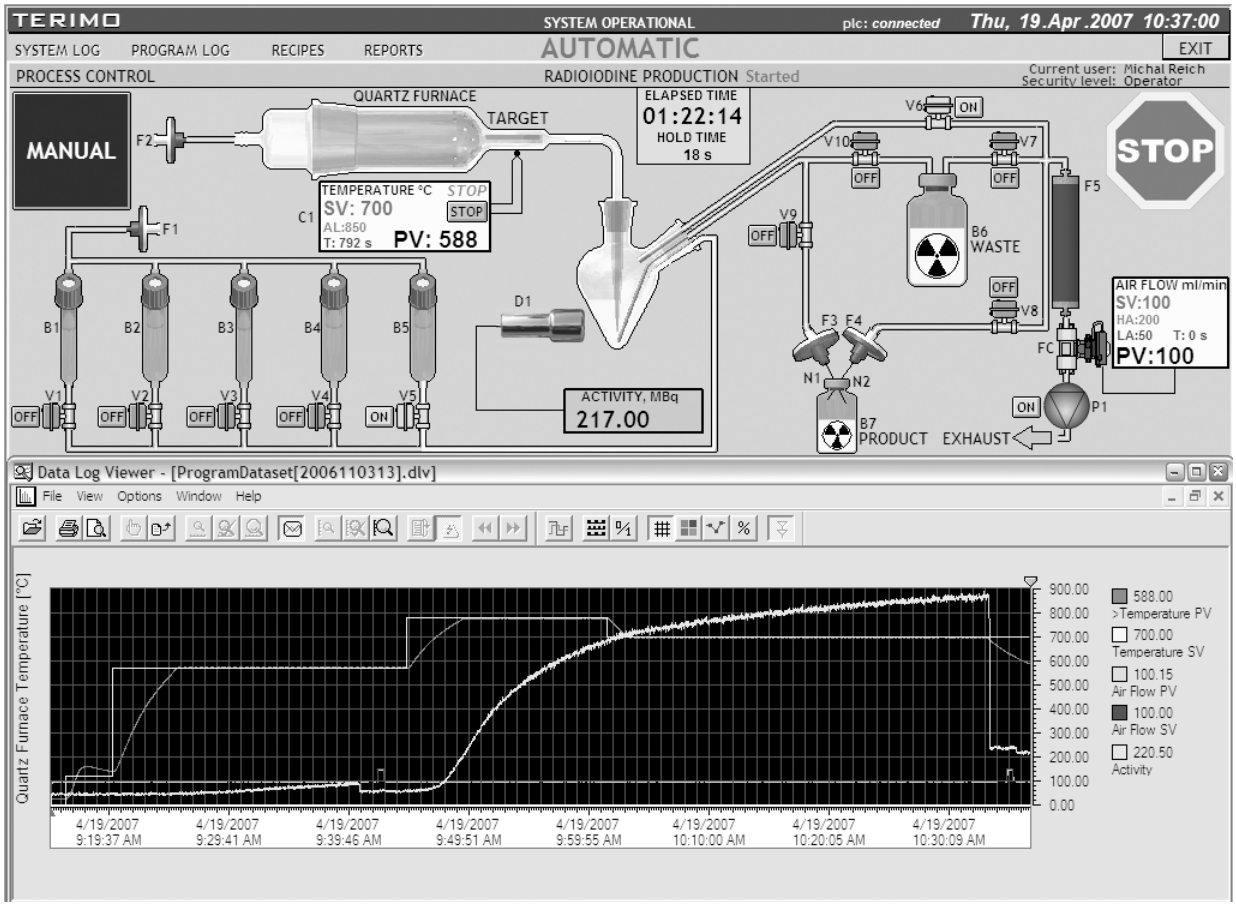
ADVANCES IN RADIOIODINE PRODUCTION BASED ON (P,N) REACTIONS

J. COMOR*[1] and G. BEYER[2]
1. Elex Commerce, Belgrade, Yugoslavia; 2. Isotope Technologies Dresden GmbH, Dresden, Germany

Objectives: Radionuclides of iodine are playing an important role in diagnostic nuclear medicine. ^{123}I is commonly produced by 30 MeV cyclotrons using gas targets but logistic problems are hampering its extensive use. There are several clinical studies under way based on ^{124}I eventually leading to routine application of this radionuclide in clinical diagnostics. However, its wide application is limited by its restricted availability. Further development of cost effective technologies for radioiodine production using medium-energy PET cyclotrons (15-18Mev) is thus justified.

Methods: A comprehensive technology for radioiodine production based on the ^{x}Te(p,n)^{x}I nuclear reaction and thermochromatographic separation of radioiodines from the irradiated TeO_2 targets has been already developed. The overall process is based on irradiation of highly enriched tellurium oxide targets ($^{124}TeO_2$/$^{123}TeO_2$) using a compact solid target irradiation system and thermodistillation of targets in a thermochromatographic aparatus (TERIMO). The final product obtained is [^{x}I]NaI that can be used for labeling or may be directly used for clinical applications. After annealing, the target can be immediately re-used for the next irradiation without further treatment.

Results: A new improved compact target system has been designed for irradiating Ø24×2mm target disks. The overall dimensions of this new target have been reduced and the cooling system has been completely changed in order to reduce the activation of the target station and increase its beam acceptance. TeO_2 targets can now withstand up to 30 μA of 18 MeV proton beams providing yields up to 15 MBq/μA-1/h-1 of 124I. A charger version of the target station is also available, allowing the user to remotely load up to three target disks into the target station. For the separation and purification of the radio-iodine from TeO_2 targets, a thermodistillation device was used. This apparatus has also been improved in terms of reliability and safety. The dedicated quartz furnace for the thermochromatographic separation has been modified in order to be less prone to rupture in case of improper handling. The safety charcoal filter's efficiency has been increased excluding any accidental release of radioiodines into the exhaust line. The overall recovery of radioiodine from the target, trapped in 0.5-1.0 ml alkaline solution, is typically >85%. The product contains <1 μg•ml-1 tellurium with radiochemical purity >95%. Loss of the target material (including handling, irradiation and radioiodine separation) is <0.4% per cycle (typically <1 mg), while batches of 2.5 GBq ^{124}I and 10 GBq ^{123}I are produced.



Conclusions: Reluctance in using solid target technology based on expected radionuclidic impurities is not justified since target materials with enrichment close to 100% are now available. Consequently, the radionuclidic purity of ^{123}I produced by the ^{123}Te(p,n)^{123}I reaction is comparable with the product obtained from ^{124}Xe gas targets. Using this technology many existing PET centers could become regional distributors of ^{123}I increasing its availability. There are already three production sites using this technology for commercial ^{124}I production.

RADIOACTIVE LABELING OF DEFINED HPMA-BASED POLYMERIC STRUCTURES: USING [18F]FETOS FOR IN VIVO IMAGING BY POSITRON EMISSION TOMOGRAPHY (PET)

M. HERTH*[1], M. BARZ[2], M. JAHN[1], V. KRAMER[2], R. ZENTEL[2] and F. ROESCH[1]
1. University of Mainz, Institute of Nuclear Chemistry, Mainz, Germany; 2. University of Mainz, Institute of Organic Chemistry, Mainz, Germany

Objectives: Polymer-based therapeutics are of increasing interest in the development of nanomedical tools for the diagnosis and treatment of many diseases. For example, micelles have been studies for drug delivery applications. Thereby, the non-specific interaction between proteins and polymer surfaces determines the in vivo fate of drug carriers. Particle-sizes, compositions, physical properties and surface chemistry influences the behaviour of nanomaterials in vivo.[1,2] To understand and fine-tune these parameters for in vivo therapies or diagnostics, appropriate imaging strategies are needed. In this respect, non-invasive, quantitative, and repetitive whole body molecular imaging techniques such as Positron-Emission-Tomography (PET) would provide a significant advance in the understanding of mentioned interactions.

Methods: Defined statistic and block copolymers were synthesized by RAFT polymerization and labeled by [^{18}F]FETos later on. The stability of the polymeric structures were determined 1 h and 2 h after the synthesis by SEC.

Results: The polymeric structures are based on the biocompatible N-(2-hydroxypropyl) methacrylamide (HPMA). In order to achieve these structures, functional reactive ester polymers with a molecular weight ranging between 25.000-110.000 g/mol were aminolyzed by 2-hydroxypropylamin and tyramin (3%) to form ^{18}F-labelable HPMA-polymer precursors. The electrophilic labeling procedure of the phenolic tyramin moieties by [^{18}F]FETos provided radiochemical yields of ~ 80% for block copolymers and > 50% for statistic polymer architectures within a synthesis time of 10 minutes and at a reaction temperature of 120 °C. Total synthesis time including synthon synthesis, ^{18}F-labeling and the final purification via size exclusive chromatography took less than 90 minutes and yielded stable ^{18}F-labeled HPMA-structures in isotonic buffer solution. Any decomposition could be detected within 2 h.

Conclusions: A new versatile ^{18}F-labeling strategy for polymeric particles has been introduced. Defined and functional HPMA based statistic and block copolymers have been synthesized by RAFT polymerization and labeled in high RCY of > 50% using [^{18}F] FETos in a reaction time of ~ 10 min. Overall synthesis including [^{18}F]FETos synthesis, polymer labeling and polymer purification via SEC was carried out in less than 90 min. The labeled polymer showed no decomposition. Further studies are planned to investigate the in vivo stability and the uptake kinetics of the ^{18}F-labelled polymers in healthy and tumor bearing rat by means of μPET imaging.

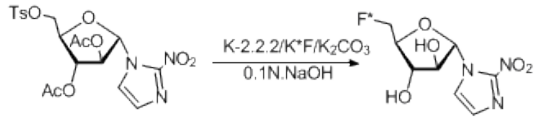
References: 1. Duncan, R. Nature Reviews Cancer 2006, 6(9), 688 2. Nahrendorf, M.; Zhang, H.; Hembrador, S.; Panizzi, P.; Sosnovik, D.E.; Aikawa, E.; Libby, P.; Swirski, F.K.; Weissleder, R. Circulation 2008, 117, 379

SYNTHESES OF 18F-FLUORINATED CLINICAL PET TRACERS USING MICROWAVE CHEMISTRY

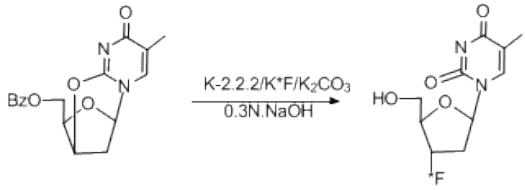
R. ORTLIEB*, P. KUMAR and L. WIEBE
University of Alberta, Department of Oncology, Edmonton, AB, Canada

Objectives: Positron Emitting radiopharmaceuticals (PERs), e.g., ^{18}FAZA (hypoxia[1-4]) and ^{18}FLT (proliferation[5]), used in PET imaging procedures, are labeled with short lived positron emitting ^{18}F-radionuclide ($t_{1/2}$ for ^{18}F=110 min) using conventional labeling procedures involving thermal heating, and are often produced in low radiochemical yields (FLT; 2-3%; FAZA; ~5-10%) due to long reaction times. These conditions frequently cause thermal decomposition and side products formation. In addition, HPLC purification, if required, extends the total production time (~1.5 h). Microwave (MW) chemistry can significantly improve the yields of these PET tracers through short reaction times. The current work is a proof-of principal for the radiochemical synthesis of ^{18}FAZA and ^{18}FLT.

Methods: ^{18}FAZA and ^{18}FLT MW labeling procedures were investigated using an in-house designed semi-automated device for reagents delivery that was attached to a commercial MW magnetron (Resonance Instruments Inc.; Model 520A) which controlled the reaction parameters. Briefly, [^{18}F]fluoride was produced by irradiating an $H_2{}^{18}O$ target for 1 h with a proton beam (19 MeV; 35 μA beam current). After preparing dry ^{18}F/K-2.2.2 complex, the corresponding protected precursor in DMSO (0.5 mL) was added to the reaction vial. MW pulses were used to drive the labeling kinetics. Protecting groups were removed by aqueous NaOH (0.1 N for FAZA, and 0.3 N for FLT) hydrolysis and the resulting solution was neutralized with 0.4M sodium phosphate buffer (pH-5.5-7.5). This mixture was analyzed by TLC and HPLC to determine radiochemical yields.



5'-O-Tosyl-2',3'-Di-O-Ac AZA — FAZA



5'-O-Benzoyl-2,3'-anhydrothymidine — FLT

Results: Both^{18}FAZA and ^{18}FLT were produced using the MW technique. Radiofluorination yields , using MW-assisted irradiations, were significantly higher (^{18}FAZA, >38% and ^{18}FLT, 5-6%) in comparison to conventional thermal technique (~6% for FAZA in 5 min, and ~2% FLT in 12 min, respectively), and required significantly shorter synthesis times (60 sec for both ^{18}FAZA and ^{18}FLT tracers). No radioactive species other that the desired product and radiofluoride were observed in the reaction mixtures. A comparison of labeling results using MW technique and the conventional procedures is provided in following table.

Conclusions: Preliminary studies using MW-assisted ^{18}F-labeling demonstrate an overall improvement in the reaction quality, significantly reduced reaction times and superior radiochemical yields for both ^{18}FAZA and ^{18}FLT. Improved quality of the reaction mixtures will subsequently lead to simpler purification procedures of these and other PET tracers. This process requires additional development of a completely automated reagent delivery and parameter control device, in order to exploit the MW process in the clinical manufacture of PERS.

References: 1) P. Kumar et al. Lett. Drug Design & Develop. 6, 82-85 (2009); 2) E.J. Postema et al. J Nuc Med. Submitted (2009); 3) M. Piert et al. J Nuc Med. 46, 106-113 (2005); 4) G. Reischl et al. Appl Radiat Isotopes. 62, 897-901 (2005); 5) P. Kumar et al. J Pharm Pharmaceutical Sci. 10, 256-265 (2007).

A comparison of conventional thermal and MW-assisted labeling of ^{18}FAZA and ^{18}FLT

Observations	^{18}FAZA		^{18}FLT	
	C	MW	C	MW
^{18}F-Drying Time (sec.)	900	720	600	780
Labeling Time (sec.)	300	60	720	60
Radiochemical Yield (%)	~6	>38	~2	5-6
Side Products	5-6	None	?	None

IN PURSUIT OF [11C]CARBON DIOXIDE WITH INCREASED SPECIFIC ACTIVITY

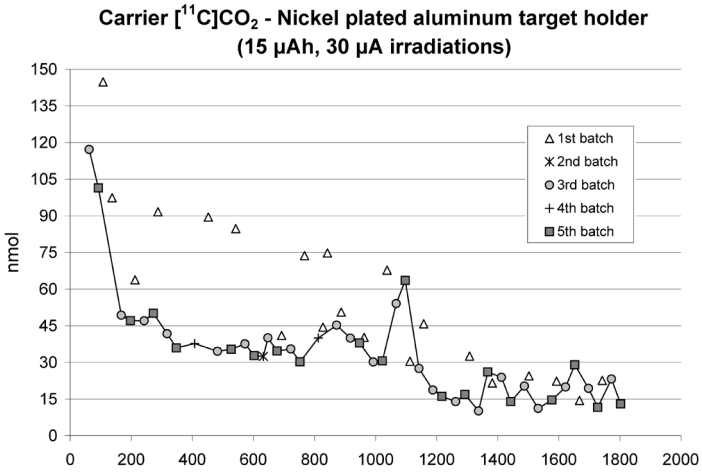
J. ERIKSSON*[1], R. MOOIJ[2], F. L. BUIJS[1], B. LAMBERT[3], L. F. VAN ROOIJ[1], P. S. KRUIJER[2] and A. D. WINDHORST[1]
1. VU University Medical Center, Department of Nuclear Medicine & PET Research, Amsterdam, Netherlands; 2. BV Cyclotron VU, Amsterdam, Netherlands; 3. IBA Molecular, Fleurus, Belgium

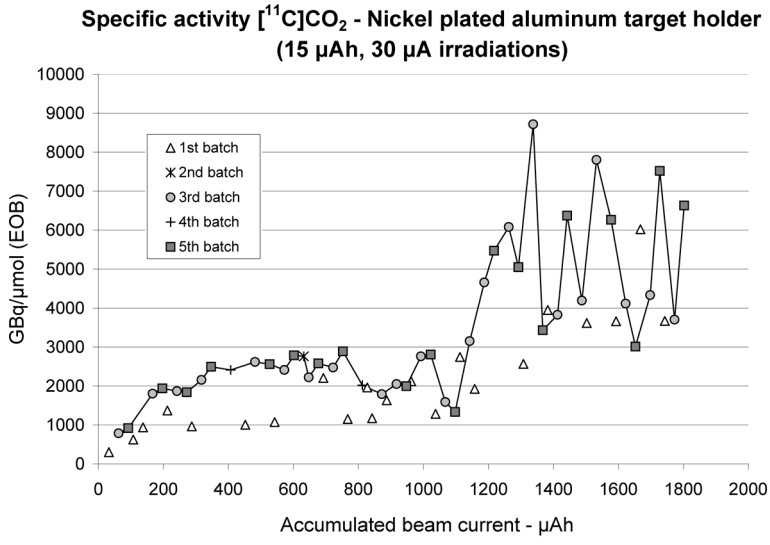
Objectives: $[^{11}C]CO_2$ used in labelling of PET-tracers is commonly produced by the $^{14}N(p,\alpha)^{11}C$ nuclear reaction in N_2/O_2 gas mixtures. During this process a significant amount of carrier can be introduced which sets the limit for the specific activity (SA) of the tracer. This study aims to increase the SA of $[^{11}C]CO_2$ by use of new target holder materials and cleaning techniques that minimizes interactions with carbonous impurities.

Methods: A remote controlled analytical system was developed for measuring the SA on whole batches of $[^{11}C]CO_2$. It included a unit for trapping the $[^{11}C]CO_2$ and subsequently concentrating it on a small volume for activity measurement using a collimated pin diode. A GC equipped with a Porapak Q column, a methanizer and a FID was used for the quantification of the carrier CO_2. The $[^{11}C]CO_2$ was produced by an IBA 18/9 cyclotron and delivered in a stream of helium via 190 m stainless steel tubing. The activity was allowed to decay to less than 200 MBq before it was injected on the GC to circumvent artifacts in the FID analysis caused by radiation. Three consecutive test periods were carried out with a standard IBA aluminium target body (50 mL), each with different configurations: A. Previously not irradiated target body, a new window foil with nitrile o-ring. B. Used foil with silver o-ring. C. New foil with silver o-ring. The previously not irradiated target holder D had the same basic build as C but with nickel plating on the aluminium surface. In total the target holders were exercised 430 times by 30 μA/15 μAh irradiations with 18 MeV protons. The SA was decay corrected to end of bombardment (EOB) and typically determined for every second batch.

Results: The initial SA was higher for the B and C configurations compared to A due to the irradiation history of the target body. Analysis of the third and later batches each day showed for configuration A, B and C a SA increase of 2.4-2.5 GBq/μmol per μAh while for D it increased significantly faster with 5.4 GBq/μmol per μAh. Configuration A reached a plateau at 2010±310 GBq/μmol, C at 1920±220 GBq/μmol and D at 2540±190 GBq/μmol after 50, 30 and 22 irradiations respectively. B developed a target leak before the plateau was established. When examining the first batch each day it was clear that it had significantly lower SA than the subsequent batches, the nitrile o-ring accounted for around 10 nmol of carrier while the helium transfer gas contributed with 30-40 nmol. After the helium feed line was separated from connections to other target systems the SA obtained with D increased to 5400±1700 GBq/μmol (first batch each day excluded). The amount of carrier was 18±5 nmol (n=17), a significant improvement compared to the 44±7 nmol (n=38) obtained with the A and C configuration. The amount of activity at EOB was practically unchanged from 85±5 to 88±2 GBq.

Conclusions: The SA has increased strongly due to the actions taken and work is in progress to improve it further.





MEASUREMENT OF THE SPECIFIC RADIOACTIVITY OF ^{11}C-LABELED PET TRACERS WITH LC-MS/MS ALONE

H. U. SHETTY*, C. L. MORSE, Y. ZHANG and V. W. PIKE
National Institutes of Health, Molecular Imaging Branch, NIMH, Bethesda, MD

Objectives: Radio-HPLC is commonly used to measure the specific radioactivity of ^{11}C- and ^{18}F-labeled tracers. Such measurements depend on two analyses, one of mass and another of radioactivity, which may each be susceptible to error. Here we report an LC-MS/MS technique that detects both ^{11}C tracer and its carrier directly, so providing specific radioactivity from mass measures alone. The utility of this technique was demonstrated with [^{11}C]PBR28, a radioligand for peripheral benzodiazepine receptors (Briard et al., J. Med. Chem., 2008; 51: 17) and [^{11}C]dLop, a P-glycoprotein substrate (Lazarova et al., J. Med. Chem., 2008; 51: 6034).

Methods: An LC-MS/MS apparatus (API 5000; Applied BioSystems) was tuned with PBR28 and dLop for m/z 349→121 and m/z 463→252 transitions, respectively (Figure 1). [^{11}C]PBR28 and [^{11}C]dLop were synthesized as reported. Each radiotracer preparation was diluted fivefold and injected (1 or 2 μL; 1.8–7.7 μCi) onto LC-MS/MS with LC running a gradient of 10 mM ammonium acetate in both acetonitrile (A) and water (B) on a reverse phase column (20 × 2 mm; 3 μm). The MS/MS instrument acquired product ions following dissociation of [M+H]$^+$ of ^{11}C and ^{13}C (carrier) species, namely m/z 120 and 122 from [^{11}C]PBR28 and m/z 251 and 253 from [^{11}C]dLop. Each preparation was analyzed ten times at intervals of 5 min. Specific radioactivities were calculated from ^{11}C/^{12}C ratios (with ^{12}C calculated from the measured ^{13}C/^{12}C ratio), and then corrected for decay. Radionuclide half-life ($t_{1/2}$) was determined from a plot of log specific radioactivity (^{11}C/^{12}C ratio) versus clock time of peak elution.

Results: LC-MS/MS of [^{11}C]PBR28 detected an m/z 348→120 transition (Figure 1A) and the LC peak for m/z 120 ion appeared at the same retention time (1.9 min) as m/z 121 and 122 from PBR28. As [^{11}C]PBR28 decayed, its mass-specific peak (m/z 120 ion) diminished and was undetectable after about six half-lives. Product ion m/z 121 from the ^{12}C-carrier saturated the detector. Thus, its true peak area was calculated from the peak area of m/z 122 ion generated from m/z 350 ion, the [M+H]$^+$ of the ^{13}C-carrier. Sequential LC-MS/MS analyses of a [^{11}C]PBR preparation gave its specific radioactivity (decay-corrected to end of synthesis) as 5,763 ± 197 (mean ± SD) mCi/μmol, in close agreement with that from radio-HPLC measurement (5,758 mCi/μmol). The $t_{1/2}$ of carbon-11 from MS/MS was 21.4 min. [^{11}C]dLop gave a product ion m/z 251. This and m/z 253 were monitored to give the ^{11}C/^{13}C ratio and thereby the ^{11}C/^{12}C ratio (Figure 1B). The determined specific radioactivity was 6,581 ± 313 mCi/μmol, in close agreement with that determined by radio-HPLC (6,431 mCi/μmol). The $t_{1/2}$ from MS/MS was 21.7 min.

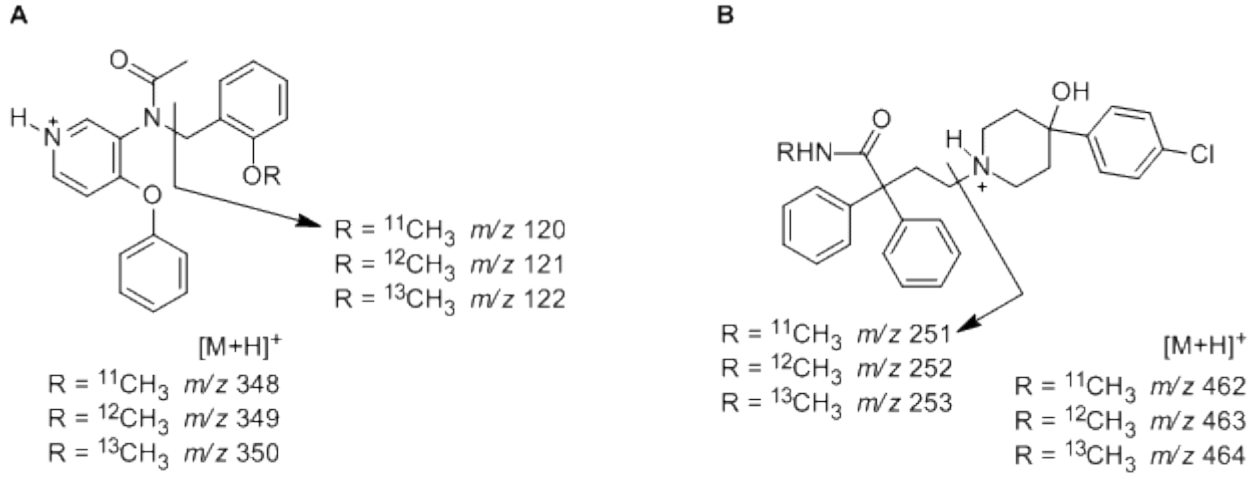


Figure 1. MS/MS of PBR28 (A) and dLop (B).

Conclusions: The MS/MS technique identified ^{11}C-labeled tracer as well as its ^{12}C/^{13}C carrier. The measurement of ^{11}C/^{12}C ratio provided specific radioactivity reliably for up to two half-lives, consistent with the $t_{1/2}$ of carbon-11 (20.4 min). The LC-MS/MS method is fast, requires only a very low activity of tracer and is useful for independently validating HPLC-based methods for determining specific radioactivities.

IMPROVED GC-FID MEASUREMENT OF [11C]METHYL TRIFLATE AND/OR [11C]METHYL IODIDE: IT'S EVEN EASIER THAN WE THOUGHT

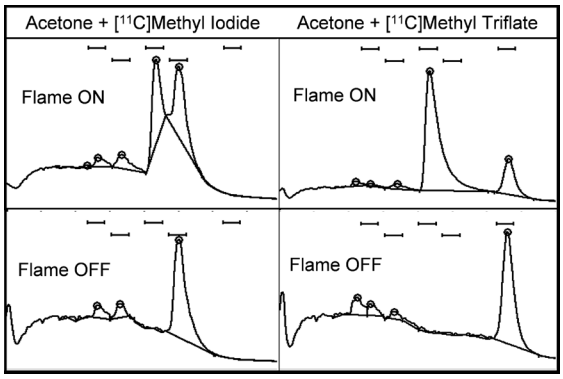
B. H. MOCK*, B. GLICK-WILSON and B. STEELE
Indiana University School of Medicine, Department of Radiology, Indianapolis, IN

Objectives: At the 2005 ISRS meeting, we introduced a simple technique for monitoring the radiochemical purity of [^{11}C]Methyl triflate with a capillary column gas chromatograph equipped with only a flame ionization detector (FID), a very sensitive device which responds to virtually any molecule with a carbon-hydrogen bond. By demonstrating that the FID also responds quite well to ionizing radiation, but with lower sensitivity than a sodium iodide crystal or Geiger-Müller detector, we had hoped to exploit this dual response to measure the specific activity of [^{11}C]MeOTf or [^{11}C]MeI. We were unsuccessful due primarily to the non-linearity of the radiation response. Instead, our continued attempts to refine the FID technique resulted in an even simpler procedure to measure radiochemical purity, and thus monitor the performance and efficiency of the silver triflate furnace used to convert [^{11}C]MeI or [^{11}C]MeBr to [^{11}C]MeOTf.

Methods: We initially used the same OVI-G43 capillary column which is recommended by the USP for the analysis of residual organic solvents. However, we observed that a large and variable portion of the injected [^{11}C]MeOTf radioactivity (but not [^{11}C]MeI) remained trapped within the capillary column, even after prolonged high temperature helium purge, thus confounding the accurate determination of radiochemical purity. Therefore, we investigated alternative capillary columns in order to minimize this retention. In addition, extraneous mass peaks were often seen in the chromatogram due to the solvents used in cleaning the delivery line from the MeOTf module to the methylation system. While such contaminants could easily be identified by their retention times, overlapping peaks often made accurate radiochemical purity analysis difficult and unreliable. We then investigated methods to diminish the mass response of the FID.

Results: The injected [^{11}C]MeOTf sample, being significantly more potent as a methylating reagent than [^{11}C]MeI, was in fact reacting with the cyanopropyl- residues of the OVI-G43 capillary column's inner siloxane coating. By switching to an equivalent RTX-20 column, containing only dimethyl- and diphenyl-polysiloxane, the in situ radiolabeling of the inner column liner was eliminated. Altering the temperature of or the gas flow through the FID had no beneficial effect in reducing the mass response of contaminating solvents. However, when the hydrogen flame within the FID was actually extinguished, the mass response of the detector was totally eliminated, leaving only the radiation response visible on the chromatogram.

Conclusions: By injecting an aliquot of the [^{11}C]MeOTf or [^{11}C]MeI gas stream onto an RTX-20 capillary GC column and monitoring the No-flame FID response, radiochemical purity can be readily determined in less than five minutes. Residual organic solvents can also be quantified using the RTX-20 column once the flame has been re-established.



IN SILICO AND IN VITRO PROPERTIES TO CONSIDER IN THE DEVELOPMENT OF PET IMAGING RADIOTRACERS

E. BRIARD*[1], Z. JIANG[2], S. DESRAYAUD[3], J. REILLY[2], B. EVERATT[2], P. MAGUIRE[4] and Y. AUBERSON[1]
1. Novartis Institute of Biomedical Research, Global Discovery Chemistry, Basel, Switzerland; 2. Novartis Institute of Biomedical Research, Global Discovery Chemistry, Horsham, United Kingdom; 3. Novartis Institute of Biomedical Research, Metabolism and Pharmacokinetics, Basel, Switzerland; 4. Novartis Institute of Biomedical Research, BioMarker Development, Basel, Switzerland

Objectives: The development of radiotracers for in vivo Positron Emission Tomography (PET) is becoming rapid and less costly. Non human primate PET studies are the fundamental experiment to evaluate the clinical fitness of CNS PET ligand candidates. The identification of in silico and in vitro properties that can predict the potential of a radiotracer candidate before radiosynthesis would reduce costs and speed the development process considerably.

Methods: A limited set of parameters have been reported in the literature to predict the success of PET ligands in the clinic. We have therefore surveyed the literature, compiled and completed a set of properties describing clinically used radiotracers, as well as unsuccessful candidates, using assays routinely applied in drug discovery programs. Among others, we examined physicochemical, permeation and pharmacokinetic properties, and last but not least, non specific binding. High non specific binding (NSB) is a common reason for failure. We will discuss several approaches that were evaluated to predict this parameter.

Results: Published parameters characterizing successful PET tracers were confirmed within this set of compounds. In addition, we evaluated high throughput HPLC methods to predict non-specific binding. RP and IAM chromatography proved very robust, and their results compared with in vitro non-specific binding data measured using a dialysis device.

Conclusions: A good correlation was found between the retention of 21 ligands on the IAM chromatography column and their in vitro NSB ($R^2 = 0.79$). Finally, we will discuss the PK parameters of a few clinically validated tracers, including their use in characterizing the washout of free radiotracer.