DEVELOPMENT OF NEW COMBINED SYSTEM FOR PRODUCTION OF FDG AND NaF RADIOPHARMACEUTICALS

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Abstract

In this work, we present a new combined system which produces FDG and NaF in separate runs. The needed ^{18}F for synthesis these radiopharmaceuticals are obtained by bombardment of highly enriched water (H_2O_{18}) with proton. The aim is development of routine systems to use with baby cyclotrons. In this study, the various chemical steps and required reagents as well as different reagent delivery methods has been investigated. This evaluation has been done with purpose of optimizing the performance of a conceptually simple device integrated into a fully automated synthesis procedure for radiosynthesis of FDG and NaF. In this system, we have used AVR microcontroller to control the process and LabVIEW software for monitoring the operation of system. Furthermore, Geiger Muller counters have been used to determine the activity to insure the accuracy of the systems operation.

Keywords: FDG and NaF radiopharmaceutical, AVR microcontroller, LabVIEW, Geiger Muller counter, highly enriched water.

INTRODUCTION

^{18}F-FDG is the most important radiopharmaceutical used in oncology for early diagnosis of cancers and for assessing response to therapy. But ^{18}F-FDG has known limitations in detecting blastic malignant skeletal lesions. The initial staging of patients diagnosed with certain cancers includes imaging with ^{18}F-FDG PET and ^{99m}Tc-methylenediphosphonate (^{99m}Tc-MDP) bone scintigraphy as separate studies. ^{99m}Tc-MDP bone scintigraphy is the method of choice for evaluation of osseous metastases, since it allows a whole-body survey at a relatively low cost.

^{99m}Tc-MDP conventional planar image have limitations related to spatial resolution and lack of specificity. However, recently the combined technology like PET-CT is used to better localizing the diagnosed cancer. Since all nuclear medicine centers are not equipped with PET-CT and/or they intend evaluate the possible bone metastasis while assessing response to therapy, the use of ^{18}F-NaF PET is considered as a suitable radiopharmaceutical for PET bone scans which has been approved by the Federal Drug Administration in February 2011. In several studies the role and efficiency of the combined ^{18}F-FDG/^{18}F-NaF PET/CT for detection of malignancy was compared to ^{18}F-FDG PET/CT and showed that the sensitivity for detection of osseous lesions or skeletal disease was increased compared to the separate ^{18}F-FDG PET/CT scans. So the simultaneous availability of ^{18}F-FDG and ^{18}F-NaF are important for PET centers. The commercially available synthesis modules like Simians EXPLORA FDG[4], GE-FDG-MX, GE-FDG-FX or GE-FDG FastLab have limitation to produce ^{18}F-NaF. So this radiopharmaceutical should be produced manually or by using a separate available kit-based module or a homemade one [1-3].

In this project we decide to design a synthesis module with capability of producing of both ^{18}F-FDG and ^{18}F-NaF by one time load to produce them in the same day.

MATERIALS AND METHODS

In order to designing and construction of an automated synthesis module, considering of following points are necessary.

Hardware

The set up of the apparatus is shown schematically in Fig. 1. Part (a) and part (b) are relevant to producing ^{18}F-NaF and ^{18}F-FDG respectively. Manipulation of all reagent solutions and solvents is performed by a vacuum and pressure of auxiliary gas (helium).

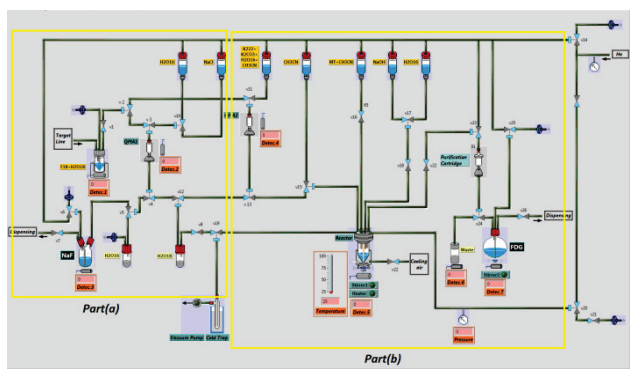

Figure 1: Schematic of the automated system for synthesis of ^{18}F-NaF (Part (a)) and ^{18}F-FDG (Part (b)).

Since the labeling of [^{18}F] fluoride onto Mannose Triflate (fluorination) is occurred at the reaction vessel, so this vessel is an important portion in a module. Therefor designed reactor must be covering several properties like

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as: high purity, chemically inert, withstand a temperature range of +20 °C to +120 °C, high thermal conductivity, good resistance to chemical corrosion, low density, impermeability to gases and liquids and small dead volume.

In this design, a cylindrical reactor with dimensions of 1.6 cm×10 cm will be made of Pyrex (Type A) and a heading in the upper region of the reactor will be made of PEEK. This heading will be sealed by an O-ring (from Bio-Chem Valve) into the glass vessel. There are 6 pieces fittings for fixing the tubes in order to entry and exit of gases and reagents into the reactor. A container made of steel will be considered around the glass vessel. Heating the reactor is done by twisting a coil around the steel case. In order to cooling the reactor, two narrow channels will be placed on the top and bottom of a Teflon container. These channels transmit compressed air into the empty space between steel case and Teflon container. Finally all the mentioned components will be surrounded by a lead shield, and a Geiger detector will be used in this shield for monitoring the activity changes within the reactor. Also, a stirrer (from Cole-Parmer) will be placed in the bottom of the reaction vessel for mixing the contents of the reactor. A diaphragm vacuum pump (down to 1.5 mbar, from KNF) and a cooling trap filled with liquid nitrogen are used to evacuate the reactor and trapping volatile radioactive substances. In order to control of pressure in different parts of the system, we use three regulators until suitable pressures (0.5 – 5 bar) are produced for desired sections. The fluids are transferred through capillary tubes (about 1 mm in diameter). These used tubes are colored (red, blue and green), so that line identification and fault detection of module will be easy. The sequence of steps in this synthesis module is managed by controlling of 27 solenoid electric valves, inclusive of 10 two-way valves (normally closed, from Cole-Parmer) and 17 three-way valves (normally closed and normally open, from Cole-Parmer). All tubing and valves were made of inert PTFE. For immediate monitoring of temperature and pressure in the reaction vessel will use suitable sensors. Two pieces of ^{18}F separation cartridges (from Isoflex) will be used. These ion exchange columns trap [^{18}F] fluoride for production of ^{18}F-FDG and ^{18}F-NaF. Also FDG purification cartridge for base hydrolysis (from Isoflex) is used for cleanup of the final product. The 7 Geiger detectors are considered in this module. All the mounted detectors will be shielded to minimize the external radiation influences. These detectors provide an opportunity to display the radioactivity level in different parts of module and determine the efficiency of production.

Indeed all the components were carefully selected to obtain best results. In other words the components of the synthesis module will be combined to achieve the shortest connections and smallest dead volumes for minimizing the production time and thus maximizing the efficiency. Also all the components (valves, tubes, vials, detectors, electronic parts, etc.) will be mounted on the panel in such a way that they can easily be eliminated or added and to reconstruct another synthesizer configuration.

Software

In the process of generating radiopharmaceuticals, due to the exposure all the stages should be carried out automatically in the hot cell. In this module, in order to reducing the expenses, microcontroller AVR (Type ATMega128) has been used.

The system consists of 27 valves with the voltage of 12 volts DC, one heater, two stirrers and one vacuum pump with the voltage of 220 volts AC. The valves and microcontroller are related to each other by a driver in Fig. 2. Also, in order to take control of rest of elements the relay is used.

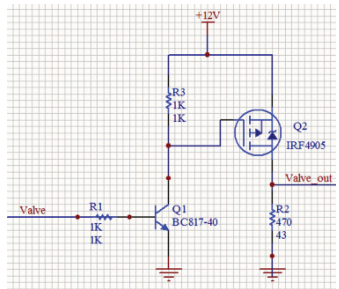

Figure 2: A driver for relating valves and microcontroller to each other.

In addition, a temperature sensor has been accommodated next to reactor which collects the temperature data every second. Also, the information regarding Geiger Muller detectors that displays the amount of activity in each stage is registered in the memory of microcontroller. Figure 3 shows the electronic design for converting the gamma rays that goes into detector, to a measurable electrical pulse. Output of this section is connected to microcontroller to counting the pulses and measuring activity.

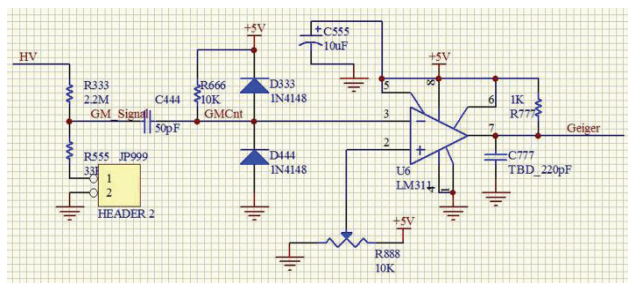

Figure 3: The electronic design for converting the gamma rays to a measurable electrical pulse.

The control system equipped with keyboard and LCD in order to entering and displaying of information. Also, the capability of sending and receiving the information from pc through RS232 enable us to carry the process for online monitoring of module. It causes to stop the system in emergency situations.

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LabVIEW software (version 2012) has been used to monitoring of our synthesis module. This program provides higher level of automation, standardization and safety. The designed program includes 4 tabs:

- Monitoring: User will be able to see the schematic of the automated system for synthesis of ^{18}F-NaF and ^{18}F-FDG, as well as the amount of activity, temperature and pressure instantly.
- Graph Acquisition: All data of detectors and sensors are collected electronically, and then they are shown in a single chart and separate charts for better monitoring and comparison of system's parameters.
- Test Results: The chart data are recorded in a table and user will be able to save them in a specified file. In fact, it provides an opportunity to compare the results of different runs.
- Setting: User can adjust synthesis parameters (time and temperature) and save the changes in a flexible manner for steps of production, washing and dispensing for both radiopharmaceuticals. Also, recorded file can be used in the next runs.

In order to access the control buttons (FDG Production, NaF Production, Stop, etc.); the Control Panel is beside the tabs. User can select the running mode in this panel. He can also select the demo button; so the whole process can be done independently of serial communication with microcontroller. This panel includes current steps of each selective mode; total process time and production time (see Fig. 4).

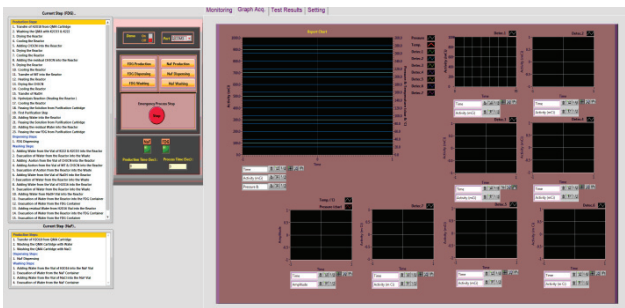

Figure 4: Graph Acq. tab and control panel in LabVIEW Software.

RESULTS AND DISCUSSION

The needed ^{18}F for synthesis these radiopharmaceuticals are obtained by bombardment of highly enriched water (H_2O_{18}) with proton at the baby cyclotron. After preloading the reagents in the module, user will be able to select the running mode (Production, Dispensing, and Washing) for ^{18}F-NaF or ^{18}F-FDG easily, only with a single click.

The main steps of ^{18}F-FDG production are described in the following:

Loading ^{18}F by opening the valve V1 on ion exchange column for separation from H_2O_{18} Eluting ^{18}F from cartridge by passing Kryptofix and K_2CO_3 into the reactor.

1. Evaporating water by heating the reactor at 88^{o}C and applying vacuum.
2. Adding CH_3CN into reactor and heating the reactor and heating the reactor at 88^{o}C.
3. Addition of Mannose Triflate and CH_3CN solution.
4. Heating the reactor at 80^{o}C to accomplish fluorination step.
5. Introduction of NaOH and heating the reactor at 50 ^{o}C for doing base hydrolysis reaction.
6. Eluting ^{18}F-FDG by adding water and applying helium pressure to pass ^{18}F-FDG from purification cartridge.

The steps of ^{18}F-NaF production are listed in the following:

1. Loading ^{18}F by opening the valve V1 ,V2 on ion exchange column.
2. Washing the QMA cartridge with water (H_2O_{16}) for more purification.
3. Eluting ^{18}F from the cartridge with NaCl as ^{18}F-NaF solution.

CONCLUSION

This design of synthesis module is feasible, user friendly and reliable.

We hope that, after fabrication this synthesis module by simply adjusting the setting (time and temperature), we can obtain high efficiency (55% for 18F-FDG and 90% for18F- NaF) by minimizing the synthesis time(30 min for FDG and 5 min for NaF).

The module has the potential to accomplish other nucleophile reactions of labeling with short lived radioisotopes.

Also user will be able to generate both radiopharmaceuticals in separate runs, consecutively by preloading reagents in the module. This is consistent with the radiation protection requirements and causes to decrease exposure of personnel.

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