P395 SYNTHESIS AND 68Ga-RADIOLABELLING OF 2-DESOXYGLUCOSE CONJUGATED MACROCYCLIC CHELATORS

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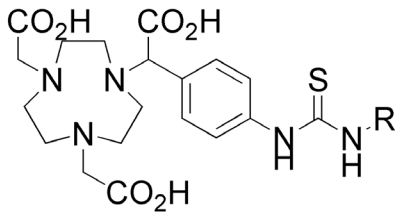
Objectives: [^{18}F]FDG is frequently used for the localization and staging of peripheral tumors and multiple other purposes. Although the approved imaging agent is readily available via reliable satellite distribution from local vendors, a generator based alternative PET-tracer would possess the potential to reduce overall cost and logistic effort. It might even increase the overall availability of the most frequently employed PET-examination, the FDG-scan.This concept has already been examined,[1] e.g. for ^{99m}Tc-labelled ECD-desoxyglucose conjugates. Encouraged by the findings reported by those investigators, we were interested in a ^{68}Ga-labelled analogue for PET.^{68}Ga provides a high positron abundance of 89 % and an intermediate positron maximum energy. With its half-life (1.13 h) lying perfectly in between the half-lives of the most frequently used ^{11}C (0.33 h) and ^{18}F (1.82 h), it provides excellent decay characteristics as a PET-radiolabel.

Methods: Multiple mono- and divalent NOTA-desoxyglucose (NOTA-DG) and DOTA-desoxyglucose (DOTA-DG were synthesised from 1,4,7-triazacyclonone and 1,4,7,10-tetraazacyclododecane in good yields. The compounds were labelled with prepurified n.c.a. [^{68}Ga]$GaCl_3$ in aqueuous solution at pH = 2.8. A DTPA-challenge experiment was conducted to verify complex stability.

Results: Yields for ^{68}Ga(III) complex formation were in the usual range.A DTPA challenge experiment indicated high complex stability, similar to the congeners DO_2A and NOTA.

Conclusions: A series of novel macrocyclic chelator-desoxyglucose conjugates can now be examined for phosphorylation in a commercial glucose-hexokinase assay. If the novel compounds are still recognized e.g. by the GluT 1 as a substrate, further systematic imaging studies seem worthwhile.

References: D. J. Yang, C. G. Kim, N. R. Schechter, A. Azhdarinia, D. F. Yu, C. S. Oh, J. L. Bryant, J. J. Won, E. E. Kim, D. A. Podoloff, Radiology 2003, 226, 465.



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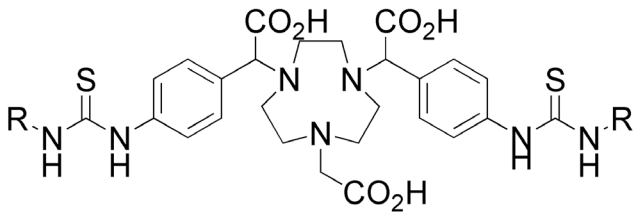

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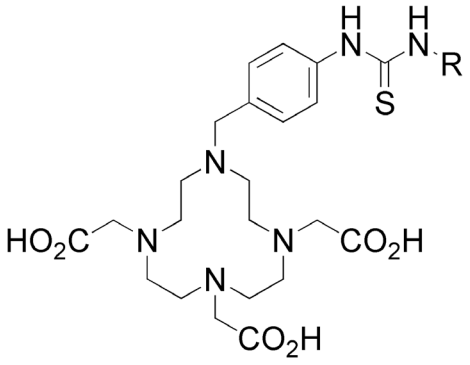

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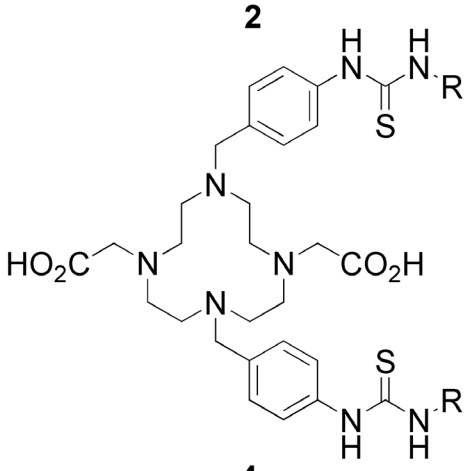

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P396 SYNTHESIS OF [^{18}F]XENON DIFLUORIDE FROM [^{18}F]FLUORIDE ION IN A COILED SILICA GLASS MICRO-REACTOR

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Objectives: ^{18}F-Labeled xenon difluoride ([^{18}F]XeF_2) is a potentially useful 'electrophilic' radiofluorination agent. [^{18}F]XeF_2 has been prepared by reaction of [^{18}F]F_2 with xenon [Schrobilgen et al. Chem Commun, 1981, 168], and by exchange of XeF_2 with either [^{18}F]HF [Chirakal et al. Int J Appl Radiat Isot, 1984, 35, 401] or [^{18}F]fluoride ion [Constantinou et al. JACS, 2001, 123, 1780]. The latter process is attractive because of the availability of [^{18}F]fluoride ion in high activity and high specific activity from the ^{18}O(p,n)^{18}F reaction on [^{18}O]water. Previously, exchange between XeF_2 and [^{18}F]fluoride ion (as ^{18}F-Cs^+/K2.2.2) was achieved in CH_2Cl_2 at room temperature (RT). However, no exchange occurred at RT with ^{18}F-K^+/K2.2.2 in CH_2Cl_2 [Vasdev et al. JACS, 2002, 124, 12863]. Here we exploited a microfluidic device to study further the influence of different conditions on this reaction.

Methods: Anhydrous ^{18}F-K^+/K2.2.2 solution (5–10 mCi; K^+/K2.2.2; 26 mM) and XeF_2 (270 mM), both in MeCN, were loaded into separate storage loops (255 μL) of the microfluidic apparatus [Lu et al. Curr Radiopharm, 2009, 2, 49]. Solution (20 μL) from each loop was infused simultaneously at 10 μL/min into the coiled silica glass micro-reactor (100 μm i.d., 4-m length). Reactions were quenched by diluting the reactor effluent with MeCN (0.4 mL) in a plastic vial. Radio-HPLC was performed on a reverse phase column (C18, 5 μ, 250 × 4.6 mm) eluted at 1 mL/min with aq. $HCOONH_4$ (25 mM)-MeCN (55:45 v/v). The procedure was repeated at higher set temperatures. Experiments with Cs_2CO_3 in place of K_2CO_3 in CH_2Cl_2 or MeCN were also performed in the microfluidic apparatus. Supplementary experiments with other conditions were carried out in glass or plastic vials. The fluorine exchange reaction between CsF and XeF_2 was also studied with quantum chemistry.

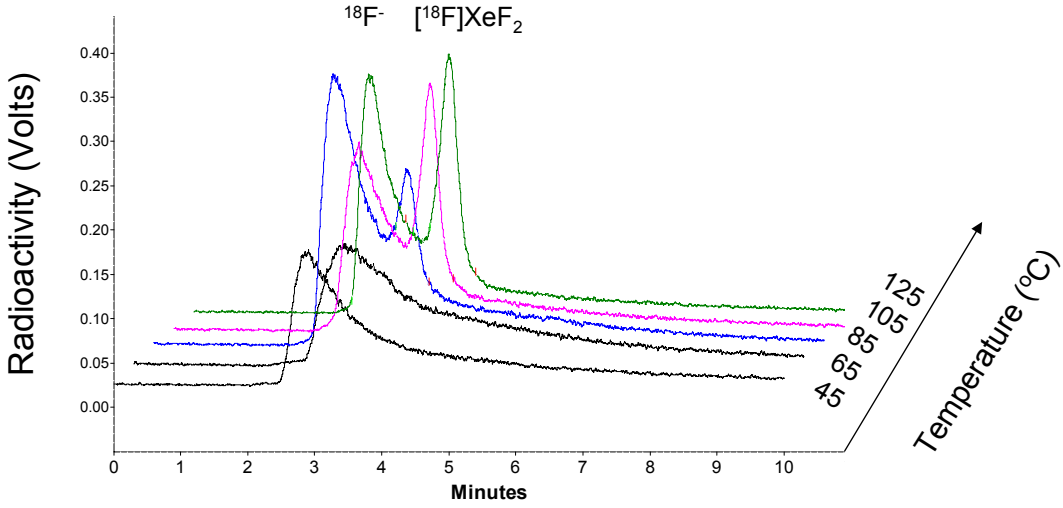

Fig 1 Effect of temperature on [^{18}F]fluoride ion (as $^{18}F^-$-K^+/K2.2.2) exchange with XeF_2 in MeCN within a coiled silica glass micro-reactor

Results: For [^{18}F]fluoride ion in the presence of K^+/K2.2.2 in MeCN, no reaction occurred up to 65 °C. At 85 °C, [^{18}F]XeF_2 was detected, co-eluting with carrier XeF_2 (t_R = 3.8 min) (Fig 1). At 125 °C, nearly half the radioactivity was incorporated into [^{18}F]XeF_2. When the counter ion was Cs^+ (K2.2.2 absent or present), exchange was clearly observable, even at 65 °C. Exchange was faster in CH_2Cl_2 than in MeCN, and slower when XeF_2 was at lower concentration. Simulation of the CsF-XeF_2 fluorine exchange reaction with quantum chemistry was consistent with experiment. Results from reactions in glass or plastic vials were as expected from our original publication.

Conclusions: The silica material of the micro-reactor was compatible with successful exchange reactions. [^{18}F]XeF_2 can be obtained in high RCY by exchange of [^{18}F]fluoride ion with XeF_2 in either CH_2Cl_2 or MeCN. In MeCN the reaction may be performed in the presence of Cs^+, with or without K2.2.2, or with K^+/K2.2.2 at elevated temperature. The use of a micro-reactor for the radiosynthesis permits a lower amount of XeF_2 (1–5 μmol) to be used in each reaction and has potential to produce [^{18}F]XeF_2 consistently and rapidly at a usefully high specific radioactivity.

P397 LABELLING OF CARBON-11 TRACERS USING A MICROFLUIDIC SYNTHESISER

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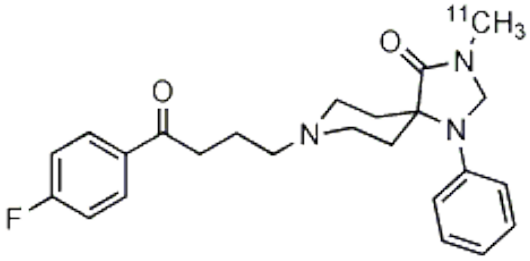
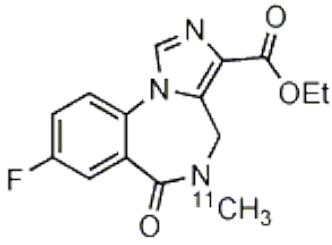
Objectives: In our search for the development of rapid and reliable methods for the production of PET radiopharmaceuticals, we are interested in investigating the use of automated microfluidic systems for our routine synthesis of radiotracers. By comparison with the conventional batch approach widely used for the production of PET radiotracers, a microfluidic method offers several appealing features: rapid optimisation of reaction conditions (multiple individual reactions with a single batch of radionuclide), low amount of expensive precursors and chemicals, flexibility and the possibility of "on-demand" single dose production of radiotracers. Furthermore, under microfluidic conditions, the product is moved away from the reagents as it is formed thus limiting side reactions that would decrease the radiochemical yield. In a previous set of experiments with a microfluidic device, we successfully produced different F-18 tracers in very high yields (e.g. 88% RCY for [^{18}F]fallypride [1]). In order to further extend the use of this approach, we present here our results obtained on the labelling of carbon-11 tracers with [^{11}C]iodomethane under microfluidic conditions.

Methods: The system used for our experiments is the Advion NanoTek Microfluidic System. This device uses a set of syringe pumps to drive the reagents at a selected flow rate through a microreactor made of fused silica tubing (31.4 µl, id=100 µm, L= 4m). Upon completion of the labelling reaction, the radiochemical yield is determined by a reversed-phase HPLC system equipped with a radiodetector. For the initial assessment of this methodology with carbon-11, our target molecules were [^{11}C] N-Methylspiperone (1) and [^{11}C]Flumazenil (2) which are being routinely used for our neuroimaging programmes.



[^{11}C]N-Methylspiperone (1)



[^{11}C]Flumazenil (2)

Results: A mixture of precursor and base in DMF were loaded into the first syringe pump and [^{11}C]iodomethane in dry DMF was loaded into a second syringe. Aliquots of both solutions were then injected into the microreactor. The amount of precursor used for each experiment was 76 nmol for [^{11}C]N-methylspiperone and 230 nmol for [^{11}C]flumazenil. Only one batch of [^{11}C]methyl iodide was required for the synthesis of each molecule. The results of these experiments are summarised in table 1.

Table 1: Labelling yields for the synthesis of [^{11}C]N-Methylspiperone and [^{11}C]Flumazenil

Tracer	Base	Reagents ratio	Combined flow rates	Temperature	Radiochemical Yield
1	0.4N tBu_4NOH	1	20 µl/min	RT	66 ± 1% (n=3)
2	15N KOH	1	20 µl/min	RT	93 ± 3% (n=3)

For both labelling experiments, the incorporation of [^{11}C]iodomethane was possible with very high radiochemical yields being obtained under mild reaction conditions.

Conclusions: Our preliminary applications of microfluidic methods for the radiosynthesis of carbon-11 tracers by [^{11}C] methylation have proven to be efficient, with high radiochemical yields. Future work will include coupling this system with HPLC and SPE purification modules with the objective of developing a fully integrated automated system for producing radiopharmaceuticals suitable for imaging studies.

References: [1] L. Brichard, A. Giamis, F.I. Aigbirhio, Eur. J. Nucl. Med. Mol. Imaging, 2008, 35 (Suppl 2): S325 (P448)

P398 RAPID [11C]METHYLATION REACTIONS USING MICROFLUIDIC TECHNOLOGY

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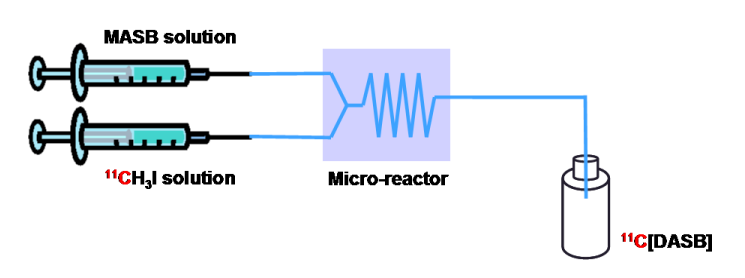
Objectives: Microfluidic devices consisting of long, narrow channels (of the order of micrometers in diameter) are emerging as a valuable tool for the preparation of PET tracers due to their potential benefits including reduced reaction times and greater yields. To date, limited research has been performed on the application of microfluidics in ^{11}C-labelling reactions, which carry a significant time constraint due to the short radioactive half-life of ^{11}C (20 minutes). As such, we have been examining the role of microfluidics in PET radiolabelling using the most widely used synthon, $^{11}CH_3I$. Here, we present our results on the labelling of N,N-dimethyl-2-(2-amino-4-cyanophenylthio)benzylamine ([^{11}C]DASB) using microfluidics. The effects of temperature, solvent, flow rate and chip dimension are investigated.

Methods: $^{11}CH_3I$ was produced from $^{11}CO_2$ using an automated gas-phase module and then bubbled through a vial containing the appropriate solvent. This solution, alongside the [^{11}C]DASB precursor, MASB, was then pumped into the microreactor, the commercially available NanoTek LF. Typically, experiments were performed using a small volume of $^{11}CH_3I$ solution, thus enabling repeat experiments to be performed with a single batch of the reagents. Control experiments were also performed in which the two reagents were premixed in a syringe before injection into the microfluidic reactor. In each case, conversions of $^{11}CH_3I$ to [^{11}C]DASB to were measured by analytical radio-HPLC of the crude product.



Results: In one set of experiments [^{11}C]methylation reactions were performed in acetonitrile solution using a 100 μL diameter, 4 m length microreactor (volume = 31 μL) heated to 130°C. Low flow rates gave the highest conversion of $^{11}CH_3I$ to [^{11}C]DASB (50% at 4 μL/min compared to 8% at 20 uL/min). Premixing the reagents before infusion into the microreactor led to improved yields under the same conditions; for example, at 4 μL/min, the conversion rose from 50 to 85% when the reagents were premixed. Addition of a 250 psi back pressure regulator to the output line from the reactor enabled these reactions to be performed at this higher pressure, leading to an improvement in yields; at the lowest flow rate of 4 μL/min, addition of a BPR increased the conversion from 50 to 73%. At 20 μL/min, the conversion increased from 8 to 35%. Conversions were found to increase with temperature, however at the device's upper limit of 200°C, DASB formation was not observed due to the degredation of MASB.

Conclusions: Microfluidic technology has successfully been used to perform ^{11}C-labelling reactions using solutions of $^{11}CH_3I$. As expected, lower flow rates lead to increased yields, due to increased time spent by the reagents in the reactor. Addition of a back pressure regulator to the product line leads to an improvement in yields but suffers the drawback of an increased dead volume, meaning that a larger solvent sweep is required in order to collect the products. The observation of increased yields in the premixing experiment compared to those in which the reactants mix within the reactor, suggests the reactions are limited by the rate of diffusion in the latter process.

P399 MICROFLUIDIC APPROACH TO THE SYNTHESIS OF [F-18]-FIAU USING AN ADVION NANOTEK-LF SYSTEM

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Objectives: [^{18}F]-FIAU as a molecular probe has shown promise in monitoring gene expression using HSV-TK as a marker. The difficulty in translating this agent has been the development of a robust and reliable synthesis. Recent methods have been described [J Label Compd Radiopharm 2003, 285-289; Nucl Med Biol 2003, 215-224] utilizing 30% HBr/HOAc to deprotect the [^{18}F]-labeled ribofuranose sugar prior to coupling the appropriately protected 5-Iodo-uracil. In approaching the synthesis of [^{18}F]-FIAU on the Advion NanoTek-LF module, we wanted to eliminate the use of HBr/HOAc and work towards shortening the overall time of synthesis. The automated approach we found successful follows the conditions described by Vorbrüggen [Tet Lett 1978, 1339-1342].

Methods: The synthesis is initiated by heating a solution of 10 mg 5-Iodo-uracil in 500 μL dichloroethane (DCE), 100 μL Hexamethyldisilazane, and 100 µL Trimethylsilyltrifluorosulfonate at 80°C in a sealed 3-mL v-vial for 1 h prior to the start of the [^{18}F]-incorporation step of the 2-O-(trifluoromethylsulfonyl)-1,3,5-tri-O-benzoyl-α-D-ribofuranose sugar. The Advion system uses a mini-MP1 exchange trap to collect the [^{18}F]$^-$ ions from the target water which are then eluted with a 10% aqueous solution of kryptofix/potassium carbonate. Once dried to remove traces of water, a 400 μL acetonitrile solution of the precursor ribofuranose is added to the dry [^{18}F]/kryptofix carbonate and passed through the microreactor on the Advion unit. The conditions for [^{18}F] incorporation call for a 2M x 100 mm column at a flow rate 50 μL/min and a temperature of 125°C. A back-pressure regulator of 250 pounds-per-square inch on the exit port of the reactor allows the 125°C temperature to be reached rapidly for the low-boiling MeCN (82°C). With a volume of 17 μL in the reactor loop, and a flow rate 50 μL/min, a residence time of 20 seconds at 125°C is achieved. This radiolabeled mixture in MeCN is delivered directly to the earlier pre-formed uracil mixture. It is then heated at 80-85°C for 60 mins. Solvents are evaporated to a thick oil at 80°C using a stream of Ar gas, followed by the introduction of 1 mL of 1M sodium methoxide in MeOH, which is mixed for 5 min and then vaporated to yield an off-white solid. Water is added and the mixture is loaded onto a semi-prep HPLC. The β-isomer is eluted at 8.3 min.

Results: In a typical run, using 90-150 mCi of ^{18}F, the radio-HPLC of the mixture shows ~67-73% of the total activity represented in the alpha and beta peak integrations with the beta isomer representing ~33% of the total. This represents ~12 mCi of the desired product produced in 115 min from only 150 mCi of ^{18}F. In a semi-prep run from 90 mCi, 6.4 mCi of beta product was isolated.

Conclusions: We have developed a robust and reliable method for producing usable quantities of [^{18}F]-FIAU using the Advion system. Work is currently underway to scale up the level of production. This method is also readily applicable for the production of [^{18}F]-FMAU and [^{18}F]-FEAU.

P400 NANO CRYSTALLINE ZIRCONIA: A NEW SORBENT FOR THE PREPARATION OF 99Mo-99MTc GENERATORS

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Objectives: Nanoparticles based sorbents have attracted a lot of attention as powerful adsorbents for the selective separation of metal ions from aqueous solutions due to their exceptionally high surface area and high surface reactivity. We have prepared nano zirconia and evaluated it's use as a sorbent for the development of $^{99}Mo/^{99m}Tc$ generator.

Methods: Nano-zirconia was prepared by reflux digestion of hydrous zirconia gel in basic solution (pH ~10). The structural characteristics of nano-zirconia were investigated by X-ray diffraction, IR spectra analysis, BET surface area analysis and TEM micrograph analysis. Determination of distribution ratio (K_d), static and the dynamic adsorption capacity, absorption and elution parameters, radiochemical and radionuclidic purity were carried out using standard radiometric techniques. The eluted ^{99m}Tc was tested by labeling established ligands such as DMSA and EC using reported procedures.

Results: Nano-zirconia could be prepared in high yields with good reproducibility. The IR absorption spectrum of the sorbent showed peaks corresponding to Zr-O-Zr groups and the X-ray diffraction pattern corresponded to tetragonal ZrO_2 phase. The surface area of this sorbent was 100 m^2/g, as determined by BET analysis. The average crystallite size of ZrO_2 was found to be 7 nm. TEM micrograph of the adsorbent revealed an agglomerated zirconia phase. The sorption capacity of the material was maximum at pH 3-4. The static adsorption capacity of the material was >250 mg/g and the breakthrough capacity was ~100 mg/g under the conditions of optimum pH, which are over 10 times greater than that of alumina. The kinetics of sorption of ^{99}Mo was very fast and equilibrium was reached within a period of 5 minutes. The loading and elution of the generator was possible within a reasonable period of 10 minutes. ^{99m}Tc could be eluted with normal (0.9%) saline solution with an elution yield of >90%. The elution performance remained consistent over a period of one week which is normally the shelf life of the generator. The eluted ^{99m}Tc had high radiochemical (>99%) and radionuclidic purity (>99.9%). The presence of zirconium metal contamination in the ^{99m}Tc eluate as evaluated by ICP-AES analysis was found to be <1 ppm. The complexation yield of ^{99m}Tc with DMSA and EC was >98%, demonstrating its suitability for preparation of radiopharmaceuticals.

Conclusions: These results demonstrate the potential of tetragonal nanocrystalline zirconia as a novel sorbent matrix for the preparation $^{99}Mo/^{99m}Tc$ column generator.

P401 ENGINEERING HOLLOW SILICA SHELLS FOR DRUG DELIVERY

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Objectives: Hollow silica shells of sub-micrometer size have been engineered for a range of applications, medicines, cosmetics, polymers and catalysis.[1] Understanding how processing changes the overall size and porosity of the particle is crucial to optimising their design and application. Many tools can estimate size and concentration of pores in porosu media, however no information on the chemistry within the nanopores is available. This study reports the synthesis and application of a library of new radiotracers or nuclear sensors for high throughput analysis of porous silica. It aims to establish the availability and charge within nanopores of silica shell, for optimum loading of desired molecules.

Methods: A new series of hexa-aza cages (L) (see Figure 1a) have been synthesized. Their Co^{2+} (spiked with a tracer amount of $^{57}Co^{2+}$) complexation behaviour was studied by dissolving the respective L (10^{-3}M) in buffer (pH 3-9) at a metal to ligand of 1:1 ratio at 21°C. The formation of the Co-L was monitored over time by instant thin layer chromatography (ITLC-SG) [mobile phase ammonium acetate (0.1M, pH 6.5); $R_f Co^{2+} > 0.9$; $[Co^{2+}\text{-}L] < 0.1$]. The Co^{2+} complex of dota was also prepared under similar conditions. The hollow silica shells (see Figure 1b) were prepared by the overcoating of sacrifical polymeric template particles with silicon precursor followed by thermal calcination in a furnace at 660 °C.[1] These silica shells (10 mg) were then exposed (10 min shaking or vortexed for 1 min) to free $^{57/nat}Co^{2+}$ and Co-L complexes (10^{-3} to 10^{-5}M) over a range of pH (3-9) conditions at 21°C. Uptake of the Co-L was monitored over time (10 min - 24 h) or until equilibrium was reached. The mixtures were centrifuged and the radioactivity associated with solutions and silica shells were measured in a gamma counter. The amount of Co-L bound to the silica shell was calculated for each time point.

Results: Subtle changes in the molecular structure L and pH were found to influence the rate of Co^{2+}complexation as well as their uptake by the hollow silica shells. Overall, positively charged Co-L complexes were selectively and rapidly taken up by the silica shells at pH 7-8, whilst negatively charged sensors were absorbed preferentially at pH 3. Selected data are illustrated in Figure 1c.

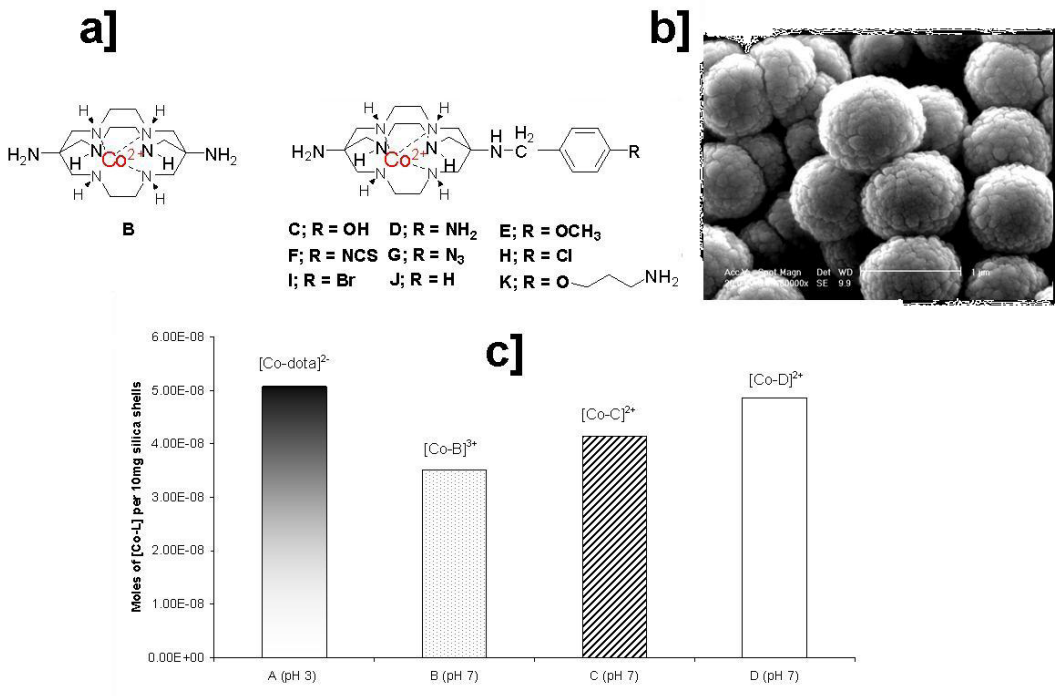

Figure 1. a] . Hexa-aza cage derivatives synthesized, b] Scanning Electron Microscope (SEM) image of hollow silica shells, c] The effect of charge and structure of nuclear sensors[a] on their uptake by the hollow silica shells
[a] Ref. to Fig.1a for compound structure

Conclusions: Surprisingly, charge as well as subtle changes in molecular structure of the nuclear sensors was found to have a significant effect on their rate and uptake by the hollow silica shells. The nuclear sensors were found to be very sensitive, fast, and required minimal material for monitoring the absorption properties of porous media. They have wider implications for high-throughput analysis of engineered porous material with the potential to predict conditions and type of target molecules that could be encapusated into the porous media.

Research Support: We wish to thank Australian Research Council funding of the ARC Centre of Excellence for Antimatter-Matter Studies.

References: [1] Lynch DE,Nawaz Y,Bostrom,Langmuir 21: 6572 (2005) [2] Guagliardo P, Uedono U, Naik R et al, Positron annihilation lifetime spectroscopy (PALS): a tool for exploring nanoporosity in biological materials,IC08 conference, Auckland, New Zealand (2008)

P402 USE OF NANO ZIRCONIA FOR POST ELUTION CONCENTRATION OF 188Re OBTAINED FROM INDIGENOUSLY DEVELOPED TITANIUM TUNGSTATE BASED 188W/188Re GEL GENERATOR

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Objectives: The objective of this investigation was to evaluate and demonstrate the potential utility of nano zirconia as an effective sorbent for the post elution concentration of ^{188}Re for radiopharmaceutical applications.

Methods: Titanium tungstate gel and nano zirconia were synthesized as per the reported procedures. About 2 g of the prepared titanium tungstate gel was irradiated in the Dhruva reactor of this centre at a thermal neutron flux of 2×10^{13} n cm^{-2} s^{-1} for 180 days. The activity of ^{188}W in the irradiated gel was assayed, packed into a column and washed with 0.1 M K_2CrO_4 solution. The ^{188}Re daughter was eluted using deionised water and the eluent was passed through a small column containing 250 mg nano zirconia for purification and concentration. Influence of pH and volume of primary eluate on the concentration efficiency, were optimized to obtain near quantitative absortion of ^{188}Re on the nano zirconia column. The ^{188}Re adsorbed on the sorbent was recovered in 0.9% NaCl solution. Radiochemical and radionuclidic purity of the product were determined using standard radiometric techniques. ^{188}Re labeled formulations with standard ligands such as HEDP and DMSA were carried out using reported procedures.

Results: Quantitative retention of ^{188}Re on the nano zirconia column was achieved at pH ~2-3. It was observed that with increase in the volume of ^{188}Re solution, the percentage of ^{188}Re retained in the column decreased. Typically 10 mL initial volume resulted in more than 98% retention while with 80mL volume, only 68% of ^{188}Re retained. In order to adsorb nearly all ^{188}Re present, the eluent from the first column was passed through a second nano zirconia column. This ensure that even at an initial volume of 80mL nearly 90% of total ^{188}Re was adsorbed in the two nano zirconia columns. Greater than 98% of ^{188}Re could be eluted with 2-3 mL of normal saline solution from the nano zirconia columns. The overall yield of ^{188}Re was >90%. The recovered ^{188}Re had high radiochemical (>97%) and radionuclidic purity (>99.99%). Using this method, 80 mL of ^{188}Re eluate could be concentrated to ~5 mL. The reproducibility of the result was evaluated for a period of three months and found to be consistent. A single nano zirconia column could be repeatedly used for more than10 times. The compatibility of the product in the preparation of ^{188}Re labeled formulations such as ^{188}Re-HEDP and ^{188}Re-DMSA was evaluated and found to be satisfactory.

Conclusions: The selective sorption property of nano material has been exploited for the concentration of ^{188}Re obtained from a gel generator. These results also indicate that nano zirconia columns could provide a basis to yield high specific volume solutions of ^{188}Re towards the end of its normal working life of an alumina generator.

P403 OPTIMIZATION OF [11C]RACLOPRIDE PRODUCTION ON A MICROFLUIDIC CHIP

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Objectives: We are interested in improving the synthesis process of [^{11}C]raclopride on a microfluidic chip. Since the C-11 radioisotope has a half-life of ~ 20.4 minutes, reducing the reaction time by using a microreactor chip can help increase the efficiency of its production. This, along with other advantages such as using smaller amounts of the reagent and producing better yields are our motivation for the microfluidic approach.

Methods: The synthesis mechanism used in this investigation involves the methylation of desmethyl raclopride (DMR) using methyl iodide (MeI) to produce raclopride (Rac). Initially the non-radiolabeled probe was synthesized on two microfluidic chips of different channel designs where the efficiencies of the synthesis were compared. One of the microfluidic chips was glass while the other was PDMS-glass chip (polydimethylsiloxane = PDMS). The glass chip is available commercially. On the other hand, the PDMS-glass chip was fabricated in our lab by first creating a molding master to produce the microchannels on the PDMS, and then by using plasma bonding to seal the PDMS layer against a glass wafer. Both microfluidic chips are 4.5 cm x 1.5 cm and can carry about 7 – 15 μl of fluid at one time. The synthesis process was carried out at ~ 70 – 100 ^{0}C using different methyl iodide concentrations. 40 – 80 ul of product were collected, neutralized and analyzed using HPLC. This HPLC was carried out using a C8 column with a mobile phase of 70% NaH_2PO_4 (with 2% H_3PO_4) and 30% CH_3CN.

Results: When comparing the cold synthesis on the microfluidic chip to the conventional process, the yields achieved were 3 - 10 times using 1/10th of reagents on the microreactor chip. When the temperature of the reaction was further increased, the yield also increased. Moreover, variation of the product collection time had showed an effect on the amount of impurities produced. Further, in comparison with a commercial Micro-Lab instrument used to carry out the radiolabeled synthesis we only produced <0.1 of the microfluidic device yield.

Conclusions: Using the microfluidic device we were able to complete the synthesis process in a shorter period of time in comparison with the conventional method. Better yields were also achieved for the cold synthesis process. By examining various conditions, we were able to optimize the cold synthesis process and to apply these optimized conditions on the microfluidic chips to synthesize the radiolabeled probe using the best microchannel design.

Table 1: Shows the cold synthesis results comparison between the microfluidic chip A and the conventional synthesis

	Temperature (^{0}C)	Time (min)	DMR (nmol)	Rac (nmol)
Conventional	80	22.6	~4.4	1.06
Microchip A	80	4.0	~0.4	2.76
	90	5.0	~0.4	4.40
	100	4.4	~0.4	8.83

P404 DETECTION OF RADIOACTIVITY TRANSPORT IN SYNTHESIS SYSTEMS

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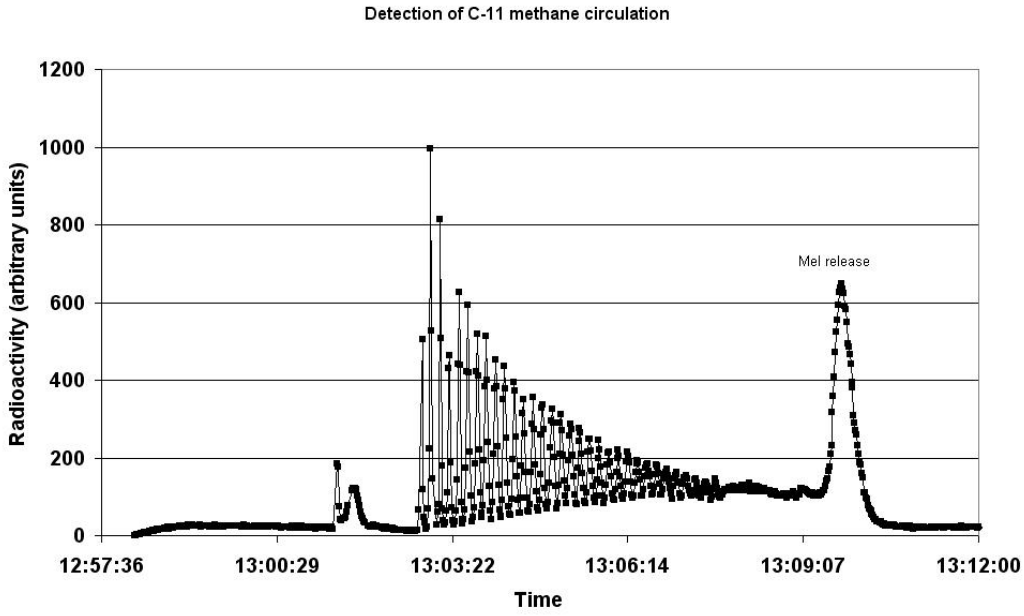
Objectives: Automatic synthesis of a radiopharmaceutical always involves the transfer of radioactive liquids or gases. The conventional synthesis systems are measuring the activity at the reactors or at various collection vessels to detect the appearing or disappearing activity. These detectors are detecting gamma radiation and require bulky shielding from their environment. With the appearance of new micro systems, the tracking of the radioactivity moving in thin tubes or micro channels would gain growing importance. Our aim was to construct a small size detector, which requires no shielding, and still not sensitive for high intensity background radiation. It was achieved with plastic scintillator coupled with photomultiplier tube.

Methods: The detector consisted of a 1 mm thick plastic scintillator (Zinsser ZA236) of 8 mm diameter, coupled to a photon sensor module (Hamamatsu H5784). The latter is comprised of a metal package photomultiplier tube, a high-voltage power supply and a low noise amplifier. The required low voltage power supply (±12 V and 0-1 V for amplification control) was constructed in house. The signal from detector was digitalized in a16 bit analog/digital converter (Advantech ADAM-5017), and the data was collected by GeniDAQ software from the same firm. The plastic scintillator was covered 2,5 micrometer thick aluminum foil. The detector was tested in a methyl iodide production module (MeI MicroLab, General Electric Medical Systems). The 1,6 mm FEP tubing of the circulation, between the methyl iodide trap and the product exit valve, passed on the surface of the plastic scintillator,

Results: The detector was tested using ^{11}C with high activity. Usually after 20 minutes irradiation with 30 μA protons, we had over 20GBq activity in our system. However there was only a very low signal coming as a background. We were able to observe the circulation of methane in the system and its decrease, as it was converted into methyl iodide, and trapped in a Porapak® Q molecular sieve. The activity of the released methyl iodide - trapped and measured in a dose calibrator - well corresponded to the peak area had shown by the detector. In other experiments the same detector could be used over more lines if the transport took place in different times. This detector can be used to detect radioactive liquids as well, the only criteria is, that there should not remain radioactive droplets in the tubing.

Conclusions: The detector measures the β^+ particles, which penetrates the tubing wall and Al foil. As was shown earlier, the plastic scintillators are significantly less sensitive for the gamma radiation than the β^+, thus it would be less vulnerable to the background radiation coming from other parts of the synthesis unit. To decrease the size of the detector further, we tried to replace the PMT to a photodiode. This idea was rejected later, because the photodiode itself shown sensitivity towards the gamma radiation, thus impair the useful signal background ratio.



P405 ELECTROCHEMICAL CONCENTRATION OF AQUEOUS [18F]FLUORIDE INTO AN APROTIC SOLVENT IN A DISPOSABLE MICROFLUIDIC CELL

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Objectives: Microfluidic technology is an attractive strategy found viable in PET radiochemistry. As PET probes demand high specific activities, this technology is predicted to find wide applications in PET radiosynthesis due to the rapid and efficient nature of its reactions. Although several microreactor systems have been developed to date, these were merely proof-of-concept studies limited from the lack of interfacing techniques in introducing target products into a microreactor. We present a novel and practical approach of transferring [^{18}F]fluoride from the target water into an aprotic solvent by means of electrochemical separation in a micro-flow cell.

Methods: A conceptual design of a disposable flow-cell with the aftermentioned method for electrochemical concentration of aqueous [^{18}F]fluoride is as illustrated in Fig. 1. The volume capacity of the utilized flow-cell is 18 μL (44 x 4.0 x 0.1 mm). Water (about 2 mL) containing no-carrier-added [^{18}F]fluoride was first flowed through the cell (0.1-1.0 mL/min) under a constant electric potential of 1-10 V applied between the Pt cathode and glassy carbon anode. The cell was then flushed with anhydrous CH_3CN (1.0 mL/min for 2 min) under the same electric potential. Voltage was then disconnected and an aprotic solvent (CH_3CN, DMSO or DMF) dissolving K.222-$KHCO_3$ complex (ca. 60 mM) was flowed into the cell and left stagnant. This was followed by heating up of the cell to a preset temperature. Accordingly, the reversed electric potential of electric field (1-10 V) was applied and cell flow was allowed to resume. A radiation sensor was used to detect the released [^{18}F]fluoride, which was then collected in a vial or sent to a subsequent chip to be used as a labeling agent.

Results: The deposition of [^{18}F]fluoride within the cell clearly depended on the flow rate and the voltage. It was rapidly increased up to 80% between 1 and 4 V followed by a gradual increase to over 90% at 10 V, while linear decrease was observed with increasing the flow rate. The optimized parameters of 10 V and 0.7 mL/min gave 90% deposition within 3 min. Efficient release of [^{18}F]fluoride from the GC surface required heating at >80°C. With a reversed voltage of 2 V and a flow rate of 0.2 mL/min, more than 70% of the trapped [^{18}F]fluoride was recovered in ca. 60 μL of the solvent within 2 min.

Conclusions: The present microfluidic method demonstrated that aqueous [^{18}F]fluoride is electrochemically concentrated in 60 μL of a solvent which is ready for nucleophilic substitution in a microreactor. A few applications to radiosynthesis of ^{18}F-radiopharmaceuticals will be presented.

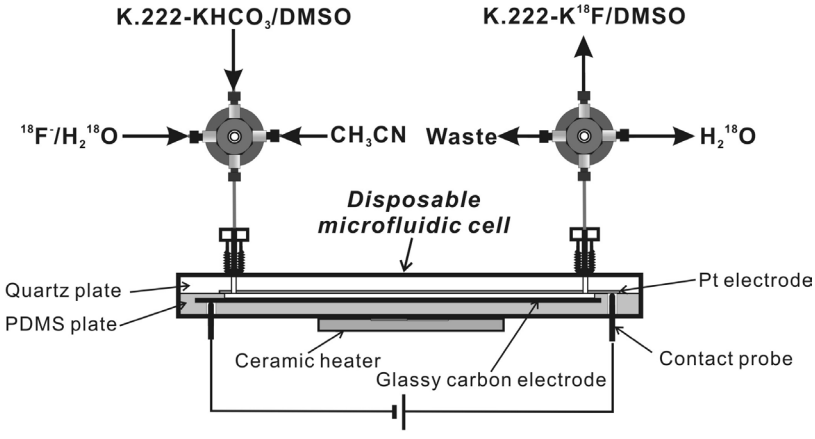

Figure 1

P406 2-[18F]-2-DEOXY-D-GLUCOSE [18F]-FDG LABELING OF PEPTIDE USING MICRO-FLUIDIC REACTOR

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Objectives: Preciously we have developed the direct labeling of amino-oxy functionalized peptides with the readily available positron emission tomography (PET) radio tracer [18F]-FDG. However, sufficient labeling yield could only be achieved at extended reaction times of 30 minutes and the use of large amounts of peptide. Micro-fluidic technology is a fascinating novel technique enabling micro-scale chemical reactions. This technology allows fast reactions in a simple experimental set-up, while using only very low amounts of starting material. The present study describes the chemoselective conjugation of [18F]-FDG to amino-oxy functionalized peptides using micro-fluidic technology.

Methods: In order to obtain optimal conditions for radiolabeling applications, the peptide concentration and the reaction time, needed to be reduced, while keeping biologically compatible conditions. Toward this goal, a potent cyclic somatostatin peptide antagonist, which was modified to display an amino-oxy functional group, was used as our standard peptide. While using our microfluidic apparatus, several factors were adapted: the temperature (from 80°C to 140°C), the flow rate (reaction time from 1min20sec to 4min), the solvent of the reaction (Water or methanol), the concentration of peptide (from 0.9 μmol.mL^{-1} to 5.5 μmol.mL^{-1}) and the pH of the solution (from neutral to 10% acetic acid).

Results: Two optimal conditions were so far obtained. The first one was achieved at 130°C for 1min20sec with a peptide concentration of 3.2 μmol.mL^{-1}, in neutral condition and a methanol/ water ratio of 2 to 1. These conditions afforded 70% convertion. The second one was achieved at 130°C for 2min40sec with a peptide concentration of 5.5 μmol.mL $^{-1}$, in neutral condition and a methanol/ water ratio of 2 to 1. These conditions afforded quasi quantitative yields convertion.

Conclusions: The time reaction and the yields of the selective amination have been greatly improved; however the temperature range upon which the reaction provides acceptable yields might not be suitable for all biologically active molecules. Furthermore, even though micro-fluidic reactor allows performing reactions at higher temperature than the boiling points of the reaction mixture, pressure variations begin to appear around 130°C. Consequently, we are currently investigating the reaction under basic conditions and different solvent systems. The reaction will also be explored with [18F] fluorobenzaldehyde as labeling precursor.

Research Support: Acknowledgements : Dr. Ralf & Esther Schirrmacher from McGill University (Montreal, ON) for providing the peptide.

P407 99mTc(CO)3-LABELED MULTIFUNCTIONAL MICELLE AS A POTENTIAL RADIOTRACER AND DRUG CARRIER TARGETING TO CANCERS

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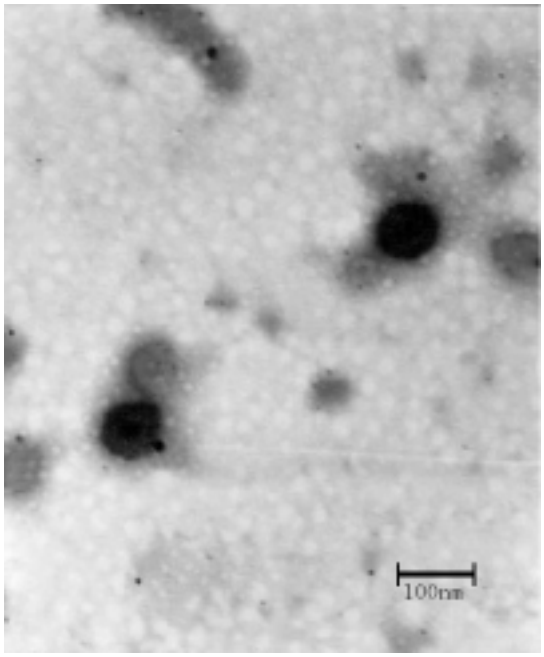
Objectives: This study is to develop a novel drug delivery system based on multi-functional block copolymer component, Aptamer-poly(ethylene glycol)-b-poly(2-Hydroxyethyl methacrylate-co-$^{99m}Tc(CO)_3$-histidine-poly(D,L-lactide) (abbreviated as Aptamer-PEG-b-P(HEMA-co-$^{99m}Tc(CO)_3$-histidine-PLA). The half-life of the micelle system consisting of the novel copolymers should be extended in blood circulation to target the cancer cells by EPR (enhanced permeability and retention) effect and active binding of aptamer with cancer receptor. The aptamer, AGRO100 is an anticancer drug on clinical trial which can bind to specific cellular proteins. This drug delivery system would have a revolutionary impact on cancer diagnosis by imaging from the labeled ^{99m}Tc. In addition, the structure of the micelle inner core would do-form from polymer phase transition induced by intracellular pH change after cancer cell uptake. We will establish this drug delivery system with advancing in this study in the use of selectively targeting aptamer for bioimaging and cancer therapy.

Methods: Histidine is characterized as a good chelator which easily and very efficiently tethers to $[^{99m}Tc(H_2O)_3(CO)_3]^+$ through the spacer at the tripodal ligand. Furthermore, histidine is a biodegradable and pH-sensitivity molecule. Aptamer-PEG-b-P(HEMA-co-histidine-PLA) was synthesized via free-radical copolymerization in a macroinitiator by combining HEMA monomer, histidine-EMA and PLA-EMA. Through a solvent exchange process by dialysis, the amphiphilic copolymer can be self- assembled to a core-shell structure micelle. $^{99m}Tc(CO)_3$ can be further labeled to histidine in the polymeric micelle.

Results: Aptamer-PEG-b-P(HEMA-co-histidine-PLA) was synthesized by free radical polymerization with yield about 84%. The chemical structure of the copolymer, PEG-b-P(HEMA-co-histidine-PLA) was verified from ^1H-NMR ($CDCl_3$, ppm): d 1.41–1.59 (m, CH_3 from PLA); d 3.40–3.63 (s, CH_2CH_2O from PEG); d 3.75–3.95 (m, CH_2OH from HEMA); d 4.16–4.21 (m, OCH_2CH_2O from HEMA conjugated with PLA or histidine); d 5.11–5.19 (m, CH from PLA); d 6.7–6.9 (m, NCHC from histidine side chain). The TEM image of the micelle suggests the dark region of the block co-polymer being the inner core and the hydrophilic segments of PEG being the extended outer shell. The micelle system would retain a hydrophilic outer shell for avoiding mononuclear phagocyte recognition and a double-layer inner core for responding bioenvironmental stimulus. The diameter of the micelle was measured to be 77.9 ± 1.9 nm by a Dynamic Light Scattering (DLS) instrument.

Conclusions: The micelle system is to be designed for the applicability in diagnosis and therapy of tumors. We have synthesized and obtained the functional copolymers. The multifunctional micelles are further successfully prepared by a dialysis process. The TEM image shown in Fig1 reveals the spherical shape and the size of the micelles which are suitable for intravenous injection. Further incorporation of $^{99m}Tc(CO)_3$ and anticancer drug into the micelles is anticipated to be readily realized.



P408 REACTOR SCALE EFFECTS ON F-18 RADIOLABELING

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Objectives: The micro-reactor system has the following reported advantages: less reagent use and, faster synthesis [1]. Proofs of the use of microfluidic technology in PET chemistry have been published [2,3]. One question posed for microfluidic technology is whether it can be used to produce large doses of ^{18}F- labeled compounds to compete with commercially available automated chemistry units used in typical PET centers [1]. In this work we explore the advantages of replacing a standard reactor (total volume in the milliliter scale) with a micro scale reactor (total volume in the microliter scale) on a commercially available automated chemistry unit for the synthesis of ^{18}F- labeled compounds.

Methods: A micro scale batch reactor (volume of approximately 60 microliters) was utilized to synthesize [^{18}F]FLT. The other components of the system, such as [^{18}F] fluoride ion isolation, and reagent delivery system are from a commercially available automated chemistry system. [^{18}F]FLT was synthesized with starting [^{18}F] fluoride ion activity of 1 mCi, 1 Ci, and 4 Ci.

Results: Our results indicate that the use of a micro-reactor in place of a conventional sized reactor leads to less reagent use, comparable yields and comparable synthesis times when producing high doses of a typical ^{18}F- labeled compound.

Conclusions: Our experimental results indicate that we can bring in the advantage of a micro scale reactor's superior heat transfer and mixing efficiency into a conventional automated chemistry system to optimize radiolabeling. On going work indicate that synthesis yields can be further improved.

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