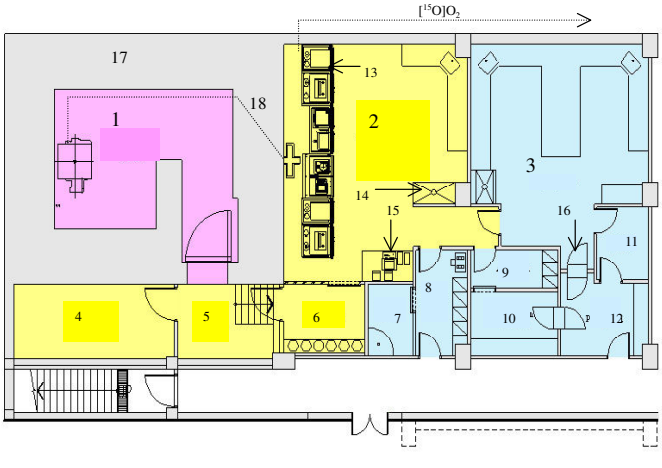
Keywords: PET, cyclotron, radiopharmacy

We at Tzu Chi Hospital have just finished the construction and equipment set-up of a new PET radiopharmaceutical production facility with a total floor area of 307 m^2 (Figure 1). The facility is the first of its kind in Taiwan, and is designed to suit the current regulatory climate in PET drug production. This brief description will provide a good reference for at least four other Taiwanese hospitals (and many more in the Asia Pacific region) which are planning similar facilities. The entire site is underneath a campus driveway, with 240 cm-thick concrete on top of the cyclotron vault. Six radiochemicals ($[^{18}F]HF$, $[^{18}F]F_2$, $[^{13}N]NH_3$, $[^{11}C]CO$, $[^{11}C]CO_2$, and $[^{11}C]HCN$) produced by the GE PETtrace system are fed into 8 air-tight hot cells (Tema Sinergie, Italy) for further procedures. Among the hot cells, two are class 100 isolators that receive radiopharmaceuticals from adjacent cells for dispensing or extra manipulation. These hot cells also equipped with radiation monitoring system and can become isolated in an event of radiation emergency. An additional laminar hood is used for the preparation of reagents, and a class 100 clean room can be used for more demanding tasks. In addition, $[^{15}O]O_2$ is pushed through a 6 cm-thick lead pipe and sent directly into the PET/CT scanning room next to the QC room for the production of $[^{15}O]H_2O$ (not shown on figure). The radiopharmaceuticals, such as FDG, once released from QC, are placed in a pass box and the PET technologist then carries them away for injections.

The entire facility is climate-controlled, including temperature, humidity and pressure controls, and can be isolated in an emergency. Flammable and harmful gas cylinders are placed in cabinets with ventilation. Harmful gas levels, including hydrogen, fluorine, and ammonia, and area radiation levels are measured continuously and can be monitored on the cyclotron control console. Ventilation from each hot cell and the air from the cyclotron vault are filtered before being released into the atmosphere. Waste water from two radioactive waste-only sinks and cooling water from any accidental leakage from cyclotron go to tanks underneath cyclotron power room, and can be released when radiation level meets the criteria. We believe our facility not only meets overall objectives for a PET radiopharmacy, but also is an efficient design.

Figure 1. Floor plan of Tzu Chi radiopharmaceutical production facility



1. Cyclotron room
2. Production room
3. QC room
4. Cyclotron power room
5. Cooling water room
6. Gas room
7. Decontamination room
8. Interlocking entry/change room
9. Ante room
10. Clean room (class 100)
11. Storage
12. Product pick-up area
13. Air-tight/laminar hot cells (class 100)
14. Laminar flow cell
15. Cyclotron control console, area gas and radiation monitors
16. Product pass box
17. 2 m thick concrete wall
18. Cyclotron product lines

CROSS SECTIONS OF PROTON INDUCED REACTIONS ON NITROGEN: DETERMINATION OF ^{14}O AND ^{13}N CONTAMINANTS IN ^{11}C PRODUCTION

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Keywords: excitation function, positron emitters, ^{11}C, ^{13}N, ^{14}O

The radionuclide ^{11}C ($T_{½}$ = 20 min) is widely used for preparing PET radiopharmaceuticals. It is mainly produced via the $^{14}N(p,\alpha)^{11}C$ reaction. As side products ^{14}O ($T_{½}$ = 71 s) and ^{13}N ($T_{½}$ = 10 min) are also formed via the $^{14}N(p,n)$ and $^{14}N(p,d+pn)$ reactions, respectively. These products considerably increase the radioactivity level in the batch. Since the available data for these reactions were rather discrepant, we performed detailed cross section measurements up to 19.2 MeV using N_2 gas and boron nitride (BN) solid targets and, for the $^{14}N(p,d+pn)^{13}N$ reaction, up to 25.6 MeV using BN targets. The beam flux was measured using monitor reactions, and the measurement of radioactive products in the targets and monitor foils was done using HPGe-detectors.

For the $^{14}N(p,n)^{14}O$ reaction, 25 cross section data points were obtained using N_2 targets and additional 6 from BN targets. The energy range covered was from threshold (6.4 MeV) up to 19.2 MeV. The measurement was based on the 2312.7 keV γ-ray of ^{14}O. Our values follow the trend of a few other literature data, but the magnitudes are generally 10 to 20 % lower. The curve through our data points serves as a good base for calculating the yield of ^{14}O.

For the $^{14}N(p,\alpha)^{11}C$ reaction, 14 cross section data points were measured from 11.5 MeV up to 25.6 MeV. In this case a decay of the annihilation peak was followed. The data are in good agreement with the recommended curve published by the IAEA [1]. This proved the reliability of the techniques used. Moreover, there is a lack of reliable data over the energy region of 22 to 26 MeV, thus our measurement extends and strengthens the existing data base. For each of the 14 energy points the cross section was also deduced for the $^{14}N(p,d+pn)^{13}N$ reaction via decay curve analysis of the annihilation peak. The shape of our excitation function curve in the energy range from threshold at 11.4 MeV to 25.6 MeV suggests that two reaction channels are involved: from threshold up to 15 MeV the $^{14}N(p,d)^{13}N$ reaction is dominant and, after 16.5 MeV, the $^{14}N(p,pn)^{13}N$ process becomes important. Our results show a discrepancy with the very limited available data [2], the present cross section values being 20-40 % higher. The cross section values in the range of 19.2 - 25.6 MeV are reported for the first time for this reaction.

From the excitation functions thick target yields were calculated for each reaction for 5 and 30 minute activations. A detailed discussion of the results is given elsewhere [3]. Here it should be mentioned that in routine production of ^{11}C the radioactivity produced will be ~ 82 % ^{11}C and ~ 18 % ^{14}O and ^{13}N at 16 MeV incident proton energy. In case of short irradiations, however, the level of contaminants may amount to 32 % at EOB. Because of the hard 2312.7 keV γ-line of the ^{14}O isotope, special shielding needs to be considered.

It should be mentioned that ^{14}O is also useful on its own, especially in astrophysics and as a PET nuclide [4]. The calculated yield of 370 MBq/μA at a low energy cyclotron (E_p < 18 MeV) could supply 10 GBq activity under practical conditions. Since the available synthesis methods for preparing labeled butanol or water are quick enough, they will allow to replace the ^{15}O with the shorter-lived ^{14}O.

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A COMPACT STACK-MONITOR RADIATION SENSOR FOR PET RADIO-CHEMISTRY LABORATORIES

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Keywords: Stack Monitor; Radiation Detector

Continuous monitoring and recording of radioactive materials released in exhaust-stack effluents is required by most State Radiologic Health Licensing Authorities. We have developed a compact, highly sensitive stack-monitor detector system which is currently being used at a number of PET radio-pharmaceutical laboratories and production facilities.

The active detector element is a 50 mm x 50 mm x 25 mm CsI(Tl) scintillating crystal coupled to a 10 mm x 20 m Si PIN photo-diode + charge-integrating preamplifier. These components are wrapped in white Teflon reflective material, and epoxy-cast inside a 65 mm x 70 mm x 35 mm aluminum enclosure to prevent encroachment of moisture and to shield against ambient light and electromagnetic intererence. The detector element is connected through a short length of coaxial cable to a post-amplifier / signal processor chassis which, in turn, drives the user's data recorder or computer-based data-acquisition system.

This detector module is much smaller than an equivalent scintillation detector using a photo-multiplier tube. Thus, it is much easier to shield the stack-monitor detector against the relatively high-photon-energy ambient radiation found in PET radio-pharmacies -- especially when a cyclotron is also being operated on the premises.

The standard detector module intended for indoor use, sheltered from the elements and from extreme temperatures. Another version of the detector -- currently under development -- incorporates internal temperature regulation to allow operation in harsh environments.

Finally, just as important as the physical properties and performance characteristics of the detector is periodic calibration and quality assurance. We shall present a straightforward 'static' method and procedure for detector calibration which does not require any releaase of radioactive material into the environment.

ASSESSMENT OF A MATHEMATICAL MODEL TO MEASURE MYOCARDIAL GLYCOLYSIS/OXIDATION BY PET AND 1-CARBON-11-GLUCOSE

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Objectives: We have recently developed a compartment model that permits non-invasive quantification of myocardial glucose uptake or utilization (GLU) using positron emission tomography (PET) and glucose labeled with carbon-11 in the one-carbon position (C-11G). However, this model does not estimate the amount of extracted glucose that is further metabolized via glycolysis/oxidation. Accordingly, a new configuration of the original model was evaluated in animal studies.

Methods: Eight dogs were studied over a wide range of GLU (12-1570 nmol/g/min). After a bolus injection of C-11G, PET data were collected for 2 hrs with concomitant arterial (ART) and coronary sinus (CS) blood sampling. ART and CS plasma levels for C-11G and C-11-metabolites (C-11-CO_2 and C-11-lactate) were used to calculate the myocardial uptake of C-11G (C-11Gu-blood), and glycolysis/oxidation (C-11MET-blood). GLU was also calculated from ART and CS glucose blood levels.

For a given study, six model transfer rates representing tracer uptake, back diffusion, phosphorylation, glycogen storage, glycogenolysis and glycolysis/oxidation were estimated from PET arterial (corrected for C-11-matabolites) and myocardial time-activity curves. After assuming true steady-state conditions, the estimated transfer rates were used to calculate myocardial uptake of C-11G (C-11Gu-model) and glycolysis/oxidation (C-11MET-model) for both 2 hrs (2HR) and 1 hr (1HR) of PET data.

Results: (C-11Gu-model) (2HR) correlated well with both GLU and C-11Gu-blood (2HR) ($y = 0.90x + 0.01$, $r = 0.96$, and $y = 0.90 x + 0.02$, $r = 0.97$, respectively, $p < .0001$ for both measurements). Moreover, MET-model (2HR) correlated well with MET-blood (2HR) ($y = 0.93 x + 0.01$, $r = 0.98$, $p<.0001$). In addition, C-11Gu-model (1HR) correlated well with both GLU and C-11Gu-blood (1HR) ($y = 0.86x + 0.01$, $r = 0.96$ and $y = 0.85x + 0.02$, $r = 0.96$, respectively, $p < .0001$ for both measurements). Similarly, MET-model (1HR) correlated well with MET-blood (1HR) ($y = 0.84x +0.02$, $r = 0.96$, $p<.0001$).

Conclusion: The results of this preliminary study demonstrate the feasibility of estimating myocardial glycolysis/oxidation of extracted glucose by PET using C-11G and 1 hr of data. Although, further studies are required to confirm these results, the ability to estimate myocardial glycolysis/oxidation non-invasively would facilitate the investigation of alterations in myocardial substrate metabolism is various cardiac disorders.

A FULLY AUTOMATED SYSTEM FOR PREPARATION OF KRYPTON-81M GENERATORS

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Keywords: krypton-81m, automation

Krypton-81m generators have been used for many years for routine lung function tests using gamma cameras. Krypton-81m (t½ = 13.1 s) results from the decay of rubidium-81 (t½ = 4.58 hours), which can be produced in a medium sized cyclotron by bombardment of natural krypton gas or enriched krypton-82 gas. The parent radioisotope is trapped on an ion exchange support which is encapsulated in a generator system. Ventilation of the generator with air releases the krypton-81m which can be inhaled directly by the patient.

Krypton-81m generators should be produced under GMP conditions under the guidance of the medicines authorities. In order to comply with the increasingly stringent demands of the authorities, to improve issues of radiation protection and to realise a more reliable production, we have constructed a new fully automated system for production of krypton-81m generators. Design of the new system was based on our existing production system, built in the late 1970's. This system enabled automatic loading of rubidium-81, on to small acrylic columns filled with zirconium phosphate ion exchanger. After subsequent flushing with water, the columns were removed from the system and tested for krypton-81m gas output by manually attaching them to a generator system connected to an ion chamber. Manual manipulations with these highly radioactive columns have lead to concerns over the radiation exposure to personnel.

The new system performs the whole loading and testing procedure fully automatically. The system is situated in a small lead cell with 50 mm walls. Additional lead shielding is placed around the bulk rubidium solution (target water flask), which is transferred directly from the cyclotron target through a teflon tube. After loading of the zirconium phosphate column with a predetermined amount of rubidium-81 solution, and flushing with water, a gas output test is performed by passing a flow of air through the column into a plastic container situated in a standard dose calibrator (Capintec, Inc.). Subsequently, the gas flow is stopped and a half-life determination is performed. This test was added in order to provide an identification test prior to release of the generator. Limits for this test comply with the European pharmacoepia (Krypton (^{81m}Kr) Inhalation Gas, p. 2326, 4th Edition, 2002). Each column is then automatically dropped through a small hole in the base of the lead cell in to a lead shielding system. A small lead plug is screwed in place using a cordless electric screwdriver before the entire lead container is sealed in a can and placed in a transport container ready for shipping. Activity levels in the target water flask and in the loaded columns are measured using Geiger-Möller tube detectors. The entire production system is controlled by a PC program written using the control and automation software, Labview (version 6.0, National Instruments Corporation).

The new system is user friendly and enables reliable prodution of krypton-81m generators with minimal radiation exposure to personnel. Production of each generator takes 5-6 min following delivery of rubidium-81 solution from the cyclotron. Full details and experiences with this system will be presented.

Preparation and HPLC Analysis of ^{177}Lu-EDTMP, ^{177}Lu-EDBMP, ^{177}Lu-NTMP

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Keywords: ^{177}Lu-EDTMP, ^{177}Lu-EDBMP, ^{177}Lu-NTMP, Preparation, HPLC Analysis

Body text

Lutetium-177 (^{177}Lu) has excellent physical properties as a potential radio-therapeutical radionuclides, which has both beta particle emissions for therapeutic effect and gamma emissions for imaging. A series of complexes of ^{177}Lu have been synthesized and evaluated using some aminomethylenephosphonate derivatives (EDTMP (ethylenediaminetetramethylene-phosphonate), EDBMP (ethylenediamine- N,N'-bis(methylenephosphonic acid)), NTMP (nitrilo-trimethylenephosphonic acid)), which have the characteristic of the high bone affinity for nuclear diagnosis or therapy. The typical labelling procedure of synthesis of ^{177}Lu-labeled complex has been established. In order to get the structural information of ^{177}Lu complexes obtained, the three ^{177}Lu complexes were analysed with electrophoresis, anion-exchange chromatography and reversed-phase ion-pair chromatography.

The ^{177}Lu-EDTMP, EDBMP, NTMP in over 97% labelling yield can be obtained at room temperature under the following conditions: [EDTMP]>0.25 mg/ml, [Lu_2O_3]=0.04676 mg/ml, pH 5-11, 30 min; [EDBMP]>25 mg/ml, [Lu_2O_3]=0.0731 mg/ml, pH 7-12.5, 30 min; [NTMP]>55 mg/ml, [Lu_2O_3]=0.0731 mg/ml, pH 2-10.5, 30 min. The results of electrophoresis were shown that all complexes were observed to migrate toward the anode, while unreacted lutetium moved toward cathode. Therefore, all of the ^{177}Lu complexes have negative charges and the large shoulders on the side of the peak toward the origin were observed for ^{177}Lu-EDBMP and ^{177}Lu-NTMP.

The unreacted ^{177}Lu and ^{177}Lu-EDTMP could not be separated using the TSK gel SAX column. Several mobile phases were studied for the appropriate retention of ^{177}Lu-EDTMP into TSK gel DEAE-2SW column. The best mobile phase of TSK gel DEAE-2SW was 0.20 M sodium acetate at 1.0 ml/min. The results were shown that a single symmetrical peak was observed for ^{177}Lu-EDTMP and multiple peaks were observed for ^{177}Lu-EDBMP (3 peaks) and ^{177}Lu-NTMP (2 peaks).

In the ion-pair reversed-phase chromatography with TBA, the good separation of ^{177}Lu-complexes was achieved. There were 2 peaks for ^{177}Lu-EDTMP, 3 peaks for ^{177}Lu-EDBMP and 2 peaks for ^{177}Lu-NTMP by the elution with the gradient system of 0.008 M TBA/10% methanol (A) and 0.008 M TBA/ 60% methanol (B) (0 min----0% B, 100% A; 5 min----50% B, 50% A; 30 min---100% B, 0% A) at 1.0 ml/min.

In conclusion, the aminomethylenephosphonate derivatives (EDTMP, EDBMP, NTMP) formed complexes with lutetium easily. As a potential therapeutical bone agent, ^{177}Lu-EDTMP has favourable chemical and physical characteristics.

PRODUCTION OF HIGHLY CONCENTRATED ^{68}GA FROM ^{68}GE /^{68}GA GENERATORS FOR LABELLING OF PEPTIDES AT NANOMOLAR LEVELS

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Keywords: ^{68}Ge/^{68}Ga generators, ^{68}Ga labelling of peptides

^{68}Ga is a short-lived positron emitter (half-life 68 min), which requires no cyclotron since it is available as a generator nuclide. ^{68}Ge/^{68}Ga generators (half-life 280 days) are commercially available as radiochemical. The ^{68}Ga solutions which can be obtained from the generators are usually too acidic and too much diluted for direct labelling procedures. The aim of this work was the development of a system to concentrate the ^{68}Ga solution and to reduce the acidity in order to make it suitable for the labelling of peptides at nanomolar levels.

Depending on the generator-matrix ^{68}Ge/^{68}Ga generators are eluted with 5M or 0.1M hydrochloric acid. The volume of the eluate varies from 4 to 20 millilitres. At hydrochloric acid concentrations > 5.5 molar, Ga^{3+}-ions form the negatively charged $GaCl_4^-$ complex which can be adsorbed quantitatively on very small amounts (< 50 µl) of strong anion-exchange resin at flow rates up to 5 ml/min. Elution of the ^{68}Ga can be achieved with < 100 µl water, which leads to decomposition of the tetrachloro-complex and release of ^{68}Ga as $GaCl_3$. The resulting solution is usually in the order of pH 1.5–2. In order to concentrate ^{68}Ga eluate of 0.1M HCl, the eluate is adjusted to 5.5m HCl with the equivalent volume of concentrated (10M) HCl in order to form the tetrachloro complex which is then treated as described above.
The handling is performed in a semi-automated system with minimal dead-volume in all components.

Two types of generators with activities of 0.4 GBq and 1.2 GBq were tested with this system. Elution yields of the generators were between 50% and 70%. Losses during the concentration process were 10% – max.15%. The ^{68}Ga solutions had a volume of 80µl –100µl at pH-values of 1.5-2. The overall time for the concentration-process was < 5 minutes. Furthermore the concentration-process cleans ^{68}Ga from any eventual ^{68}Ge breakthrough and from other cations which if present will interfere with the labelling of peptides, especially at nanomolar levels. Test-labelling procedures with DOTA-derivatised model-peptides at 20nMol levels gave 70% ± 10% yields.

In conclusion we developed a semi-automated system for concentration and cleaning of ^{68}Ga solutions which can be used successfully for routine labelling of DOTA-derivatised peptides at nanomolar levels.

^{68}GA-LABELLED DOTA-DERIVATISED PEPTID-LIGANDS

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Keywords: ^{68}Ge/^{68}Ga generator, ^{68}Ga-labelling of peptides, DOTA-derivatised peptides

^{68}Ga-labelled peptides form a new class of PET-radiopharmaceuticals, which may be produced independently from a cyclotron. Since the specificity of peptides can be optimized to a very high degree, the synergistic effects of high image resolution and high target specificity may lead to a widely available improvement in diagnostic efficacy. For triple loaded cations DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tretaaceticacid) has proven to be a very suitable chelator, which can be attached to peptide-ligands without loss of specificity. However, beside the challenge of preparation of DOTA-derivatised peptides, the labelling of these compounds at nanomolar concentration levels is difficult. Since the concentration of peptide receptors are usually in the order of nMol/l, higher concentrations of peptide ligands tend to override the specific targeting by unspecific distribution. At these small concentration levels other cations need to be rigorously excluded and all handling should be carried out in small volumes in order to maximize the labelling yield.

The DOTA derivatised peptides Tyr-Octreotide (TOC), Naphtylanilin-Octreotide (NOC) und Bombesin (all at 20 nmol amounts) were labelled with the concentrated eluate of a ^{68}Ge/^{68}Ga generators (< 100 µl) at pH 4,5 within 4 min at 90°C. For the adjustment of the pH we used 400µl 1m HEPES-solution as a non-ionic buffer. Purification was achieved with RP18 mini-cartridges within 10 Min. Quality control was carried out by HPLC. The overall elution-, concentration-, labelling-, and purification-procedure took less than 30 min. and was carried out in an elsewhere described semi-automated system.

The optimal complexation yield for Ga^{3+} in the DOTA-cage is achieved in the pH range of 4.3-5.0. At higher pH Gallium tends to form hydroxy-aquato-complexes, while the complex formation with DOTA becomes small and reversible at low pH-values. Because even Sodium-ions compete with Ga^{3+} for complex formation with DOTA the overall cation level needs to be controlled quite strictly. In order to control the pH we therefore used the non-ionic buffer HEPES, which was adjusted to pH 5.0 with small amounts of HCl. HEPES, although considered to be non-toxic, is removed from the reaction mixture by absorption of the labelled peptide on RP18 mini-cartridges and washing with water, followed by elution of the labelled peptide with ethanol. Ethanol is finally removed by evaporation. The labelling yield for all three peptides was > 80%. The radiochemical purity was >98%.

In conclusion we established a fast and reliable semi-automated procedure for the preparation of ^{68}Ga-labelled DOTA-derivatised peptide-ligands at nanomolar levels. The overall yield was 300 – 350 MBq (EOS) using a 1,2 GBq ^{68}Ge/^{68}Ga generator. We have used these new radiopharmaceuticals in a series of human tumour-diagnostic procedures and have shown the superiority in comparison with classic commercial radiopharmaceuticals such as In-111 labelled somatostatine derivatives (1).

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MOLYBDENUM – ALUMINA INTERACTIONS ASSOCIATED WITH MOLYBDENUM-99 PURIFICATION

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Keywords: Molybdenum, Alumina, Purification

The Australian Nuclear Science and Technology Organisation (ANSTO) has been producing ^{99}Mo from the irradiation of low enriched uranium dioxide pellets (2.2% ^{235}U) for over thirty years. The ANSTO process purifies ^{99}Mo by:- dissolution of targets in nitric acid; primary separation of ^{99}Mo from the uranium and some fission products using an alumina column; volatilisation of some fission products during a boildown process and final purification of ^{99}Mo on a smaller alumina column.

With the advent of the Replacement Research Reactor (RRR), ANSTO plans to modify the process for the production of ^{99}Mo. These modifications involve changing the enrichment and chemical form of the target and ensuring that the chemical purification process is compatible with the new targetry and anticipated scale of production. Design of a low enriched uranium metal foil (~19.75% ^{235}U) target for ^{99}Mo production and results of preliminary irradiations are presented at this meeting by Donlevy *et al.*.

Studies have also been conducted in order to establish if optimisation of ^{99}Mo recovery from the alumina column is possible, and to assess if the existing ^{99}Mo purification process is compatible with the new targets.

This paper focuses on studies undertaken to establish conditions for optimum ^{99}Mo recovery from alumina column separation, in particular investigating the nature of the molybdenum (Mo) species that remains bound to the alumina column after "stripping" by ammonia solution. In solution, Mo rapidly equilibrates to form a mixture of polyoxo- species dependent on pH of the solution, concentration of Mo and the presence of other ions. Moreover, the active sites of an alumina solid phase are expected to interact with the adsorbed species, so that the reason(s) for incomplete desorption of Mo from alumina is not completely understood.

A reference library of polyoxomolybdates has been synthesised according to literature methods. Spectra of the reference compounds, both as pure solids and as polyoxomolybdate anions in aqeuous solution has been obtained. A similar reference library has also been developed for molybdenum adsorbed onto alumina as a function of pH and as a function of Mo concentration. The collection of reference data allows the identification of the molybdenum species on the alumina support during the current process as well as to determine the nature of species retained on the support after stripping. These results may also be used to evaluate the current adsorption mechanisms proposed in the literature and their significance to the 99Mo purification process.

Preliminary Raman results show evidence for the Anderson species on the alumina support The Anderson species, $[Al(OH)_6Mo_6O_{18}]^{3-}$ ($AlMo_6$), is thought to form from complexation of polyoxomolybdate anions with free Al^{3+} ions, resulting from support dissolution. These species may then bind to the bulk alumina. Extended X-ray Absorbtion Fine Structure (EXAFS) studies to yield cordination geometery of molybdenum dispersed on a high quantity of alumina support have also been conducted.

The results of these examinations will be presented and outcomes as they relate to potential improvement of ^{99}Mo recovery from alumina, discussed.

WATER SUPPRESSED ^{1}H NMR AS A RELEASE TEST: ADDRESSING THE CHEMICAL PURITY OF PET RADIOPHARMACUETICALS.

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Keywords: Water suppressed ^{1}H NMR, FDG, Altanserin, Quality Control

Introduction: NMR spectroscopy is often associated with long acquisition time and extended data analysis sessions and thus often neglected for routine analysis of the short lived PET radiopharmaceuticals. Proton NMR can however often be used as a quick and general method to resolve the chemical purity of many injection-ready radiopharmaceuticals, giving adequate attention to the optimization of analytical conditions and sequence set-up. We have previously reported(1) how non-edited, simple FID spectroscopy can document both the precise composition of ethanol containing injectables and the absence of other (more toxic) residual organic solvents. We have now extended the method to include water suppression in a two-step analytical process.

Methods and results: The samples are first 10 fold diluted with D_2O and spiked with 500 ppm tetramethylsilane (TMS). Then the overall sensitivity and sample composition relative to both water and TMS signal is established in a few, non-solvent suppressed and totally relaxed acquisitions. Subsequently, a simple narrow band presaturation water suppression sequence is applied for 128 acquisitions, followed by automatic filtering, Fourier transformation, phase and baseline correction, peak detection and signal integration. The overall acquisition and analysis time is less than 15 minutes on a Varian 400 MHz NMR spectrometer.

Given the absence of other gross constituents with strong proton signals (such as ethanol), organic residuals can be identified and quantified, first relative to the TMS, and secondly directly to the water signal, down to the 10 ppm level, thus constraining the chemical purity of the product within limits acceptable by modern toxicological standards.
Results obtained from the routine analysis of ^{18}F-Altanserin and ^{18}F-FDG will be presented.

Conclusion: Proton NMR can be a method of first choice in the arsenal of release tests for PET radiopharmaceuticals. In terms of total analysis time, repeatability and sensitivity, especially in the presence of multiple constituents, it can compare favourably with the time-honoured method of gas chromatography. In comparison to the latter method, the results are unequivocal in the identification of the occasional impurity.

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QUANTIFICATION OF ^{48}V PRODUCED BY THE PROTON ACTIVATION OF THE TITANIUM ENTRANCE FOIL DURING $^{16}O(p,a)^{13}N$ REACTION

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Keywords: ^{13}N-ammonia, ^{13}N-nitrite, ^{13}N-nitrate, Vanadium-48

Nitrogen-13 labelled ammonia has been used as tracer to measure myocardial perfusion and myocardial ischemia. Gatley and Shea (1) have used DeVarda=s alloy reduction of ^{13}N-labelled $NO_3^!$ and $NO_2^!$ formed during the proton irradiation of pure water to produce radiochemically and radionuclidically pure [^{13}N]NH_3. We now report the separation of radiochemical and radionuclidic impurities, using a Sep-Pak®, from [^{13}N]NH_3 and the quantification of ^{48}V produced due to the proton activation of titanium entrance foil during $^{16}O(p,a)^{13}N$ reaction.

A Siemens 11 MeV negative ion cyclotron (RDS-112) was used to produce ^{13}N by the proton irradiation of 0.1 mM solution of aqueous ethanol at 400 psig. The aluminum target chamber with an internal beam strike volume of 2.8 mL was fitted with 0.001" aluminum vacuum window and a 0.001" titanium target window. After the irradiation, the target was emptied at a constant flow rate of 2 mL per min. for 3 minute. The effluent from the target was passed through first an anion Sep-Pak® (Waters Accell Plus QMA) that had been pre-treated with 4 mL of ethanol followed by 10 mL sterile water and a 0.2 µM Millipore filter before it was collected in a sterile vial.

Radiochemical purity of $^{13}NH_3$ was checked using radio-HPLC. A Ge(Li) detector (Canberra Model 7229) operating at 2000 V and the Aptec PCMCA/WIN programme for data analysis and a high purity germanium detector (Oxford Instruments Inc.) with relative efficiency 18.7% and FWHM of 1.72 KeV at 1.33 MeV were used to monitor the radionuclidic purity of ^{13}N-ammonia.

After a typical production run (20 µA, 3 min.), 800 100 MBq of ^{13}N was produced at 3 min. from EOB. Radio-HPLC of the effluent from the target (before Sep-Pak purification) showed only one peak at the void volume ($^{13}NH_4^+$) and no additional peaks due to $^{13}NO_2^!$ and $^{13}NO_3^!$ were observed. ?-Ray spectrum of the effluent from the target showed photo peaks at 511, 983 and 1312 KeV. Decay curve analysis of photo peak (511 KeV) confirmed the presence of ^{13}N as the major component and ^{18}F and ^{48}V as minor components. The amount of ^{48}V (2.78 KBq) on the Sep-Pak® was determined by integrating the 983 KeV photo peak.

Statistically significant quantities of ^{48}V were eluted from ^{13}N target with titanium window. Radiochemical and radionuclidic contaminants were increased with increased irradiation dose (: Ahr). Irradiation of the target with low dose ((: Ahr) produce sufficient quantities of ^{13}N, for repeat deliveries of $^{13}NH_3$ for cardiac PET studies, without any radiochemical impurities such as ^{13}N-labelled nitrite and nitrate (2). Use of Havar instead of titanium as target window would also eliminate the formation of ^{48}V without affecting the yield of ^{13}N.

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^{211}At PRODUCTION AND RECOVERY

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Aim: ^{211}At is the only alpha-emitting isotope which can be introduced into organic molecular structures by covalent chemical binding and possesses superior decay characteristics for therapeutic applications when compared with other alpha emitters. However, its production requires a minimum of 27,5 MeV alpha-particles, which are relatively rarely available. In view of the revival of alpha-therapy approaches, a production system for ^{211}At has been set up at the MHH cyclotron (MC-35). The first aim of this project was to establish a target- and work-up-system for the reliable production of several ten MBq-quantities of ^{211}At for animal- and cell-research.

Methods: An aluminum-target-system holds a 1.3cm diameter Bi-disc of 0,25 mm thickness. The disk is pressed onto the aluminum backing with 2 tons/cm^2. The front is covered with a 12,5 µm Al foil, cooled by a He-jet which is separated from the vacuum by a 25µm Ti foil. Starting with 27.5 MeV alpha-particles the resulting target-energy is 25 MeV. This relatively low energy is chosen to avoid any contamination with ^{210}At and ^{210}Po (1) in the first experimental period. A beam current of 10µA for 15 min (9 mCoulomb) yields 16.4 MBq ^{211}At theoretically. Astatine is recovered from the target by a dry distillation technique, using various gases as a transport support-medium. The small all-quartz distillation-apparatus is heated up to 900°C. Astatine is recovered in a small coolable vessel containing various trapping media. Distillation and trapping can be monitored with small radioactivity monitors. The whole system fits in a cubical 0.5m glove box.

Parameter Testing: Continuous monitoring of the distillation process allowed to optimize the heating rate, the transport support-medium and its flow-rate. Various trapping solutions were tested for their efficiency.

Results: Different beam dispersion in the target seems to influence the release and distillation of Astatine from the molten Bismuth-target. Two different release patterns were observed. The first pattern resulted in a first slow, than rapid release, while the other pattern was a continuous release of Astatine. Both patterns were independent of the transport support-medium, (air (oxidizing) or nitrogen (inert)), with no significant difference in the overall release rate of Astatine. The flow rate had a significant effect on the over all distillation time as well as on the trapping efficiency in the trapping medium. These effects were reversely related. The overall distillation time needed for optimal recovery was 30 min. The overall recovery of Astatine in the trapping vessel using pure water was ca. 80%, with 20% usually escaping the trapping solution. Only under strongly reducing trapping conditions (e.g. 0.1M Sulphite) the recovery was quantitative. Under these conditions Astatide was characterized quantitatively by HPLC. All of the Astatine, escaping under less reducing conditions could be trapped in activated charcoal. The current production conditions yield 13 MBq ^{211}At in aqueous solution.

First experiments with genetically modified cell-cultures and animals carrying genetically modified tumour cells have demonstrated that Astatine is actively transported by the iodide symporter system (2). Incorporation into organic precursors for labelling of peptides was achieved in 60% to 80% yields by destannylation, dediazotation and direct labelling of aniline derivatives.

Conclusion: A target and a recovery system have been installed which yields about 13 MBq ^{211}At with only 15 min. beam-time (9 mCoulomb). Production yield improvements of a factor of 3 are anticipated after installation of a new target-system which is in the testing phase currently and which is capable of withstanding higher beam currents. Using a slightly higher energy and considerably longer irradiation times we anticipate to raise the production to several hundred MBq.

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ROBOTIC SYNTHESIS OF 3'-DEOXY-3'-[^{18}F]FLUOROTHYMIDINE ([^{18}F]FLT)

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[^{18}F]FLT, PET, Robotics

At the Massachussets General Hospital an Anatech RB-86 robot supplemented with workstations is used routinely for automated production of ^{18}F and ^{11}C radiopharmaceuticals for human use. [^{18}F]FLT is a promising PET radiopharmaceutical for the imaging of tumor proliferation. By using the available workstations and modifying existing programs we synthesized [^{18}F]FLT based on the method developed by Machulla et al (1). ^{18}F in $H_2{}^{18}O$ (1 ml) was added to a 5 ml reactivial containing 5.5 mg of potassium carbonate and 15 mg of Kryptofix 2.2.2. The solution was then dried by evaporation under nitrogen at 130°C. Four portions of 1 ml acetonitrile were added and each in turn evaporated. To the vial was added 0.5 ml of dimethylsulfoxide (DMSO) and solution was heated at 170°C for 5 minutes. A solution of 5'-O-(4,4'-dimethoxytriphenylmethyl)-2,3-anhydrothymidine in DMSO (25 mg/0.5 ml) was added and heated for 10 minutes at 170°C. The solution was cooled to 100°C, 1N HCl (0.35 ml) was added and the solution was heated for 3 minutes. A solution of sodium acetate (1.5 ml, 0.5 M) was added. The solution was passed through a neutral Al SEP-PAK and eluted with 2 ml of water. The eluate was purified by semipreperative HPLC on a Luna C-18 column (10 um, 25cm x 1cm, Phenomenex) eluted with 17% methanol in water at a flow rate of 8 ml/min. [^{18}F] FLT was eluted after 7 min. The collected solution was evaporated to dryness. To the dried product 9 ml of 0.9% sodium chloride in water for injection was added and the solution was passed through a 0.22 um membrane filter (Millex GV). The synthesis time was 90 min and the radiochemical yield was 6.4±0.42 % (EOS). Radiochemical purity, chemical purity and specific activity were determined by HPLC. A Beckman system gold model 126 pump, diode array detector model 168 and radioisotope detector model 171 were used to perform HPLC. A C-18 Prodigy column 25 cmx4.6 mm (Phenomenex) was eluted with acetonitrile: water, 10:90 at a flow rate of 2.5 ml/min. UV detection wavelength was 254 nm. [^{18}F]FLT eluted after 5.5 min. The radiochemical purity was 97.20±2.9 %. The specific activity was 2157±927 mCi/ mol (EOS). The UV trace showed the FLT peak, the solvent peak and a minor unidentifiable peak that eluted after the solvent peak. [^{18}F] FLT was identified by co-injecting with a standard. The amounts of methanol and acetonitrile in the formulations were found to be 11.14±4.1 g/ml and < 3.9 g/ml respectively. The formulations were tested for Kryptofix by TLC. No Kryptofix was found (detection level 0.1 mg/ml). From our experience we conclude that reliable automated synthesis of [^{18}F]FLT for clinical use can be done using the robot and the workstations.

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ELECTROLYTIC PURIFICATION OF [^{18}O]WATER

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Keywords: [^{18}O]water, purification, electrolysis

Irradiated [^{18}O]water contains organic impurities which originate from the preconditioned anion exchange cartridge used for the separation of [^{18}F]fluoride. The organic contaminants consist mostly of ethanol, acetonitrile and soluble resin oligomers which are usually oxidized in refluxing aqueous $KMnO_4$. Purification of this solution by conventional destillation results in [^{18}O]water that can be used again for [^{18}F]fluoride production. However, GC analysis of the destillate shows significant amounts of ethanol and acetonitrile. To remove these contaminants a crystal water method has recently been suggested.[1] Here we describe an alternative procedure for the purification of used [^{18}O]water using an electrolysis method.

Impure [^{18}O]water is transferred into the hydrolysis cell by means of a syringe module (Figure 1). The supply of water into the cell is controlled by electronic level indicators. The volume of the chamber can be kept at 4 ml. Electrolysis is performed at 1.9V and 0.6 A and [^{18}O]oxygen and hydrogen are transferred separately into a fuel cell or as shown here into a flow-through reactor where the elements are catalytically recombined.

More than 99.9% of the solvent impurities were removed by a single purification pass. Thus, ethanol concentration of 5 mg/ml (Fig. 2) was reduced to 4 µg/ml (Fig. 3). The capacity of this device amounted to 2 ml/d and the recovery of [^{18}O]water was >98 %.

In conclusion, electrolysis in combination with fuel cell technology represents an effective improvement on the destillation method used for [^{18}O]water purification.

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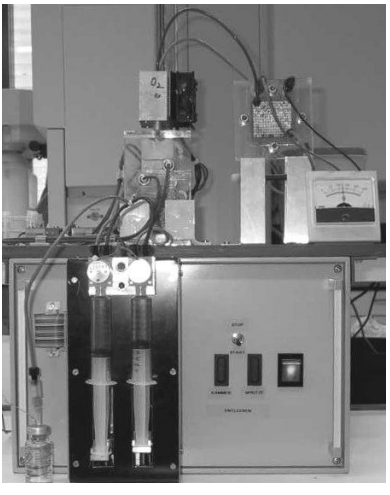

Fig. 1: Electrolysis device

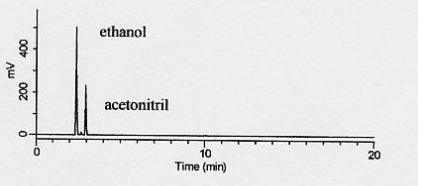

Fig. 2: [^{18}O]water before hydrolysis

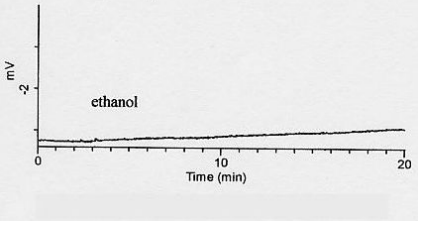

Fig. 3: [^{18}O]water after hydrolysis

VIRTUAL VOLUME REACTORS: A GENERAL APPROACH TO MULTIPHASE MICROSCALE REACTIONS FOR PET TRACERS

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Keywords: Virtual-volume reactor, captive-solvent

Captive solvent reactions (1) are accomplished in a small volume of liquid retained on or in a solid phase. This allows reliable mass transfer between gas and liquid phases while keeping the volume small. Subsequent reactions (2) or chromatography are simplified, especially if the reaction can be done in the column's injection loop (3). However such linear reactors may require careful attention to proper application of the liquid phase to the solid phase, and to the flow rate of the gas phase for satisfactory yields.

In contrast, virtual volume reactors employ a small volume of solvent dispersed on a relatively large volume of highly polished 0.8 mm zirconia balls. This approach has the robust advantages of conventional microreactors. For example 40 microliters of a reaction mixture are applied to 4 g (1.5 mL volume) zirconia balls in a 3 mL conical glass flask. The flask has a 1.0 mm neck and a septum seal. All access is by way of a 20 gage needle. This allows easy introduction and removal of liquids or gases while keeping the balls confined. A strong vortical motion is applied to the reactor by an AC/DC motor via an eccentric torlon coupling. Power to the motor is pulsed at about 1 Hz. This results in very strong mixing shear and mass transfer between phases. Rapid heating and cooling are accomplished by a heat gun and a carbon dioxide jet. Evaporations are substantially accelerated by the very high rates of shear and heat and mass transfer. The zirconia balls are very hard and resistant to contamination but do not scratch the reactor.

The first application has been the synthesis of [^{11}C]cyclohexanecarbonyl chloride, the precursor to WAY 100635. The concept appears to be adaptable to a microwave cavity. Virtual volume reactors should be especially useful for [^{18}F]fluoride exchange reactions where it is sometimes desirable to evaporate high-boiling solvents.

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AUTOMATED SEPARATION, PURIFICATION AND LABELING SYSTEMS FOR COPPER ISOTOPES (^{60}Cu, ^{61}Cu AND ^{64}Cu)

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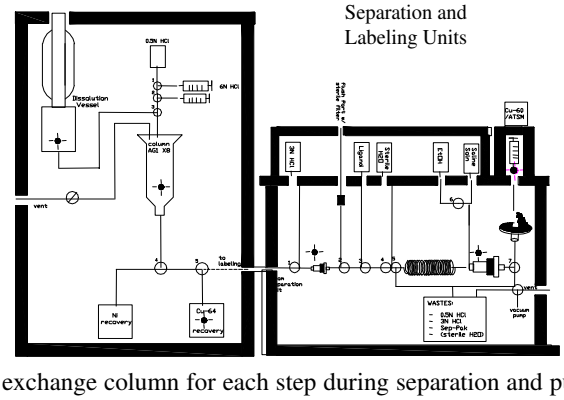
Keywords: Automation, Separation, Labeling, Copper, ATSM

Copper-64 is routinely produced at our facility in large quantities for collaborative research and service projects. An automated processing system is essential for the handling of large batches of radioactivity. As previously described (1), enriched ^{64}Ni is plated onto a gold disk and irradiated to produce ^{64}Cu via the ^{64}Ni(p,n)^{64}Cu nuclear reaction. The resulting irradiated material is then dissolved in acid. The acidic solution is loaded onto an ion exchange column for separation of ^{64}Ni for recycling and purification of ^{64}Cu for further use. In addition, ^{60}Cu-diacetyl-bis(N^4-methylthiosemicarbazone) (ATSM) has been approved at WUSM for several human investigations studies of tumor hypoxia in cancer (2). Thus, an automated labeling unit is also necessary to make this compound in an efficient and reliable manner to reduce absorbed radiation doses to personnel. (3,4)

Preliminary trials with commercially available accessories have shown excellent results in the separation and purification of Cu isotopes. Labeling results confirmed the feasibility of using a simple reaction line for this synthesis eliminating a number of steps. Thus, a self-contained and self-shielded unit is under construction to allow the remote separation and purification of Cu isotopes. Another self-contained and self-shielded unit is under construction to permit the labeling of the copper isotope with ATSM. These two automated units are designed to be used independently or in-line. The use of disposable accessories (syringes, tubing, 3-way stopcock valves) minimizes preparation time and eliminates cleaning procedures. New accessories and reagents will be placed in the units before each process. The activity transfer between different steps will be monitored with radioactivity detectors placed at strategic locations. Rotary actuators will be used to operate the stopcock valves. Linear motion actuators will be used with syringes to dispense reagents into the ion exchange column for each step during separation and purification. Vacuum will be used to transfer the reagents at different steps for the labeling. The final sterile labeled compound will be collected into a syringe for patient administration. A graphical user interface and a PC will be used to operate each unit and for keeping records. This work is supported by the NCI grant R24 CA86307.



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A NEW $^{72}Se/^{72}As$ ISOTOPE GENERATOR BASED ON SOLID PHASE EXTRACTION

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Keywords: ^{72}Se, ^{72}As, generator

The isotope generator $^{72}Se/^{72}As$ consists of the long-lived mother, ^{72}Se ($T_{1/2}$ = 8.5 d, 100% e) and the short-lived daughter, ^{72}As ($T_{1/2}$ = 26 h, 88% ß$^+$). Different radiochemical no-carrier-added (nca) generator procedures have been discussed [1,2,3]. However, in each case complexity, separation quality or operating expense is too high to be handy for any practical application. Therefore the development of a new and more reliable $^{72}Se/^{72}As$ isotope generator was necessary prior to the development of a new ^{72}As-labelling chemistry.

The ^{72}Se was produced at the Forschungszentrum Juelich via (^3He,3n)-reaction on natural germanium at a beam current of 5 µA for 12 h, giving a yield of 5 mCi. To simulate the behaviour of ^{72}Se, ^{75}Se was used in some cases, which was produced via (n,?)-reaction at the nuclear research reactor at the HMI Berlin.

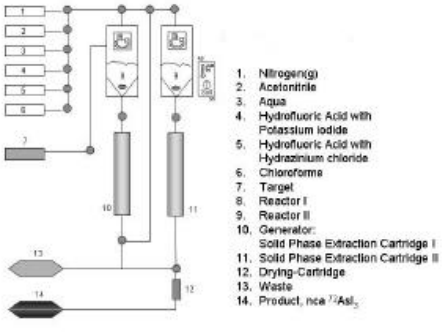

Fig.1: Scheme of an $^{72}Se/^{72}As$-Isotope generator based on solid phase extraction

100 mg of irradiated natural germanium are dissolved in 5 ml HF_{conc} and 500 µl HNO_{3conc} at T = 50°C within 3 hours. Aliqouts of 100 µl were added to 5 mg of hydrazine dihydrochloride in 900 µl HF_{conc} and the mixture was stirred for 30 min. An ENV-solid phase extraction cartridge was preconditioned with 5 ml of MeOH, 5 ml H_2O and 5 ml HF_{conc}. The mixture was transferred to the cartridge. $^{72}Se^{(0)}$ is fixed to the solid phase, while macroscopic Ge is eluted with the mobile phase as $[GeF_6]^{2-}$. The produced daughter ^{72}As can be eluted subsequently using 2 ml $HF_{conc.}$. To this eluent, 10 mg KI are added, forming nca $^{72}AsI_3$ and the mixture is stirred for 10 min at room temperature. Then it is transferred to a second solid phase extraction cartridge where $^{72}AsI_3$ is fixed to the solid phase. It is eluted with chloroforme and dried with $CaCl_2$.

The concept of the new generator is based on the reduction of in-target produced ^{72}Se to $^{72}Se^{(0)}$ with hydrazine dihydrochloride. This metallic nca selenium can be fixed up to 99% by a standard solid phase extraction system based on a polystyrol matrix. The daughter is eluted by $HF_{conc.}$ giving > 50% yield already in the first 2 ml. The amount of selenium remaining in the product fraction is less than 0.01%. For subsquent radiopharmaceutical synthesis the arsenic has to be transformed in a suitable chemical form. With KI, nca $^{72}AsI_3$ is formed quantitatively. As this compound is soluble in organic solvent, the product fraction of the new generator can be used directly for organic synthesis.

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SYNTHESIS OF 1,3-DIMERCAPTOPROPYL ARSENIC-BOC-CYSTEINE-O-BZL AND DIPHENYL ARSENIC-BOC-CYSTEINE-O-BZL AND FIRST RADIOARSENIC LABELLING

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Keywords: arsenic, cysteine, mercaptanes

The long-lived ^{72}As represents an interesting positron emitter with potential for PET. The amino acid cysteine was chosen as a first molecule, suitable for labelling with no-carrier-added (nca) arsenic isotopes as delivered from a new ^{72}Se/^{72}As-generator-system, based on solid-phase extraction [1]. Because cysteine is SH-functionalized, a high affinity to arsenic and formation of stable covalent bonds is expected. The amino acid cysteine is involved in peptide biosynthesis. The protein synthesis rate increases in tumor growth, and hence, it should be possible to use either ^{72}As-cystein for the diagnosis of tumor processes with long biological half-lives via PET, or ^{77}As-cystein for therapeutic treatment of some tumor sorts.

To simulate the behaviour of nca ^{72}As, nca ^{77}As was used as produced at the TRIGA reactor at the University of Mainz via following reaction: ^{nat}Ge(n,)^{77}Ge($T_{1/2}$=11.3 h) $\xrightarrow{-}$ ^{77}As($T_{1/2}$=38.8 h)

S-1,3-dimercaptopropylarsenic-N-tert-butyloxycarbonyl cysteine benzyl ester:

100 mg (0.32 mmol) 1,3-dimercaptopropylarsenic iodide are synthesized according to [1] and without further purification 95 mg (0.32 mmol) of N-tert-butyloxycarbonyl cysteine benzyl ester and 25 µl pyridine (0.32 mmol) are added at T= 0°C. The mixture is stirred for 30 min at room temperature and is then washed with water to give a pale yellow liquid after filtration. Solvent is removed in vacuo giving 47 mg of oily product (30% yield).

Diphenylarsenic-N-tert-butyloxycarbonyl cysteine benzyl ester:

330 mg (0.94 mmol) diphenylarsenic iodide are synthesized according to [1] and without further purification 293 mg (0.94 mmol) N-tert-butyloxycarbonyl cysteine benzyl ester and 75 µl pyridine are added at T=0°C. The mixture is stirred vigorously for 10 min and is then allowed to warm up to room temperature. Ice is added and after phase separation, the organic layer is 3 times extracted with water. Solvent is removed in vacuo giving 340.5 mg of oily product (69% yield).

The products could be analyzed via FD-MS, ^{1}H- and ^{13}C-NMR. The synthesis of nca dimercapto arsenic and diphenyl arsenic cysteines was performed according to the procedures above, using nca $^{77}AsI_3$ giving radiochemical yields more then 60 % each.

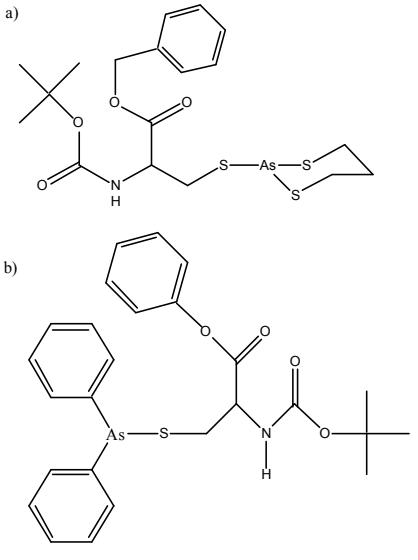

Fig.1:
a) S-1,3dimercaptopropylarsenic-N-tert-butyloxycarbonylcysteine benzyl ester
b) Diphenylarsenic-N-tert-butyloxycarbonyl cysteine benzyl ester

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UPGRADING AN OLD TWO REACTOR POT FDG BOX TO A VERSATILE F-18 RADIOLABELLING MODULE

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Keywords: PET, F-18, radiolabelling, automation

Modern F-18 synthesis modules for FDG production use a single reactor pot for radiolabelling and solid phase hydrolysis for deprotection. This limits their usefulness for other syntheses requiring multiple steps and subsequent processing. Alternative commercial-built modules are extremely expensive. We choose to modify and upgrade an old two pot FDG box from IBA (1990 model) into a versatile and reliable F-18 synthesis module that can also be used for labelling [^{18}F]A-85380, [^{18}F]MPPF and [^{18}F]FLT.

The new module includes additional features such as integrated QMA SepPak recovery of the enriched water, isolation of the intermediate compound, automatic loading and injection on a 2mL loop, HPLC column purification, radioactive peak collection and formulation of the final product. Two shielded PIN diode radiation detectors have also been added in front of each reactor pot to monitor the activity during the synthesis. The control of the module has been achieved by connecting a dedicated PLC (Siemens S7 CPU224), interfaced to a PC using Siemens "ProTool/Pro" visualisation software (Figure 1& 2). A versatile program has been developed, which allows easy changes to synthesis parameters, as well as displaying real-time trends of radiation levels and UV absorbance with full archiving of trend data. In addition, an estimation of the activity of the radiopharmaceutical produced and its specific activity is displayed.

For production of [^{18}F]A-85380, the labelling reaction was done at 150^{o}C in DMSO for 5mins in reactor 2, followed by trapping of the crude product on a C-18 SepPak cartridge located between the two pots. After flushing the product into reactor 1 and hydrolyzing, the mixture was injected into the preparative HPLC column for automated purification and reformulation. The total synthesis time was 55 minutes, with a radiochemical yield of ~30% decay corrected. [^{18}F]MPPF was synthesized in 90 minutes with a radiochemical yield of ~15% decay corrected.

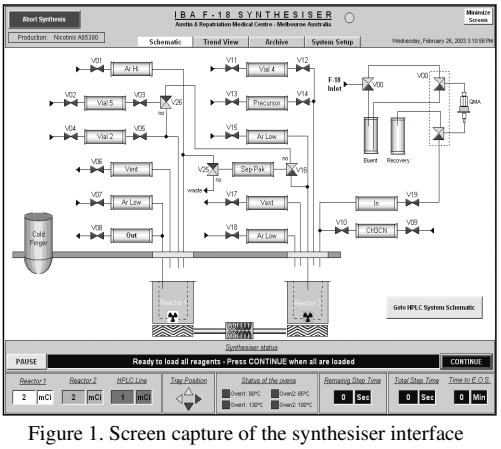

Figure 1. Screen capture of the synthesiser interface

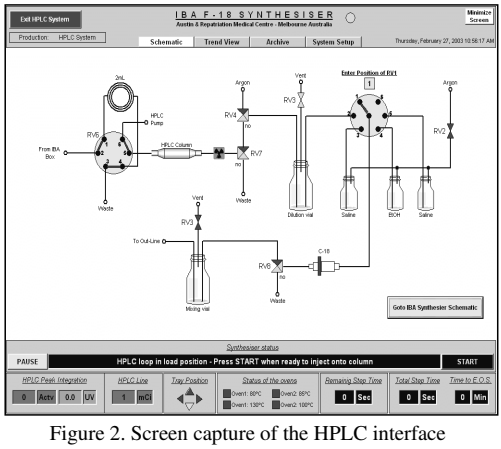

Figure 2. Screen capture of the HPLC interface

QUALITY CONTROL OF PET RADIOPHARMACEUTICALS USING HPLC COUPLED WITH AN ELECTROCHEMICAL DETECTOR

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Keywords: Quality control, PET radiopharmaceuticals, HPLC, electrochemical detection

In the quality control of PET radiopharmaceuticals, it is often required to examine radiochemical purity, specific radioactivity and chemical impurities in the product before human administration, to assure the quality and the safety. The method with HPLC/UV, which is most commonly used for this purpose, dose not always provide sufficient sensitivity for all compounds. One of the alternatives is the method with LC/MS. However, this method is very complicated, too time-consuming and requires quite expensive equipment, therefore, it is not suitable for the routine analysis of the short-lived PET radiopharmaceuticals.

On the other hand, the electrochemical detection method, which is widely accepted as a sensitive and selective technique for the analysis of electro-active substances, has been used for sensitive detection of FDG and ClDG in the ^{18}F-FDG injection. We intended to evaluate this technique from the view point of simplicity, sensitivity and selectivity in the quality control of PET radiopharmaceuticals. In this study, we have analysed [^{11}C]MP4A and [^{11}C]MP4P, useful radiopharmaceuticals for measuring acetylcholinesterase activity, as model compounds since the compounds and their desmethyl substrates have no available UV absorbance and have aliphatic amine structure.

The chromatographic separation was performed using a C18 column (Waters Xterra RP 18, 3.9mm i.d.×150mm) and acetonitrile/20mM phosphate buffer (0/100 for [^{11}C]MP4A, 15/85 for [^{11}C]MP4P) as the mobile phase with a flow rate of 1.0ml/min. The eluent from the column was directly introduced into an electrochemical detector (Waters 464) equipped with a glassy carbon single electrode and an Ag/AgCl reference electrode. The influences of pH value (2.0, 4.7, 7.0 and 9.3) of the buffer solution and the applied potential (0.8-1.5V) on the detector response were examined. Standard solutions of the authentic samples were prepared in acetonitrile and diluted with water to the desired concentration of 0.02, 0.05, 0.1, 0.2, 0.5, 1, 2 and 5μg/ml. [^{11}C]MP4A and [^{11}C]MP4P were synthesized with [^{11}C]CH_3I according to the method commonly used at NIRS.

In an acidic buffer solution, the detector response was observed to reduce. The baseline noise level was increased with increasing pH or potential. Therefore, we applied pH 7.0 for a buffer solution and +1.15V for an applied oxidation potential, in which comparably high responses and low backgrounds were obtained for each compounds. For both radiopharmaceuticals, product and desmethyl substrate could be successfully detected in high sensitivity. At the same time, triethylamine could be also detected, which is used in the synthetic process of these radiopharmaceuticals. Other possible contaminants such as DMF and acetonitrile in the final product gave no peak under the present conditions, even at the concentration of 100μg/ml. The calibration curves were linear over the range of 4-100ng/20μl injection volume with the correlation coefficients more than 0.996. The detection limits for desmethyl substrates (secondary amines) and products (tertiary amines) were ng and sub-ng levels for a 20μl injection volume, respectively. The precisions were within 8% (R.S.D.) for 10ng/20μl injection volume. These results showed that the method with an electrochemical detector might be a powerful tool for the analysis of PET radiopharmaceuticals with no appropriate UV absorption. Moreover, it will be expected to be applied for the analysis of other PET radiopharmaceuticals with electro-active groups, such as aliphatic amines, phenols and aromatic amines.

Practical Production of ^{61}Cu via ^{nat}Co (a , 2n) ^{61}Cu reaction and Preparation of ^{61}Cu-ATSM

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Keywords: ^{61}Cu, ^{nat}Co (, 2n) ^{61}Cu reaction, separation, ^{61}Cu-ATSM

Recent developments in the field of labeling of radiopharmaceuticals with copper radionuclides such as Cu-ATSM, which is used for imaging of blood flow, tumor and hypoxia, has also increased the interest of new production methods of positron emitting copper radionuclide. Several useful positron emitters such as ^{60}Cu ($^{+}$; 92%, EC; 8%, $T_{1/2}$ = 23.2 min), ^{61}Cu ($^{+}$; 61%, EC; 39%, $T_{1/2}$ = 3.41 h), ^{62}Cu ($^{+}$; 97%, EC; 3%, $T_{1/2}$ = 9.7 min), ^{64}Cu ($^{+}$; 18%, EC; 45%, $^{-}$; 37%, $T_{1/2}$ = 12.7 h) are available among the Cu nuclides. Since ^{61}Cu has relatively longer half-life, that enable to trace the relatively longer biological processes, its effective production ways become very important. Until now the production of ^{61}Cu has been performed using enriched ^{60,61,62}Ni target with low energy proton beam, however, utilization of expensive enrich Ni target requires the recovery of the irradiated Ni target. In our previous study, effective production methods have been investigated, utilizing the cost effective natural Co as target via ^{nat}Co (, 2n) reaction instead of expensive enriched Ni target (1). In the present study we produced ^{61}Cu with practical amount for PET study using ^{nat}Co (, 2n) ^{61}Cu reaction, and applied the ^{61}Cu solution to the preparation of ^{61}Cu-ATSM.

Alpha beam (40 MeV, 5-10 A) was irradiated on Co target (thickness 165 m, corresponding energy range: 39-18 MeV) for 1 hr. The irradiated Co target was dissolved in c-HNO_3. Serially connected two columns, packed with cation exchange resin (AG50W-X8) and anion exchange resin (AG1-X8), respectively, were used for the separation ^{61}Cu from Co. The dissolved solution was passed through the first cation exchange resin column to remove NO_3^-. The cation exchange resin was washed with pure H_2O to remove NO_3^- until eluate became almost neutral. Metal ions (^{61}Cu and Co) absorbed on cation exchange resin were eluted with 4N-HCl, and then transferred on the second anion exchange resin column preconditioned by 4N-HCl. After elution of target Co with 4N-HCl, ^{61}Cu was eluted from the column with 0.1N HCl to collect into a vial. The ^{61}Cu solution was concentrated to dryness to remove excess HCl, and then pure H_2O was added. ^{61}Cu-ATSM was prepared by adding glycine buffer (100 L, 0.1 mol/L) and H_2ATSM (0.1 mg/100 L DMSO) to the ^{61}Cu solution. Radiochemical purity of ^{61}Cu-ATSM was determined on reversed phase HPLC column using MeCN/H_2O (1/1) as mobile phase.

Removal of NO_3^- from the dissolved target solution by cation exchange resin was necessary, since NO_3^-, which has stronger affinity to anion exchange resin and interfere the formation of $CuCl_4^-$ complex, disturbed the separation of ^{61}Cu and Co on anion exchange resin. Separation of ^{61}Cu from Co on the anion exchange resin with 4N HCl (Cu; $CuCl_4^-$, Co; Co^{2+}) gave ^{61}Cu solution with a recovery efficiency of 80% and Co contaminant of ca. 10 ppm. In practical, about 40 mCi of ^{61}Cu could be obtained within 1.5hr from EOB by irradiation of 40 MeV beam at 10 A for 60 min. Major nuclidic impurities were ^{60}Cu and ^{62}Cu and the nuclidic purity was about 96% (after 1.25hr. EOS). ^{61}Cu-ATSM was prepared simply by adding H_2ATSM solution in ^{61}Cu solution after pH adjustment. The radiochemical purity of ^{61}Cu-ATSM was greater than 99%. In conclusion, we could successfully isolate ^{61}Cu form irradiated Co target using ion exchange resin, and the isolated ^{61}Cu was applicable to preparation of ^{61}Cu-ATSM.

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PRODUCTION OF ^{34m}Cl, A NEW PET RADIONUCLIDE

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Keywords: ^{34m}Cl, [^{34m}Cl]ClDG, Positron Emitter, Production, Purification

The short-lived radionuclides, such as ^{18}F, ^{75,76,77}Br, ^{123,124}I belonging to the halogen group have been widely used in the field of the nuclear medicine. However, no radionuclide of the chlorine has been used in this field, in spite of its importance. Chlorine-34m (half-life = 32.0 min, β^+ 57%) is an only candidate for this purpose since other radionuclides of chlorine are not suitable under the criteria of half-life and decay characteristics for the PET study. Although many nuclear reactions, such as ^{35}Cl(n,2n), ^{35}Cl(p,pn), ^{34}S(p,n), ^{34}S(d,2n) and ^{32}S(α,d) are known for the production of ^{34m}Cl (1,2), quite limited number of reports on ^{34m}Cl production have been published, specially on the high specific activity ^{34m}Cl production, probably due to the difficulty of separating the generated ^{34m}Cl from the irradiated target material (3, 4). In the present study, we have intended to investigate a new production method, as well as a remote production system for the practical production of no carrier added ^{34m}Cl.

Chlorine-34m was produced by the nuclear reactions of ^{32}S(α,pn)^{34m}Cl and ^{34}S(p,n)^{34m}Cl. Yellow crystals of sulfur was melted in a specially designed target chamber and irradiated by the alpha beam (50 MeV, 1 μA) or by the proton beam (18 MeV, 1 μA) from the NIRS cyclotron. After irradiation, the sulfur target was melted again at 130 °C and then pure hot water was introduced into the target chamber at a flow rate of 1 mL/min, using a specially designed production system. ^{34m}Cl$^-$ could be successfully extracted from the irradiated sulfur, condensed on a Sep-Pak light(Waters, Accell QMA) and eluted with 0.3 mL of 66 mM K_2CO_3 solution. The radionuclidic and radiochemical purity of ^{34m}Cl was confirmed with a pure Ge detector and a radio-ionchromatograph, respectively. 2-deoxy-2-[^{34m}Cl]chloro-D-glucose ([^{34m}Cl]ClDG) could be synthesized with the obtained ^{34m}Cl$^-$, according to the same procedure as [^{18}F]FDG synthesis.

By the irradiation of 50 MeV α particles at 1 μA for 30 minutes on the thick sulfur target, 9 mCi (330 MBq) of ^{34m}Cl$^-$ could be obtained at the nuclidic purity of >99% and the radiochemical purity of >99% within 30 minutes from EOB. All the procedures could be performed remotely with the apparatus developed in this study. [^{34m}Cl]ClDG with the radiochemical purity of >98 % was synthesized at the radiochemical yield of ~70 % (decay corrected). It might be possible to produce more than 100 mCi (3.7 GBq, EOB) of ^{34m}Cl by irradiating the sulfur target with higher energy of α particles (e.g. 70 MeV) at higher beam current (e.g. 10 μA) for longer time (e.g. 1 hour). Improvement of the target chamber and the production system and optimization of the separation condition of ^{34m}Cl from the irradiated sulfur target are currently under way.

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^{68}Ge/^{68}Ga GENERATOR CHARACTERISATION

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Keywords: ^{68}Ga, ^{68}Ge/^{68}Ga generator

^{68}Ga is employed in preparation of radiopharmaceuticals for diagnostic imaging by PET. Production procedures, radiation and chemistry characteristics of ^{68}Ga are very attractive for clinical use. First of all it is generator produced and does not require a cyclotron and, moreover, 271day half-life of ^{68}Ge provides a relatively long generator life span. The ^{68}Ga decays to 89% by positron emission of 2.92 MeV energy. Its 68 min physical half-life is enough to follow many biochemical processes without unnecessary radiation. From the chemistry point of view, ^{68}Ga has oxidation state of +III and forms stable complexes with chelators containing oxygen and nitrogen donor atoms. ^{68}Ga-radiopharmaceuticals have been used for brain, renal, bone, blood pool, lung, vascular pool, tumor imaging (1).

Some of the restrictions for wider use of ^{68}Ga have been the chemical form in which it is obtained from the generator and the contamination of the generator eluate with the generator column material. The advantage of the generator (2) characterized in this work is two-fold. First, ^{68}Ga is eluted in an ionic form allowing diverse and fast further chemistry. Second, the ^{68}Ge is loaded onto a titanium dioxide, so that the column material leach is not toxic, in contrast to tin or aluminum dioxide used in other generators. The characterization of the generator is essential for better understanding and efficient utilization of ^{68}Ga chemistry and further production of radiopharmaceuticals.

Elution efficiency, radionuclide purity, chemical purity, biological purity were measured and analyzed on the base of Inductively Coupled Plasma Atomic Emission Spectroscopy (ICP-AES) analysis, well-counter radioactivity measurements, energy spectrum as well as microbiology analysis. The elution efficiency was defined simply as the proportion of the ^{68}Ga present in the system that was separated during the elution process, usually expressed as a percentage. In practice, the amount of ^{68}Ga separated was less than the amount predicted by theory. The elution optimization was done considering contamination with competing metal ions. Calculations (based on measured data) of theoretical specific activity and specific activities considering isotopic dilution and pseudo carriers indicated that the largest contribution into the specific activity drop came from the pseudo carriers. A method for the generator eluate purification from the competing metal ions is under development.

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A COMPETITIVE METHOD FOR SIMULTANEOUS DEUTERON-CYCLOTRON PRODUCTION OF *NO-CARRIER-ADDED* COPPER-64 AND GALLIUM-67,66 FOR APPLICATIONS IN PET RADIODIAGNOSTIC AND METABOLIC THERAPY OF TUMOURS.

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Keywords: Radioisotope production, Copper-64, Gallium-67,66, PET, Metabolic Therapy.

Copper-64 is a radionuclide suitable for labelling of radiopharmaceuticals for PET imaging, as well as metabolic radiotherapy of tumours. Among the several methods for production of *no carrier added* ^{64}Cu (^{61}Cu), we investigated the deuteron irradiation on Zn targets via (d,αxn) plus (d,2pxn) nuclear reactions in the energy range up to 19 MeV with *simultaneous* production of ^{66}Ga, ^{67}Ga and ^{65}Zn, ^{69m}Zn. A few data were present in the literature about these reactions.

The irradiations were carried out with the SCANDITRONIX MC40 cyclotron of the Joint Research Centre-Ispra (Italy) of the European Union, whose maximum energy is 38 MeV for both proton and α beams and up to 19 MeV for deuteron beams.

Some thick targets (total absorption) were irradiated at the maximum energy available, to determine the thick target yield. Moreover, the excitation functions in the energy range 3-19 MeV have been experimentally determined. A comparison will be made between the integrated thin-target excitation function and Thick-Target yield, that was previously measured. In collaboration with ENEA of Bologna, Italy and the LLNL, USA it was possible to compare the experimental cross sections with the ones calculated with some computer codes and in particular with the results obtained with PENELOPE code and a new version of ALICE program.

Finally, a very effective and fast radiochemical separation of No Carrier Added ^{64}Cu (^{61}Cu) from both ^{67}Ga (^{66}Ga) radionuclides and ^{65,69m}Zn (labelled Zn target) was pointed out and will be resumed in some details, together with the necessary and related quality controls tests.

At 19 MeV energy, an appreciable experimental thick-target yield of 8560 ± 240 MBq C^{-1} at the End Of an Instantaneous Bombardment (EOIB), corresponding exactly to 833 ± 23 μCi $\mu A^{-1}h^{-1}$ is achieved. After a 25.4 hours irradiation (2 half-lives of ^{64}Cu) with a beam current of 100 μA of a thick Zn target of natural isotopic composition, could be produced theoretically 42 GBq (1.1 Ci) of ^{64}Cu at the EOB. With present radiochemical yield of 80 %, the practical activity achievable for NCA ^{64}Cu (containing the shorter-lived ^{61}Cu) would be 34 GBq (0.9 Ci) that is an activity suitable for both PET imaging and radioimminotherapy of several patients. After a proper cooling-time, a ^{64}Cu with a radionuclidic purity suitable for high-resolution PET imaging is achievable.

As a relevant by-product of ^{64}Cu, we must remember ^{67}Ga, whose applications in nuclear medicine radiodiagnostic are known since a long time.

MONITORING OF GAS TARGET PRESSURE AND INTEGRITY DURING RADIONUCLIDE PRODUCTION

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Keywords: radionuclide production, gas target, pressure monitoring, enriched isotopes

Gaseous target materials are used extensively in radionuclide production for PET and SPECT. Typically, a metallic target chamber, equipped with a thin entrance foil, is filled with a target material to an elevated pressure of up to several MPa. During irradiation with a charged particle beam, a rise in pressure is seen. This pressure increase is proportional to the intensity of the particle beam. The absolute increase depends on the particular gas (target material), the initial filling pressure, the energy range of the particles absorbed in the gas, the temperature and the target chamber design.

The possibility of a foil rupture during irradiation is present in case of malfunction of the equipment or if the beam intensity and consequent heat absorption exceeds limits of the entrance foil capabilities. The foil rupture has consequences on radiation safety, schedules of pharmaceutical production and if expensive enriched materials are used, also on economics. We have now developed a system where the target pressure is monitored during irradiation, and the actual pressure seen is compared with a calculated pressure based on initial parameters. In case of deviation between these two values appropriate action can then be taken.

The monitoring equipment consists of pressure, beam intensity and temperature transducers connected to a programmable logic controller with data collecting capabilities, and a suitable user interface. For a particular irradiation procedure data on pressure, beam intensity and temperature are collected.

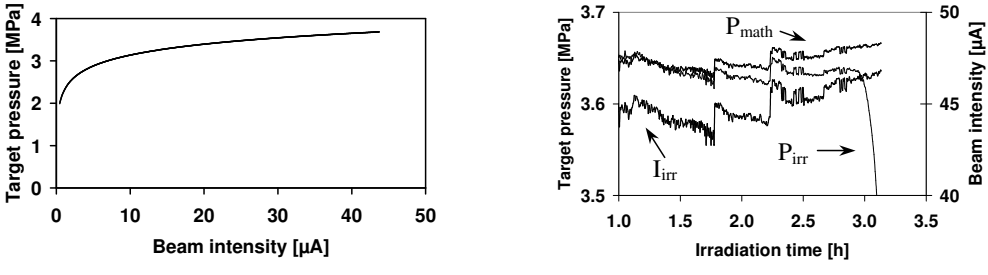

Figure 1. Example of Xenon gas target pressure as a function of beam intensity in left panel. On the right a demonstration of the development of a pinhole leak in the target foil with subsequent deviation of P_{irr} from P_{math}.

The function $P_{irr}=A(I_{irr})^{\delta}$ can then be fitted to pressure-beam intensity relations, see fig. 1 left panel. The factor A is linearly related to the target filling pressure by the relation $A=B*P_{fill} - C$. The exponent δ was found to be approximately constant for a particular gas. We then get a relation between the target filling pressure and the beam intensity that predicts the pressure during irradiation:

$$P_{math}(I_{irr}) = (B* P_{fill} - C)*(I_{irr})^{\delta}$$

where B, C and δ are constants. Taking into account the effect of a varying target cooling, the equation takes a form, where T_{fill} is the initial temperature of the target chamber before irradiation and T_{irr} is the chamber temperature during irradiation.

$$P_{math}(T_{irr},I_{irr}) = (B* (T_{irr}/T_{fill})*P_{fill} - C)*(I_{irr})^{\delta}$$

A RAPID IMPROVED METHOD FOR GAMMA-SPECTROMETRY DETERMINATION OF THALLIUM-202 IMPURITIES, IN [THALLIUM-201]LABELLED RADIOPHARMACEUTICALS

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Keywords: Radiopharmaceutical, ^{202}Tl impurities, Gamma spectrometry, Radioisotopic impurity

Since the late 1970s, the readily commercially available univalent cation [^{201}Tl]Tl(I) ($t_{1/2}$ = 72.912 h) in "very high specific activity" No Carrier Added form, is a radionuclide of widespread diffusion, for use in infarction radiodiagnostic and several other cardiovascular and even cerebral Nuclear Medicine investigations by -camera and SPECT; even if its *whole body excretion half-life* can be considered as long 10 days.

In despite of the cyclotron production method and the efficiency of radiochemical processing adopted, the long–lived *radioisotopic* impurity ^{202}Tl ($t_{1/2}$ = 12.23 d) is always present in [^{201}Tl]labelled radiopharmaceuticals (RP) together with other short-living impurities like, ^{200}Tl ($t_{1/2}$ = 26.1 h.), ^{199}Tl ($t_{1/2}$ = 7.42 h) and ^{198m,g}Tl. It is evident that in despite of the lower yield, the medium-lived ^{202}Tl constitutes the main problem from radioisotopic contamination point of view. In our experimental measurements during about 20 years, on a *wide range of commercial samples* of [^{201}Tl]thallium(I) chloride RP for i.v. injection, we found variable amounts of the various radionuclidic impurities,in particular, most of them contain ^{202}Tl, in percentages varying from 0.5 up to 5 %, *before the expiration* time of the RP itself. Apart the dose to the patients, medical and paramedical personnel and total population, the medium-lived ^{202}Tl emits some -rays of medium energies (**439.56**, 520.13 and 959.7 keV), which contribute in increasing the S/N ratio and the degradation of -camera and SPECT images contrast. Moreover, the emission intensities *ratio* of 439.56 (^{202}Tl) to 167.43 keV (^{201}Tl) -peaks of 0.941/ 0.10 = **9.41**, is a further disadvantage from this point of view. Conversely, ^{200}Tl content is negligible in most cases due to its the short half-life and normally does not constitute a problem from both dosimetric and rad-waste point of views.

We point out a rapid determination of ^{202}Tl impurity, carried out by HPGe gamma spectrometry of ^{201}Tl samples, shielded by a 5 mm thick envelope of lead. DT correction errors, random pile-ups, Compton continuum and X-ray fluorescence background, are very efficiently avoided and suppressed. Some experimental results on DT correction performances of a commercial HPGe counting cha in are reported.

The method described allows determination of ^{202}Tl impurities in ^{201}Tl radiopharmaceuticals with high sensitivity and short counting times. The same method could be applied in Nuclear Medicine routine, to determine ^{201}Tl radioisotopic pur ity by means of a ionization chamber dose calibrator (like Capintec CRC-30, USA). The same method is effective in order to evaluate contamination by the short-lived ^{200}Tl, even if in practical cases this radionuclide is present in negligible amounts.

DESIGN AND IMPLEMENTATION OF A RADIOLIGAND LABORATORY AT COLUMBIA UNIVERSITY IN NEW YORK CITY

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During the mid 90's the PET community was in the process of preparing to meet the requirements of new FDA regulations concerning the manufacturing of [F-18]FDG. Columbia University's PET Center in New York City was no exception, the program was preparing to start up an expanded research program while still accommodating a commercial distribution center operated by PETNET Pharmaceuticals. The routine production of short-lived radioligands has challenged not only the chemist but also the regulatory community. Basic concepts of cGMPs that are applied to the large pharmaceutical industry became highly challenging when applied to PET drug production. In order to manufacture/compound radioligands the USP published its own guidelines, while the FDA was developing newer guidelines devoted specifically to short lived radioligands. These series of documents, as well as the guidelines being produced by the European community and the International Committee on Harmonization, became an important resource when considering the design of a new facility. The design of a facility to prepare PET radiopharmaceuticals must also consider environmental regulations requiring minimal release of radioactivity into the environment. Performing research in our licensed radiopharmacy was deemed to be too difficult and the decision was made to set-up a research laboratory adjacent to the existing cyclotron and radiopharmacy. Columbia University made available an 800 sq ft space to construct a research facility. In designing the laboratory the area was divided into four main zones. The first area is a multiple use cold preparatory area, for the preparation of reagents, validation and quarantine of incoming reagents, etc. The second area is where the hot cells are located and is carefully monitored for radioactive contamination and exposure levels. The third area is a quality control area where final testing of radiopharmaceuticals such methods as HPLC, pyrogenicity, sterility and GC. The final area, which is separated from the main production lab, is the metabolite and small animal imaging room where blood metabolite analysis and animal microPET imaging studies using a Concorde microPET R4 are performed. Since the opening of Columbia University's PET research laboratory in August of 2000, over 1,820Ci (67.4 TBq) have been processed. There have been 730 production runs for human use, 393 for non-human primate and 750 general research and development preparations. Although only 800 sq. ft. in size, the lab design and practical set-up has provided Columbia investigators with an efficient resource that provides 12 radiotracers under approved protocols for human use and has enabled individual researchers the ability to develop approximately 50 new radiotracers. As PET centers are growing in numbers across the world architects and chemists are reviewing the literature and finding limited practical information, hence the purpose of this presentation is to provide such information. The presentation will cover the design aspects of Columbia University's Radioligand laboratory and its attempt to meet the needs of investigators and cGMP.

AN AUTOMATED RADIOSYNTHESIS OF 1-(5-[^{18}F]FLUORO-5-DEOXY-α-D-ARABINO-FURANOSYL)-2-NITROIMIDAZOLE [^{18}F]-FAZA: A POTENTIAL TUMOUR HYPOXIA IMAGING AGENT

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Keywords: Automated, radiosynthesis, [^{18}F]-FAZA, Hypoxia

An automated radiosynthesis of the potential tumour hypoxia imaging agent [^{18}F]-FAZA has been developed using the Coincidence FDG Synthesizer (GEMS-Coincidence) and disposable kit system.

Typically, [^{18}F]-FAZA is prepared by treating 1-(2,3-*O*-diacetyl-5-*O*-tosyl-α-D-arabinofuranosyl)-2-nitroimidazole with a [^{18}F]fluoride/Kryptofix 2.2.2 complex in dimethyl sulfoxide (DMSO) and heating the mixture at 160 °C for 5 minutes. Hydrolysis with 0.1N NaOH and subsequent high performance liquid chromatography (HPLC) purification provides [^{18}F]-FAZA with an average 14 % radiochemical yield. This is performed with the aid of a general-purpose automated fluorination module. In the absence of such a module we chose to investigate the possibility of performing this synthesis using the Coincidence FDG Synthesizer.

The standard disposable kit for [^{18}F]-FDG was used without modification. The recovery of [^{18}F]fluoride from [^{18}O]enriched water and subsequent conditioning with Kryptofix 2.2.2 and potassium carbonate was performed without modification to the controlling program. It was only from this point onward that the program required modification. After drying the [^{18}F]fluoride/Kryptofix 2.2.2 complex, 1-(2,3-*O*-diacetyl-5-*O*-tosyl-α-D-arabinofuranosyl)-2-nitro-imidazole was introduced to the reaction vessel as a solution in acetonitrile. Acetonitrile was used owing to the incompatibility of the disposable kit with DMSO. Radiofluorination was achieved by heating the contents of the reaction vessel at 100 °C for 50 minutes. The reaction mixture was then diluted with water for injection and passed through a Sep-Pak tC-18 cartridge. In the process, the radiofluorinated intermediate was trapped on the tC-18 cartridge and unreacted [^{18}F]fluoride and Kryptofix 2.2.2 were flushed to waste. While still retained on the tC-18 cartridge, the radio-fluorinated intermediate was treated with 0.1N NaOH to affect hydrolysis of the acetyl protecting groups and provide [^{18}F]-FAZA. [^{18}F]-FAZA was recovered and the resulting solution neutralized by elution from the tC-18 cartridge with buffered phosphate solution. Purification of [^{18}F]-FAZA was by way of semi-preparative HPLC (Partisil ODS 3, 250 mm x 10 mm x 10 μm; 5 % EtOH in 0.9 % normal saline; 4.0 mL/min). Total radiosynthesis time was approximately 100 minutes from EOB and the non-decay corrected radiochemical yield was approximately 5 %.

In the absence of a general-purpose automated fluorination module, this FDG Synthesizer has proven to be a suitable alternative. The software modification required to perform this procedure was made straightforward by the use of an excel spreadsheet programming tool provided by GEMS-Coincidence.

The optimisation of reaction parameters and the integration of a radio-HPLC system are currently being investigated.

PRODUCTION AND SUPPLY OF RADIOISOTOPES FOR MEDICAL RESEARCH AT THE UNIVERSITY OF MISSOURI RESEARCH REACTOR

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Keywords: Sm-153, Ho-166, Lu-177, radiolanthanides, radiotherapy

The University of Missouri Research Reactor Center [MURR] was instrumental in the development of two commercialized radiotherapeutic agents: Sm-153 EDTMP [Quadramet®] for the palliation of pain due to metastatic bone cancer, and Y-90 labeled glass microspheres [TheraSphere™] for the treatment of liver cancer.

Quadramet®, a therapeutic radiopharmaceutical approved for use in the US in 1997 that relieves the excruciating pain associated with human metastatic bone cancer. Samarium-153 produced at MURR is attached to a special molecule that is attracted to actively growing bone. Once injected, it delivers beta radiation to the tumor, relieving the pain and in some cases even shrinking the tumor. Available in other parts of the world as well, this drug is a significant improvement over the use of morphine and other opiate drugs otherwise needed to ease the patient's pain. It is neither addictive nor causes the extreme drowsiness that degrades the quality of life of those using opiate drugs.

TheraSphere™ is approved in Canada and the US for the treatment of liver cancer and currently being investigated for treatment of other diseases. These microscopic, highly insoluble, radioactive glass beads are arterially injected into the patient and become lodged in the tumor's capillaries, delivering large doses of radiation to the cancer while sparing normal tissue. The microspheres are manufactured in Rolla, MO, and irradiated at MURR to generate the short-lived isotope yttrium-90. The radiopharmaceutical improves the quality of life of liver cancer patients who other wise have few alternatives and extends their survival.

MURR is now actively developing other radioisotopes with potential for use in radiopharmaceuticals. We currently supply Curie quantities of various radiolanthanides—including Sm-153, Ho-166 and Lu-177—for use in human clinical trials. These have shown potential for treating diseases such as multiple myeloma and rheumatoid arthritis. We are also developing methods for the production of very high specific activity radioisotopes suitable for receptor targeting radiopharmaceuticals such as radiotherapeutic generator production. The development of these and other radioisotopes will be discussed in the context of their physical and chemical properties as related to their potential utility in medical research.

The University of Missouri has formed the Radiopharmaceutical Sciences Institute (RSI) in conjunction with MURR, the MU Chemistry Department, the MU Medical School, and the Comparative Oncology Group of the MU Veterinary School to wage a comprehensive attack on the problem of cancer. The University of Missouri RSI benefits from being the only institution in the U.S. to combine research departments of Medicine, Veterinary Oncology, Chemistry, Nuclear Engineering, and a high flux nuclear reactor to support this effort.

NEW PROCESS FOR THE SEPARATION OF ^{111}IN FROM ^{112}CD AND SIMULTANEOUS PURIFICATION OF THE ^{112}CD TARGET

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Keywords: ^{111}In, Separation, Radiochemistry, ^{112}Cd, Targetry

In-111 has favourable characteristics [= 171 keV (87.6 %) and 245 (94.2 %)] for both diagnosis and therapy. It is generally produced by alpha particle irradiation of silver or proton and deuteron irradiation of enriched cadmium targets.[1-3] Yields via the latter two routes are considerably higher (3 - 5 times at 22 MeV) than the former and are generally employed by production facilities.

Various methods of purification have been reported.[1-4] They generally employ the use of strong acid such as, hydrobromic acid with anion and cation exchange columns or aqueous organic solvent extractions. In each case the challenge is to reduce the contaminating metal ions, such as iron and long lived radionuclidic impurities. The contamination by Fe(III), presents a particular problem for radiolabelling of proteins and peptides while radioisotopic impurities create problems with shipment of product and expiry times. The ability to purify expensive target material quickly is also of interest for cost-containment of inventory.

We have previously reported the extraordinary separation power of organic acid mixtures for the separation of radioisotopes. Here we systematically investigated the use of acid/organic mixtures for the separation of ^{111}In from proton irradiated ^{112}Cd. Distribution coefficients for In, Cu, Co, Ni, Cd, and Zn were determined over a range of hydrochloric acid concentrations (0.1 – 3M) and organic solvent mixtures (35% - 95%) with AG1-X8 resin. From distribution data a method of separation was devised that allowed isolation of carrier-free ^{111}In and the simultaneous recycling of the target material ^{112}Cd using an anion exchanger AG1-X8. The copper target plate was re-designed to reduced the contamination of radioisotopic impurities in the ^{112}Cd.

Six ^{112}Cd targets (650 – 750 mg) were irradiated with 26 MeV protons for 3 hours at approximately 200 A. After irradiation the target was digested with 10.3 M hydrochloric acid, evaporated to dryness and then dissolved in 0.2 M hydrochloric acid / 98.3% ethanol. The mixture was then loaded on to an AG1-X8 column and contaminating radioisotopes were removed by various acid/organic mixtures. The ^{111}In was eluted quantitatively in a mixture of 0.3 M hydrochloric acid / 65 % ethanol and then evaporated to dryness and resuspended in 0.05 M hydrochloric acid. The ^{112}Cd was quantitatively removed from the column with 0.005 M hydrochloric acid.

The radioisotopic purity of the ^{111}In was > 98 % at calibration (> 200 hr after EOB) with ^{114m}In $\leq$ 0.1 % at calibration (60 hours EOB). The chemical impurities for cadmium were < 0.03 g per 37 MBq and for nickel, copper, iron and lead < 0.1 g per 37 MBq).

To our knowledge this is the first reported use of acid/organic mixtures for the separation of ^{111} In and the simultaneous purification of ^{112}Cd. Significant benefits include use of less corrosive solvents resulting in a reduction in metal ion contaminants, faster evaporation times, faster recycling of ^{112}Cd target, reduction in dose to staff and reduction in ^{112}Cd inventory required to maintain weekly production.

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PRODUCTION OF MULTIPLE RADIOISOTOPES FROM A SINGLE IRRADIATION OF A MULTI-LAYERED TARGET

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Keywords: Radioisotopes, Separations, Anion Exchange, Targetry

Multi-layered targets provide an opportunity to optimise use of cyclotron irradiation time. Other advantages are a reduction in radioactive waste and an increase in the range and yield of isotopes from a single irradiation. The challenge is to design compatible electroplated targets and the separation of multiple radioisotopes on a single column.

Cu-64 and ^{67}Cu were reported to be co-produced during routine commercial production of ^{67}Ga from enriched ^{68}Zn.[1] Preliminary work by us demonstrated for the first time separation of ^{64}Cu from the ^{67}Ga production process.[2] During this study, waste from the ^{67}Ga process was analyzed by gamma spectrometry and found to contain significant amounts of contaminating radioisotopes, including ^{57}Co, ^{57}Ni and ^{65}Zn. The production of the ^{57}Ni and ^{57}Co was from the Ni-coating on the copper target plate. The presence of ^{65}Zn with its 1115 keV emission was considered most undesirable as its contamination of the enriched ^{68}Zn slowed its recycling time and increased the demand for a larger inventory of enriched ^{68}Zn. Evaluation of the cross section of the relevant nuclear reactions and calculation of proton beam energies entering and exiting enriched ^{68}Zn showed that ^{65}Zn was primarily produced by activation of the copper target plate. Hence it was of interest to assess the impact of increasing the nickel coating on the copper target plate.

Over 90 copper target plates were first electroplated with varying amount of natural nickel (100 mg – 800 mg) and then enriched ^{68}Zn (600 mg - 750 mg). Each multi-layered target was then irradiated with protons of 27 MeV. The ^{68}Zn was digested off with 8M hydrochloric acid and the ^{67}Ga separated using the cation exchange method reported in the literature.[3]

A comprehensive study on the binding affinity of above mentioned radioisotopes with anion and cation exchange resins and acid / organic solvent mixtures was conducted. Acid concentrations were varied from 0.2 – 3.0M and the percentage of organic solvents ranged from 35% to 95%. Distribution coefficients plotted highlighted solvent systems that could be used to progressively elute each radioisotope identified. Separation processes were developed that could elute ^{57}Ni, ^{57}Co, ^{64}Cu ^{67}Ga and ^{65}Zn from a single column.

The electroplated nickel coating was then removed with concentrated nitric acid and the resultant digest analyzed for Zn, Co and Ni radioisotopes. Yields of each Co and Ni radioisotope increased by 10 fold with increase in nickel coating from 100mg – 800 mg. The ^{65}Zn on the copper target and in the enriched ^{68}Zn was substantially (more than 4 fold) reduced. Most notable was the significant reduction in ^{65}Zn in the irradiated ^{68}Zn target material that allowed its removal from the hot-cells at the end of processing; previously ^{68}Zn targets would be stored in hot cells for 6 – 9 months prior to recycling.

This study demonstrates the feasibility of multiple targets, where the production of radioisotopes requiring lower energies can be “piggy backed” onto a routine production process such as that of ^{67}Ga. It also provides an opportunity to prevent radioisotopic contamination of target material, (e.g enriched ^{68}Zn) and reduce dose to operators. Novel separation processes allows separation of multiple radioisotopes from a single column, as well as the full characterisation of radioactive waste.

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FABRICATION OF URANIUM FOILS FOR Mo-99 IRRADIATION TARGET BY COOLING-ROLL CASTING METHOD

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Keywords: uranium foils, Mo-99 irradiation target, cooling-roll casting, medical diagnosis, cooling roll

As the uranium foils for Mo-99 irradiation target charged into a reactor can be conventionally fabricated at laboratory scale [1-2], but not yet at a commercialized scale by the hot rolling method due to some problems in foil quality, productivity and economic efficiency, attention has shifted to the development of new technology. Under these circumstances, an alternative fabrication method of uranium foil has been developed in KAERI using a cooling roll, in order to produce fission isotope ^{99}Mo, the parent nuclide of ^{99m}Tc. In order to develop the fabrication technology of the wide foils with reliability, the fabrication and characterization of the uranium foils by the cooling-roll casting method have been carried out in this study.

Uranium lumps (99.9 % pure) were charged and induction-melted in a high-temperature-resistant ceramic nozzle. The superheated molten U metal was fed through a small orifice onto a rotating cooling roll on a vertical axis. The liquid metal was then rapidly solidified with the rotating roll driven by an electric motor in an inert atmosphere. The rapidly solidified foils were collected in a container.

Uranium foils had a good roughness on the surface, without cracks and impurities. Cooling-roll casting process exhibited a very high yield (above 95%) and productivity (large amount of the foils in a few seconds). Continuous and uniform uranium ribbons with thickness ranging from 100 to 200 μm were produced exceeding 5m in length for one batch (Fig. 1), by adjusting the process parameters of the cooling-roll casting apparatus. Uranium foils had fine and uniform grains below 10 microns in size with the a-U phase (Fig. 1). It is expected to be able to prevent the uranium foils from excessively swelling by an-isotropic growth behavior during irradiation. Conclusively, major advantages of the cooling-roll casting process were obtained as follows: 1) a simplified process without the hot-rolling process and heat-treatment process, 2) an improvement in productivity and yield in foil fabrication, and 3) a high purity and a high quality of the foils, 4) a very fine polycrystalline structure.

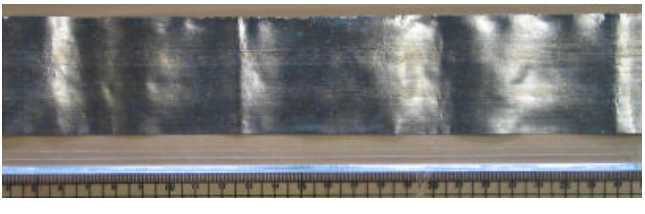

Fig. 1. Uanium foil produced by cooling-roll casting apparatus.

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DENSITY FUNCTION STUDY ON O-IODOHIPPURIC ACID

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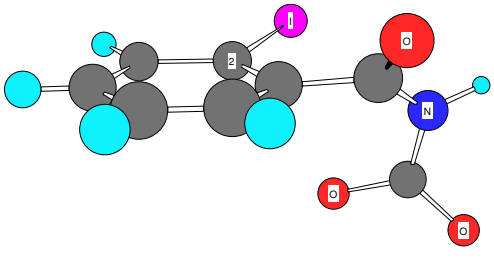
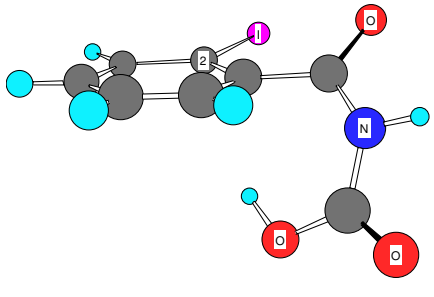
Keywords: o-iodohippuric acid, o-iodobenzoic acid, B3LYP calculation, $^{*}I^{-}$-exchange

The density function study of the widely used renal imaging agent o-iodohippuric acid (OIHA) was performed, using Gaussian-98 program at the B3LYP/CEP-4G level. Considering the practical labeling condition, o-iodobenzoic acid (OIBA), and both acidic and basic forms of every compound were separately treated. Full geometry optimization of the compounds in vacuo was executed, and that in 19 different solvents was done utilizing Onsager model. For the optimum structures in solvents, Polarized Continuum model CPCM was used to obtain the solventizing free energy ΔG_{sol} and other structural parameters in solution. The results show that the conformation of OIHA changes evidently as comparing the two forms of OIHA and as the dielectric constant of solvent shifting, but OIBA maintains the conformation unchanged. The negative charge on C2 atom in both compounds suggests a SN1 nucleophilic substitution path of $^{*}I^{-}$ ion exchange with OIHA and OIBA. The over strong solventization of OIHA under basic aqueous solution reflected in a 4.7 ΔG_{sol} radio of basic value to acidic one results probably in the lower labeling ratio under the same condition in experiment. Better oxidative-reductive stability of both compounds in acidic solution than in basic one indicates that the acidic labeling condition is suitable for usage as well. Our work is helpful to understand the properties of OIHA and OIBA better. Further calculation is being done.



o-iodohippurate



o-iodohippuric acid

LOW ENRICHED URANIUM FOIL TARGETS FOR ^{99}MO PRODUCTION

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Keywords: target, molybdenum-99

The Australian Nuclear Science and Technology Organisation (ANSTO) has been producing ^{99}Mo from the irradiation of low enriched uranium dioxide pellets (2.2% ^{235}U) for over thirty years. The ANSTO process purifies ^{99}Mo by:- dissolution of targets in nitric acid; primary separation of ^{99}Mo from the uranium and some fission products using an alumina column; volatilisation of some fission products during a boildown process and final purification of ^{99}Mo on a smaller alumina column.

With the advent of the Replacement Research Reactor (RRR), ANSTO plans to modify the process for the production of ^{99}Mo. These modifications involve changing the enrichment and chemical form of the target and ensuring that the chemical purification process is compatible with the new targetry and anticipated scale of production. Low enriched uranium (LEU) metal foil (19.75%) has been chosen as the ideal target material for ^{99}Mo production in the RRR.

The ^{99}Mo target development program has been conducted in two phases. The purpose of the demonstration phase was to evaluate the use of LEU foils for ^{99}Mo production. A prototype target (LEUFR) was designed to fit existing irradiation facilities in HIFAR and a small amount of LEU foil was irradiated, processed and ^{99m}Tc generators prepared and evaluated according to ANSTO protocols. The second phase of the program is directed at HIFAR validation of an annular LEU target that will be similar to that used in the RRR. This part of the program is in progress and irradiations are scheduled for 2004.

This paper will:- report on the design and supporting data (neutronics, computational and experimental fluid dynamics etc) for the prototype LEUFR target, the new annular LEU target and the new HIFAR irradiation rig for the annular target; summarise the key engineering requirements for an acceptable LEU target; compare experimental temperature data collected during irradiation of the first LEUFR target (upto 0.4g ^{235}U) with theoretical estimates; report on the ^{99}Mo processing and quality control results of ^{99}Mo (Table 1) and ^{99m}Tc generators prepared from prototype LEUFR targets; report on the schedule for irradiation of annular LEU targets in HIFAR prior to RRR start-up.

	Specification		UEO3	UEO5	UEO6
Radionuclidic Purity (%)	^{99}Mo	>98	99.98	100	100
	^{131}I	<0.0002	ND	ND	ND
	^{132}I/^{132}Te	<0.002	ND	ND	ND
	^{112}Ag/^{112}Pd	<0.01	ND	ND	ND
	^{239}Np	<1.0	ND	ND	ND
	^{103}Ru	<0.05	ND	ND	ND
	^{127}Sb	<0.5	0.0143	ND	ND
	^{95}Nb/^{95}Zr	<0.01	ND	ND	ND
	^{140}La/^{140}Ba	<0.01	ND	ND	ND
	Others	<0.01	<0.01	<0.01	<0.01
Separated Iodines	^{131}I	<0.0002	ND	ND	6.78×10^{-5}
	^{132}I	<0.002	4.0×10^{-7}	1.8×10^{-6}	1.48×10^{-5}
Specific Activity	>180 TBq/g Mo		yes	yes	Yes
Appearance	A clear liquid		Yes	Yes	Yes
Pass/Fail			Pass	Pass	Pass

Table 1: Mo-99 purity obtained from irradiation of nickel coated LEU (19.81%) foils

EFFECT OF PARTICLE SIZE OF DTPA-DEXTRAN DERIVATIVES ON SENTINEL LYMPH NODE UPTAKE

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Keywords: Sentinel Lymph Node, In-111, DTPA, Dextran, rat

Sentinel lymph node (SLN) is the first lymph node draining a tumor site and being metastasized tumor cells. Tc-99m-colloid is recently used for clinical SLN imaging. Vera et al. have reported Tc-99m labeled mannosyl dextran with the particle size of about 7 nm for SLN imaging(1,2). It is said that the transition ability of a compound into a lymph node is affected by the particle size. A particle with the size of less than 5 nm doesn't retain in the lymphoduct and a particle with the size of more than 150 nm is unlikely to enter into the lymphoduct. In this paper, dextran derivatives conjugated with DTPA as a chelating site were synthesized in order to obtain difinite-sized particles. The dextran-DTPA conjugates were labeled with In-111 and the effect of the particle size of the compounds was evaluated using rats.

DTPA was introduced in dextran of various sizes using DTPA anhydride. The particle size of the DTPA conjugated dextrans was measured using DLS (dynamic light scattering) system. The DTPA conjugated dextrans were labeled with In-111-$InCl_3$. The radiochemical purity was evaluated using HPLC, paper chromatography and electrophoresis. The obtained labeled dextran derivatives were injected into a footpad of rats and in vivo kinetics of the radioactivity was imaged using a scintillation camera for animal use.

Three different-sized DTPA-dextran conjugates were obtained (10, 70 and 120 nm). DTPA introducing efficiency was about 0.1 per one glucose moiety of each dextran derivative. After injection of In-111 labeled DTPA-dextran derivatives, popliteal lymph nodes were clearly imaged. All compounds showed a rapid clearance of the radioactivity from the injection site. 10 nm DTPA-dextran showed a fast clearance from the lymph nodes. The highest uptake of the radioactivity was observed using 120 nm DTPA-dextran. Almost radioactivity was excreted into urine.

Dextran derivatives can provide particles of various sizes. An optimal sized particle can be selected depending on the site characteristic for diagnosis. Moreover, an application of the compounds as MRI contrast agents is promising using Gd chelating DTPA-dextran derivatives and now under consideration.

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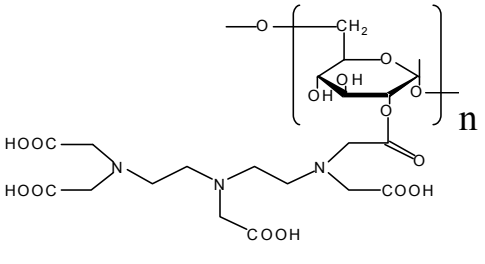
2. Vera D.R, Wallace A.M., Hoh C.K., Mattrey R.F. *J Nucl Med* 2001; 42: 951-959.

Chemical Structure of DTPA-Dextran



^{99}MO PRODUCTION FROM LOW ENRICHED URANIUM FOIL TARGETS

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Keywords: molybdenum-99, distribution co-efficient, ion-exchange chromatography

The Australian Nuclear Science and Technology Organisation (ANSTO) has been producing ^{99}Mo by neutron bombardment and subsequent fission of uranium dioxide pellets (2.2% ^{235}U) in the High Flux Australian Reactor (HIFAR) for over thirty years. Upon commissioning the Replacement Research Reactor (RRR), ^{99}Mo will be produced by irradiation of Low Enriched Uranium (LEU) metal foils (~19.75% ^{235}U).

In the current process, the irradiated pellets are dissolved in nitric acid and the solution is loaded onto an alumina column. Unwanted species are washed from the column using nitric acid and the ^{99}Mo is finally stripped from the column using ammonia solution. Recovery of ^{99}Mo is approximately 80%. Related experiments concerning the identification of the molybdenum (Mo) species bound to the alumina substrate, with a view towards subsequent recovery, are presented at this meeting by Syna *et al.*

It is essential that the ^{99}Mo chemical purification process is compatible with the new targetry and increased scale of production in the RRR. An extensive series of experiments has been conducted to determine the affinity of ^{99}Mo for alumina (as well as some other substrates) under a wide range of conditions. These conditions have been chosen in order to elucidate which parameters most affect the loading of ^{99}Mo onto the column and the recovery upon stripping. Those parameters include:

- contact time between ^{99}Mo and substrate (*e.g.* alumina)
- Mo concentration
- pH
- nature of alumina (particle size distribution, surface area, 'surface acidity', porosity *etc.*)
- nature of other species in solution (total ionic strength, concentration of individual species, chemical interactions)
- ratio of alumina to liquid
- temperature
- radiation field

Identification of the critical parameters and their effect on the performance of the processing unit will allow us to optimise the existing process in terms of speed and ^{99}Mo recovery. Furthermore, this knowledge should allow us to predict the effects of the increased enrichment and therefore determine the optimal physical parameters for the new processing unit as well as to optimise the ^{99}Mo purification procedure with respect to speed, yield and purity.

We report herein our findings and discuss the implications for the improved chemical processing procedure.

NOVEL APPROACHES IN NUCLEAR MEDICINE

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Keywords: Solid Targetry, Radiofullerene, Radiopharmaceutical

Among the many research activities planned following the commissioning of a negative ion medical cyclotron at Sir Charles Gairdner Hospital, in Perth, Western Australia, various aspects of solid targetry and investigations into novel delivery methods of radiopharmaceuticals using fullerenes show tremendous promise.

Fullerenes are molecules composed entirely of carbon atoms arranged in closed, cage-like structures and represent a form of ordered carbon like graphite and diamond. Due to their hollow structure, however, atoms can be placed inside the molecular cage, forming an "endofullerene." Using endofullerenes as carriers of radioisotopes has already been suggested, but research into the synthesis of such compounds for such a purpose is lacking.

Because fullerenes are capable of both physically and chemically isolating radioisotopes from their environment it is plausible that one might achieve a greater degree of flexibility in developing a new class of radiopharmaceuticals for tracer or therapy applications than is currently possible. What is certain is that radiofullerenes have biodistributions which could be modified simply by altering the nature of the chemical substituent on the fullerene surface. Radionuclides suitable for use in medical diagnosis and cancer therapy would typically include ^{86}Y and ^{64}Cu as these are within the energy range for production in an 18 MeV cyclotron.

Producing, extracting and purifying fullerenes produced under various presents in itself a great challenge to current research. Incorporation of radioisotopes adds another dimension to this challenge.