The design and construction of an automated synthesis system for radiopharmaceuticals labeled with $^{18}$F has been reported. This apparatus was constructed at IFIN-HH for research of short lived radioisotopes for PET investigation. $^{18}$F fluoride was produced at the IFIN-HH cyclotron by irradiation of H$_2$O enriched 97% in $^{18}$O, with deuterons of 13 MeV or protons of 8 MeV. The irradiated H$_2$O was transferred (injected) into the radiochemistry full automated processing systems which ensure the separation of $^{18}$F-from H$_2$O, the labeling with $^{18}$F of a precursor compound by an acid or basic hydrolysis; then it is transformed in the radiopharmaceutical with $^{18}$F and finally purified as selective absorbants. The system is easy to operate and contain a programmable logical controller which manages the entire operation program stored in its internal memory. The computer is used to assist the operator during the different steps of synthesis and to allow visualization of the process and printing the report. The device served for the production of $^{18}$F FDG at the IFIN-HH cyclotron, one of the most used radiopharmaceutical in PET investigations. The synthesis module has configured so that it is enough flexible to accomplish and other nucleophile reactions of labeling with short lived radioisotopes.

Key words: FDG, PET, radiopharmaceutical.

PACS: 87.58.Ji, 07.05.Dz

1. INTRODUCTION

History. In the 1970s, Tatsuo Ido at the Brookhaven National Laboratory was the first to describe the synthesis of $^{18}$F-FDG, the most commonly used PET scanning isotope carrier. The synthesis of FDG is also the most complicated and thus successful automation of this process offers the greatest challenge.

Nuclear medicine in Romania encountered difficulties concerning the use of short lived radioisotopes for therapy and diagnosis because of lack of appropriate production lines and to the impossibility of procurement from outside owing to short life time of these radioisotopes. Until now, in IFIN-HH Radioisotopes Production...
Center processed only long lived radioisotopes produced in nuclear reactor facilities existing in Romania or imported from outside. Our U-120 Cyclotron existing in IFIN-HH has its basic parameters (beam energy and intensity of accelerated ions) which fit well with the requirements of small/medium sized four particle cyclotrons with regard to medical radioisotopes production.

Why a home made system for synthesis of [18F] FDG? The extensive clinical and research application of PET in the past few years has stimulated a great interest to development of fully automated systems for PET radiopharmaceuticals [1]. Our system is dedicated for research and it is designed to provide maximum flexibility for easy and fast PET tracer development. It is an automated versatile synthesizer for easy and efficient production of [18F] tracers via nucleophilic substitution with [18F] F-Fluoride trapped from [18O] water. All the components (valves, tubes, vessels, electronic parts, I/Os, GM detectors, etc.) are easy to move and to reconstruct another synthesizer configuration. It is possible to add or eliminate a large number of such components. PC based systems controlled via LabView software (National Instruments) provide higher level of automation, standardization and safety. PC operation using text base LabView program is very simple and provides the opportunity to adjust synthesis parameters in a flexible manner, reprogramming for different syntheses is possible within a short time. In addition, the software allows more working arrangements: fully automated, manual, automated combined with manual sequences.

2. MATERIALS AND METHODS

HARDWARE

The set up of the apparatus is shown schematically in Figure 1. All reagent solutions and solvents are manipulated within the module by vacuum or auxiliary gas (helium). The reaction mixtures in the reaction vessels can be stirred, heated, cooled evaporated, and pressurized. Evacuation of the reactors is performed with a vacuum pump via a cooling trap filled with liquid nitrogen. Volatile radioactive substances are thus trapped. Radioactivity detectors display the radioactivity level in the reactors and in the vessel for the final product. The modules of the system are combined to achieve the shortest connections and smallest dead volumes.

All the components were carefully checked to obtain best results. The Tubes are Teflon (from BOLA), the valves are air-actuated and Teflon membrane (from Burkert), Pressure Transmitter type 8320 and proportional valve type 2822 (from Burkert). The central part of the apparatus is the reactor vessel. This is a Glassy Carbon tube (SPI-Glas™ Brand) with internal diameter of 20 mm and 100 mm longer.
Fig. 1. – Schematic of the automated system for synthesis of [18F]-FDG for PET investigation.

Special remark: Glassy Carbon Test Tubes exhibit some very unusual properties:

- High Purity;
- High thermal conductivity;
- Corrosion resistance;
- Impermeability to gas and liquids;
- High hardness and strength, almost like that of a ceramic;
- Low density;
- High surface quality with excellent polishing characteristics (to a black mirror reflective finish);
- No adhesion;
- Good resistance to thermal shock;
- Biocompatibility;
- Physical and chemical properties are isotropic.

For example, the SPI-Glas™ Brand Glassy Carbon Test Tubes, relative to quartz test tubes, exhibit far higher thermal conductivity and show very little adhesion. Thermal cycling times are reduced, sometimes substantially. This also means that the heater coils can be operated at lower temperatures than would otherwise be mandated if ceramic or quartz test tubes were being used. Because of the lack of any porosity and high purity, and high temperature properties, glassy
carbon is the ideal material for fabrication into evaporation boats. Its non-wetting characteristics make it the ideal approach for certain otherwise difficult-to-evaporate materials.

The top of the Carbon tube is closed by a Teflon special design cover (see Figure 2) to ensure all the necessary connections tubes. The reactor vessel is introduced in a copper cylinder and the small space between it and the carbon tube is filled with silicone oil. In this small place is mounted the thermocouple Type E to monitors the temperature. On the outside of the copper cylinder is the heater. The cooling of the reactor is provided by a system of tubes with small holes for an adiabatically detenta of the compressed air flow. In Figure 3 we can see a Photographic view of the system.

Fig. 2. – The design of the cover of the glassy carbon tube and a photo of the copper cylinder (middle) and the glassy carbon tube with the special Teflon cover mounted (right).

FLUID TRANSFERS

The fluids are transferred through capillary tubes (as 1 mm in diameter) by vacuum or by helium pressure of high purity (99.99999%). All connections were made via Teflon tubing and valves. The pressure transmitter M3 provides signal blocker to the valves V2, V3, V4, V5, V6 and V19 when a growing set pressure in the reactor vessel reach the threshold of about 1.4bar, this means that the liquid has been completely transferred.

All chemicals (reagent grade) were obtained from commercial suppliers and used without further purification.
The Geiger detectors are type 713 LND, Inc, 500 volts operating voltage, Minimum dead time 45 micro sec. All the 6 detectors are shielded mounted to minimize the external radiation influences. The detector GM5 has a major role: at the beginning at the purification process the liquid follows the way to the waste recipient, and if the number of counts/sec is more than the set threshold the valve V17 switch to the way “a”, and the liquid e is collected in the final recipient.

The data acquisition system. We use for data acquisition an analogue NI6221(National Instruments) PCI bus with 32 analog inputs at 16-bit, 250 kS/s, and a digital NI 6509 with 96-bidirectional channel digital I/O interfaces for PCI and PXI systems, with high-current-drive capabilities (24 mA), and is completely jumper-free.

SOFTWARE

The software is PC based systems controlled via LabView version 7.1 (National Instruments). The traditional process for designing embedded machine control systems typically involves multiple stages of development that each requires specialized electronic design automation (EDA) tools such as state-diagram and flowcharting tools, SPICE circuit simulation, board layout and routing, control design tools, finite element analysis (FEA), C and VHDL languages, multiple target-specific compilers, and human-machine interface (HMI) tools [2].

Fig. 3. – Photographic view of the system.
3. RESULTS AND DISCUSSION

[18F] Fluoride occurs at the U-120 IFIN-HH cyclotron by irradiation of 97% 18O enriched water with 13 MeV deuterons, or 8 MeV protons. After irradiation the 18F-water is injected through the valve V10 (with vacuum) in the automated system to obtain after a synthesis process 2-[18F] FLUORO-2-DEOXY-D-GLUCOSE. Before starting the synthesis, a cleaning program for the system was carried out. The 4 main stages of the [18F] labeled are short described in the following:

(i) the separation of 18F- from H218O in the QMA column-ion Exchange Sep-Pak that ensure the recovery of water that has not been used and which can be used for other courses of irradiation;
(ii) the fluoridation reaction by nucleophilic substitution with [18F] of the mannose triflate precursor;
(iii) acid hydrolysis of the groups protective of precursor, which leads to the formation of gross radiopharmaceutical [18F] FDG.

The last two stages occur in the glassy carbon vessel provided with heating system (iv) purification of the labeled product what is done by converting it by Sep=Paks absorber. Finally the solution is passed through a sterile filter (Millipore 0.22micron) and the isotonic 2-[18F] FDG solution is apportioned into evacuated ampoules [3].

The Gamma radiation spectrum corresponding to the solution of 18F is presented in Figure 4. The active impurities, such as 24Na, as well as the inactive impurities can be removed by absorption on a column of resin, not present in that experiment. The main purpose of this spectrum was to determine the 18F activity in the solution in order to calculate the radiochemical yield.

Fig. 4. – Gamma radiation spectrum corresponding to the solution of 18F.
Measurement Time 136.12 sec, Dead Time 12%, Distance source-detector 44.5 cm.
4. CONCLUSIONS

Installation of automatic synthesis presents a number of advantages including:

− minimizing the time needed for the radiopharmaceutical synthesis, something very important for marking isotopes with very short life as $^{18}\text{F}$ ($T_{1/2}=109.6$ min);
− provides simplicity in operation and flexibility;
− does not require a specific qualification in chemistry – may be used as sets of reagents ready for use;
− all necessary chemicals are preloaded in exact quantities – on the vessels or cassette;
− installation is compact and easily shielded in accordance with the radioprotection requirements;
− allows the creation of several sequences for nucleophilic fluoridations which may broad range $^{18}\text{F}$ labeled products used in PET procedures.

Acknowledgments. This study was partly supported by a research project (contract 19/2006) of the Romanian national program viasan.

REFERENCES
