A Systematic Review of Medical Cyclotron, Producing F-18 & FDG Radio Isotopes for Pet Scan Imaging

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***Abstract* — Alzheimer's Disease is the most common form of dementia (memory loss). More than 5 million people are currently living with Alzheimer's and experts predicts this number could be tripled by 2050. Early detection of AD through molecular imaging techniques will assist the development & the evolution of medication to slow down the progression of the disease & optimize patient care. The most commonly used medical imaging for diagnosing & guiding the treatment of Alzheimer's disease is Positron Emission Tomography (PET) Scanning. PET scans are very useful diagnostic scans and are obtained through the use of neutron deficient radioisotopes. In order to emit positron, fluorine-18 (^{18}F) isotope is prepared from water enriched with the ^{18}O isotope using high energy protons by a cyclotron. A cyclotron is a particle accelerator. These particles are then focused onto a target O18 and the bombardment causes the production of the desired radioisotope i.e. F18. F-18 is then attached to a form of glucose called 2-deoxyglucose. This forms a radiolabeled pharmaceutical called 2-fluoro-2-deoxyglucose (FDG) and when given to a patient the body assumes it is glucose. Being radioactive, FDG assist in molecular imaging of the body. The purpose of this study is to present the systematic review of evidence based literature concerning the production of F18 labeled FDG Radioisotopes by medical Cyclotron.**

***Index Terms*—Cyclotron, Radio isotopes, Positron, Fluorodeoxyglucose (FDG).**

I. BACKGROUND

In the modern era, where Healthcare meets the technology, PET Scan are generally using as molecular imaging tool for the body & assist the physician to understand the existence, progression and aggressiveness of disease. In a PET scan the patient is given a dose of medicine containing a positron emitting neutron deficient isotope. The resultant coincident pairs of gammas from the annihilation are detected by PET cameras. The cameras are arranged in a ring through which the patient is moved. From this process a series of 'slice' images are obtained and these can then be combined to give a 3-dimensional picture.

II. RADIOTRACERS FOR PET SCAN IMAGING

Positron Emission Tomography requisite the emission of positron particles that are generally acquired by neutron deficient radio isotopes like Flourine-18 (F18) & injected to the body in the form of 2-deoxy-2-[18F] Fluoro-D glucose (FDG), because of very short half-life, these radioisotopes are usually produces on site by a particle accelerator called 'cyclotron' **[1]**.

III. PRODUCTION OF RADIOTRACERS

The low-molecular-weight PET radioisotopes (C-11, N-13, O-15, and F-18) are all produced by charged particle bombardment. Typically, the radioisotopes are produced in a cyclotron, although other charged particle accelerators can be used. The charged particles that are used are usually the nuclei of very low weight isotopes, hydrogen, deuterium, or helium. The hydrogen nucleus is a single proton; the deuterium nucleus is one proton and one neutron; and the helium nucleus is two protons and two neutrons.

A cyclotron is a particle accelerator. It is an electrically powered machine which produces charged particles in an ion chamber in the center of the machine. As the name suggests, a cyclotron accelerates the beam of charged particles in a spiral path. These particles are then focused onto a 'target' or starting material and the bombardment causes the production of the desired radioisotope.ie. [18F]. The [18F] F- target system is designed to produce [18F] fluoride ion from the interaction of the accelerated beam with the [18 O] water target material. Because of its short half-life (109 min), this isotope must be used as soon as possible after production **[2]**.

IV. LOADING THE TARGET MATERIAL

In a typical system for F-18 production, the target is typically loaded with a pre-determined amount of O18 water by means of a syringe or pump. The volume of water in the target is about 0.8 ml, but another 1-2 ml is required to fill the lines leading to the

target. The water delivery system is then isolated from the target by means of a valve and the target is irradiated. This can be described as a "static" target, meaning that the target material remains in the target throughout the irradiation time **[3]**.

V. THEORY OF CYCLOTRON OPERATION

The cyclotron operates by accelerating negative hydrogen ions in quasi-spiral orbits to the extraction energy of MeV (million-electron-volts). The negative hydrogen ions (H-) are produced by an internal axially-mounted modified Penning Ion Gauge (PIG) ion source. The ions are then injected into the acceleration region, where they gain high energy as they cross the edges of the electrodes, called dees. Beam acceleration occurs in a magnetic field produced by a single-coil electromagnet. The magnetic field provides the bending force that causes the beam particles to travel in a quasi-spiral path toward the extraction radius. This focusing produces high beam transmission efficiencies and therefore low internal activation, resulting in reduced personnel radiation exposure. As the accelerated ions reach the trailing edge of the dees, the alternating voltage potential of the dee changes to a negative value, and the negative ions are repelled by the now negatively-charged dee electrode. As the beam travels toward the next dee, the dee potential changes to a positive value, which attracts the negative ions. The alternating polarities of the dees and the bending effect of the magnetic field move the H- ions from dee to dee in a spiral path.

During acceleration, the H- ions move farther and farther from the center of their orbit, until they reach the extraction radius. Here, a thin carbon foil is rotated on a carousel to intercept the ion beam. The two loosely- bound electrons are stripped from the H- ion producing H+ ions, or protons. The change in the electric charge of the beam particles reverses the bending force exerted on them by the magnetic field, and the proton beam arcs outward, toward the designated exit port **[5]**.

VI. NUCLEAR REACTIONS

When accelerated to high energies, these charged particles can be smashed into nuclei of other elements. The high energy is used to overcome the electrical forces which keep the positively charge nuclei apart. After overcoming these forces, the nucleons can interact using nuclear forces to form new isotopes. Typically, a high-energy particle smashes into an isotope of an element and some other high-energy particle is emitted. The nuclear reactions are written with the target isotope on the left, the product isotope on the right, along with the incoming and outgoing particles. An example of a typical reaction for producing fluorine-18 is

$$_{8}O^{18} + {}_{1}P^{1} \_\_\_\_\_ {}^{8}F^{19} + {}_{0}n^{1} + \Upsilon$$

Where p indicates a proton & n stands for neutron. The high-energy proton interacts with the oxygen-18 nucleus. A high-energy neutron is emitted, leaving a fluorine-18 isotope. Since the incoming and outgoing particles each represent one nucleon, the mass number (N) of the product, fluorine-18, is the same as the target, oxygen-18. However, a proton replaces a neutron, thus the atomic number (Z) of the isotope increase and the chemical species changes from oxygen to fluorine **[2]**.

VII. TARGETS

Although cyclotron currents are quite low, the energy of each particle is quite high. Thus, the amount of energy in the beam is quite high. This high energy poses several problems for cyclotron targets. The targets must be able to dissipate the heat from the beam. The beam must pass through a "window" to reach the target material. In order to minimize loss of energy in the window, it is desirable to have a thin window. But the window must also be able to withstand the high energy in the beam. Various target materials are used. In the case of FDG, the target material is water that has been enriched in the oxygen-18 isotope **[3]**.

VIII. PRODUCTION YIELD

The nuclear reaction rate varies depending up the energy of the incoming charged particle. The dependence of this rate on energy is different for each nuclear reaction. Fortunately, there are practical reaction rates for production of all the low-weight positron emitters at relatively low energies. That means that these isotopes can be produced with relatively inexpensive cyclotrons. For example, a "medical" cyclotron which can accelerate protons to 10–15 MeV and deuterons to 5–7.5 MeV can be used to produce C-11, N-13, O-15, and F-18. The production yield depends on how likely a particle of a certain energy is to react with a particular nucleus. It also depends on how many particles there are in the accelerator beam. The number of particles in the beam is given in terms of current, typically in units of micro amps.

IX. DELIVERY OF F18

The irradiated water become radioactive, i.e. labeled F-18 and is then removed from the target, typically by means of inert gas (Argon) pressure, that preserve it and transported over a delivery line leading outside the cyclotron shielding to a collection vial. The F-18 isotope is then separated from the water and processed for production of a radiopharmaceutical agent FDG through an ^{18}F extraction device **[3]**.

X. FDG SYNTHESIS

The Chemical Process Control Unit (CPCU) is used to produce 2-deoxy-2-[18F] fluoro-D glucose (FDG). The CPCU typically receives aqueous [18F] F- from the target and, through a multi-step process, creates a (F18) labeled glucose analog, 2-deoxy-2-[18F] fluoro-D-glucose (i.e. [18F] FDG).

The basic steps in the FDG synthesis process include:

- Isotropic drying of the [18F] fluoride ion in the presence of Krypto fix 222 and potassium carbonate.
- Substitution of [18F] fluoride ion into the glucose precursor compound (mannose triflate).
- Purification of the labeled glucose precursor.
- Hydrolysis of the glucose precursor yielding [18F] FDG.
- Purification of the [18F] FDG product. **[4]**

XI. PROCESS

The [18F] is delivered to the first reaction vessel where the drying and substitution steps are performed. Purification of the labeled glucose precursor occurs during the transfer between the first and second reaction vessel. A silica gel cartridge mounted in the transfer tube removes unreacted Krypto fix 222 and [18F]. Hydrolysis occurs in the second reaction vessel.

The final purification occurs during the [18F] FDG transfer to the collection vial. Removal of unwanted products take place. The first purification component removes hydrochloric acid by use of an ion retardation resin. The second purification component removes any un-hydrolyzed glucose precursor. The third purification component removes synthesis decomposition products.

XII. DOSE

The Dose that is injected to the patient contains FDG (fluorine-18 labeled 2-flouro-2-deoxy-D-glucose) which is about 96 to 99% pure (as per QC).

This Radioactive dose decays by emitting a positron. A positron is the anti-particle of an electron and therefore it is antimatter. When a positron collides with an electron a very short lived particle called a positronium is formed which then undergoes annihilation. In annihilation two gamma (γ) emissions of equal energy (511 Kev) are produced and they travel in opposite directions. The two gamma emissions are called a coincident pair and each pair is detected by a circle of detectors or PET cameras.

XIII. LIMITATIONS & LOSSES

A considerable amount of O-18, typically 25-30%, is lost after each run. The O-18 isotope is used up in three ways. First, a very small amount, on the order of Nano liters, is actually converted to F-18. The next most important loss of O-18 is due to a combination of leakage and isotopic exchange with ^{16}O oxides in the target, transport lines and storage vessels. After one run of an hour or two, the enrichment factor can drop from 95% to 85-90%. This is still high enough to be economical to run a cyclotron, but the amount of contamination is too high, as will be explained below.

The third loss is due to leakage of target material from the pressurized target and attached tubing which may lead to a reduced water level in the target and, if severe enough, to a catastrophic failure. Target cooling relies on the liquid water material present in the target to function as a heat conductor. A typical 1 ml target must dissipate over 500 W of heat for as long as 2-3 hours. Many target systems are pressurized to as high as 500 psig or higher to improve target thermal stability. In these conditions, containment of a small amount of water becomes a significant technical problem. Loss of a very small amount of target material may have dramatic consequences such as target foil rapture, target body degradation, and loss of target yield.

Although 70-75% of the initial O-18 water remains, the biggest effective loss is due to contamination. Any contamination in the liquid water increases the formation of super-heated steam with increased leakage and loss of cooling. Because the consequences are so adverse, the water recovered after only one run in a static target system must be sent back to the supplier for reprocessing to remove contaminants.

Existing static target systems do not provide any mechanism to timely detect the critical loss of target material during irradiation. In addition, in a static target it is impossible to monitor the amount of radioactive F-18 being produced with any certainty. The result of a production run may not be known until after its completion, up to several hours after start of production. Given the fact that production and delivery schedules do not allow much flexibility due to the extremely short half-life of the F-18, this uncertainty results in a decrease in reliability and availability of the product **[5]**.

XIV. CONCLUSION

Study reveals the ways, how a medical Cyclotron prepare the labeled Pharmaceutical product for PET Scanning. This labeled Isotopes by particle accelerator likely, medical cyclotron not only assist to establish the diagnosis along with other clinical & investigative tools but also helps to monitor the effect of treatment & progression of disease.

As the research has demonstrated the production & synthesis of Radioisotopes for PET Scanning, still further enhancement can lead the technology to the greater levels.

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