F-18 production by means of ^{20}Ne(d,^{4}He) reaction at ININ

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Fluor-18 is one of the most useful radioisotopes for positron emission tomography (PET), so the means to produce and process it turns out to be of great importance. In order to test the feasibility to produce this tracer in our laboratory at ININ, provided with an EN-tandem accelerator, we constructed a gas cell to contain a Ne gas target and bombard it with 6.5 MeV deuterons. In this work we report the production of some mCi of F-18 obtained through the ^{20}Ne(d,4He)^{18}F reaction, the experimental setup employed, with some practical implications related to the use of the alternative ^{18}O(p,n)^{18}F reaction.

Keywords: radioisotope production; positron emission tomography.

El fluor-18 es uno de los radioisótopos más útiles en la tomografía por emisión positrónica, y en consecuencia la metodología para producirlo y procesarlo es de gran importancia. Con el fin de explorar la posibilidad de producirlo en nuestro laboratorio en el ININ, provisto de un acelerador de partículas (EN-tandem), construimos una celda gaseosa para contener el neón como blanco y bombardearlo con deuterones a 6.5 MeV. En este trabajo reportamos la producción de varios mCi de F-18, obtenidos a partir de la reacción ^{20}Ne(d,4He)^{18}F y detalles del arreglo experimental empleado, junto con algunas consideraciones prácticas relacionadas con el uso de la reacción ^{18}O(p.n)^{18}F como alternativa.

Descriptores: producción de radioisótopos; tomografía por emisión de positrones.

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1. Introduction

As a consequence of technological improvements, Proton Emission Tomography (PET) has acquired an increased importance for health applications. By using this technique, a short lived positron-emitting radioisotope, commonly known as a radiotracer, is incorporated into a patients' body, usually into the blood circulation system. The radiotracer is introduced into the subject once it is fixed to a metabolically active molecule, like fluorodeoxyglucose (FDG). In this case, after a period around one hour, the modified sugar will end up preferably concentrated in the illed organ or sick tissue, moment at which the patient should be placed in an image scanner.

The most common radioisotopes used in PET are typically isotopes with short half-lives, such as ^{11}C ($\sim$20 min), ^{13}N ($\sim$10 min), ^{15}O ($\sim$2 min), and ^{18}F ($\sim$110 min). From these, according with the tissue of interest to be scanned, one introduces an enough amount of radiotracer taking into account the time required for the metabolically active molecule, to be concentrated in the tissue or organ of interest. It is clear that for a shorter half life, the initial required activity should be bigger.

Once the radiotracer is fixed in the organ of interest, we look for the beta plus annihilation, which follows from the tracer decay once that the positron is stopped (up to a few millimeters) and encounters an electron. This annihilation gives place to the emission of two anti-coincident gamma rays of 511 keV each. At this point a detector arrangement (surrounding the patient) and an associated electronic system must be prepared to register the coincidence events of these photons, using time of flight techniques in order to define the annihilation position. Coincident events are stored, rejecting those which arrive outside the resolution time imposed, and once a sufficient number of events are taken, a computer image can be reconstructed, giving a morphological map of the organ under study.

In Mexico there are only two institutions capable of producing ^{18}F for PET applications. In both cases, the radiotracer is obtained by ^{18}O(p,n)^{18}F reactions using a cyclotron as accelerator. The scanning system is close or aside the producing radiotracer facility, permitting an efficient use of the tracer. The application of the ^{18}F radiotracer requires the processing of nucleophylic aqueous [^{18}F]fluoride, obtained from the bombardment of [^{18}O]H_2O with protons, in order to incorporate it to a metabolically active molecule. Though the high cost of [^{18}O]H_2O, this technique has been taken as the established method for the production of radiofarmaceuticals for positron emission tomography. However, electrophylic ^{18}F in the form of [^{18}F]F_2 is still used in the investigation of new radiochemistry requiring electrophylic substitution and clinically in the synthesis of other useful compounds [1].

Many efforts have been conducted in order to improve the production of electrophilic ^{18}F in the form of [^{18}F]F_2. One of the most common production methods makes use of the ^{20}Ne(d,4He)^{18}F reaction, which has lower production rates

and obviously requires a deuteron beam. A limiting factor with this reaction comes from the construction of adequate target assemblies, for containing the Ne gas and the produced fluorine, assuring its recuperation. Until now, the use of several metal containers like Ni, stainless steel and aluminum have been reported [1].

We intend to use a copper sealed tube as a container for the Ne gas and employ our tandem accelerator in order to produce F-18 through the ^{20}Ne(d,4He)^{18}F reaction at 6.5 MeV deuteron energy. The production of ^{18}F by means of this reaction will be presented in what follows.

2. Experimental setup

This work was performed at the Nuclear Center of the Instituto Nacional de Investigaciones Nucleares (ININ), located 36 km at the East of México City, México. Our Laboratory is provided with a Tandem Van de Graaff accelerator (EN-model from HV Eng. Corp., Mass., USA), which delivered the deuteron beams employed for the Fluorine-18 production. The use of the ^{20}Ne(d,^{4}He)^{18}F reaction, required the construction of a gas cell to contain the neon gas, and thus, in Fig. 1 we present a simplified drawing showing its relevant characteristics once it was terminated. The body of this cell comprises a 23.7 cm long copper tube, 2.54 cm inner diameter (1"), with an appropriate flange at one extreme to support a thin (19 μm thick) aluminum window for the beam entrance. The other extreme of this tube is closed by a 0.6 mm Cu plate, which serves as a beam stop, as well as for taking, through it, the activation (decay) measurements.

Figure 2 shows a schematic diagram of the gas driving circuit employed to fill the gas cell with a spectroscopically pure Ne gas (Tube Light Co. Inc., N. J., USA). This arrangement permitted us to evacuate and fill the cell, purging it twice to remove atmospheric residues, to a pressure of 460 mm of Hg of neon. The cell was then fixed to an open 2.25" (5.7 cm) diameter beam pipe of the accelerator, using a Lucite isolator in between to integrate the deuteron beam charge arriving to the cell.

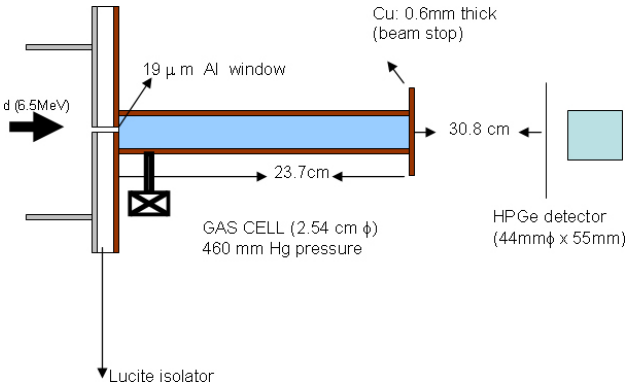

FIGURE 1. Schematic drawing of the gas cell characteristics used for F-18 production, accompanied by the experimental post-irradiation gamma-ray counting conditions.

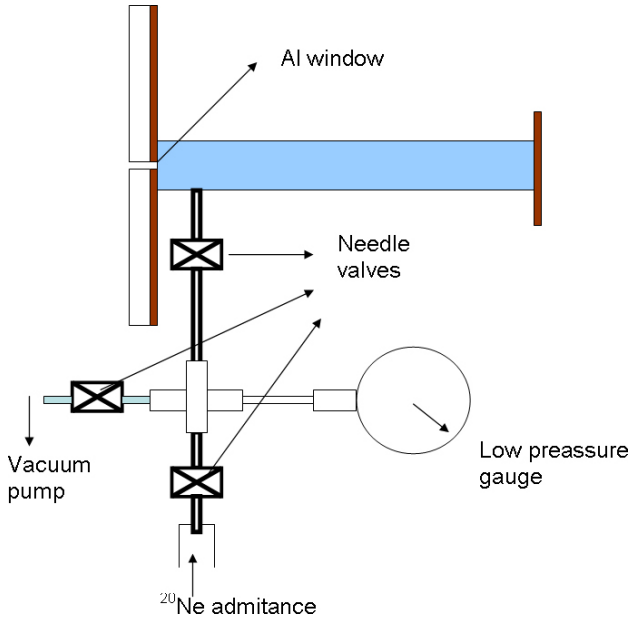

FIGURE 2. Simplified drawing of the gas circuit used for evacuating the cell and for the filling of the neon gas up to 460 mm Hg pressure.

3. Bombardment, activation and results

As it is illustrated in Fig. 1, the accelerator deuteron beam arrives with 6.5 MeV energy to the 19 μm thick Al window, where it looses approximately 400 keV before reaching the gas target (using a density of 2.7 g/cm^3 for Al and usual energy loss calculations in agreement with Ziegler et al. values [2]). For a neon gas pressure of 460 mm Hg, a density of 0.54 g/cm^3(or 1.63×10^{19}atoms/cm^3) is obtained by applying ideal gas relations, which, after taking into account the cells' length (23.7 cm), a target thickness of 12.9 mg/cm^2 is deduced. Now, for an initial deuteron energy of 6.1 MeV, an energy loss of 1.22 MeV is obtained for the deuteron ions to traverse the gas target (by applying calculations in agreement with values of reference [2]) and end up stopped, finally, at the copper plate with a residual energy of 4.88 MeV.

The production of F-18 was taken during 2 hours and 54 minutes, with a deuteron beam current close to 100 nA as a mean, without corrections due to electron losses at the Al entrance window. Owing to this last fact, the derived total deuteron fluence would be overestimated taking these values as a basis (we presume, between 1.5 and a factor of two). Thus, no further attempt was made to obtain a normalized yield of F-18 production for these experimental conditions, *e.g.*, mCi per deuteron unit charge (mC).

Once that the irradiation took over (defined as our initial decay time, and consequently, the related initial activity of the sample), we left a 2 hour decay period before taking the first counting rate measurement. A HPGe coaxial detector from "Tennelec" (Tennessee, USA), 44 mm diameter by 55 mm long crystal, fixed 30.8 cm away from cell and aligned along the cells' axis (as shown in Fig. 1), was used to per-

form the F-18 decay measurements (511 keV gamma counting rates) as a function of time. In Fig. 3, we present a gamma energy spectrum taken 2 hours and 15 minutes after the irradiation was suspended, showing the 511 keV peak originated from the beta pluses' annihilation.

A compilation of the counting rate measurements, comprising up to nearly four days after the irradiation, is presented as a graph in Fig. 4, where the solid line added is an aid to show up the presence of two radionuclides which decay by β+ emission. Besides F-18, the other radioisotope identified was copper-64, which was produced by the ^{63}Cu(d,p)^{64}Cu reaction at the beam stop plate. After subtracting the background counts of other β+ emitters naturally present in our laboratory (0.18 counts per second, measured independently), the decay of Cu-64 was properly adjusted with the last point taken 93.5 hours after the irradiation, using a half-life value of 12.7 hours for this purpose. In this way,

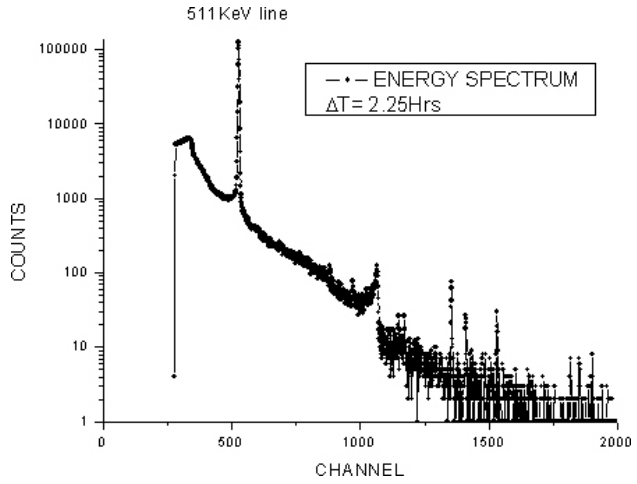

FIGURE 3. Gamma ray energy spectrum taken with a HPGe detector 2.25 hours after the irradiation, showing the 511 keV peak coming from β+ emitters.

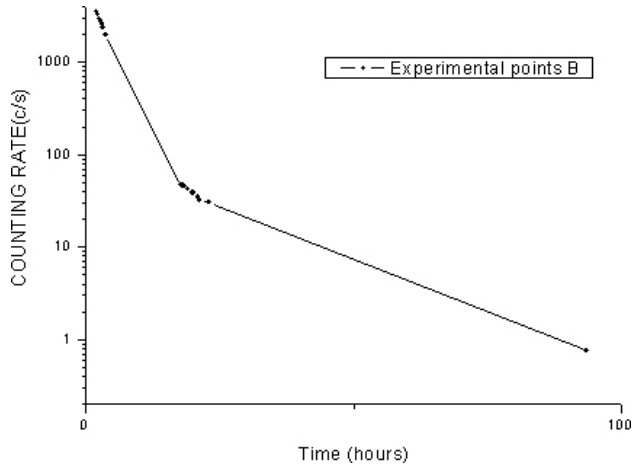

FIGURE 4. Graph of the counting rate measurements of 511 keV gamma rays as a function of time. The continuous line, added to the experimental points, is an aid to show up the presence of two β+ emitters.

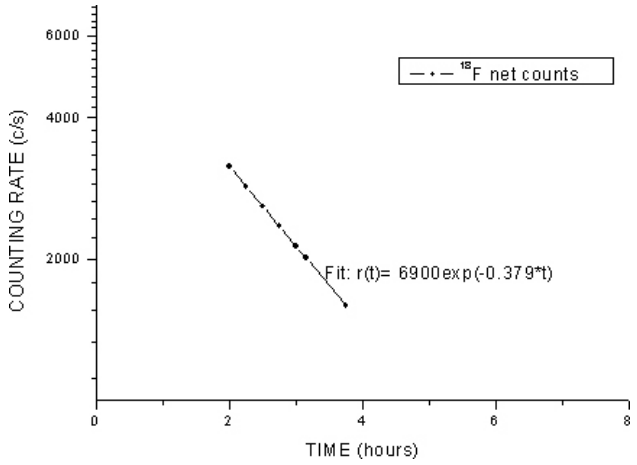

FIGURE 5. Histogram of F-18 (net) decay data, obtained after the subtraction of Cu-64 contribution and the background events from other β+ emitters.

the initial counting rate obtained for Cu-64 was 95.6 counts per second, permitting us to explain the long term counting events presented in Fig. 4.

Once the natural background and the Cu-64 contributions are taken care of, the F-18 net counts are left alone, and a linear least square fit is possible to apply (taking the natural logarithm of the counting rate as a function of time). Applying this fit to the first counting interval data points (between 2.0 and 3.75 hours after the irradiation), an initial counting rate of 6900 counts/sec is obtained from the F-18 decay data (supposing a half-life equal to 109.8 min), with a linear correlation coefficient of 99.8%. In Fig. 5, this fit is shown as a linear-log graph for the fluorine-18 decay countings.

From this initial counting rate, it is now possible to obtain the initial activity of the sample, if the detector efficiency is known for the energy of interest (511 keV) and a properly weighted solid angle is obtained. From the efficiency calibration of this detector, we found an efficiency value of 6.1×10^{-3} for this energy (511 keV), as given elsewhere [3]. On the other hand, if we suppose a uniform distribution of F-18 along the interior of the cell, as seen from the detector, this can be approximated as a string of (constant) point sources distributed along the cells' length. Thus, upon applying an inverse distance-squared function for each line segment, a weighted (mean) distance of 40.4 cm is obtained. From this value, a net solid angle of 9.3 msr is calculated as equivalent to that subtended by the HPGe detector. Besides, since the 511 keV photons exit the cell through its base (0.6 mm Cu plate), a transmission of 0.956 is obtained using the NIST attenuation coefficients given in reference [4].

Finally, with these parameters at hand, it is easy to prove that the initial counting rate (C_0) and the initial activity (A_0) are related by: $C_0 = A_0 \quad \varepsilon \quad \Omega$ T, where ε, Ω, and T stand for the efficiency, the mean solid angle and the copper plate transmission, respectively. Thus, a 3.4 mCi initial activity was obtained through the ^{20}Ne(d,^{4}He)^{18}F reaction, under these (rather unfavorable) experimental conditions. An estimated 3% uncertainty is estimated for this measurement.

4. Conclusions

The use of the ^{20}Ne(d,^{4}He)^{18}F reaction to produce F-18 aimed for PET medical applications is still a valuable alternative in relation to the, now most effective, ^{18}O(p,n)^{18}F reaction based on ^{18}O-enriched water to produce no-carrier-added [^{18}F]fluoride [5]. Nevertheless, in both cases these reactions require a moderate projectile energy and a moderate beam current to give useful yields of Fluorine-18.

The activity that we measured (3.4 mCi) is about one half the quantities required for standard PET scans. No especial effort was taken to improve our experimental conditions, which, on the contrary, were much limited on projectile energy and current, and by the use of a low neon gas pressure (< 1 atm). Quite better experimental conditions, using this reaction at different centres, are summarized in a review article by M. Guillaume et al. [5], where pressures exceeding 10 atm, deuteron beam currents greater than 10 μA and energies above 11 MeV are employed. However, this method, which has proven its value, opens the possibility to be implemented at our laboratory as a complementary activity, once that the experimental conditions are taken care of.

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1. A.D. Roberts *et al.*, *Appl. Radiat. Isot.* **46** (1995) 87.

2. J.F. Ziegler, J.P. Biersack, and U. Littmark, "*The stopping and range of ions in solids*", Pergamon Press, (New York, NY, USA 1985). Using 1991 actualized values.

3. E. Martinez-Quiroz *et al.*, Proceedings: *VII Congreso Anual de la Sociedad Nuclear Mexicana (SNM), Boca del Río, Veracruz, México* (1996) 70.

4. J.H. Hubbel and S.M. Seltzer, "NIST X-ray Mass Attenuation Coefficients", Web reference: http://physics.nist.gov/PhysRefData/XrayMassCoef/cover.html

5. M. Guillaume *et al.*, *Appl. Radiat. Isot.* **42** (1991) 749.