RADIOCHEMISTRY AND RADIOPHARMACEUTICALS

Anhydrous F-18 Labeled Elemental Fluorine for Radiopharmaceutical Preparation

Vito Casella, Tatsuo Ido, Alfred P. Wolf, Joanna S. Fowler, Robert R. MacGregor, and Thomas J. Ruth

Brookhaven National Laboratory, Upton, New York

Interest in fluorine-18 as a label in radiopharmaceutical studies has led to the development of a method for the production of decicuries of anhydrous ^{18}F-F_2 using the $^{20}Ne(d,\alpha)^{18}F$ reaction. The amount of anhydrous ^{18}F-F_2 that can be removed from the target is a function of target pressure and carrier concentration increasing with rising target pressure and decreasing with decreasing carrier concentration. At a target pressure of 24 atmospheres and a carrier concentration of 0.1% F_2, nearly 95% of the theoretical yield of fluorine-18 produced can be removed and up to 85% delivered through a 10-m stainless steel tube to the reaction chamber. Other functions affecting yield—including target design, target-gas handling and purity—have been addressed. Thick target yields for 14.0- and 9.4-MeV deuterons on target were measured to be 82 and 67 mCi/μA at saturation. With the BNL 60-in. cyclotron, production of 600–800 mCi of ^{18}F-F_2 with a specific activity of ~10 mCi/μmole has been in effect since 1976.

J Nucl Med 21: 750–757, 1980

Radiopharmaceuticals labeled with fluorine-18 have been described a number of times and their advantages have been detailed in the literature (*1–4*). A reagent showing considerable promise as a labeling agent is anhydrous ^{18}F-F_2 (*2,5–8*). Furthermore, recent procedures using highly diluted F_2 and/or low reaction temperatures have avoided many of the problems associated with this highly reactive halogen and have renewed interest in its use in organic synthesis (*9–11*). The need for decicurie quantities of ^{18}F-F_2 at high specific activity prompted a modification and extension of methods in use (*1,2,8*). Also, it became clear that at the high activities contemplated (>500 mCi), and because of the requirements at sites having medical cyclotrons, automated or semi-automated devices would be needed to allow safe handling of the reagent. The $^{20}Ne(d,\alpha)^{18}F$ reaction is suited to this purpose. The $^{18}O(p,n)^{18}F$ reaction also shows promise (*12*), but it introduces the added complication of using the F_2 reagent in an oxygen atmosphere. It will be the subject of another paper.

Received Nov. 26, 1979; revision accepted Feb. 22, 1980.

For reprints contact: Alfred P. Wolf, PhD, Dept. of Chemistry, Brookhaven National Lab., Upton, NY 11973.

Fluorine-18 from the $^{20}Ne(d,\alpha)^{18}F$ reaction has been used for radiopharmaceutical synthesis (*5–7,13–15*). Winchell et al. (*16*) have described a method for producing large quantities of F-18, but they did not identify the chemical form of the F-18 recovered. The excitation function up to 24 MeV for this reaction has been published by Nozaki et al. (*17*) and reinvestigated by Guillaume (*18*), but a complete review of this field is outside the scope of this paper. We report here the development of a system for establishing the targetry conditions in order to produce ^{18}F-F_2 in high activity, and a simple method for the routine production of high-activity ^{18}F-F_2 by remote handling.

MATERIALS AND METHODS

FLUORINE IS A HIGHLY TOXIC AND REACTIVE GAS. THE READER IS DIRECTED TO A SERIES OF ARTICLES (*19,20*) ON THE MANIPULATION AND HANDLING OF GASEOUS FLUORINE IN ORDER TO BECOME FULLY AWARE OF THE HAZARDS IN HANDLING THIS DANGEROUS GAS.

The evolution of the present system has followed two tracks. First, the optimum operating conditions had to be determined. This required the development of a safe, reliable method of handling pure F_2 (following section). The second approach was to develop

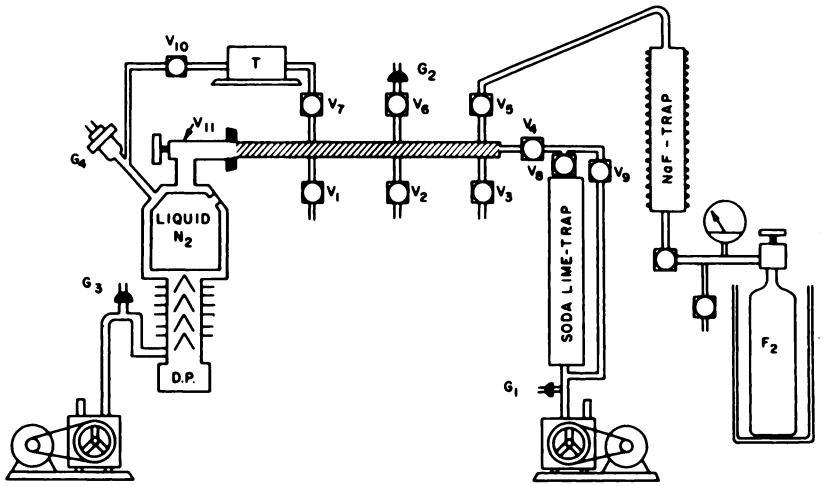

FIG. 1. Vacuum manifold for handling pure F_2. V_1, V_2, V_3—valves used in loading targets; V_4—valve isolating manifold from roughing vacuum system; V_5—valve isolating manifold from pure F_2 supply; V_6—valve isolating thermocouple gauge from manifold; V_7—valve isolating pressure transducer (T) from manifold; V_8—valve to soda-lime trap and roughing vacuum system; V_9—by-pass valve to roughing vacuum system; V_{10}—valve isolating pressure transducer from high-vacuum system; V_{11}—valve isolating manifold from high vacuum (diffusion pump) system; G_1—thermocouple gauge monitoring roughing vacuum system; G_2—thermocouple gauge monitoring manifold pressure; G_3—thermocouple gauge monitoring roughing pump for diffusion pump; G_4—discharge vacuum gauge monitoring high-vacuum system; T—differential pressure transducer with monel diaphragm; DP—diffusion pump.

a system that could be handled remotely in a production mode, with minimal operator intervention. This system (viz., target-gas handling system for production) was developed after the operating parameters had been determined.

Gas-handling system for pure F_2. The metal line illustrated in Fig. 1 is a modified version of the line previously described (*8*). The principal changes were to use nickel or monel materials and to weld all of the connections where possible. A monel reagent tank containing fluorine* was kept in a shielded facility in the hood housing the vacuum line. It was filled when required at a remote handling facility that stored the high-pressure tank obtained from the manufacturer. At present the storage pressure in the reagent tank is kept below 2 atm. While it appears that the tank and valve system can be operated at much higher pressures, we felt that the lower pressure was safer for laboratory use. The manufacturer states the purity of the gas to be about 97%, with the major impurities being N_2 and O_2. No attempt was made to remove these gases. However, any traces of HF were removed before entry into the vacuum manifold by using a sodium fluoride scrubber or cold trap (Fig. 1). The neon* used was research grade, with a stated purity of 99.999%. All metal tubing in contact with fluorine was either nickel or monel. The main manifold had a diameter of 1.51 cm. All connecting lines were 0.95 cm in diameter. The whole system was evacuated by means of a roughing pump and a diffusion pump† charged with a silicone-fluid.‡ When fluorine is absent, pressure in the system is measured using a discharge-type of vacuum gauge.‖ Fluorine pressure is measured with a diaphragm-type differential pressure transducer (*2*) especially made for use with corrosive gases,§ and having a nickel-plated interior and no silicates in the ceramics. Pressure readings are obtained from an electric manometer¶ attached to the sensor. An auxiliary thermocouple manometer is attached directly to the manifold. Monel diaphragm valves** are used wherever pure or highly concentrated F_2 may come in contact with the system. Note, however, that some valves have begun to leak after about a year of continual use.

The resistance to fluorine of the monel and nickel surfaces of this system depends on the formation of a coherent fluoride film. This is obtained by admitting 1 atm of F_2 and electrically heating the system to ~300°C (*8*). The pressure in the system generally ceases to fall after several hours, indicating no further wall reaction. Conditioning is nevertheless continued for 48 hr to ensure thorough passivation. The line is then ready for use. Excess F_2 is removed through the soda-lime trap using roughing pump No. 2 (right, Fig. 1). Great care should be exercised while the line is being passivated. When the system has been conditioned and careful vacuum techniques are practiced, the manifold system can maintain a vacuum of 10^{-6}–10^{-7} torr. After passivation, the manifold is used for transferring F_2 to targets. The fluorine pressures in targets ranged from 0.01 to 760 torr.

Targets. The target materials used for fluorine-18 production must be chemically inert, have reasonable heat-transfer properties, and be stable under irradiation conditions. The current target design is shown in Fig. 2. The body of the target is constructed of the purest nickel commercially available†† in pipe form, with a 2.5-cm i.d. The interior of the target is honed to a mirror finish before passivation in order to ensure a continuous, smooth nickel fluoride surface. The rear of the target is a polished nickel plate containing a 6.4 mm o.d. nickel exit port, electron-beam welded to the body. A stainless steel flange, welded to the target chamber, contains a groove machined to hold a metal O- or C-ring that is used to secure the front window and provide a vacuum-tight seal by pressure applied from a brass or aluminum flange-connector assembly. The O-ring and C-ring materials used thus far are silver-plated or gold-plated nickel.‡‡ Both materials provided an excellent seal at target pressures of 20–25 atmospheres. Teflon O-rings have been used in the past (*2,8*), but heat decomposition may cause them to introduce carbon into the system.

The target chamber and window are cooled by water passing through a brass jacket around the target chamber and through copper tubing soldered to the front flange. There is no evidence that more efficient cooling is needed; the target pressure returns rapidly (≤1 sec) to the initial pressure even after a 2-hr irradiation, indicating little or no thermal heating of the target body.

The front window consists of a sandwich of 0.025 mm Ni foil (facing the target gas) backed with 0.787mm aluminum foil. In searching for the best window material, a series of Ni and Havar foils of varying thicknesses (0.13–0.33 mm) were hydrostatically tested to failure. The thinnest foils failed at 82–92 atm and the thickest was still intact at 235 atm. While all of the foils could withstand the static pressures within the target, the thicker foils (0.25–0.33 mm) invariably failed under moderate (10 μA) irradiation conditions. Nickel and Havar have very poor heat conductivity, which probably contributes to their failure since as much as 90 watts are deposited in the window. The 0.13 mm Ni window was not tested under irradiation conditions. It may also fail when subjected to high pressure and beam currents, so its use as a target

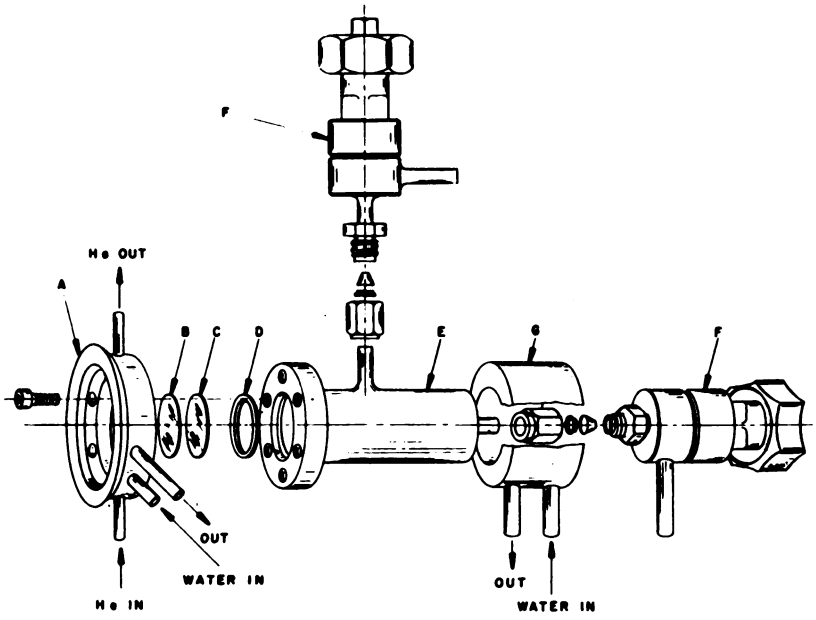

FIG. 2. Target for production of ^{18}F-F_2. (A) Front cooling flange constructed of brass or Al, cut to fit Marmon flange (o.d. 9.68 cm). (B) Aluminum degrader foil; 0.81 mm. (C) Nickel foil; 0.025 mm. (D) Nickel pressure ring "O" or "C", plated with gold or silver (0.318 × 2.9 cm i.d.). (E) Target body: nickel pipe 2.5 cm i.d., 10 cm in length; "O" ring groove dimensions (0.25 cm deep, 2.7 cm i.d., 3.5 cm o.d.). (F) Hoke diaphragm valves constructed of monel; KEL-F insulators connect stainless steel transport line to these valves. (G) Brass cooling jacket; sliding fit with rubber "O" rings for sealing.

window should be tested before use in a production system. The Al/Ni sandwich can withstand static pressures in excess of 70 atm and has the added advantages of using Al, a good conductor, as the beam degrader while providing a material that does not become extremely active with long-lived radionuclides upon irradiation. The sandwich window is bowed out by applying 40 atm Ne pressure to the target system before passivation and use. The dome shape increases pressure stability. The target has two monel diaphragm values[11] attached to it (Fig. 2). Whereas the passivation procedure described above for the manifold could be used with targets, the following was faster and more convenient. The assembled target, minus the water jacket, is passivated by filling with 50 torr of F_2 and heating to a dull red glow (400–600°C) in a gas-air flame with water cooling on the front flange, followed by filling of the target with 10–20 atm of 1% F_2 in Ne and its irradiation with a 5-μA beam for 10 min. The front window is cooled during bombardment by flowing helium over it at a rate of 100 ml/min; the target body and flange are water cooled. Repassivation of the target is not required if the system is only briefly exposed to air—for example, when values are replaced.

Because the availability of nickel is difficult to predict, other materials were sought in the construction of the target. Inconel 600 was the most readily available at the time, and several targets were constructed of this material in the manner described above. The results of testing these targets will be discussed later.

Thick target yield determinations. Because there appeared to be some question as to which excitation function was the most reliable, it was remeasured at the Brookhaven tandem Van de Graaff accelerator using techniques similar to those reported elsewhere (*21*). There is excellent agreement between our results (*22*) and those of Nozaki et al. (*17*).

For the production runs, the BNL 60-in. variable energy cyclotron was used to provide deuterons at beam currents up to 15 μA and energies of either 18 or 23 MeV. In order to determine experimentally the amount of F-18 that could be produced under thick-target conditions, direct yield measurements were made using a target similar to that shown in Fig. 2, except that it was constructed of aluminum instead of nickel. The thickness of the aluminum front window was adjusted to provide 9.4- and 14.0-MeV deuterons on target from incident 18- and 23-MeV deuterons, the same energies used in the production mode. The target was loaded with 24 atm of Ne and bombarded at each energy, first with a 1-μA beam for 5 min and later with a 14-μA beam for 2 min. This was done to see whether there was any marked difference in the production as a function of dose rate. After each bombardment the target chamber and windows were washed with a solution of 0.25 *N* NaOH containing 0.1% by weight of NaF, to remove the fluorine activity for counting. Under the conditions of bombardment only 0.2% of the activity was in the gas phase.

Fluorine-18 activity was assayed in a calibrated NaI(Tl) well counter. The radionuclidic purity was assayed with a Ge(Li) solid-state detector and multichannel analyzing system. The only photons present were the 511-keV gamma-ray due to positron annihilation, and the gamma rays associated with Na-22 and Na-24. The sodium activities accounted for <0.1% of the total activity, and do not present a radionuclidic impurity problem since they are not present in the gaseous phase when a nickel target is used. Under the stated conditions, beams of 9.4- and 14.0-MeV deuterons were found to produce, respectively, saturation activities of 67 and 82 mCi of F-18 per μA of current (*22*), irrespective of dose rate. The values agree to within 15% of the excitation function published by Nozaki et al. (*17*) and its counterpart determined here.

Target-gas handling system for production. The need for a simple system for the loading and emptying of the targets is paramount when such a system is to produce 0.5 to 1 Ci of activity at a time on a daily basis. In such a system the first consideration is to have the target handled as little as possible. This was accomplished by permanently mounting a target on a 2-m collimated beam pipe in the cyclotron target area. This beam pipe is connected to the cyclotron target area by a short beam pipe (60 cm), which is removed to provide access to the target area when other users need the cyclotron. The target end of the F-18 beam pipe is isolated from the cyclotron's target area by a shielding wall (1.7 m). The target is loaded and emptied by way of a 3.2 mm stainless steel line connecting the target and a simple manifold in the chemistry hood some 10 m away. This manifold and line were initially conditioned with 2 atm of 1% F_2/Ne mixture for several hours before the transfer of ^{18}F-F_2. Further conditioning has not been found necessary unless the line has been exposed to air. Teflon tubing proved to be wholly unsatisfactory, becoming permeable to F_2 after short-term use.

Using premixed, commercially available 1% F_2 in neon* (research purity) to add the carrier, and research purity neon as a diluant, the target can be loaded remotely to the desired pressure and F_2 concentration. A schematic of this system is shown in Fig.

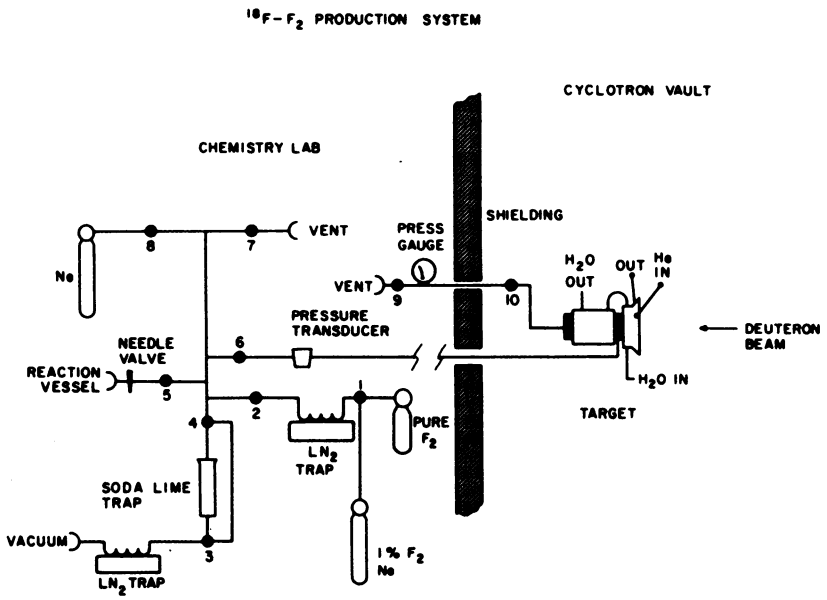

FIG. 3. Schematic of target-gas handling system for $^{18}F-F_2$ production. Valve 1 allows introduction of F_2 carrier as either pure F_2 or premixed 1% F_2/Ne. Valve 2 is used in conjunction with Valve 1 for isolating gas impurities in LN_2 trap when necessary. Valves 3 and 4 control soda-lime trap/by-pass in vacuum line. Valve 5 controls access from target to chemical reaction vessel. Valve 6 isolates target from manifold. Valve 7 is used to vent manifold. Valve 8 is used to introduce Research Purity Neon. Valve 9 is the target vent, used for flushing target. Valve 10 is used for flow-through flushing of target before loading. It is closed for target loading and irradiation.

3. The manifold shown is constructed of 6.4 mm stainless steel tubing welded at all joints. The valves are stainless steel bellows of the H series type.[§§] In an earlier version using monel valves, it was discovered that the passivated monel offered no advantage over either passivated brass or stainless steel valves. Since the brass valves contain Teflon seats and may be a source of stable CF_4, which undergoes exchange producing $^{18}F-CF_4$, only stainless steel valves are used in contact with the $^{18}F-F_2$. It is emphasized that this system uses a $\leq 1\%$ F_2-in-neon mixture. The use of higher concentrations of F_2 in the system would require additional precautions and modifications. Pure F_2 must not be allowed to come in contact with brass valves or packed valves of any kind.

In preparing for an irradiation, the back port of the target (valve 10, Fig. 3) is opened and the entire system is purged for a few minutes with neon and vented to 1 atm. The back port of the target is then closed and 1% F_2/Ne mixture is added to the line to give the desired amount of carrier. For example, raising the residual 1 atm of neon to 2.6 atm by addition of 1% F_2/Ne results in the introduction of ~50 μmol carrier (F_2), as determined by iodometric titration (*23,24*). Neon is then added to the target to give a final pressure of 23.8–25.9 atm, and the target is valved off *in the chemistry lab* (Valve 6, Fig. 3). The pressures in the target/transfer line are monitored by a pressure transducer with a monel diaphragm and digital readout.[¶¶] Note that the transducer monitors the pressure of the target/transfer line system during irradiation. This serves as a direct indication of whether the beam is striking the target gas or not. If it is, the pressure rises immediately and is proportional to the intensity of beam.

After irradiation the dead volume of gas is vented. The pressure at this point is ~15 atm. The $^{18}F-F_2$ can then be used as a reagent for labeling by using a needle valve to control the flow rate into the reaction vessel and purging to a final pressure of 1 atm. The unused residual gas (target and line) is ~8.5% of the initial amount. If necessary, this small amount could be recovered by a slight modification in the system to allow the target and line to be flushed with neon after the initial purge.

Activity balance and fluorine (F_2) assay. By purging the contents of the target through a series of traps, measurements can be obtained for the total fluorine-18 activity recovered from the target, the relative amounts of useful $^{18}F-F_2$ and volatile inert F-18 activity, and the quantity of carrier F_2 delivered from the target. The traps consist of 15 ml of ~1 *M* KI solution with starch indicator, followed by a small soda-lime trap (2 × 8 cm, 4–8 mesh), and finally a charcoal trap (5 × 16 cm, 4–6 mesh Columbia activated carbon) cooled with dry ice. The traps are fabricated from glass with connections made from 3.2 mm o.d. Teflon tubing and swagelok fittings. For convenience the size of the traps is chosen so that they fit into the well of an ionization chamber for convenient radioassay. The charcoal traps are reusable with no activation being necessary. The F-18 recovered from the target is a sum of the activities in the three traps, decay corrected. The relative amounts of usable $^{18}F-F_2$ and F-18-labeled inert gaseous com-

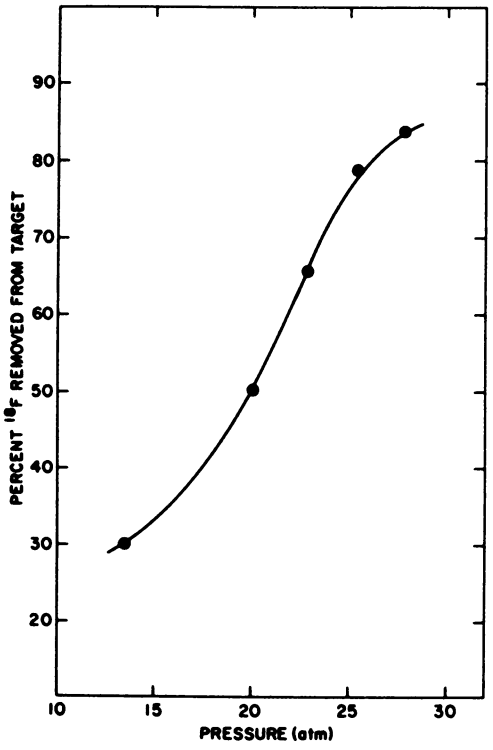

FIG. 4. Percent of F-18 removed from target as function of initial target pressure. (15-μA deuteron beam for a dose of 1.25 μA-hr.) Extraction efficiency based on experimentally determined value of 82 mCi/μA at saturation.

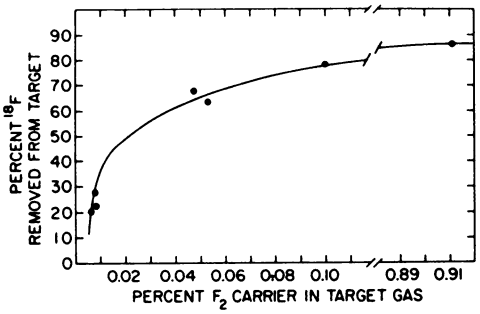

FIG. 5. Percentage of F-18 removed from target as function of quantity of F_2 carrier present. (15-μA deuteron beam for dose of 1.25 μA-hr.) Extraction efficiency as in Fig. 4.

pounds are obtained from the activities in the KI + soda lime and activity in the charcoal. The amount of carrier F_2 can then be obtained by titrating the KI solution with standard thiosulfate ($F_2 + 2KI \rightarrow I_2 + 2KF$; $I_2 + 2S_2O_3^{-2} = 2I^- + S_4O_6^{-2}$) (*23,24*). Note that the activity in the soda lime is usually <1%.

Target parameters. The initial experiments using the pure F_2 system to load the neon targets indicated that the F-18 recovery was a function of carrier concentration, initial target pressure, dose rate, and total dose (*8,22*). It was also noted that absolute yields varied from one target system to another. Therefore, when the target system was located in its present permanent position, the aforementioned parameters were studied for the particular system.

The targets were always loaded in the manner described in the section on "Target-gas handling system for production." The assays of the various activities and their chemical forms were performed as described in the section on "Activity balance and fluorine (F_2) assay." The pressure and carrier studies used a 15-μA deuteron beam, for a dose of 1.25 μA-hr.

The effect of initial target pressure was studied by loading the target with 1.6 atm of the 1% F_2/Ne mixture (60 μmol of F_2) and adding sufficient neon to bring the target to the desired pressure. The pressures studied ranged from 13.5 to 28 atm.

The carrier studies were performed by varying the pressure of the 1% F_2/Ne mixture added from 0.14 (5 μmol F_2) to 19 atm (710 μmol F_2). Because it was difficult to reproduce the loading of the lower concentrations, the results were expressed in terms of the amount of F_2 recovered.

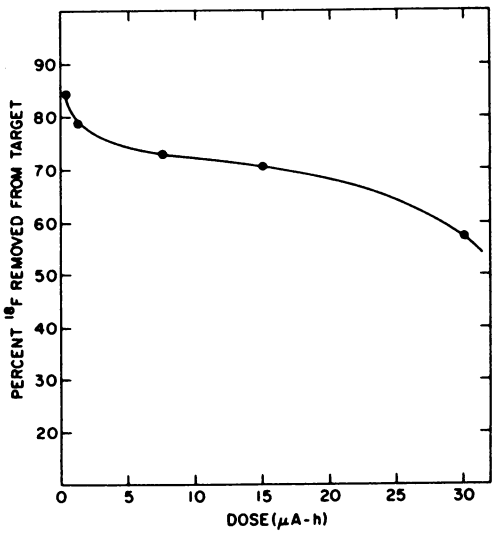

FIG. 6. Percentage of F-18 removed from target as function of total dose to target (constant dose rate at 15 μA). Extraction efficiency as in Fig. 4.

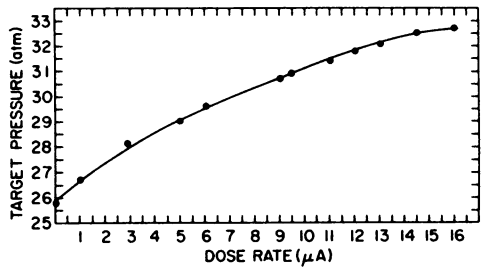

FIG. 7. Pressure rise in neon target gas as function of dose rate (initial pressure = 25.8 atm).

From the pressure and carrier studies it appeared that the optimum operating conditions for the production of ^{18}F-F_2 for use in labeling radiopharmaceuticals were 25.9 atm and 0.1% F_2 carrier. Thus, the studies on the effect of dose rate and total dose were performed under these conditions. In order to keep as many variables as possible constant, the dose-rate studies were done at constant total dose (0.25 μA-hr). The dose rates ranged from 1 to 15 μA.

RESULTS AND DISCUSSION

The effects of the various parameters on the recovery of F-18 are shown in Figs. 4, 5, and 6. In Fig. 7 the effect of dose rate on target-gas pressure is illustrated.

The rise in pressure as a function of beam current has been attributed to beam heating in gas targets (*25–27*). This increase in temperature causes a reduction in gas density and thus decreases the number of target nuclei in the beam, resulting in a lower production rate. This is consistent with the results shown in Fig. 4. While the lower initial pressure represents a thick target, the 15-μA beam probably reduces the density to such an extent that the target is no longer sufficiently thick to stop the beam. Moreover, the carrier studies (Fig. 5) point toward a competition reaction for the F-18 between the carrier F_2 and the Ni walls of the target. By increasing the gas pressure, the thick target condition can be maintained at higher beam currents, and the mean free path of the F-18 produced is also reduced, tipping the balance in favor of labeling the F_2 molecule.

A more complete study of the interplay between beam current and target-gas density is currently under way.

The results of the dose-rate effect studies indicate that the recovery remains constant (>90% of theoretical) for low to moderate dose rates (1–10 μA) but then begins to decrease, so that at 15 μA the recovery is ~83% of theoretical, these determinations being made at constant total dose. Whether this small variation can be attributed to the reduction of gas density at the higher dose rates is not clear at this time.

The total dose to the target gas appears to have the most dramatic effect of the recovery of F-18 (Fig. 6). Beam currents were limited to 15 μA as a precaution

TABLE 1. TYPICAL OPERATING CONDITIONS FOR ^{18}F-F_2 PRODUCTION

Parameter	Value
Machine energy	23 MeV
Deuteron energy on target	14.0 MeV
Target pressure (Ne)	25.8 atm
Carrier concentration	0.1% F_2
Beam current	15 μA
Dose on target	30 μAh
Theoretical yield	655 mCi*
Recovered yield	367 mCi

* Based on the experimentally determined yield of 82 mCi/μA at saturation. Note that the calculated theoretical yield (92 mCi/μA) is somewhat higher since 100% ^{20}Ne was used in calculation. Naturally occurring neon is 90.5% ^{20}Ne.

because of the large increase in target pressure with increasing dose rate (Fig. 7). Although one would expect higher yields at a lower dose rate, the added irradiation time required to obtain an equivalent production of F-18 is prohibitive.

A comparison of the F-18 recovery was made at low and high doses for the Inconel and nickel targets. The results show that at low dose the recovery of F-18 from the Inconel target is ~50%, whereas for the Ni target it is >80%. However, at the high doses (>15 μA-hr) the recovery from the Inconel is unacceptably low (15–20%) whereas that for the Ni target is still good (~60%).

Note that for all these studies (except those investigating carrier) and quantity of ^{18}F-F_2 averaged ~95% of the total recovered F-18 activity. The high recovery of F-18 as F_2 is maintained with frequent target irradiations. When the target is not used for several days, there is frequently a decrease in ^{18}F-F_2 production of approximately 20% and a corresponding rise in F-18-labeled, chemically inert, gaseous compounds. The factors responsible for this target behavior have not been determined, although target leakage has been excluded as a cause. The problem is easily avoided by carrying out a short irradiation and discarding the target gas before a production run (*28*).

CONCLUSION

The routine production of large quantities (200–500 mCi) of ^{18}F-F_2 with either the system described in this paper or its earlier version (*22*) has been in progress since 1976. Typical operating conditions and parameters are listed in Table 1.

The decicurie quantities of ^{18}F-F_2 produced are needed for particular radiopharmaceutical production. Most production runs are used for the production of 2-[^{18}F]fluoro-2-deoxy-D-glucose (^{18}FDG) for use in the study of regional brain glucose metabolism (*29*). Under the production conditions of Table 1, sufficient ^{18}FDG can be synthesized for two patient studies in the same afternoon (~30 mCi at end of synthesis).

TABLE 2. CALCULATED THICK-TARGET SATURATION YIELDS FOR THE $^{20}Ne(d,\alpha)^{18}F$ NUCLEAR REACTION

Energy (MeV)*	Yield (mCi/μA)†	Range in Ne (mg/cm^2)‡
2	1.2	6.8
3	3.6	12.6
4	8.6	20.0
5	17.2	28.8
6	28.1	39.0
7	40.1	50.5
8	51.1	63.3
9	60.6	77.4
10	68.9	92.7
11	76.1	109
12	82.3	127
13	87.5	146
14	91.9	166
15	95.6	187
16	98.7	210
17	101	233
18	104	258
19	106	283
20	107	310
21	108	338
22	110	367

* Deuteron energy incident on target gas.
† Based on the excitation function as determined by Nozaki et al. (*17*) and Casella et al. (*22*).
‡ To threshold. (The quantity of neon necessary for thick target is dependent upon the dimensions of the target being used. In the described system, the target is 10 cm long and 2.5 cm in i.d. Calculations used 100% ^{20}Ne.)

Note that because of the high reactivity of F_2 various components of the system begin to fail and must be replaced. Also, moisture in the system will convert nearly all the F_2 into aqueous HF: $H_2O + F_2 \rightarrow HOF + HF$; $HOF + H_2O \rightarrow HF + H_2O_2$ (*30,31*). The largest contamination problem appears to stem from any source of carbon or nitrogen, which results in production of F-18-labeled, chemically inert, gaseous compounds at the expense of ^{18}F-F_2. Therefore, it is of utmost importance to monitor and check all reagents including the higher-purity neon and F_2/Ne gases. The accompanying paper discusses this problem in detail (*28*).

With respect to the applicability of a similar system to use with medical cyclotrons, Table 2 has been constructed to illustrate the theoretical yield at saturation of F-18 as a function of energy. These calculations are

based on the excitation function determined here, which is in agreement with Nozaki et al. (*17*).

In general, medical cyclotrons have deuteron energies in the 7.5–15-MeV range with beam currents on the order of 50–100 μA. Therefore, it becomes a more difficult job to select a beam window system what will not degrade the beam energy significantly and yet be sufficiently strong to withstand the higher beam currents. With the lower energy cyclotrons, the quantity of gas necessary to make a thick target is reduced, and the pressure rise associated with higher beam currents may be small enough to allow the use of thinner windows. However, running at higher beam currents may not be advantageous, as is illustrated in Fig. 6, which shows the percentage of F-18 recovery as a function of total dose. As mentioned earlier, the reasons for this phenomenon are not fully understood, and studies in progress address this problem.

Even with these constraints it is reasonable to expect a small medical cyclotron to be able to produce sufficient ^{18}F-F_2 for radiopharmaceutical preparation.

FOOTNOTES

* Matheson Co., Rutherford, NJ.
† Veeco EP-2A
‡ Dow Corning 704
‖ Model GPH-100A, Consolidated Vacuum Corp., Springfield, NJ.
§ Model 5730-1000 T4C1H5, Datametrics Corp., Wilmington, MA.
¶ Barocel
** Hoke type 4621N4M
†† KLM metals, Plainview, NY.
‡‡ Custom made by Pressure Science, Inc., Beltsville, MD.
‖‖ Hoke type 4618N4M
§§ Nupro
¶¶ Sensotec, Columbus, OH.

ACKNOWLEDGMENTS

The authors are grateful to Dr. David Schlyer for helpful discussions and to Dr. Barclay Jones for his help in the implementation of the new target system.

REFERENCES

1. WOLF AP, CHRISTMAN DR, FOWLER JS, et al: Synthesis of radiopharmaceuticals and labelled compounds utilizing short-lived isotopes. In *Radiopharmaceuticals and Labelled Compounds*, Vol. 1, Copenhagen, IAEA, 1974, pp 345–381
2. LAMBRECHT RM, WOLF AP: Cyclotron and short-lived halogen isotopes for radiopharmaceutical applications. In *Radiopharmaceuticals and Labelled Compounds*, Vol. 1, Vienna, IAEA, 1973, pp 275–290
3. ROBINSON GD: Prospects for ^{18}F radiopharmaceuticals. In *Radiopharmaceuticals*, Subramanian G, Rhodes BA, Cooper JF, and Sodd VJ, eds., New York, Society of Nuclear Medicine, 1975, pp 141–148
4. PALMER AJ, CLARK JC, GOULDING RW: The preparation of fluorine-18 labelled radiopharmaceuticals. *Int J Appl Radiat Isot* 28: 53–65, 1977
5. FOWLER JS, FINN RD, LAMBRECHT RM, et al: The synthesis of ^{18}F-5-fluorouracil. *J Nucl Med* 14: 63–64, 1973
6. IDO T, WAN C-N, CASELLA V, et al: Labeled 2-deoxy-D-glucose analogs. ^{18}F-labeled 2-deoxy-2-fluoro-D-glucose, 2-deoxy-2-fluoro-D-mannose, and ^{14}C-2-deoxy-2-fluoro-D-glucose. *J Label Cmpd Radiopharm* XIV: 175–183, 1978
7. SHIUE C-Y, FOWLER JS, MACGREGOR RR, et al: The synthesis of [^{18}F] 5-fluorouridine (F-18-5-FUR) as a probe for measuring RNA synthesis and tumor growth rates *in vivo*. In *Radiopharmaceuticals II*. Sorenson, JA, ed. New York, Society of Nuclear Medicine, 1979, pp 259–264
8. LAMBRECHT RM, NEIRINCKX R, WOLF AP: Cyclotron isotopes and radiopharmaceuticals. XXIII. Novel anhydrous ^{18}F-fluorinating intermediates. *Int J Appl Radiat Isot* 29: 175–183, 1979
9. MERRITT RD, JOHNSON FA: Direct fluorination. Addition of fluorine to indenes and acenaphthylenes. *J Org Chem* 31: 1859–1863, 1966
10. BARTON DHR, HESSE RH, MARKWELL RE, et al: Fluorination at saturated carbon. 1. Direct substitution of adamantanes. *J Am Chem Soc* 98: 3034–3035, 1976
11. BARTON DHR, HESSE RH, MARKWELL RE, et al: Fluorination at saturated carbon. 2. Direct fluorination of steroids. *J Am Chem Soc* 98: 3036–3037, 1976
12. RUTH TJ, WOLF AP: Absolute cross sections for the production of ^{18}F via the $^{18}O(p,n)^{18}F$ reaction. *Radiochimica Acta* 26: 21–24, 1979
13. HARPER PV, LEMBARES N, KRIZEK H: Production of ^{18}F with deuterons on neon. *J Nucl Med* 12: 362–363, 1971 (abst)
14. TEWSON TJ, WELCH MJ, RAICHLE ME: [^{18}F]-labeled 3-deoxy-3-fluoro-D-glucose: Synthesis and preliminary biodistribution data. *J Nucl Med* 19: 1339–1345, 1978
15. WELCH MJ, LIFTON JF, GASPAR PP: Production of ^{18}F for bone scanning from the $^{20}Ne(d,\alpha)^{18}F$ reaction via fluorine-18 labeled nitrosyl fluoride, A selective fluorinating agent. *J Nucl Med* 12: 405, 1971 (abst)
16. WINCHELL H, WELLS D, LAMB J, et al: U. S. Patent 3,981,769 (1976)
17. NOZAKI T, IWAMOTO M, IDO T: Yield of ^{18}F for various reactions from oxygen and neon. *Int J Appl Radiat Isot* 25: 393–399, 1974
18. GUILLAUME M: Production en routine par cyclotron de fluor-18 et potassium-43 a usage medical au moyen d'une cible gazeuse télécommandée. *Nuclear Instruments and Methods* 136: 185–196, 1976
19. *Matheson Gas Data Book*. Rutherford, NJ, Matheson Co., Inc., 1971, pp 211–215
20. *Chemical Hazards Bulletin, No. C-61, Fluorine*, New York, American Insurance Association
21. COLLÉ R, KISHORE R, CUMMING JB: Excitation functions for (p,n) reactions to 25 MeV on ^{63}Cu, ^{65}Cu, and ^{107}Ag. *Phys Rev* C9: 1819–1830, 1974
22. CASELLA VR, IDO T, WOLF AP: Production of anhydrous ^{18}F for nuclear medicine. *J Label Cmpds Radiopharm* XIII: 209, 1977 (abst)
23. RODDEN CJ: *The Analytical Chemistry of the Manhattan Project*, New York, McGraw-Hill, 1950, p 231
24. SKOOG DA, WEST DM: *Analytical Chemistry—An Introduction*. New York, Holt, Rhinehart, and Winston, 1965, pp 397–398
25. ROBERTSON LP, WHITE BL, ERDMAN KL: Beam heating effects in gas targets. *Rev Sci Instr* 32: 1405, 1961
26. MCDANIELS DK, BERGQUIST I, DRAKE D, et al: Beam heating in gas targets. *Nucl Inst Meth* 99: 77–80, 1972
27. OSELKA M, GINDLER JE, FRIEDMAN AM: Non-linear behavior of gas targets for isotope production. *Int J Appl*

Radiat Isot 28: 804-805, 1977

28. BIDA GT, EHRENKAUFER RL, WOLF AP, et al: The effect of target-gas purity on the chemical form of F-18 during ^{18}F-F_2 production using the neon/fluorine target. *J Nucl Med* 21: 758-762, 1980
29. REIVICH M, KUHL DE, WOLF AP, et al: The [^{18}F]fluorodeoxyglucose method for the measurement of local cerebral glucose utilization in man. *Circ Res* 44: 127-137, 1979
30. STUDIER MH, APPELMAN EH: Hypofluorous acid. *J Am Chem Soc* 93: 2349-2351, 1971
31. APPELMAN EH: Nonexistent compounds: Accounts of two case histories. *Chem Res* 6: 113-117, 1973