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DESIGN, DEVELOPMENT AND EVALUTION OF A SIMPLE SEMI-AUTOMATED SYSTEM FOR [^{18}F]-FLUOROCHOLINE SYNTHESIS

(Reka bentuk, pembangunan dan penilaian sistem pensintesis [^{18}F]-Fluorocholine separa automatik)

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Abstract

Positron Emission Tomography (PET) scanning are usually conducted with [^{18}F]-fluoro-2-deoxyglucose (FDG) as tracer. The [^{18}F]FDG exhibits several weakness in detecting certain type of tumours such as brain tumour and prostate metastasis. In this study, [^{18}F]-fluorocholine (FCH) has been identified as an alternative to [^{18}F]FDG. The absence of specific synthesizer for FCH production hampers the application of this tracer in PET studies at local premises. This study focuses on the development of the [^{18}F]FCH synthesizer prototype and the [^{18}F]FCH synthesis. The design would emphasize on its simplicity, relatively low cost, semi-automated synthesis and purification, as well as good reliability and safety. The [^{18}F]FCH was synthesized in two steps approach; reacting [^{18}F]-fluoride with dibromomethane into [^{18}F]-fluorobromethane before purification using Sep-Pak silica cartridges and finally converted into [^{18}F]FCH by reacting with N,N-dimethylaminoethanol. The synthesizer are successfully developed and able to achieve decay-corrected radiochemical yield of 10.131 % in under 110 minutes. Optimization of the radiochemical yield is still underway.

Keywords: [18F]-fluorocholine, remotely operated synthesizer, positron emission tomography, radiopharmaceutical

Abstrak

[^{18}F]-fluoro-2-deoxyglucose (FDG) secara amnya digunakan sebagai penyurih dalam imbasan menggunakan tomografi pancaran positron (PET). Penyurih ini mempunyai beberapa kelemahan dalam mengesan jenis kanser seperti tumor otak dan tumor prostat. Disebabkan oleh faktor ini, [^{18}F]-fluorokolina (FCH) telah dikenal pasti sebagai penyurih alternatif. Namun disebabkan tiada pensintesis FCH yang khusus, ia tidak dapat diaplikasikan sebagai penyurih PET di hospital tempatan. Kajian ini dijalankan bertujuan untuk menghasilkan prototaip pensintesis [^{18}F] FCH dan mensintesis [^{18}F] FCH. Reka bentuk prototaip ini tertumpu pada keringkasan, kos yang rendah, sintesis dan penulenan secara separa automatik, serta faktor keselamatan.[^{18}F]FCH telah di sintesis menerusi dua peringkat; [^{18}F]-fluorida di tindakbalas dengan dibromomethana menghasilkan [^{18}F]-fluorobromethana sebelum penulenan menggunakan kartrij silica Sep-Pak. Kemudiannya [^{18}F]-fluorobromethana di tindakbalas dengan N,N-dimethylaminoethanol menghasilkan [^{18}F]FCH. Pensintesis [^{18}F]FCH telah berjaya dihasilkan dan [^{18}F]FCH dapat dihasilkan pada kadar 10.131 % dalam 110 minit. Penghasilan FCH secara optima masih dalam kajian.

Kata kunci: [18F]-fluorokolina, pensintesis kawalan jauh, tomografi pancaran positron, radiofarmaseutikal

Introduction

Cancer has becomes an increasing health problem in Malaysia. It is estimated that one out of four people in Malaysia will develop cancer at certain age of one's life [1, 2]. In order to provide improved quality of life for the cancer patient and ultimately to reduce the mortality, emphasis has been given to detect and delivers effective treatment at early stage of cancer development. In recent years, positron emission tomography (PET) has gained

considerable interest as a mean of cancer imaging tool in Malaysia. PET studies can provide functional information using radio-labelled tracer, especially using [^{18}F]-fluoro-2-deoxyglucose ([^{18}F]FDG) [3].

It is undeniable that [^{18}F]FDG alone is insufficient in solving all diagnostic oncological problems faced by mankind. There are other PET radiopharmaceuticals with large potential that can be used as a tool to explore various metabolic pathways [4, 5] such as [^{18}F]-Fluorocholine ([^{18}F]FCH). According to Hara [6], the radiopharmaceutical has been proven to be of usefulness, if not beyond doubt, but because there is no specific synthesizer to produce [^{18}F]FCH available in local hospitals and institutes, the production of the pharmaceutical in Malaysia has been hampered.

Even though it has been proven that [^{18}F]FDG is quite competent to be used as PET tracer, it still has several weaknesses. Reports such as by Price et al., Picchio et al., and Reske et al. [7-9] have shown that [^{18}F]-Fluorocholine or [^{18}F]FCH is more capable than [^{18}F]FDG to detect both primary and metastatic prostate cancer. Other reports also suggested the clinical usefulness of [^{18}F]FCH compared to [^{18}F]FDG, especially in brain metastases [10].

The [^{18}F]FCH was first successfully synthesized by DeGrado et al. [11] by reacting N, N-dimethylaminoethanol with 1-[^{18}F]fluoro-2-bromomethane ([^{18}F]]FBM). To the best of our knowledge, there are two methods of [^{18}F]FCH synthesis reported so far. The first method [11, 12] involves the reaction between [^{18}F]-fluoride with dibromomethane, at temperature 100 °C to produce [^{18}F]FBM. The precursor is then purified by Gas Chromatography (GC) before it is allowed to react with 2-dimethyl aminoethanol (DMAE), thus producing [^{18}F]FCH. The radiochemical yield was reported to be 20 -40 % (not decay-corrected) under 40 min.

The second method employs the use of [^{18}F]-fluoromethyl triflate. Iwata et al. [13] has reported a method to purified [^{18}F]FBM simply by just using disposable Solid Phase Extraction (SPE) cartridges before the [^{18}F]FBM is conveniently converted to more reactive [^{18}F]fluoromethyl triflate, in order to synthesize [^{18}F]FCH. The [^{18}F]FBM is converted to [^{18}F]fluoromethyl triflate by passing the freshly purified [^{18}F]FBM through a preheated (200 °C) column impregnated with silver triflate (AgOTf). The radiochemical yield at the end of synthesis is within 54-67 %. The time of synthesis is less than 30 minute.

Other choline-analogues such as [^{18}F]fluoroethylcholine ([^{18}F]FEC) and [^{18}F]propylcholine have been synthesized by using ethyl bromide and propyl bromide respectively [12]. Another method involves the use of ethyl tosylate as precursor has been used to synthesize [^{18}F]FEC [14-16]. However, [^{18}F]FEC has so far seemed holds no significant clinical advantages over [^{18}F]FCH [12, 14]. DeGrado et al. reported that the uptake of FCH and choline in cultured prostate cancer cells were comparable, whereas uptake of FEC was approximately one fifth of FCH. Therefore, [^{18}F]FCH has potential to be used in PET technique.

Currently, cyclotron-PET facilities in Malaysia have only produce [^{18}F]FDG for their routine clinical use. In order to address this deficiency there is effort to synthesis other tracer such as 3, 4-dihydroxy-6-^{18}F-fluoro-L-phenylalanine ([^{18}F]FDOPA) by Hospital Putrajaya. From the practical points of view, it is hoped that with a home-made synthesizer that is competitively simple and low cost, that the best solution for the problem could be paved.

Materials and Methods

Components of the Synthesizer

The [^{18}F]FCH synthesizer module consists of two separate plant; namely processing plant and reagent plant. The processing plant is installed inside the hot-cell, where all the process that involves contact with radioactive material are being done, while the reagent plant is use to introduce non-radioactive chemicals into the processing plant. The reagent plant is connected to the processing plant via tygon silicon tubing through special ports at the side of the hot-cell.

Two-way (PN: EW-98302-12) and three-way (PN: EW-98302-12) solenoid operated pinch valves, tygon silicone tubing (PN: EW-95702-01), as well as needles with non-coring deflected tips (PN: EW-25701-32) were purchased from Cole-Palmer. Stainless steel straight barbed connectors (PN: EW-31208-00), y barbed connectors (PN: EW-

31209-55) and tee barbed connectors (PN: EW-31208-31) from Cole-Palmer are used to connect between tubing wherever tolerance to chemical and high temperature are required. We use stainless steel female luer lock with hose barb (PN: EW-31507-29) and male luer lock with hose barb (PN: EW-31507-26) from Cole Palmer to connect Sep-Pak cartridge and needle to tubing. In the same manner, polypropylene straight barbed connectors (PN: P-06365-11), y barbed connectors (PN: EW-30726-41) and male luer lock with hose barb (PN: P-45503-00) are used in less demanding area.

The electrical parts of the synthesizer consist of toggle switches (PN: 320-922), control panel (PN: 580-411), junction box (PN: 580-398), LED indicator (PN: 250-106); all purchased from RS Component, and DC power supply (PN: RS-75-24) from Mean Well. The air process heaters (PN: 200-2496), digital temperature controllers (PN: 461-206) and thermocouple type J (PN: 455-4270) were purchased from RS Component to form the heating system for the synthesizer. The pinch valves were connected to the power supply, toggle switches, LED indicators and manually operated by opening the switches. By applying pressure and vacuum through the tubing, and opening the desired valves, the movement of the fluid is controlled inside the synthesizer from one point to another.

Reagents for Synthesis

Anhydrous acetonitrile, dibromomethane, N,N-dimethylaminoethanol, potassium carbonate, ethanol, 0.85% saline solution, Kryptofix 2.2.2, and ethanol were purchased from Sigma-Aldrich. All chemical were used without any further purification. Sep-Pak plus tC18, Sep-Pak plus Silica, Sep-Pak plus Accell plus CM, and Sep-Pak light QMA Carbonate cartridges were obtained from Waters. The Sep-Pak Accell plus CM cartridge was conditioned with 5 mL HCl 0.5N and were rinsed with 10 mL ethanol prior to synthesis. The Sep-Pak Silica and QMA Carbonate were used without preconditioning.

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[^{18}F]-Fluoride Production

The no carrier added [^{18}F]-fluoride was produced by using a PETtrace cyclotron (GE, Uppsala) at Hospital Putrajaya. A beam of 16.5 MeV proton was allowed to bombard the target material, [^{18}O]-water; thus producing the [^{18}F]-fluoride via ^{18}O(p,n)^{18}F nuclear reaction. The [^{18}F]-fluoride was then delivered into the GE TRACERlab MX FDG synthesizer and collected into a 10 mL sealed vial, readily put inside a lead pot. The lead pot was then placed inside a transport box before transported to Malaysian Nuclear Agency. Upon arrival (transit time ~ 30 min), the radioactivity of [^{18}F]-fluoride will be determined using radioisotope calibrator (Capintec CRC-712MH) before being transferred into the hot-cell prior to synthesis.

Results and Discussion

Development of the Synthesizer

The [^{18}F]FCH synthesizer are based from several criteria as following: a) relatively easy to develop, b) user friendly, c) high radiochemical yield and purity, d) relatively low cost, as well as e) safe and reliable.

The basic functions of the synthesizer are: a) introduction of [^{18}O]-water into the system, b) separation of [^{18}F]-fluoride from [^{18}O]-water; the most commonly method to do it is by using an anion exchanger resin, c) elimination of water traces by using azeotropic distillation, d) nucleophilic substitution between [^{18}F]-fluoride and precursor forming radiolabeled intermediate, e) intermediate purification using silica cartridges, f) methylation process of N,N-dimethylaminoethanol (DMAE) with intermediate, g) product purification by using cation-exchange resin, and g) purification of final product.

Based on the literature review, several models of the synthesizer specific for the [^{18}F]FCH would be designed and considered. From these models, a final model would be carefully selected and further modified. Materials needed for the development of the synthesizer were identified and purchased and materialization of the synthesizer was based on the final design.

The synthesizer is consists of two major parts. The first part is the processing plant, where all processes that involved radioactivity were done in a hot cell (Figure 1). The other part is the reagent plant (Figure 2), where all the chemicals, stored in conical vials were transferred into the hot cell via tygon silicon tubing through special ports at the side of the hot-cell. This design has some advantages over single, non separated design especially during

synthesis. It allows reagents to be freshly prepared or changed even when the synthesis process has started. It also contributes to smaller dimension, allowing it to fit into smaller hot cell, since almost all the reagents were located outside of the hot cell.

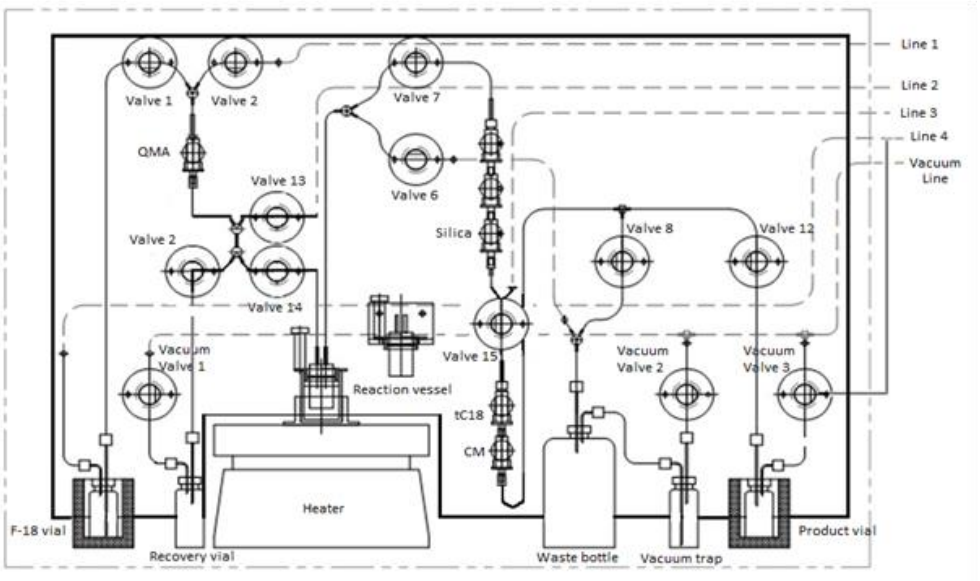

Figure 1. The processing plant of the synthesizer for [^{18}F]-FCH. The synthesizer is remotely operated by opening certain valves allowing the pressurized carrier gas to transfer the fluid from reagent plant into certain part of synthesizer for the desired process to happen

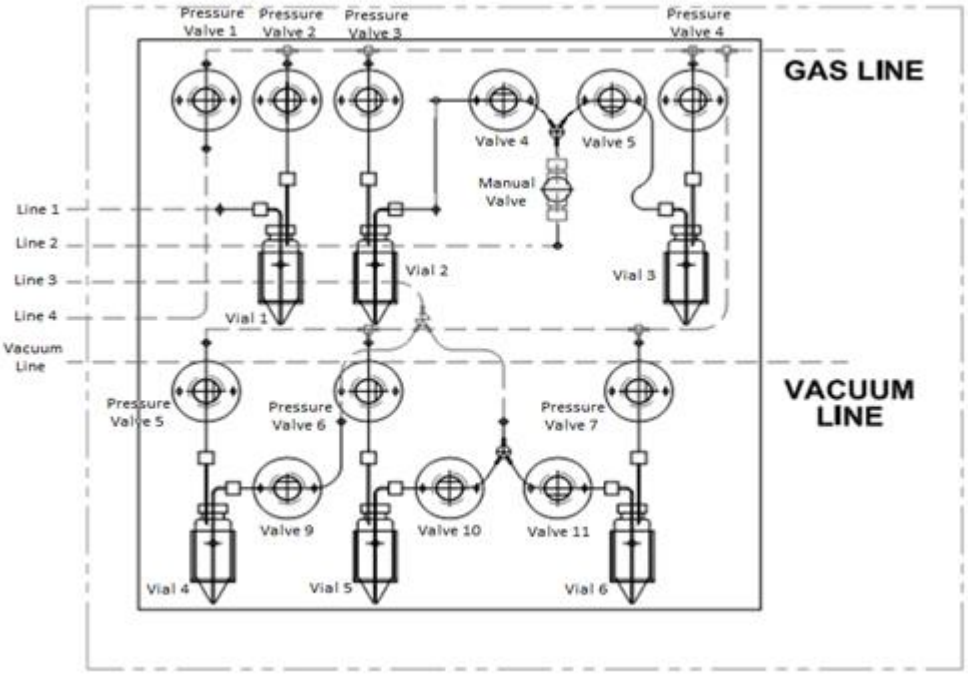

Figure 2. The reagent plant acts as a loading station for the [^{18}F]-FCH synthesizer where all the chemicals except for *N*,*N*-dimethylaminoethanol are loaded into their respective vials.

All seven reagents except DMAE were put into disposable 20 mL glass vials and sealed using butyl rubber septa and aluminium crimps. In order to optimize extraction from the flat bottom vials, they are later modified into conical vials with the assistance of the glassblower team. B1 vial contains K_2CO_3 solution, B2 contains acetonitrile, B3 contains primary precursor, B4 contains ethanol, B5 contains purified water, and B6 contains saline solution. Each vial was punctured with a pair of needles prior to synthesis, which one of the needle will penetrate until it reach the bottom of the vial and the other will penetrate just deep enough for the gas to flow.

The fluids are transferred into the processing plant through tygon tubes (internal diameter 1/16 inch) by blowing carrier gas (in our case, oxygen-free nitrogen) and under suction of vacuum, created using a mini venturi pump, connected to L5 line. When VP1 valve is opened, the nitrogen gas will flow through the tubing and creating positive pressure at [^{18}F]-fluoride vial. By opening V1, V2, VC1 valves, the positive pressure inside the vial and the negative pressure created by vacuum would force [^{18}F]-fluoride into tubing. The [^{18}F]-fluoride would be trapped at Sep-Pak QMA cartridge (anion exchange resin) while [^{18}O]-water would passed through the cartridge and finally collected in the water recovery vial. In the same manner, by controlling which valves to be opened, the direction of the fluid flow can be precisely manipulated for any desired process.

Simulations were run using sterile water to verify that the synthesizer; a) have proper tubing connections and ensure no leakage occurred as well as b) showed intended flow direction. Correction actions were taken to rectify the problems founds. The finished prototype is shown in Figure 1. The dimension of the synthesizer is 0.46m (length) x 0.5m (height) x 0.14m (wide) for the reagent plant and 0.74m (length) x 0.50m (height) x 0.5m (wide). The cost of the synthesizer is estimated around RM 30, 000.

Calibration of the Heating System

One of the critical components of the synthesizer is the heating system. In the [^{18}F]FCH synthesizer, there are at least two occasions where heating are required. The first heating event happened during the azeotropic distillation, where the mixture of [^{18}F]-fluoride, solution of 33 mM K_2CO_3 and acetonitrile are heated. The second heating are required for reaction between anhydrous [^{18}F]-fluoride with dibromomethane. Therefore, the heating system must be able to achieve accurate and consistent required temperature in order for the synthesizer to function as it should be.

There is a wide range of suggested temperature for the first heating process (evaporation process) from 110 ºC [13], 100 ºC [14], 95 ºC [17] and 90 ºC [18]. The second heating process did not have specific temperature, as the reaction temperature is the manipulated variable for the synthesis. Based from Kryza et al. report, we set the temperature range to be within 70-90 ºC.

It is worth mentioning that since both heating process were not done simultaneously and both processes were done at the same vessel, normally only one heating system is required to do both jobs. Among the heating methods use for synthesis PET fluoro-compound are oil bath for example use by Iwata et al. [13], stream of heated air such as showed by Cheung and Ho [19] and heating tape for example use by Ahmed et al. [20].

We have tested oil bath method using 20 mL silicone oil as heating medium in a custom-made glass cup. The temperature controller was connected to a hotplate and the controller would receive input from a thermocouple soaked in the medium, where once the targeted temperature has been achieved, the controller would cut off power supply to the hotplate. Unfortunately, reliable temperature could not be achieved by using this configuration since temperature fluctuations were high (data not shown). Thus the air process heater is used as an alternative, as it was proven as a success in previous studies.

The new heating system using the air process heater worked principally the same as the hotplate system, instead of using hotplate, air process heater was used where hot air passed through a custom-made inner glass tube (open at the top) surrounded by a glass jacket. The heated air is circulated within the jacket and the heat is transfer from the glass tube to the silicone oil (Figure 3). Once this heating concept has been proved successfully, the glass tube and the jacket were replaced with stainless steel tube and jacket.

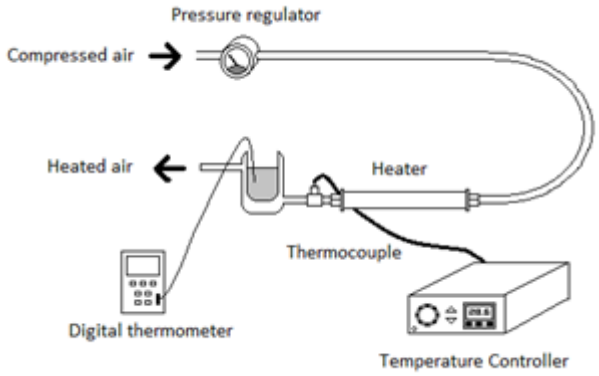

Figure 3. Simplified diagram of the air process heater for the synthesizer. The compressed air is passed through the heater and the temperature of the air is measured with thermocouple probe, which is connected to the temperature controller. The actual temperature of heating medium is measured using digital thermometer.

The heating system was tested and calibrated using a digital thermometer. The heating system showed good accuracy, consistent performance and stable temperature. However, it is found later that the heater required about 30 minute to achieve designated temperatures from ambient temperature (Figure 4), thus two set of heaters are used, one is for evaporation process (Heater A) and the other is for the fluorination process (Heater B). Nevertheless the results showed that the temperature has to be set higher than the required temperature, as a result of heat loss. Therefore, through a series of try and errors, a balance of temperature set and actual temperature of the heating medium is obtained (Figure 5). The calibration curve is then tested and the results are showed in Table 1.

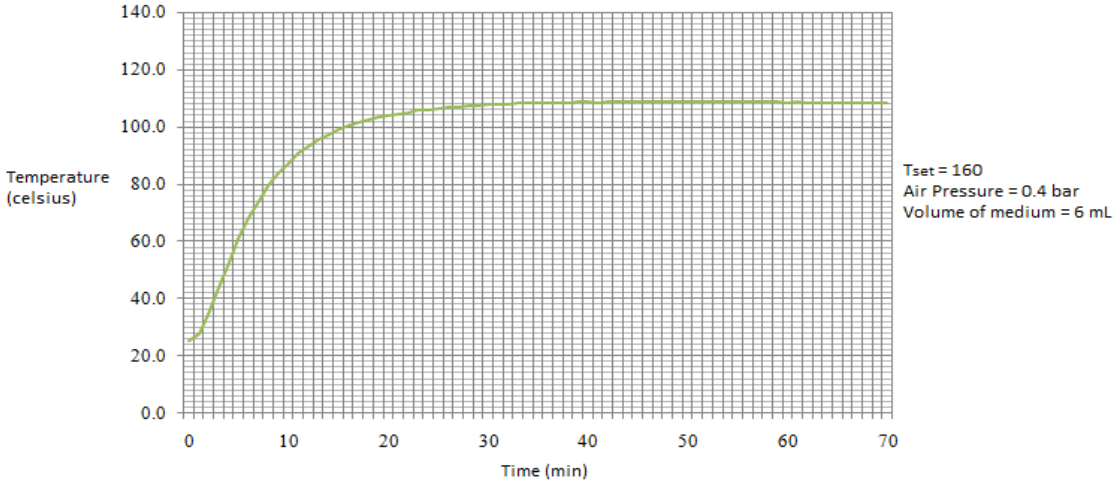

Figure 4. Temperature profile of heating system of the synthesizer. Note that the heating system required about 30 min before it reached equilibrium, thus making double heater system a necessity in order to achieve consistent heating for both the azeotropic distillation and fluorination process.

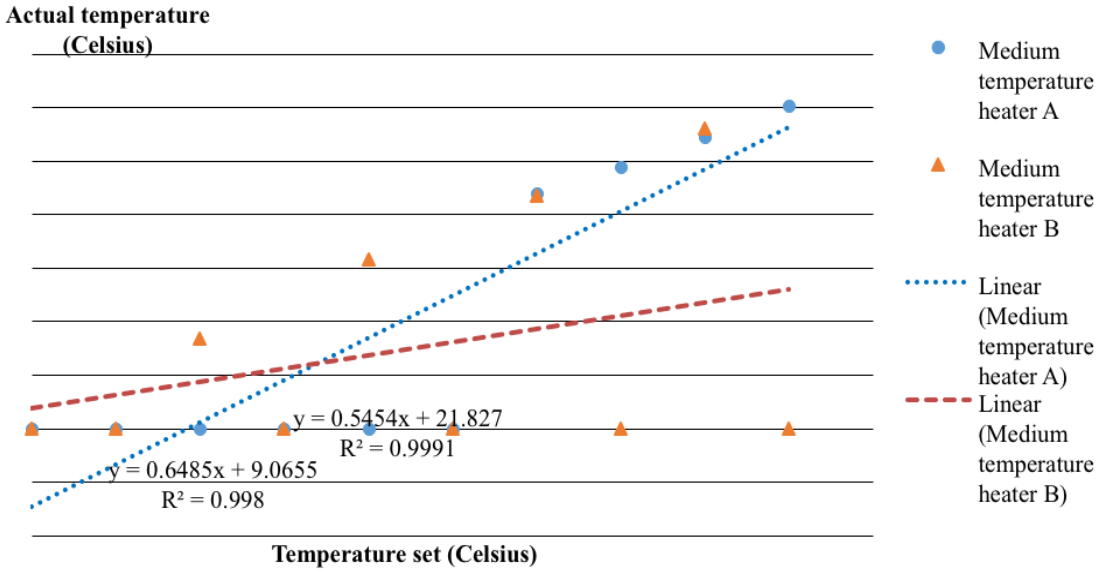

Figure 5. Calibration of the heating system of the synthesizer. The required temperature of the heating medium is achieved by increasing the temperature set at the temperature controller.

Table 1. Validation of the heating system based on value calculated from calibration curve of the heating system.

$T_{require}$	T_{set} (°C)	$T_{measure}$ (°C)[b]
110	161[a]	111.342 ± 0.149
90	125	90.630 ± 0.333
80	109	80.822 ± 0.263
70	94	72.498 ± 0.272

a – Data obtained from heater A. The rest are performed on heater B,
b – Measurements were made from 30th to 90th min after the heater is on.

Synthesis of [^{18}F]FCH

The trapped [^{18}F]-fluoride was eluted from the cartridge by using 1 mL K_2CO_3 solution (33 mM) at B1 vial into the reaction vessel. Then 1 mL acetonitrile was added inside the vessel and the mixture was heated at 80-90 °C until dried. The process is repeated three times to ensure no residual water was left for the next process. Primary precursor (CH_2Br_2) was added to reaction vessel and allowed to react for 6 minute at temperature of 80-90 °C (based from Kryza et al.). The labelled intermediate was then transferred to triple Sep-Pak silica cartridges for separation of labelled and unlabelled compounds. The labelled compound were directed to tC18 cartridge containing 400 µL DMAE and the product is trapped at Sep-Pak CM cartridge by 10 mL ethanol elution. The cartridges were rinsed with 15 mL purified water. Final step is involving the elution of the product into the product vial by 3 mL 0.85% saline solutions. Data of the synthesis is shown in Table 2.

The resulted radiochemical was lower than originally anticipated. The highest yield achieved is only 1.446 %. In contrast to Kryza et al. [17], they reported non-corrected yield of 15-25 %. Since manipulating the amount of

precursor and solvent, reaction temperature and time, as well as evaporation temperature and time did not give significant increase in radiochemical yield, we suspect the problem lie in QMA carbonate cartridge that we used, compare to ordinary QMA cartridge used by other groups. However, further study proved that was not the case as more than 80% of the activities were collected at the reaction vessel and less than 0.2 % was trapped at the cartridge after elution (Table 3). Another study showed that there is still a significant activity left at the reaction vessel, 78.923 % after a complete synthesis was done (Table 4). The result suggested that the low yield was probably contributed by incomplete reaction between [^{18}F]-fluoride and the precursor.

Table 2. Effect of quantity of precursor, reaction temperature, evaporation time on radiochemical yield of [^{18}F]FCH

Quantity of CH_2Br_2 (µL)	**Reaction Temperature (°C)**	**Evaporation Temperature (°C)**	**Evaporation time (min)**	**Corrected Yield (%)**
300	80	90	10x3 (+ 15 mg K_{222})	0.089
700	80	90	10x3 (+ 15 mg K_{222})	0.193
700	80	90	15x3 (+ 15 mg K_{222})	0.100
700	80	80	15x3 (+ 15 mg K_{222})	0.291
700	90	80	15x3 (+ 15 mg K_{222})	0.334
100/1 mL asetonitrile	90	80	15x3 (+ 15 mg K_{222})	0.024
200/0.5 mL asetonitrile	90	80	15x3 (+ 15 mg K_{222})	0.206
1000	90	80	15x3 (+ 15 mg K_{222})	1.446

Table 3. Activity distribution of [^{18}F]F vial, Sep-Pak light QMA Carbonate cartridge, collection vial and reaction vessel after elution

Component	**Radioactivity (decay corrected), mCi**		
	Sample 1	**Sample 2**	**Sample 3**
[^{18}F]F vial before elution	7.610	5.550	7.080
[^{18}F]F vial after elution	0.154	0.030	0.076
Cartridge after elution	0.008	0.004	0.007
Collection vial	0.033	0.023	0.025
Reaction vessel	6.750	5.000	5.890

Table 4. Activity distribution of components of the synthesizer after a complete synthesis run. Note that majority of the remaining activity is concentrated at reaction vessel

Component	Measured radioactivity (mCi)	Corrected radioactivity, A (mCi)	A/initial activity x 100%
[^{18}F]F$^-$ vial	2.110	5.893	8.007
QMA cartridge	0.042	0.132	0.179
Reaction vessel	19.900	58.087	78.923
Silica cartridges	0.459	1.491	2.026
tC18 cartridge	0.004	0.012	0.016
Accell CM cartridge	0.001	0.003	0.004
Product vial	0.069	0.188	0.255

Table 5. Effect of reaction temperature and flow rate of carrier gas on radiochemical yield of [^{18}F]FCH

Quantity of CH_2Br_2 (µL)	Reaction Temperature (°C)	Evaporation Temperature (°C)	Flow rate (mL/min)	Corrected Yield (%)
600	80	90	140	1.636
600	90	90	140	2.427
600	80	90	30	7.719
600	90	90	30	8.113
600	100	90	30	10.131

The results listed in Table 2 were obtained when the radiopharmaceutical was produced under high flow rate setting (>100 mL/min of carrier gas). When the flow rate decreases to 25mL/min during elution process from the triple Sep-Pak silica cartridges, it was observed that there was a significant increase of radiochemical yield (Table 5). These results suggest that low flow rate allows more time for the radiolabelled intermediate to react with DMAE, thus increasing the yield. However, all our attempts to further increase the yield were unsuccessful.

The product was analyzed using HPLC system (column C18 4.6 x 150 mm^2, acetonitrile: ammonium formiate 0.1 mol/L at 79:21). From the radiochromatograph, it is clear that the radiochemical purity of the [^{18}F]-fluorocholine produced by using our synthesizer is high; >99% (Figure 6). No other peaks were found. Retention time is 4.32 min. When we injected a pure [^{18}F]-fluoride into the HPLC system, we find a good separation between [^{18}F]-fluoride and [^{18}F]-fluorocholine, with retention time = 1.56 min.

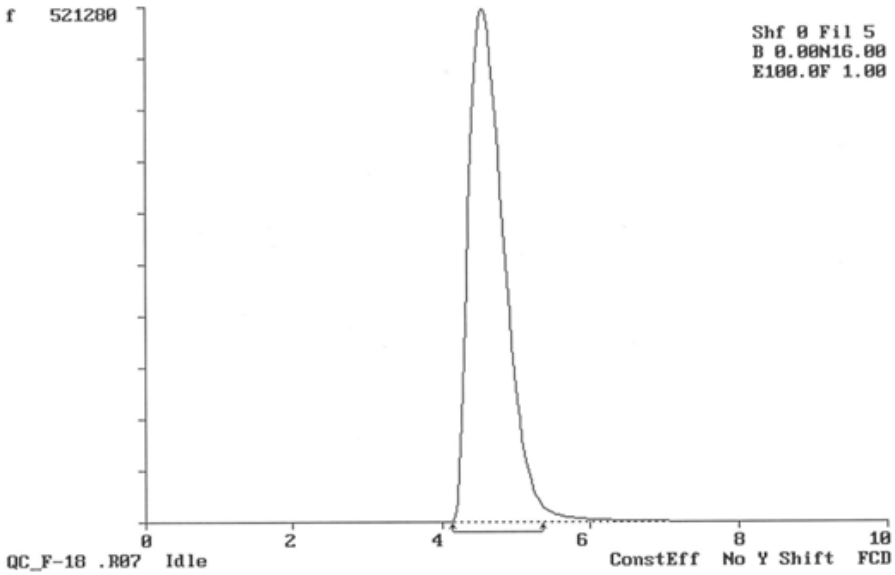

Figure 6. Radiochromatogram of the [^{18}F]FCH synthesized

Conclusion

We have managed to develop a remotely controlled lab-scale [^{18}F]FCH synthesizer that is relatively low cost and simple to operate. The synthesizer is divided into two major parts, namely the processing plant where all the processes of synthesis are done and the other part is the reagent plant that serves to introduce the chemicals into the processing plant. Two set of air process heaters are used for the synthesizer and the heating system provides good accuracy, consistent performance and stable temperature. Synthesis of [^{18}F]FCH were done with two steps approach, by adding dried [^{18}F]-fluoride with dibromomethane to produce [^{18}F]-fluorobromethane before converted the radiolabeled compound into [^{18}F]FCH by reacting with N,N-dimethylaminoethanol. We were able to achieve decay-corrected radiochemical yield of 10.131% under 110 min and the radiochemical purity achieved is high; >99%. The low radiochemical yield warrants further analyses and optimization is still underway.

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