

# **Radiation Environment in Medical Cyclotron Facility & Optimization of Synthesis Parameters of Flouro-Deoxy Glucose**

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**DOCTOR OF PHILOSOPHY  
IN APPLIED PHYSICS**

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2016

# **Declaration**

*This is to certify that the work embodied in this thesis entitled “Radiation Environment in Medical cyclotron Facility & Optimization of Synthesis parameter of Flouro-Deoxy Glucose” is original and free from any form of falsification, fabrication and plagiarism. I have not violated any of the provisions under the acts of Copyright/Piracy/Cyber/IPR etc. amended from time to time. I shall be solely responsible for any such dispute arising out of my doctoral work.*

**Rajeev Kumar**  
**Research Scholar**

# CERTIFICATE

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We certify that Rajeev Kumar has prepared his thesis entitled “Radiation Environment in Medical Cyclotron Facility & Optimization of Synthesis Parameters of Flouro-Deoxy Glucose” for the award of Ph.D. degree of the Babasaheb Bhimrao Ambedkar University (Central University) Lucknow, Utter Pradesh under our supervision. He has carried out his work at Department of Nuclear Medicine and Cyclotron Facility, AIIMS New Delhi and Department of Applied Physics, School of Physical Sciences, Babasaheb Bhimrao Ambedkar University (Central University) Lucknow, Uttar Pradesh, in PET Radiochemistry as a Ph.D. Scholar under our supervision. The candidate has completed the research work for the full period prescribed and that the thesis embodied the result of his investigation conducted during the period he worked as a Ph.D. Scholar.

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*Dedicated to three most important  
ladies in my life my Mother, Wife  
& Daughter*

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*The life of a Ph.D. student is described as always difficult, sometimes dark but never dull. My career path has largely fulfilled this promise. So it is with a sense of immense satisfaction that I turn to the pleasant task of acknowledging the help of all those who made this work possible. The actual task required a clock work like precision among different departments and would not have been possible without the unconditional support and unflinching support of all team members.*

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**Rajeev Kumar**

# **LIST OF ABBREVIATIONS & SYMBOLS**

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AERB	Atomic Energy Regulatory Board
AAPM	American Association of Physicists in Medicine
AVF	Azimuthal Varying Field
ALARA	As Low As Reasonable Achievable
BOP	Beam on Post
BL	Beam Line
CT	Computed Tomography
CA	Competent Authority
CMC	Chemistry Manufacturing and Controls
CFM	Cubic Feet Meter
CRT	Cathode Ray Tube
CSE	Control Standard Endotoxin
DP	Diffusion Pump
E P	European Pharmacopeia
<sup>18</sup> F-FDG	Fluorine-18 Labeled Flouro-Deoxy-Glucose
<sup>18</sup> F	Fluorine 18
FDA	Food and Drug Administration
FRL	Federal Regulatory Limits
GE HC	General Electric Healthcare
GC	Gas Chromatography
GSH	Glutathione
GPM	Gallon per Minute
HPLC	High Performance Liquid Chromatography
HP	High Performance
IAEA	International Atomic Energy Agency
JRC	Joint Research Centre
KeV	Kilo Electron Volt
LAL	Limulus Amoebocyte Lysate
mCi	Milli Curie
μCi	Micro Curie
MBq	Mega Becquerel

μA	Micro Ampere
μSv	Micro Sievert
MeV	Mega Electron Volt
MHO	Maleimidehexyloxime
MP	Medical Physicist
MCF	Medical Cyclotron Facility
MC	Medical Cyclotron
MMOF	Main Magnetic Offset
NM	Nuclear Medicine
NMP	Nuclear Medicine Physicians
PET	Positron Emission Tomography
PSI	Pound Square Inch
PIG	Penning Ion Gauge
PTS	Portable Test System
QA	Quality Assurance
QC	Quality Control
QMA	Quaternary Ammonium Anion
RSO	Radiation Safety Officer
RDS	Radioisotope Delivery System
RF	Radio-Frequency
SPECT	Single Photon Emission Computed Tomography
SCCM	Square Cubic Centimeter
TLC	Thin Layer Chromatography
USP	United States of Pharmacopeia

*Abstract of Ph.D.  
Thesis*

# **ABSTRACT OF Ph.D. THESIS**

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## **“RADIATION ENVIRONMENT IN MEDICAL CYCLOTRON FACILITY & OPTIMIZATION OF SYNTHESIS PARAMETERS OF FLOURO-DEOXY GLUCOSE”**

### **INTRODUCTION:**

Positron Emission Tomography is a nuclear imaging modality of nuclear medicine department that has rapidly gained favor. PET is powerful imaging modalities, which are mainly used for oncological, cardiological and neurological patients. Most important application of PET is in the staging and management of cancers. PET accurately determines the extent of the spread of disease in a cancer patient. PET scanning is a simple, non-invasive procedure. For undertaking a whole body PET scan, a small intravenous injection of the radiopharmaceutical injected (i.e. Flouro-Deoxy Glucose).

For production of Flouro-Deoxy Glucose, we need F-18 which is radioactive in nature. This F-18 produced on-site in a special machine called medical cyclotron. During production of F-18 we checked any radiation leakage is found or not. On the same time we also monitored the irradiation parameters of the medical cyclotron. During this monitoring we optimized the working principle of medical cyclotron and irradiation parameters. After production of F-18 it was transferred in to the Radiochemistry module Explora FDG4. Where actually Flouro-Deoxy Glucose synthesized.

This work includes the radiation safety of the patients, patient attendants and radiation safety personals, Radiation environment of the medical cyclotron Facility. Radiation safety personal include the staff working at the site. Which include Nuclear

Medicine Physicians, Medical Physicist, Radiation Safety Officer, Nuclear Medicine Technologist, Nurse and Nursing attendant. In this study on Radiochemistry module Explora FDG4 synthesis parameter optimized.

## **OBJECTIVE OF RESEARCH**

This was carried out in the Department of PET Scan and medical cyclotron Facility, where actually cyclotron was installed. Basically three major equipments were involved in this study. Those were medical cyclotron, Radiochemistry Explora FDG4 Module and PET scanner. The cyclotron is the most widely used particle accelerator for producing medically important radio nuclides. The name of this cyclotron is Eclipse RDS111 from Siemens Limited, Germany. Many medical centers in India have installed compact medical cyclotrons for on-site production of short-lived positron-emitting radio nuclides. The energy of the medical cyclotron was 11 MeV. This means the charge particle will rotate about by this speed. The maximum target current of this cyclotron was 40  $\mu$ A.

A mandatory requirement for cyclotron installation is radiation control permit from AERB. Cyclotron radiation survey is an integral part of the overall radiation safety in the cyclotron facility.

Since this is a very new modality in the India. So the motivation behind this work is to understand the processes which start with cyclotron start and up to patient's scan.

The purpose of this work is to optimize the working principle of medical cyclotron and synthesis of parameters of FDG. In this study the knowledge of

Physics, Nuclear Physics, Chemistry and Radiochemistry and Nuclear Medicine involved. This work was basically related with Nuclear PET Radiopharmacy

In summary, the following work has been carried out:

1. To optimize the working principle of medical cyclotron
2. To optimize the irradiation parameters of medical cyclotron for maximum yield
3. To study the radiation safety aspects in medical cyclotron, Radiochemistry lab and Quality Control area
4. To study to minimization of radiation dose to staff and attendant of the patients minimize in PET scan.
5. To optimize the synthesis parameters of Positron Emitting Fluoro-Deoxy Glucose in Cyclotron Facility

The present work is organized into following five chapters:

**Chapter-1** It is include the introduction of the study. Its deals with the basics of PET Pharmacy and medical cyclotron. Importance of irradiation in the field of Nuclear Science is explained. In this chapter also discussed about aims of the study. A review of literature on present experimental work on the medical cyclotron and FDG is carried out. The objectives and future scope of the present work have been given at the ending of this chapter.

**Chapter-2** Gives the information about the material used and experimental technique used in present work. This chapter gives the information about the medical cyclotron, FDG and Radiation safety aspects. In this chapter optimize the working principle of

medical cyclotron and optimize the irradiation parameters of medical cyclotron for maximum yield also mentioned.

**Chapter-3** This chapter includes the comprehensive studies of synthesis of FDG and its quality control and optimization of parameters of Synthesis of. The effect of optimization of FDG parameters also mentioned. The advantage of optimization includes Yield, Chemical consumed and Time. It consumed lesser chemicals, lesser time and maximized the yield of FDG by new method. Further, all quality control was done of produced FDG and showing excellent results.

**Chapter-4** In this chapter the radiation level of the deferent points of the medical cyclotron, Radiochemistry synthesis area and Quality Control areas were tabulated and analyzed. In cyclotron area radiation monitoring was done before bombardment, during bombard and after bombardment. In case radiochemistry area, it was done before synthesis, during synthesis and after synthesis. In quality control area radiation exposure level was noted before and during quality control. It also tells us about the layout of the radiation surveillance. Deferent point were recognized for radiation monitoring

**Chapter-5** This chapter concludes the findings of this research work and presents a discussion of their implications in the context of present and future effects of medical cyclotron and FDG. The future scope of the present work has also been presented.

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# *Chapter 1*

# *Introduction*

# **CHAPTER 1: INTRODUCTION**

---

## **1.1 BACKGROUND**

The principle of Cyclotron was first conceived by Ernest Orlando Lawrence in 1929 (1). M. Stanley Livingston was students of Ernest Orlando Lawrence, translated this idea into working hardware (2). They had build First functional cyclotron in 1932 at University of California, Berkeley and for this invention Ernest Orlando Lawrence got Noble prize in Physics (3).

## **1.2 ACCELERATOR**

Accelerator is a device which accelerates the charged particles to produces a high-energy, precise high intensity beam. Its uses electromagnetic field to thrust charge particles to approximately speed of light, by which we can get well classify beam. Accelerator is used for particle therapy in oncology department, radioisotope production for medical diagnostics and therapeutics, ion implanters for manufacture of semiconductor and accelerator mass spectrometer for measurement of rare isotope such as radiocarbon. In present situation more than 30000 accelerators are equipped all over the world (4).

### ***1.2.1 TYPES OF ACCELERATORS***

There are two types of accelerators: (a) Electrostatic and (b) Electromagnetic

#### ***1.2.1.1 ELECTROSTATIC ACCELERATOR***

It uses static electric fields to accelerate particles. The example of this class is the Cathode ray tube (CRT) in an ordinary old television set, Cockcroft-Walton generator and Van de Graff generator.

### *1.2.1.2 ELECTROMAGNETIC ACCELERATORS*

It uses altering electromagnetic fields whichever by magnetic induction or field of oscillating radio frequency. It accelerates particles and minimized the breakdown problem.

Rolf Wideroe, Gustav Ising, Leo Szilard, Max Steenbeck, and Ernest Lawrence were pioneers in the field of accelerator (5).

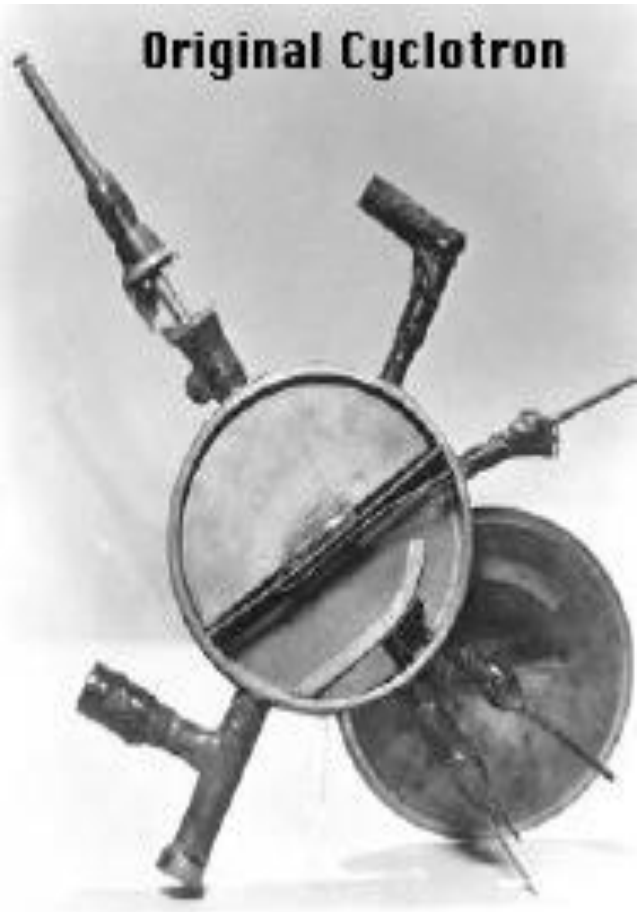
## **1.3 LINEAR ACCELERATOR**

This is a device which uses high Radio-Frequency (RF) electromagnetic waves to accelerate charged particles to high kinetic energies in a linear path, inside a tube like structure called the accelerator waveguide. In short form it is called LINAC.

Linacs have numerous applications, few of them are mentioned here. The high energy electrons and X-rays are generated by LINAC for treatment of various cancers in radiotherapy department. The Linac is used to treat all parts of the body.

## **1.4 BETATRON**

For acceleration of electrons it is invented by Donald Kerst. It is circular magnetic induction accelerator. The concept originates eventually from Norwegian-German scientist Rolf Wideroe. In Betatron the electrons moving at approximately the speed of light in a very small radius trajectory.



**Figure 1.1: Picture of Ernest Lawrence and original cyclotron (courtesy by MLA style “Ernest Lawrence- Biographical” Nobel prize.org.Nobel Media AB 2014.)**

## **1.5 CYCLOTRON**

In cyclotron the charge particle rotate in cyclic path way. It is mainly used for the production of isotopes which emits positrons ( $^{18}\text{F}$ ,  $^{15}\text{O}$ ,  $^{13}\text{N}$ , and  $^{11}\text{C}$ ). For installation of medical cyclotron lots of necessary equipment and documentations are required. In India Atomic Energy Regulatory Board (AERB) is the proficient authority for regulatory approval of the Cyclotron Facility (4, 6).

### ***1.5.1 CYCLOTRON STALK***

Generally it is positioned away from the public occupied places. Its length as suggested by AERB is approximately 2.5 times taller than the surrounding structures.

The stacks are generally inbuilt with filters and charcoal, which absorb the produced activity during normal operations (7).

## **1.6 TYPES OF MEDICAL CYCLOTRON ON THE BASIS OF SHIELDING**

On the basis of shielding medical cyclotrons are two types: (a) Self shielded medical cyclotron and (b) Bunker type medical cyclotron (4, 6, 8).

### ***1.6.1 SELF SHIELDED***

For production of positron emitting radioisotopes self-shielded cyclotron is always preferred. The energy of Self-shielded cyclotron is generally of 11-16 MeV. Self-shielded cyclotron is made of retractable interlocked shield with concrete walls.

### ***1.6.2 BUNKER TYPE***

The energy of Bunker type Cyclotron is 16-30 MeV. It is located in a vault and the bunker is made up with concrete walls of generally two meter thick. Its entry looks like maze wall. It is design to meet the regulatory guideline i.e. the dose rate at the surface of the inner wall of cyclotron room should be less than or equal to 2 mSv/hr during operations.

## **1.7 TYPES OF MEDICAL CYCLOTRON BASED ON ENERGY**

On the basis of energy the cyclotrons can be classified into three categories (a) Low (b) Medium and (c) High energy cyclotron. Each of one mentioned below one by one (9, 10):



**Figure 1.2: Picture of Medical Cyclotron without Shielding (Courtesy Siemens Ltd)**



**Figure 1.3: Picture of Medical Cyclotron with its Shielding (Courtesy Siemens Ltd)**

### ***1.7.1 LOW ENERGY***

The range of proton energy up to 11 MeV for low energy cyclotron, it is dedicated for medical positron emission tomography and mainly it is used for in-house production.

### ***1.7.2 MEDIUM ENERGY***

The range of proton energy from 12-30 MeV for medium energy cyclotron machines, it is dedicated for positron emission tomography and it is used for outsourcing of  $^{18}\text{F}$ -FDG for distance centres.

### ***1.7.3 HIGH ENERGY***

The range of proton energy 30 MeV and above than 30 MeV for high energy cyclotron machines, it is primarily used for radiotherapy of malignant tumors.

## 1.8 GENERAL WORKING PRINCIPLE OF CYCLOTRON

Moving charged particles emitting electromagnetic radiations and it is deflected by a magnetic field. The Lorentz force perpendicularly acts on the particles. By which they emerges radiation by the accelerating proton undergo in a spiral path way around the lines of the magnetic field. In cyclotron the charge particle moves on circular orbits to accelerate the charged particles exhibit in a uniform magnetic field (4, 10-13).

The force experienced by a charge particle in an electrical field is expressed by

$$F = q E \quad (1)$$

And the force experienced by a charge particle in magnetic field is expressed by

$$F = qVB \quad (2)$$

Where F is a force, q is a charge particle, V is the velocity and B is magnetic field.

If charge particle moving on circular path the centrifugal force explained by

$$F = \frac{mv^2}{r} \quad (3)$$

Where m = mass of the particle to be accelerated and

r = radius of the circular path.

$$r = \frac{mv}{qB} \quad (4)$$

$$V = Wr \quad (5)$$

Where W is angular velocity, and

$$W = 2\pi f r^2 \quad (6)$$

Where  $f$  is the angular frequency of the movement, so using equation 2 and 3

$$\frac{mv^2}{r} = qVB \quad (7)$$

Because PE converted in to become KE, so

$$qV = \frac{mv^2}{2} \quad (8)$$

Where  $V$  is the potential between the dees where the particle gain energy

$$v^2 = \frac{2qV}{m} = vB \quad (9)$$

Where  $V = Er = vB$  (10)

So,  $v = \frac{rqB}{m} = Wr = 2\pi fr$  and finally

$$F = \frac{qB}{2\pi m} \quad (11)$$

## 1.9 CYCLOTRON OPERATION

Two computers are used to control the operation of a cyclotron. One located in the console room for operator and the second located inside the cyclotron room that actually executes various commands given by the operator. Before initializing the system various parameters such as temperature, humidity, vacuum status, gas pressure, exhaust system, electric current/UPS system and chiller plant status have to be checked and should be ensured that their water level at optimal working levels in the Target Supporting Unit (TSU) chiller plant. After initialization, the target is dried and checked for leaks. After passing the leak test, the bombardment is started by selecting the F-18

radionuclide through master computer, Required proton beam current, Bias voltage, Ion source gas flow, Ion source current and RF amplitude are selected and the bombardment process is started for desired duration. The duration of bombardment depends upon the amount of activity required. Once the F-18 is produced it is unloaded from the target and transferred to radiochemistry synthesis module for further synthesis of  $^{18}\text{F}$ -FDG (7, 14).

We used Eclipse RDS 111 cyclotron. This brand of cyclotron is influential an adequate amount of Curie levels radioisotopes. PET scanner is one of the best ever developing areas of nuclear medicine imaging technique for both research and clinical applications in the field of oncology.

## **1.10 MEDICAL CYCLOTRON PRODUCED RADIONUCLIDE**

Medical cyclotron is used to produce short lived radiotracers such as  $^{18}\text{F}$ ,  $^{11}\text{C}$ ,  $^{15}\text{O}$ ,  $^{13}\text{N}$  etc. in which most commonly used radiopharmaceuticals is  $^{18}\text{F}$ -FDG which gives information about metabolic activity of the biological cells of humans being. It is widely used in Nuclear Medicine Department. Currently  $^{18}\text{F}$ -FDG is the most important PET tracer is used in Medical Oncology for treatment of cancers (14-16).

## **1.11 ACCIDENTAL ASPECTS**

Careful analysis and various safety issues are required in case of accidental conditions. One of the accidental conditions is target rupture which can happen due to improper cooling of cyclotron parts or may be some other reasons. During target rupture personal radiation safety is major concern and it is ensure that the operating personnel do not receive unwanted and unnecessary radiation exposure (17-20).

## **1.12 GENERAL CHARACTERISTICS OF RADIOCHEMISTRY MODULE**

Radiochemistry modules are equipped within separate areas along with medical cyclotrons. The produced activity transfer is carried out pneumatically or through Argon gas through tubes rooted under floor with sufficient shielding to prevent the radiation exposure to the working personnel. Mechanical robotic arm are used for the dispensing of radiopharmaceuticals. Some centers are using automatic dispenser for dispensing. In general, very high amount of activity is produced in a single run of medical cyclotron, it may be up to Curie level. Very small amount of activities usually in micro-Curie level are transferred to quality control area for quality control purposes (7)

### **1.13 HANDLING OF RADIOPHARMACEUTICALS AND MODULE**

Negative pressure needs to be provided in the medical cyclotron and the chemistry module area. So the air containing the radioactive materials escapes into the vault and chemistry module environment are expelling in to the environment through a stack after passing through filters. Some companies provide nitrogen trap system in which nitrogen trap to remove the radiation from the radiochemistry laboratory and then released through the stack (7, 14).

In our system the radiochemistry module has a charcoal filter, which absorbs the air born fluoride gas which was produced during evaporations in the synthesis.

### **1.14 FLOURO DEOXY GLUCOSE**

$^{18}\text{F}$ -FDG cannot undergo further metabolism unlike glucose, because the hydroxyl group at the two number of carbon is a requirement for the process.  $^{18}\text{F}$ -FDG is a good indicator of glucose uptake and cell viability. 3-Deoxy Glucose and 4-Deoxy Glucose were not retained inside the cells. Similarly, 3-FDG and 4-FDG do not accumulate in living cells as much as  $^{18}\text{F}$ -FDG. Historically the electrophilic method of

fluorination has a key role in the synthesis of  $^{18}\text{F}$ -FDG, although the nucleophilic substitution method is used most of the manufacturer (20-22).

## **1.15 RADIATION APPLICATION**

Medical cyclotron produced radionuclides plays major and valuable applications for human being. The largest part among them is in the medical field are diagnosis and therapy. PET is a nuclear imaging modality of nuclear medicine department that has rapidly gained good turn for diagnostics and therapeutics purposes. PET is a most powerful imaging modality, which has far triumph implications for patient care and management in almost all branches of medicine especially oncology, cardiology and neurology (17, 19).

## **1.16 POSITRON EMISSION TOMOGRAPHY**

PET scanning is a simple effortless, non-invasive imaging procedure. For undertaking an  $^{18}\text{F}$ -FDG-PET scan, a small intravenous injection of the radioisotope ( $^{18}\text{F}$ -FDG), produced on-site from a special machine called cyclotron and radiochemistry module is given to the patient in a nuclear medicine department after which the patient undergoes the scan through a PET scanner. Patient has to report about 4-hour fasting for this procedure. Diabetics need extra precautions (12, 23).

PET scan is an extremely safe procedure. The radiation dose to the patient is minimal. The radioisotope used, which in most cases is  $^{18}\text{F}$ -Fluorodeoxyglucose ( $^{18}\text{F}$ -FDG) is nothing but a simple glucose molecule whose atom has been substituted by a radioactive fluorine atom, has a short half life and is rapidly eliminated from the body. The amount of a single adult dose of  $^{18}\text{F}$ -FDG is approximately 10 mCi and it may vary according to body weight.  $^{18}\text{F}$  decays principally by positron emission, which leads to

annihilation process. In this process of a pair of coincident 0.511 MeV photons emitted (24)

## **1.17 RADIATION SAFETY**

During the routine operation of medical cyclotron, it is compulsory to assess the radiation levels in and around the medical cyclotron. Radiation Safety Officer (RSO) and Medical Physicist (MP) are responsible to keep the radiation exposure to minimum level because during the operation of cyclotron, high level of radiation is produced and it is mandatory to measure the radiation level in and around the medical cyclotron (25).

Routine cyclotron radiation survey is an important part of overall radiation safety in the cyclotron facility. The RSO/MP maintains the record of radiation levels and should inform to AERB whenever any radiation accident happens. He can prevent unjustifiable radiation exposure to occupational worker and patients. For measurement of radiation level Ionization Chamber and Geiger Muller (GM) counter based survey meter are widely used (26).

## **1.18 REVIEW OF LITERATURE**

M A Dell (27) suggest that with the advent of high-energy collimators and dual-head coincidence cameras, standard nuclear medicine centre will very rapidly start imaging with PET radiopharmaceuticals. The use of 511-keV emitters raises new radiation safety concerns for nuclear medicine professionals conventionally restricted to handling  $^{99m}\text{Tc}$  and other low-energy isotopes. This is a basically evaluation of positron emitters, extent concerns, exposure rates, shielding necessities and external radiation exposure improvement. Recently developed PET shielding products are accessible and regulatory status is discussed briefly.

JC Hung (28) gives the details idea about the quality assurance requirements, which include test procedure, acceptance criteria, and testing schedule for  $^{18}\text{F}$ -FDG injection listed in the USP, the draft CMC issued by the U.S. FDA and the EP were compared. The FDA transformation Act of 1997 needs that the Quality Assurance of compounded PET medicine goods is in observance with the PET compounding principles and representative monographs incorporated in the USP. But, the “twilight” clause of the PET part inside the FDA transformation Act of 1997 stipulates so as to all PET medicine goods, in owing way, have to get together the requirements for drug consent trial and recent good manufacturing carry out, and the FDA has issued a summary CMC that includes QA specifications for  $^{18}\text{F}$ -FDG injection.

Sushil Sharma et al (29) described about the radiation safety was resolute to uphold quality control in the cyclotron laboratory. In the study they did 438 runs in the Faraday cup (20  $\mu\text{A}$  for 10 min), 20 runs on  $^{18}\text{O}$ -water target (40  $\mu\text{A}$  for 2 h) and 10 runs on  $^{18}\text{O}$ -gas targets (30  $\mu\text{A}$  for 45 min), They have established that occupationally exposed workers remain  $10 \pm 5$  times lower federal regulatory limits (FRLs) in the cyclotron,  $30 \pm 8$  times lower FRL in the radiochemistry lab and  $200 \pm 10$  times lower the FRL exterior the cyclotron laboratory for the period of beam function. (The FRL for unrestricted area are  $<20 \mu\text{Sv}$  in 1 h.) The non occupassional exposed personnel allocation in offices in the surrounding area of the cyclotron area surrounded by 100 m distance remained two hundred times lower the FRL irrespective of beam would be on or off, suggestive of usual beam current of 40  $\mu\text{A}$  for 2 hours once a day during office hours is safe provided QC and system presentation trial as discussed in this report are strictly maintained.

G. S Pant et al (25) had detail study on a self-shielded medical cyclotron. It was commissioned to produce positron emitters, namely,  $^{18}\text{F}$ ,  $^{15}\text{O}$ ,  $^{13}\text{N}$  and  $^{11}\text{C}$  for positron

emission tomography (PET) scanning. Currently the cyclotron has been wholly used for the making of  $^{18}\text{F}$  for  $^{18}\text{F}$ -FDG imaging. The operational parameters which influence the yield of  $^{18}\text{F}$  production were measured. The radiation value in the cyclotron and radiochemistry laboratory was also measured to evaluate the radiation safety position in the centre.  $^{18}\text{O}$  water is bombarded with proton beam from the cyclotron to produce  $^{18}\text{F}$  that is used for the synthesis of  $^{18}\text{F}$ -FDG. The operational parameters which influence the yield of  $^{18}\text{F}$  were observed during 292 production runs out of a total of additional four hundred runs. The radiation exposure value was also calculated in the centre at different point through cyclotron production and in radiochemistry room during of  $^{18}\text{F}$ -FDG syntheses. It was found that after the Target rinse increased the number of runs of a given target, as well as resulted in an improved connection between the duration of bombardment and the end of bombardment  $^{18}\text{F}$  activity with completely fresh target after rebuilt. According to article the radiation levels in the cyclotron and radiochemistry laboratory was monitored to be healthy inside set limits with secure work put into practice.

Frank Wuest et al (30) give the thought that  $^{18}\text{F}$ -FDG as the mainly significant PET radiopharmaceutical is available in every PET center. However, there are only very few examples by means of  $^{18}\text{F}$ -FDG as a construction mass for the synthesis of  $^{18}\text{F}$ -labeled compounds. This study tells us to use of  $^{18}\text{F}$ -FDG as a building block for the synthesis of  $^{18}\text{F}$ -labeled peptides and proteins.  $^{18}\text{F}$ -FDG was converted into  $^{18}\text{F}$ -FDG-maleimidehexyloxime ( $^{18}\text{F}$ -FDG-MHO), a novel  $^{18}\text{F}$ -FDG-based for the mild and thiol group-specific  $^{18}\text{F}$  tagging of peptides and proteins. This reaction was performed at 100 °C for 15 min in a sealed vial having  $^{18}\text{F}$ -FDG and *N*-6-aminoxy-hexyl maleimide in 80 percent ethyl alcohol.  $^{18}\text{F}$ -FDG-MHO was got in 45–69% radiochemical yield after HPLC purification in a total synthesis time of 45 min. Chemo discriminatory conjugation of  $^{18}\text{F}$ -FDG-MHO to thiol groups was investigated by the reaction by the tripeptide

glutathione and the single cysteine having protein annexin A5 (anxA5). The annexin A5 radiolabeled ( $^{18}\text{F}$ -FDG-MHO-anxA5) was obtained in 43–58% radiochemical yield (based upon  $^{18}\text{F}$ -FDG-MHO,  $n = 6$ ), and  $^{18}\text{F}$ -FDG-MHO-anxA5 was used for a pilot small animal PET study to review in vivo biodistribution and kinetics in a HT-29 murine xenograft model.

P. Zanzonico et al (31) tell us that PET and SPECT are now a day's well established and indispensable imaging modalities in the modern Nuclear Medicine. Computed Tomography Scanners have now been integrated in to multiple modality PET/CT and SPECT/CT devices, and these devices, Particularly PET/CT scanner are dramatically impacting clinical practice. FDG most widely used radiopharmaceutical for clinical PET imaging.

The AAPM provides a comprehensive summary of shielding design and related considerations, along with illustrative calculations. Whether It is in the form of a PET/CT or a SPECT/CT device, the introduction of CT scanners into a nuclear medicine location has shaped new and compound radiation protection issues relating to the radiation load and assistant dangerous accrued by patients. In addition, because PET is dependent on the availability of short-lived  $^{18}\text{F}$  ( $T_{1/2} = 110$  min) mainly in the appearance of FDG, and other momentary positron emitters such as  $^{11}\text{C}$  ( $T_{1/2} = 20$  min),  $^{13}\text{N}$  ( $T_{1/2} = 10$  min), and  $^{15}\text{O}$  ( $T_{1/2} = 2$  min), cyclotrons for production of medically applied radionuclides and linked radiochemistry centre are now extensive and present their own radiation safety issues. In addition to the radioactive product, sources of exposure consist of neutrons and radioactive activation products in the various cyclotron components and surrounding shielding.

J Kozirowski (32) did the study on Quality Control. Most automated synthesis modules synthesis  $^{18}\text{F}$ -FDG in half an hour, except the quality control involving up to

three separate methods and three unlike investigative systems is time uncontrollable. The utilize of HPLC, TLC, and GC for the quality control of  $^{18}\text{F}$ -FDG is both time consuming and expensive. In reference number 33, it is presented that single HPLC system for all three analyses.

H.H.Coenen et al (33) described that Positron emission tomography (PET) is a rapidly expanding clinical modality universal due to the ease compact medical cyclotrons and automated chemistry for the production of radiotracer. Though, the majority of the  $^{18}\text{F}$ -tracers other than  $^{18}\text{F}$ -FDG are in less than optimum human use and there is significant extent to bring potentially helpful  $^{18}\text{F}$ -tracers for clinical use. The Expert Nuclear Medicine Physicians reviewed the developments together with the artificial approaches for the preparation of  $^{18}\text{F}$ -tracers for oncology and neurology. An assortment of three groups of  $^{18}\text{F}$ -tracers that are constructive either in oncology or in neurology was done based on well-defined criteria and application, lack of toxicity, availability of precursors and effortlessness of production.

From recommendations of the consultant cluster gathering, IAEA started a synchronized investigative development on “Expansion of  $^{18}\text{F}$  radiotracer for exercise in oncology and neurology” in which 14 countries are participat in a 3-years joint plan. The outcomes of the synchronized research project are expected to catalyze the wider application of numerous  $^{18}\text{F}$  radiotracers away from  $^{18}\text{F}$ -FDG for diagnostic applications in oncology and neurology.

According to K. Abbas et al (34) the MC40 Cyclotron is productively used for usual  $^{18}\text{F}$ -FDG manufacture in fulfillment with the promotion approval under a profitable joint venture between JRC and GE HC. The commercial production has been operational since April 2004 without any interruption. This radiopharmaceutical site has been the 1<sup>st</sup> producing site authorized in Italy.  $^{18}\text{F}$  production, the cyclotron is operating every night

through about six hours. The  $^{18}\text{F}$ -FDG radiopharmaceutical is circulated to hospitals and investigating centres in the Italy. The radiopharmaceutical is commercially recorded under the brand name Steri PET.

Shane B. Claggett et al (35) suggest that many automated radiosynthesizers for producing PET probes provide a means for the operator to form traditional synthesis programs. The consumer is still accountable for adding steps to bring up to date the graphical demonstration of the organization. In spite of these unnecessarily complex approaches, we have formed software to carry out radiochemistry on the ELIXYS radiosynthesizers with the goal of being intuitive and easy to use.

P.P.Silva et al (36) shown in his study that the activated accelerator cyclotron components and the radioisotope making may bang on the workers radiation exposure of the personnel through the custom maintenance and emergency fix events and any alteration of the equipment. Since the adherence of the principle of ALARA constitutes a major objective of the cyclotron management, it has noted that imperative to investigate the radiation levels at the place of work and the likely wellbeing effects to the employee caused by radiation exposure. This study was based on the entity monitoring report for the duration from 2007 to 2011. Monitoring of the workplace was also performed by means of gamma and neutron detectors to conclude the dose rate in different predetermined spots.

V. Anticl et al (37) proposed to evaluate the exposure to staff in the two PET/CT centres in Serbia and to examine the chances for dose lessening. Dose levels in terms of  $H_p(10)$  for entire whole body and  $H_p(0.07)$  for upper extremities of NM personnel were monitored by thermo luminescence and electronic personal dosimeters. The doses per process in terms of  $H_p(10)$  were 4.2 to 7 and 5 to 6  $\mu\text{Sv}$ , in two centres, correspondingly, while the extremity (lower or upper) doses in terms of  $H_p(0.07)$  in one

of the centres was 34–126  $\mu\text{Sv}$  procedure. The whole-body doses per unit activity was 17 to 19 and 21–26  $\mu\text{Sv GBq}^{-1}$  in 2 centres, respectively, and the normalized finger dose in one of them was 170 to 680  $\mu\text{Sv GBq}^{-1}$ . The maximal expected annual whole-body doses in 2 centres were 3.4 and 2.0 mSv, while the consequent extremity (lower or Upper) dose in the later one was 45 mSv.

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## *Chapter 2*

*Experimental*

*Technique &*

*Methodology*

# **CHAPTER 2: EXPERIMENTAL TECHNIQUE AND METHODOLOGY**

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## **2.1 GENERAL**

The Eclipse RDS from Siemens limited is an automatic, self-shielded, dual beam medical cyclotron, installed in the Cyclotron Facility. It is a fixed-energy isochronous cyclotron, capable of accelerating protons to 11 MeV energy (1).

## **2.2 MEDICAL CYCLOTRON**

Cyclotrons are types of particle accelerator in which charge particle accelerate in cyclic path way from centre to outwards. The all six components of medical cyclotron kept under high vacuum. The value of vacuum level is  $10^{-7}$  Torr. The brief description of each constituent and their functioning principle are discussed below (2-5).

## **2.3 COMPONENTS OF CYCLOTRON**

### ***2.3.1 ION SOURCE SYSTEM***

Hydrogen gas is used for production of ion source. Negative hydrogen ion produced from hydrogen gas in ion source system. It is axially mounted in the cyclotron tank and consist a very special design called penning ion gauge (PIG). PIG consist two tantalum cathode these electrode are connected negatively potential (1-3 kV). Inside the PIG hydrogen gas flow from 4-10 SCCM. It is controlled by the software during normal automatic operation. The hydrogen accepts an electron and becomes negatively charged hydrogen ions. The ionized hydrogen gas forms the plasma from which negative ions are extracted for acceleration by applying positive bias voltage. During normal operation, the control system regulates the ion source arc current to maintain the desired target current.



### ***2.3.2 RADIO FREQUENCY SYSTEM***

RF system is the most significant and responsive part of the cyclotron can also called heart of cyclotron. The voltage difference between the electrodes accelerates the negative hydrogen ions inside the dees, which in turn imparts energy to the negative H<sup>-</sup> ions. The structure is composed of four pie-shaped electrodes, which are mounted in the magnet valleys and supported by Dee-stems extending down from mounting plates at the top of the magnet yoke.

### ***2.3.3 VACUUM SYSTEM***

The vacuum system consists of a vacuum chamber or tank contained within the magnet yokes. There are three or four diffusion pumps with one mechanical and depends upon model of cyclotron, which help in creating and maintaining, desired vacuum in the tank by constantly removing gas from the ion source and surfaces inside the vacuum chamber. The vacuum is essential in the key acceleration area of the cyclotron to uphold the preferred acceleration to the ion beam without any loss of ions and their energy.

### ***2.3.4 MAGNET SYSTEM***

The magnet system provides the bending force that confines the beam to the circular orbit centered between the upper and lower magnet poles. The magnet system includes the upper and lower magnet yokes with integral pole pieces, the magnet coil, and the magnet power supply. The field generated by the magnet coil is concentrated in the small gap between the upper and lower poles where the beam is accelerated.

### ***2.3.5 EXTRACTION SYSTEM***

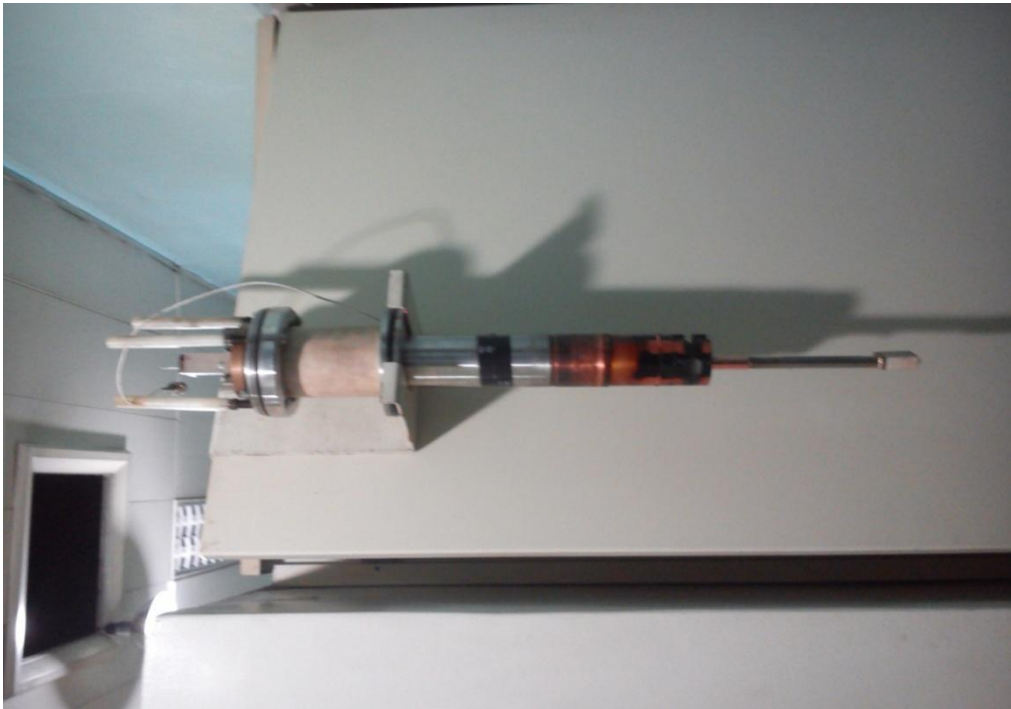
The dual beam option allows two extractor foils in between the path of charge particle, thus splitting the beam between two targets. The extraction system consists of one, or optionally two, beam extractors that intercept the accelerated negative hydrogen beam (i.e. negative hydrogen ions) with a carbon foil (thickness 5  $\mu\text{m}$ ). In negative ion cyclotron consist of a carousel with dimension of only around 4 cm. It holds three carbon foils. When accelerated negative hydrogen ion reaches periphery of dee it intercepted in carbon foil. Carbon foil absorbs two electrons and convert it into proton ion this proton ion curve outward due to its polarity. This polarity change from negative to positive ions reverses the bending force exerted on the beam by the magnetic field. Once stripped of electrons, the positively charged beam arcs outward toward the exit port and target.

### ***2.3.6 TATGET SYSTEM***

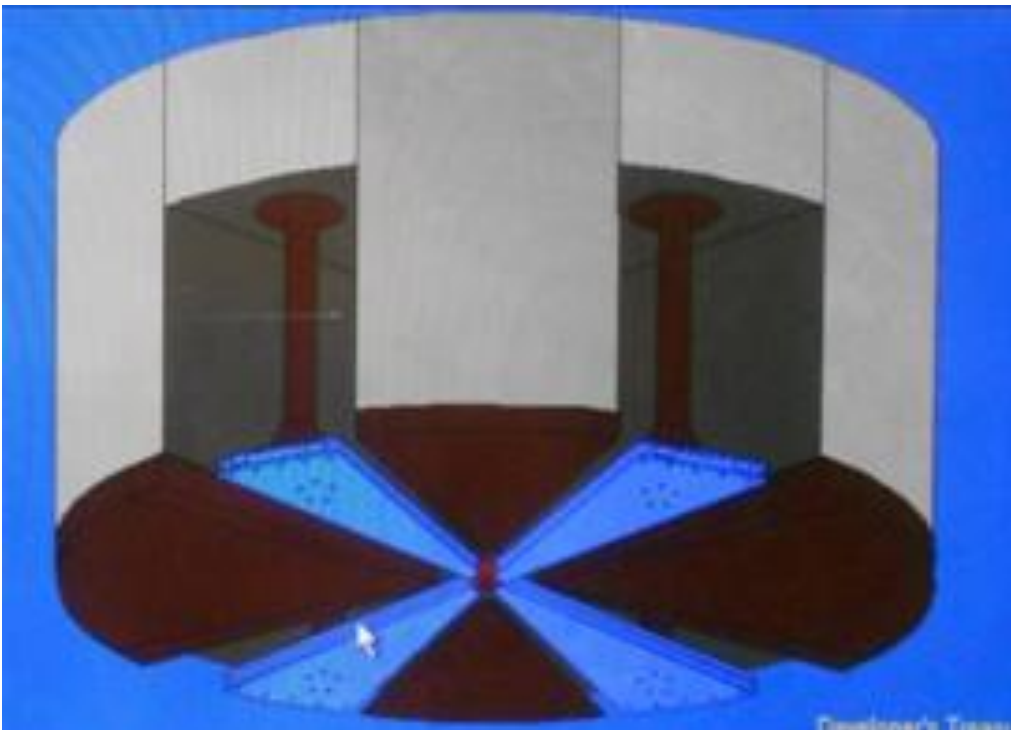
Target assembly is part of a cyclotron for the irradiation of target material it has four components Target Material, Target Body, Target Changer and Collimator Assembly. There are four clinically useful positron emitting radionuclides such as  $^{18}\text{F}$ ,  $^{15}\text{O}$ ,  $^{13}\text{N}$ , and  $^{11}\text{C}$ -are produced with RDS-111 target system.

#### ***2.3.6.1 TARGET MATERIAL***

The liquid or gases material that undergoes nuclear transformation on being bombarded with protons. For example the production of  $^{18}\text{F}$ ,  $^{18}\text{O}$  is the target material.



**Figure 2.1: Schematic diagram of Ion source (Courtesy Siemens Ltd)**



**Figure 2.2: Schematic diagram of Radiofrequency system (Courtesy Siemens Ltd)**

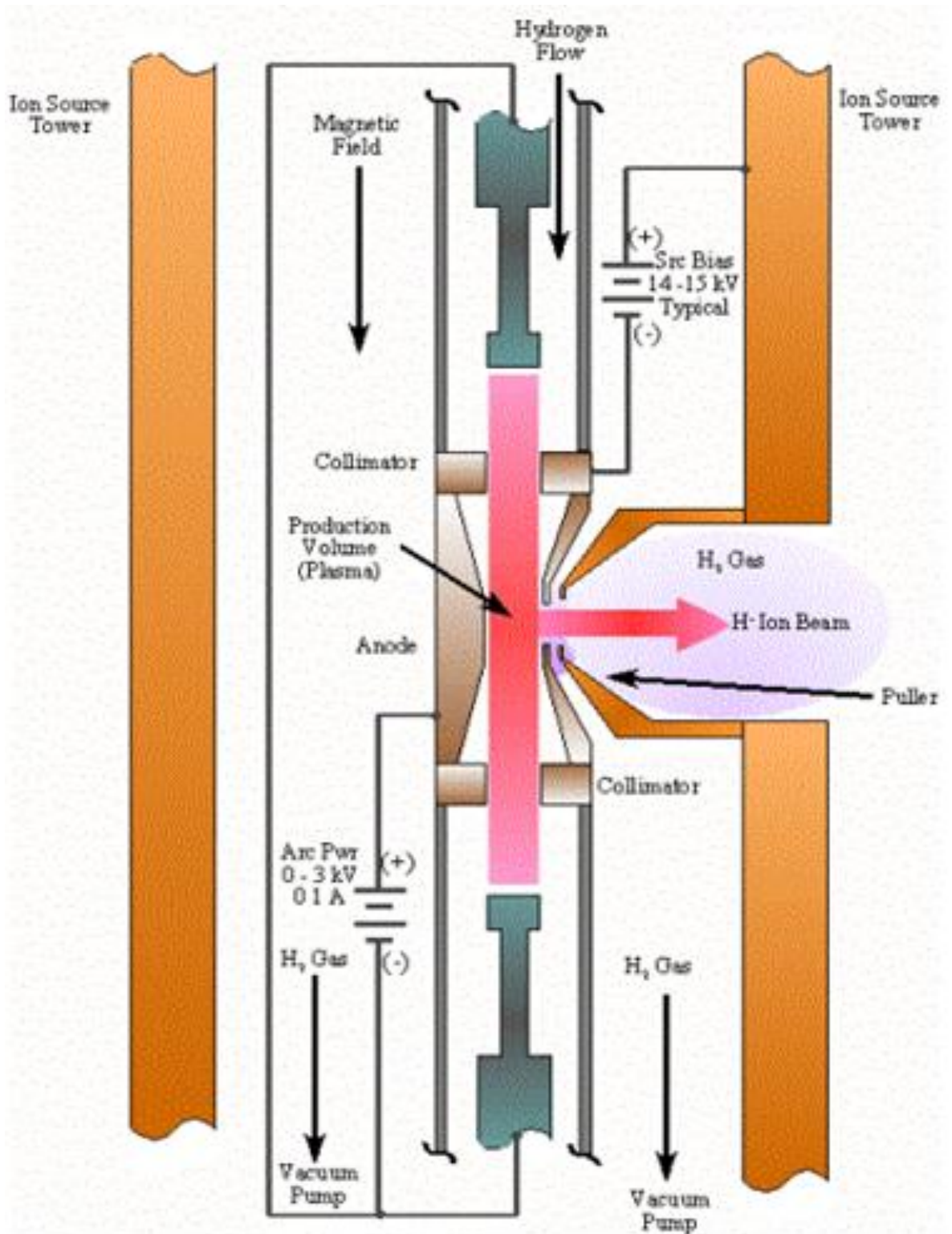
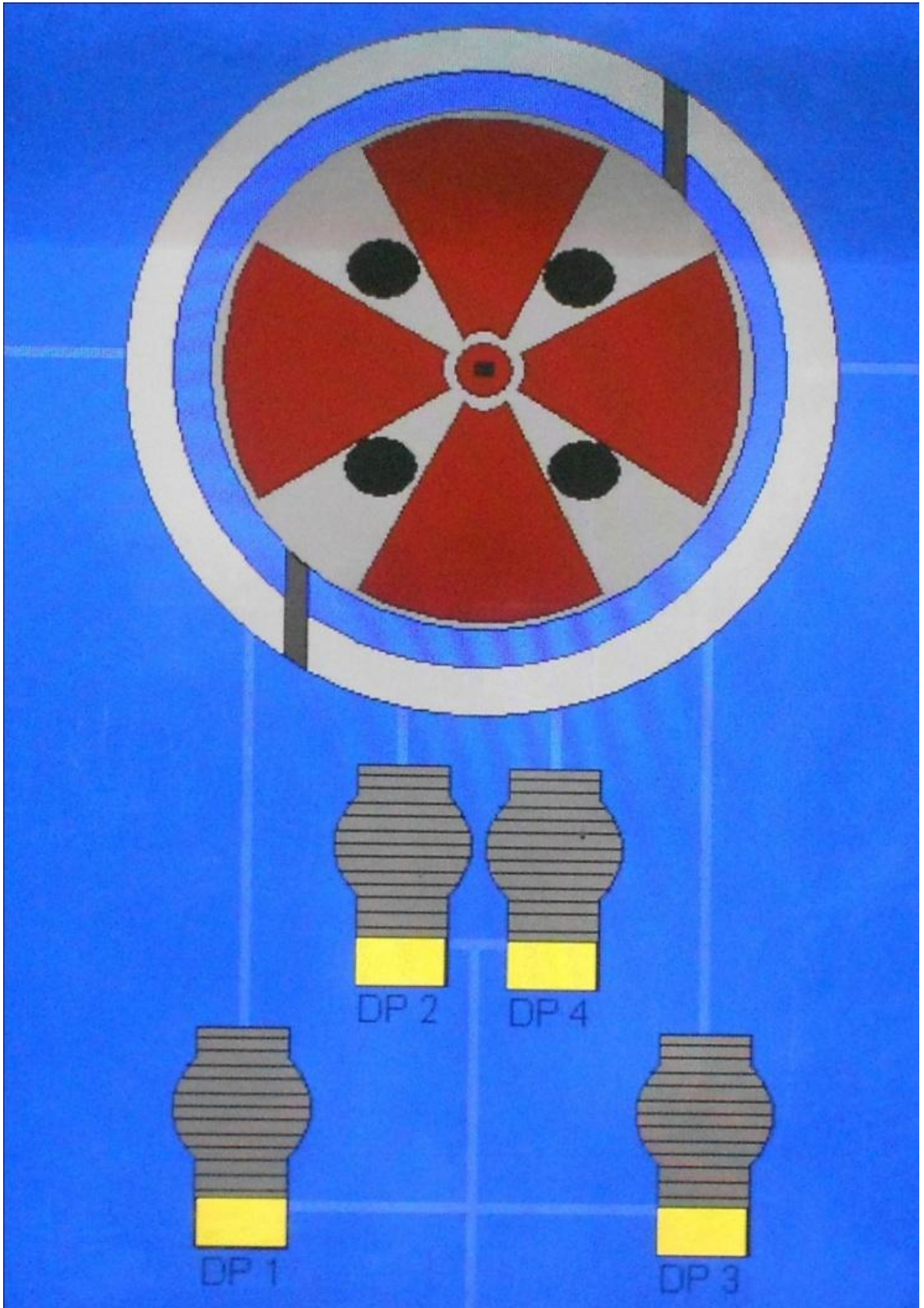
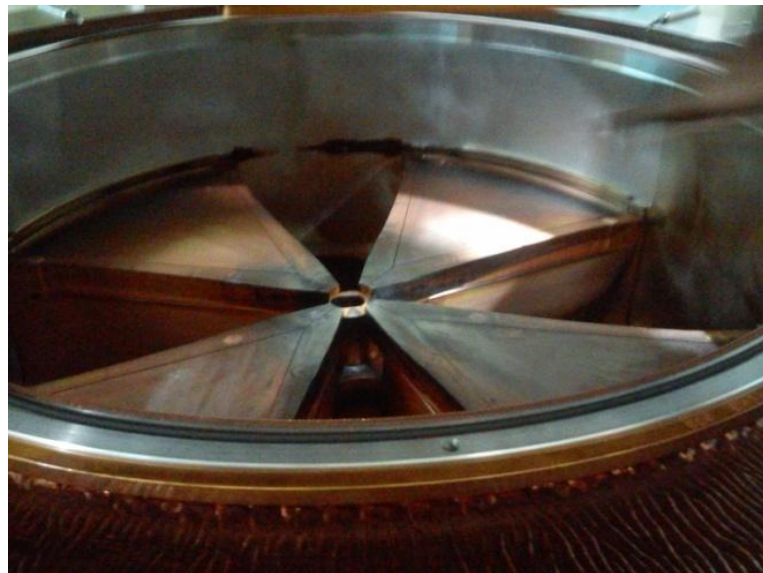
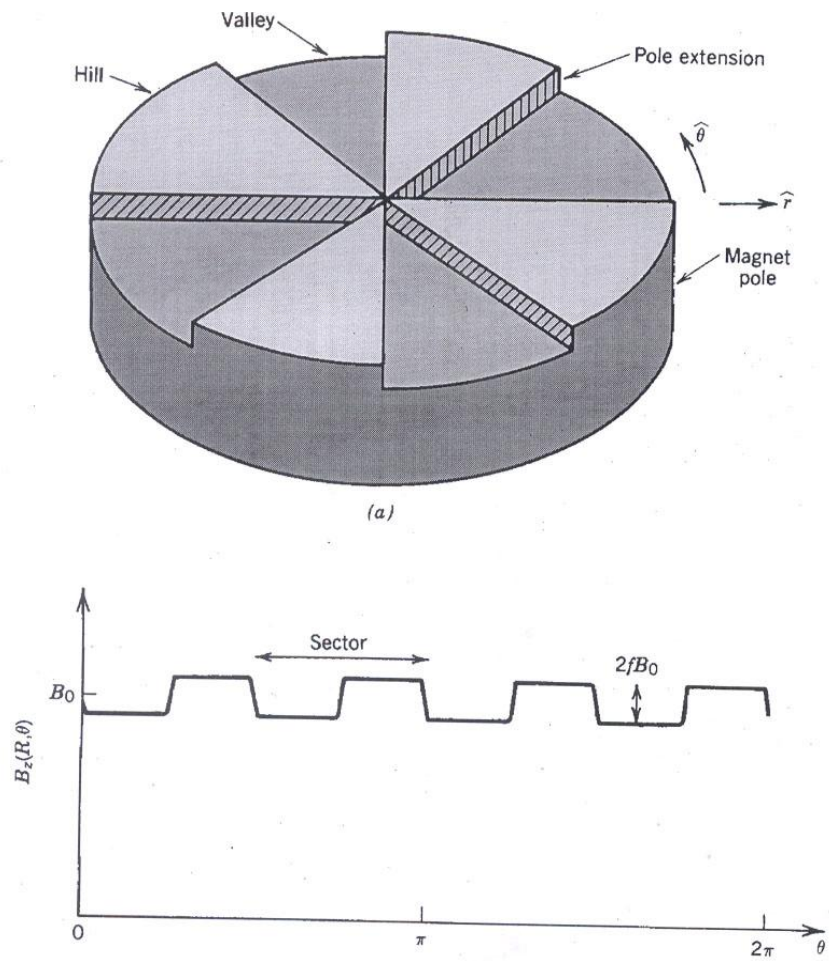


Figure 2.3: Schematic diagram of production of Hydrogen ions in the ion source

(Courtesy Siemens Ltd)



**Figure 2.4: Schematic diagram of Vacuum System (Courtesy Siemens Ltd)**



**Figure 2.5: Picture a and b are schematic diagram of Magnet System (Courtesy Siemens Ltd)**

### *2.3.6.2 TARGET BODY*

This holds the target material during irradiation and is usually made of silver/tantalum. During target irradiation the beam passes through a vacuum window, helium cooling space, target window and the target material. As the ion beam travels from one end to others end of the windows it lose the energy.

### *2.3.6.3 TARGET CHANGER*

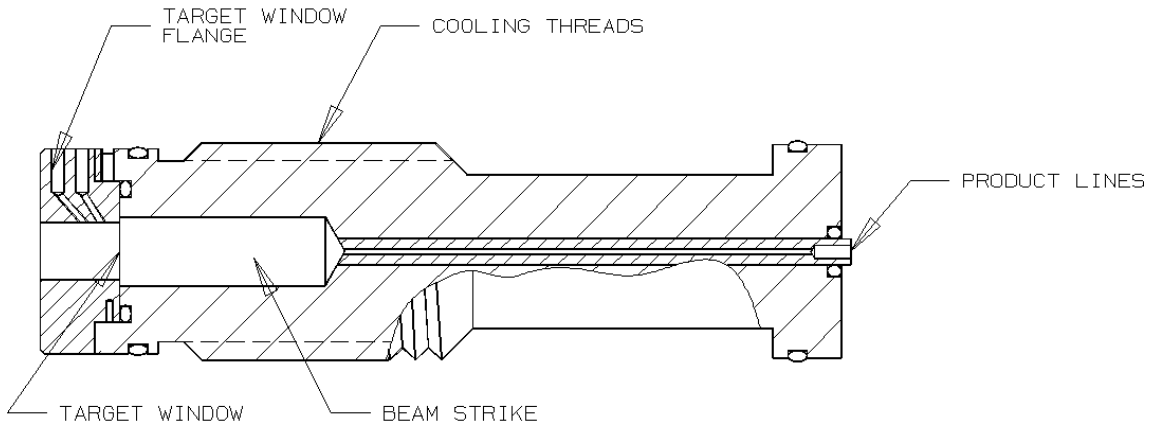
This includes a collimator and single vacuum window assembly. The target changer gearshift the revolving of the selected target into bombardment position and accommodates as many as eight targets. The ports that have not occupied by any target are packed with Faraday cups, made up of aluminum cylinder. Water and helium are distributed all the way through the target changer to remove heat from the targets, which is generated during cyclotron operations.

### *2.3.6.4 COLLIMATOR ASSEMBLY*

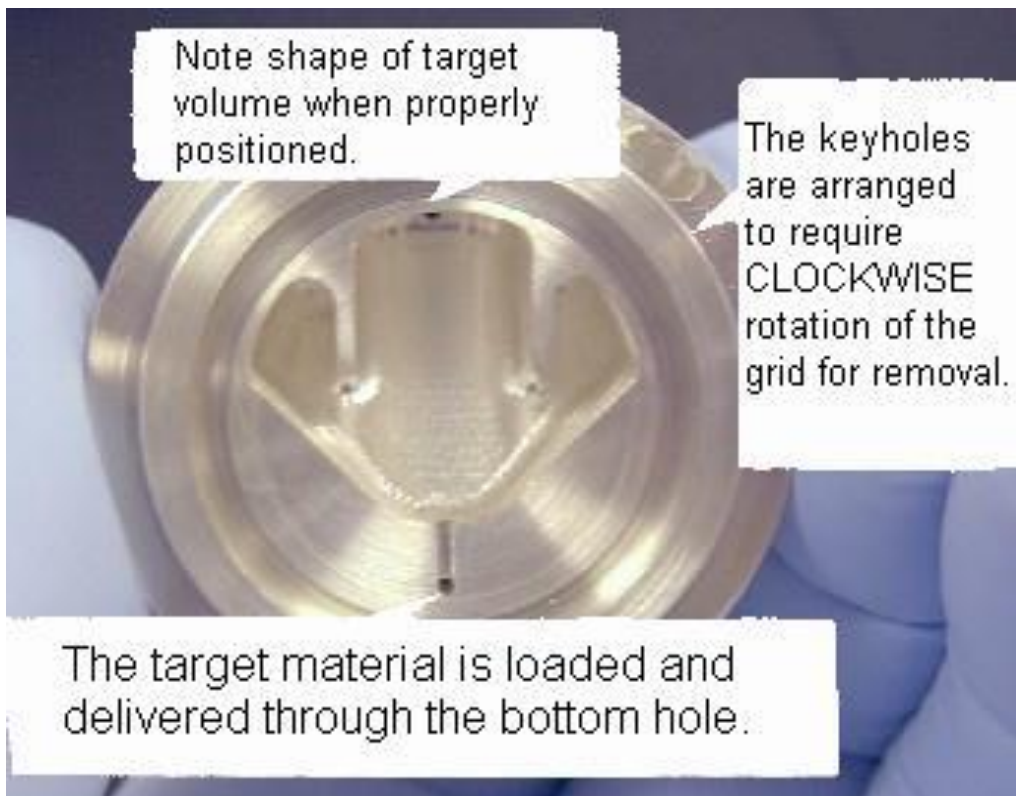
The collimator is mounted at the target changer entry to make sure a comparatively homogeneous beam profile across the target diameter.

## **2.4 DEE VOLTAGE**

It is defined as the voltage difference between the dees to accelerate the charge particles to gain the desired energy. When the dee voltage is small the ion makes a larger numbers of turns that when the voltage is large. However in modern cyclotrons, a large dee voltage (30-100kV) is generally used. In any event, the final energy attained by the ion is the sum of the individual energies gained at each crossing of the gap between the dees. At a dee voltage of 35 kV, the energy gained by a proton in each revolution, in a cyclotron with a magnetic field of 1.8 tesla, is approximately 0.1 MeV. Thus to reach a



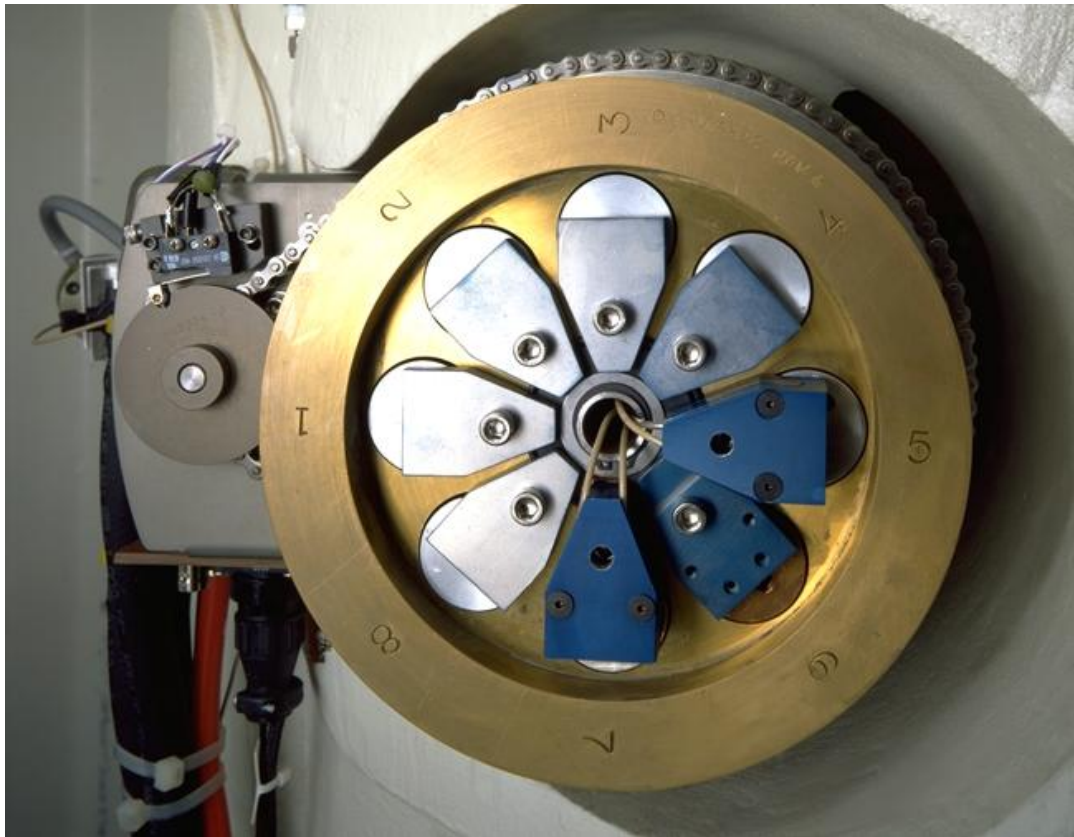
**Figure 2.6: Schematic diagram of Target (Courtesy Siemens Ltd)**



**Figure 2.7: Schematic diagram of space for target material in the Target (Courtesy Siemens Ltd)**



**Figure 2.8: Schematic diagram of Extractor System (Courtesy Siemens Ltd)**



**Figure 2.9: Schematic diagram of Targetry system (Courtesy Siemens Ltd)**

maximum energy of 11 MeV, the proton will have to go through  $11\text{MeV}/0.1\text{ MeV}$  or 110 revolutions.

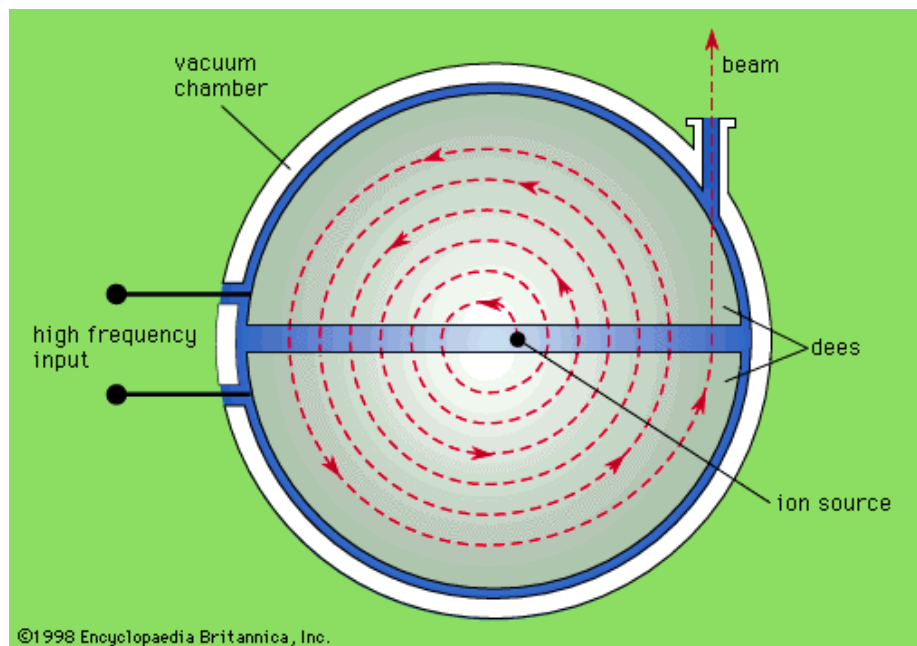
## **2.5 AXIAL FOCUSING AND AZIMUTHAL VARYING FIELD CYCLOTRON**

Median plane: - Charged particle revolves in a circular orbit in a plane between two magnetic poles.

Axial focusing: - Particles differing from median plane are enforced by putting off magnetic field to remain in the median plan for this magnetic field should decrease at larger radius. This force known as axial focusing restores the ions, when necessary, to the median plane. For this force to prevail the magnetic field must decrease at the larger radius. Axial focusing of orbiting charge particles is compulsory for appropriate performance of cyclotron (6-8).

## 2.6 ECLIPSE HP CYCLOTRON

The Eclipse family of PET cyclotrons is Siemens complete solution for entire radioisotope production. The Siemens Eclipse High Performance (HP) medical cyclotron made of 11 MeV, -ve ion, solo particle accelerator. The produced activity by this cyclotron approximately 10 Ci) of  $^{18}\text{F}$ . In this system radiotracers such as  $^{18}\text{F}$ ,  $^{18}\text{F}$ -2,  $^{11}\text{C}$ ,  $^{13}\text{N}$  and  $^{15}\text{O}$  using a four position automated target carousel. It was designed specifically to optimize fluoride production. The automated, compact Eclipse HP medical cyclotron produces the highest quality output and is designed for commercial production and distribution of  $^{18}\text{F}$  radiopharmaceuticals (9).



**Figure 2.10: Sketch of a particle being accelerated in a cyclotron, and being ejected through a beamline (courtesy by MLA style “Ernest Lawrence- Biographical” Nobel prize.org.Nobel Media AB 2014.)**

### 2.6.1 MAIN FEATURES

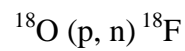
Some main features of this medical cyclotron are mentioned below

- Flexible design targets with four target carousel accomplished of running  $60\ \mu\text{A}$ .
- Compact & self-shielded
- Automated system control

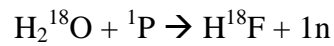
- Ease of serviceability
- The HP system can produce small volume targets with high production yields using up to 8 targets and 60  $\mu\text{A}$  current. It further supports solid targets and uses water cooling only for the elimination of helium (1).

## 2.6.2 PRODUCTION METHOD FOR $^{18}\text{F}$

$^{18}\text{F}$  produced by a nuclear reactions that is given below



- $^{18}\text{O}$  water used as target material for production of  $^{18}\text{F}$  and this  $^{18}\text{F}$  is further incorporated by a nucleophilic substitution for production of  $^{18}\text{F}$ -FDG (10-12).



**Figure 2.11: Schematic diagram of self -shielded cyclotron (Courtesy Siemens Ltd)**

## **2.7 AUTOMATED RADIOCHEMISTRY SYNTHESIS MODULE**

### **2.7.1 MAIN FEATURES**

Some main features of this Explora FDG-4 radiochemistry module are mentioned below

- Reduction of radiation exposure to personnel
- Better reproducibility of the synthetic method and
- Overall cost savings.

In this study the FDG synthesized on FDG4 Explora radiochemistry automated module by Siemens LTD (13-14).

### **2.7.2 FDG4 EXPLORA RADIOCHEMISTRY AUTOMATED MODULE**

Explora FDG 4 can produce four sequential FDG runs without user intervention with a single preparation. The interaction of radiochemist with the module is least, and with just a 20-minute setup, it can produce more than Ci of  $^{18}\text{F}$ -FDG by a single run (15).

### **2.7.3 KEY BENEFITS**

- 4 runs; single setup
- Adaptive evaporations with infrared temperature measurement

### **2.7.4 MULTI-RUN FLUDEOXYGLUCOSE (FDG) SYNTHESIS MODULE**

Explora FDG 4 is a radiochemistry module which synthesized up to four run without manual intervention, automated glucose synthesis radiochemistry module for the production of  $^{18}\text{F}$ -FDG compound through nucleophilic substitution (16).

### ***2.7.5 TYPICAL TRACERS & RESEARCH APPLICATION***

$^{18}\text{F}$ -FDG: Glucose Metabolism (Oncology, Cardiology, Neurology)

### ***2.7.6 TYPICAL SYSTEM PERFORMANCE***

- Synthesis time: = 45 -50 minutes
- Set-up time: Typically  $\leq 20$  minutes
- Clean-up time: < 35 minutes
- Time between two production runs: 45 minutes



**Figure 2.12: Automated Explora Radiochemistry module with readymade column (a and b) courtesy Siemens Ltd.**



**Figure 2.13: Automated Explora Radiochemistry module with manual column (d) courtesy Siemens Ltd.**

## **2.8 RADIATION MEASUREMENT**

Before radiation measurement the layout drafted. The radiation survey done by using survey meters. Radiation levels were measured by two radiation detector, one is portable radiation detector and other is online ROTEM's Medi SMARTS system. Radiation levels has been monitored in and around Cyclotron RDS 111 self shielded Hot shell, Explora.

The radiation levels in the cyclotron and radiochemistry laboratory will also monitor to assess the radiation safety status in the facility. The radiation dose levels have been also measured in the facility at different points during cyclotron operations and in the radiochemistry laboratory during  $^{18}\text{F}$ -FDG syntheses (9, 17).

## **2.9 RADIATION DETECTOR**

The radiation detector in the lab keeps workers safe. Exposure of radiation of radiation personnel by contamination or irradiation can be a foremost hazard. Even small amounts over a long time can increase the hazard for human being. A personal radiation detector monitors in the lab, alert users if any leakage takes place. Depending on the type they can detect and measure types of radiation, levels of radiation, counts, accumulated dose, and dose rates.



**Figure 2.14: Pictures of Portable Radiation survey Meter (courtesy Ludlum)**

## **2.10 OPTIMIZE THE WORKING PRINCIPLE OF MEDICAL CYCLOTRON**

It is observed more than 900 batch run of cyclotron to optimize the working principle of cyclotron in a medical cyclotron facility. Before initialization of cyclotron it is noted down the parameters Left Control Cabinet, Vacuum Control Chassis, Right Control Cabinet, Heat Exchanger Cabinet, Water System Control Chassis, Exhaust System, Power Distribution Cabinet, Basic System Gas Pressures and Gas Purity Levels. All above mentioned parameters are mentioned in below in tabulated form.

**Table 2.1: Left Control Cabinet**

<b>Sl No.</b>	<b>Parameters</b>	<b>Typical value</b>	<b>Exact Value</b>
1	Extractor drive chassis power ON lamp	Lit	Lit
2	Beam current integrator toggle switches	Down	Down
3	Magnet power supply controller ON Lamp	Lit	Lit

4	Magnet power supply controller dial setting (record value)	Coarse/Fine	Coarse
5	Magnet power supply voltage and current controls	Fully clockwise	Fully clockwise
6	Bias power supply voltage and current controls	Fully clockwise	Fully clockwise
7	Rear cabinet door	closed and Latched	closed and Latched
8	Ion source power supply voltage and current controls:(DV25and later)		

**Table 2.2: Vacuum Control Chassis**

<b>Sl No.</b>	<b>Parameters</b>	<b>Typical value</b>	<b>Exact Value</b>
1	vacuum tank pressure	less than $2 \times 10^{-7}$ torr	less than $10^{-7}$ torr
2	Foreline pressure	less than $2 \times 10^{-1}$ torr	less than $2 \times 10^{-1}$ torr
3	24 CDC indicator	Lit	Lit
4	5 VDC indicator	Lit	Lit
5	Start Timer diab indicator	Not Lit	Not Lit
6	Mech Pump indicator	Lit	Lit
7	Foreline pressure high	Not Lit	Not Lit
8	Start Seq Act indicator	Not Lit	Not Lit
9	DP water OK indicator	Lit	Lit
10	TTC OK indicator	Lit	Lit
11	Quick cool disable indicator	Not Lit	Not Lit
12	DP 1 not ready indicator (DV2-DV14 )	Not Lit (yellow LED)	Not Lit (yellow LED)
13	DP 2 not ready indicator (DV2-DV14 )	Not Lit (yellow LED)	Not Lit (yellow LED)
14	DP 3 not ready indicator (DV2-DV14 )	Not Lit (yellow LED)	Not Lit (yellow LED)
15	DP 4 not ready indicator (DV2-DV14 )	Not Lit (yellow LED)	Not Lit (yellow LED)
16	DP 1 Ready indicator (DV14 and later)	Lit (green LED)	Lit (green LED)
17	DP 2 Ready indicator (DV14 and later)	Lit (green LED)	Lit (green LED)
18	DP 3 Ready indicator (DV14 and later)	Lit (green LED)	Lit (green LED)
19	DP 4 Ready indicator (DV14 and later)	Lit (green LED)	Lit (green LED)
20	DP 1 OCT indicator	Not Lit	Not Lit
21	DP 2 OCT indicator	Not Lit	Not Lit
22	DP 3 OCT indicator	Not Lit	Not Lit
23	DP 4 OCT indicator	Not Lit	Not Lit

**Table 2.3: Right Control Cabinet**

SI No.	Parameters	Typical value	Exact value
1	PTS X 10 Frequency synthesizer Remote Lamp	Lit	Lit
2	PTS X 10 Frequency synthesizer level control	3/4 turn to full clock wise (+10 to +13 dbm)	3/4 turn to full clock wise (+10 to +13 dbm)
3	Rear cabinet door	closed and Latched	closed and Latched

**Table 2.4: Heat Exchanger Cabinet**

SI No.	Parameters	Typical Value	Exact Value
1	Main water flow meter	Approximately 1.0 gpm	Approximately 1.0 gpm
2	Deionization Column water flow meter	Approximately 1.0 gpm	Approximately 1.0 gpm
3	Supply water temperature	Less than 65°F	Less than 65°F

**Table 2.5: Water System Control Chassis**

SI No.	Parameters	Typical value	Exact Value
1	Water Level	Green Norm indicator lit	Green Norm indicator lit
2	Temperature	Green Norm indicator lit	Green Norm indicator lit
3	Pump	Green Norm indicator lit	Green Norm indicator lit

4	Flow switch	Green Norm indicator lit	Green Norm indicator lit
5	Conductivity OK	indicator Lit	indicator Lit
6	Make up water ON	indicator not Lit	indicator not Lit
7	Quick Cool water ON	indicator not Lit	indicator not Lit

**Table 2.6: Exhaust System**

Sl. No.	Parameters	Typical value	Exact Value
1	Flow	more than 500 Cfm	more than 500 Cfm

**Table 2.7: Power Distribution Cabinet**

Sl. No.	Parameters	Typical Value	Exact value
1	Circuit Breakers	All circuit breakers ON	All Circuit Breakers ON

**Table 2.8: Gas as Pressure of Gas Bottles**

Sl No.	Gas Bottle	Bottle Pressure	Secondary Pressure	Bottle valve position
1	Ion Source Hydrogen	> 100 psi	20 psi +/- 5 psi	Open
2	Target Helium recirculation	> 100 psi	7psi +/- 1 psi	Open
3	Argon bottle	> 750 psi	650 psi	Open
4	Vacuum tank venting Nitrogen	> 100 psi	5 psi	Open

**Table 2.9: Gas Purity Levels**

<b>Sl No.</b>	<b>Cyclotron Location</b>	<b>Gasses used</b>	<b>Purity Level</b>
1	Ion Source	Hydrogen	99.9999% minimum Purity
2	Vacuum Tank	Nitrogen	Extra Dry nitrogen, 99.9% minimum purity
3	Air Valve Actuation and cooling water line purging	Compressed Air	Dry Compressed Air

### **2.10.1 DISCUSSIONS**

For best operation of medical cyclotron there should be trained and qualified personal required. The qualification of cyclotron operator was only in the area of nuclear medicine personnel who is either DMRIT from BARC, Mumbai or M.Sc. Nuclear Medicine Technology from AIIMS, New Delhi and others recognize universities. Now it has been revised by AERB that B.Sc. Physics from any recognize university can operate the medical cyclotron after some grooming from a qualified trainer.

There are more than 900 batches observed of cyclotron run. Before initialization it was looked into lots of parameters of cyclotron for every foot race. As noted in table one all parameters are placed in the left control cabinet. Extractor drive chassis power should be ON and lit should be glowing. Beam current integrator toggle switch should be down. The magnet power supply controller lamp should be ON and lit should be glowing. Magnet power supply controller dial setting in record value i.e. coarse or fine range. Magnet power supply voltage and current controls should be fully clockwise. Bias

power supply voltage and current controls should be fully clockwise. Rear cabinet door should close before the start of the bombardment.

Table two is related with vacuum. The tank pressure should be less than  $2 \times 10^{-7}$  Torr and the fore line pressure should less than  $2 \times 10^{-3}$  Torr. The 24 CDC indicator , 5 VDC indicator , Mechanical Pump indicator , DP water OK indicator , TTC OK indicator , DP 1 Ready indicator (DV14 and later) , DP 2 Ready indicator (DV14 and later) , DP 3 Ready indicator (DV14 and later) , DP 4 Ready indicator (DV14 and later) all should be lit glow. Start Timer diab indicator, Foreline pressure high, Start Seq Act indicator, Quick cool disable indicator, DP 1 not ready indicator (DV2-DV14), DP 2 not ready indicator (DV2-DV14), DP 3 not ready indicator (DV2-DV14), DP 4 not ready indicator (DV2-DV14), DP 1 OCT indicator, DP 2 OCT indicator, DP 3 OCT indicator, DP 4 OCT indicator in all case lit should not be glow.

Table three located at right control cabinet. PTS X 10 Frequency synthesizer Remote Lamp should be illuminated. PTS X 10 Frequency synthesizer level control should be 3/4 turn to full clockwise (+10 to +13 dbm).The rear cabinet door should be shut down and latched.

Table four for heat exchanger cabinet. Main water flow meter should be approximately 1.0 Gallon per Minute (GPM). Deionization column water flow meter approximately 1.0 GPM. Supply water temperature should be less than 65°F.

Table five for water system control chassis .The green norm indicator lit for Water level, Temperature, Pump, Flow switch. Conductivity OK indicator should be blinking. Water makes up ON and water quick cool ON indicator should not lit for normal operation.

Table six for exhaust system and the precise value of exhaust would not less than 500 Cubic Feet Meter (CFM). It will produce negative pressure inside the cyclotron room. If any radioactive leakage found in the cyclotron room, the all radioactive contaminants will go outside from cyclotron room with fumes.

Table seven dedicated for power distribution cabinet. All circuit breakers should be ON

Table eight dedicated for gas pressures of gas bottles. Hydrogen gas used to produce ion source and it should be more than 20 Pound Square Inch (PSI). The valve of the hydrogen gas bottle should open before the initialization of the cyclotron. Recirculation of helium gas for target cooling should open. Target becomes hot during bombardment because of heat generated by nuclear reactions. If there is no helium gas in the helium bottle we cannot begin the bombardment. Its bottle pressure should not less than 100 psi and its secondary pressure should not less than 7 psi. The valve of the helium gas bottle should open before the initialization of the cyclotron. The argon gas is use for swipe the produced radioisotope. If there is no Argon gas in the bottle we cannot transfer the produced radioisotopes. Its bottle pressure should not less than 750 psi and its secondary pressure should not less than 650 psi. It is use because of its inert in nature. The valve of the argon gas bottle should open before the initialization of the cyclotron. The Nitrogen gas is used for venting the vacuum tank. There is vacuum level of  $2 \times 10^{-7}$  torr inside the tank. If something went wrong inside the tank then there is a need to open the tank of cyclotron. For opening of tank vacuum should be break. For breaking of vacuum nitrogen gas fill inside the tank, so there is minimal possibility of air molecule to stay put on the wall of cyclotron tank. Its bottle pressure should not less than 100 psi and its secondary pressure should not less than 5 psi. It is use because of its inert in nature. The valve of nitrogen gas bottle should open before the venting of cyclotron.

Table nine used for gas purity levels. Purity level hydrogen, helium and argon are minimum 99.999 %. This is also called five nine. The purity level of nitrogen gas is not less 99.9 % and it should be extra dry. The compressed air should be dry, it is used for air valve actuation and cooling water line purging.

If all above discussed limit are fulfilled then only we can initialize the cyclotron. If cyclotron not initialized through automatic mode then there is second option of manual mode. In that respect is surely some reason for cyclotron not initialized in manual mode. First, we had marked off all gas cylinders. Because if gas cylinder empty cyclotron will not initialize. The following step to check for cyclotron initialization fail due to bias voltage. If bias voltage is not coming we have to check ion source parameter. In this case we have to do ion source conditioning.

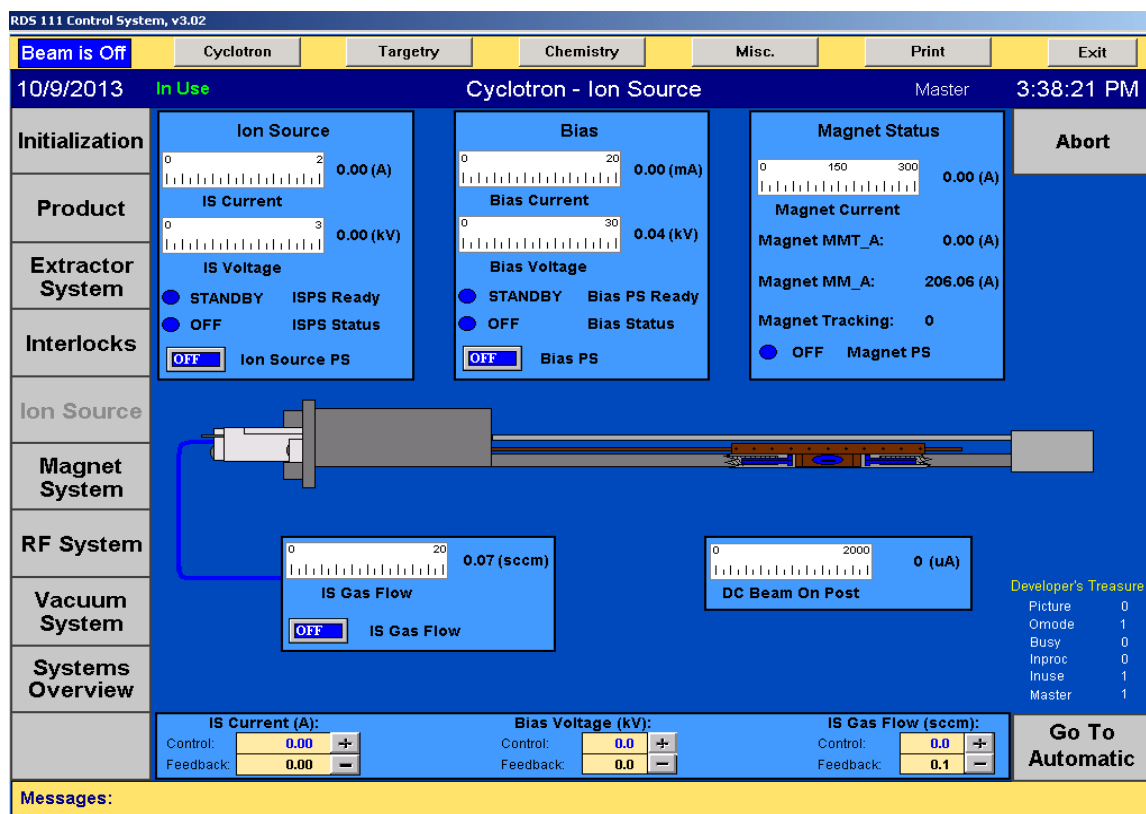
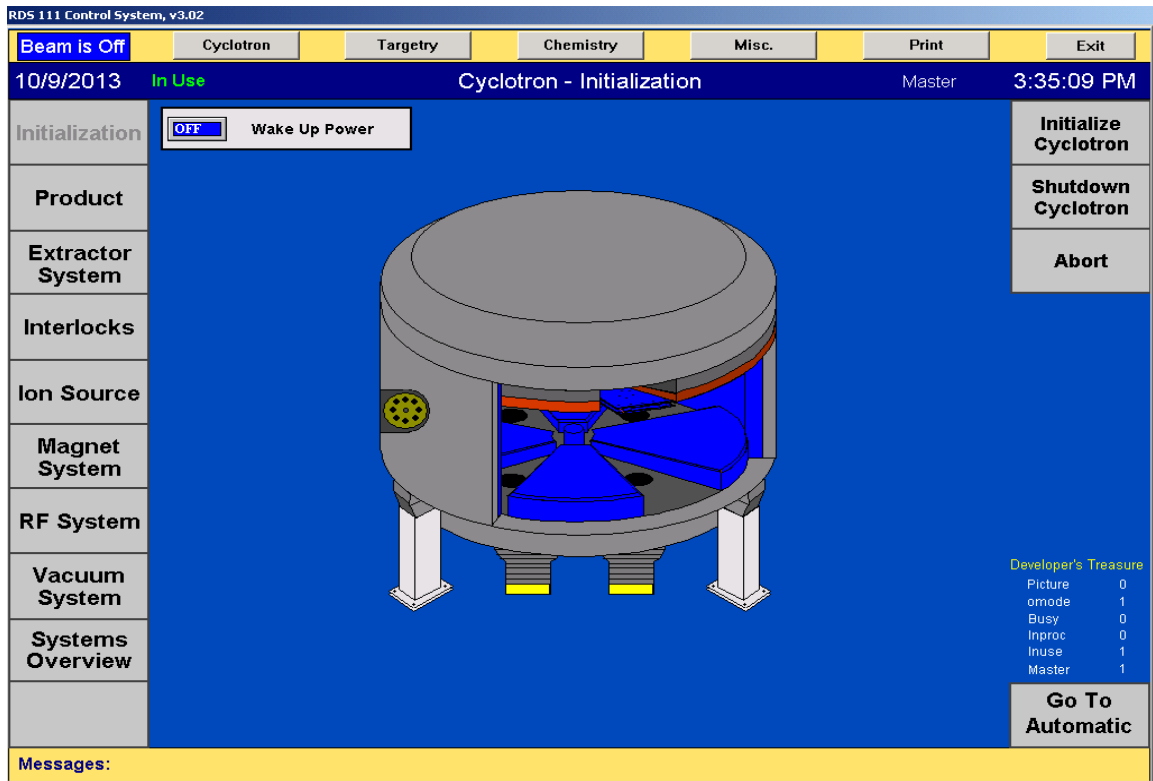


Figure 2.15: Schematic diagram of Parameters of Ion source (Courtesy Siemens Ltd)



**Figure 2.16: Schematic diagram of home page of Cyclotron (Courtesy Siemens Ltd)**

## **2.10.2 METHOD OF ION SOURCE CONDITIONING**

For ion source conditioning cyclotron initialization not required

Wake up power ON.

Magnet ON.

Put gas level 5 SCCM (after put gas be careful about the vacuum level).

Increase the ion source gas flow.

Keep eye on vacuum level (it should be  $10^{-6}$  not  $10^{-5}$ )

We can put 10 SCCM for 10 minutes (This will removed flake if present within the ion source).

Bring back gas to 5 SCCM.

Switch ON ion source.

Start by put 0.025 A.

Switch ON the bias power supply (start with 10 KV then increase up to 15 KV).

Simultaneously see the BOP for best output (0.15 is safe).

Now increase Ion Source Current value (Like 0.1, 0.11, 0.12.....up to 0.4A).

This will increase Beam on Post (BOP 800 value is the best value).

Now Put Ion source current value 0 (ZERO).

Put Bias power supply OFF.

Now cyclotron is ready for bombardment.

May adjust the puller gap and find a good transmission (be careful RF should not be switched OFF, It's better to do when RF is stable).

### **2.10.3 STEPS FOR MANUAL BOMBARDMENT**

Wake power ON.

RF ON

Change the frequency value accordingly so that the feedback of RF comes.

Wait for 20 minutes.

Rotate the selected target from the selected beam line.

Put Helium flow and Helium pressure ON.

Load the  $^{18}\text{O}$  water in the concerned target.

Control during the loading of  $^{18}\text{O}$  water, on that point should be no air bubble present in the syringe.

Watch the loading pressure of the target and wait five minutes, if it is stable go to next step.

Put magnet tracking OFF.

Put Ion source gas flow ON and the value of ISGF is 4-5 SCCM.

Put magnet ON.

Set the value of MMOF is between 2.5 to 3 (in older cyclotron it may increase).

Set the foil rotation, either  $90^\circ$ ,  $180^\circ$  or  $270^\circ$ . Whatever foil available.

Put Ion Source Current ON and its value i.e. 0.08 A.

Finally Put Bias Voltage ON and Its value should be 14-15 KV.

Now beam will come and bombardment being started. Now increase the ion source current for best performance. For best transmission and output should be adjusted by three point adjustments, which include Main Magnetic Offset (MMOF), Foil rotation and target current.

During bombardment cyclotron operator must watch parameters page to see the pressure fluctuation. If anything wrong with pressure i.e. sudden increase in pressure or sudden decreases in pressure just abort the bombardment. By aborting bombardment transfer the produced activity for  $^{18}\text{F}$ -FDG synthesis. The advantage quick abort of bombardment is to prevent the vacuum window blow. If the vacuum window will blow the all activity present in the target will go into the tank of the cyclotron. To remove this activity and rectify the problem it will require a minimum of three days.

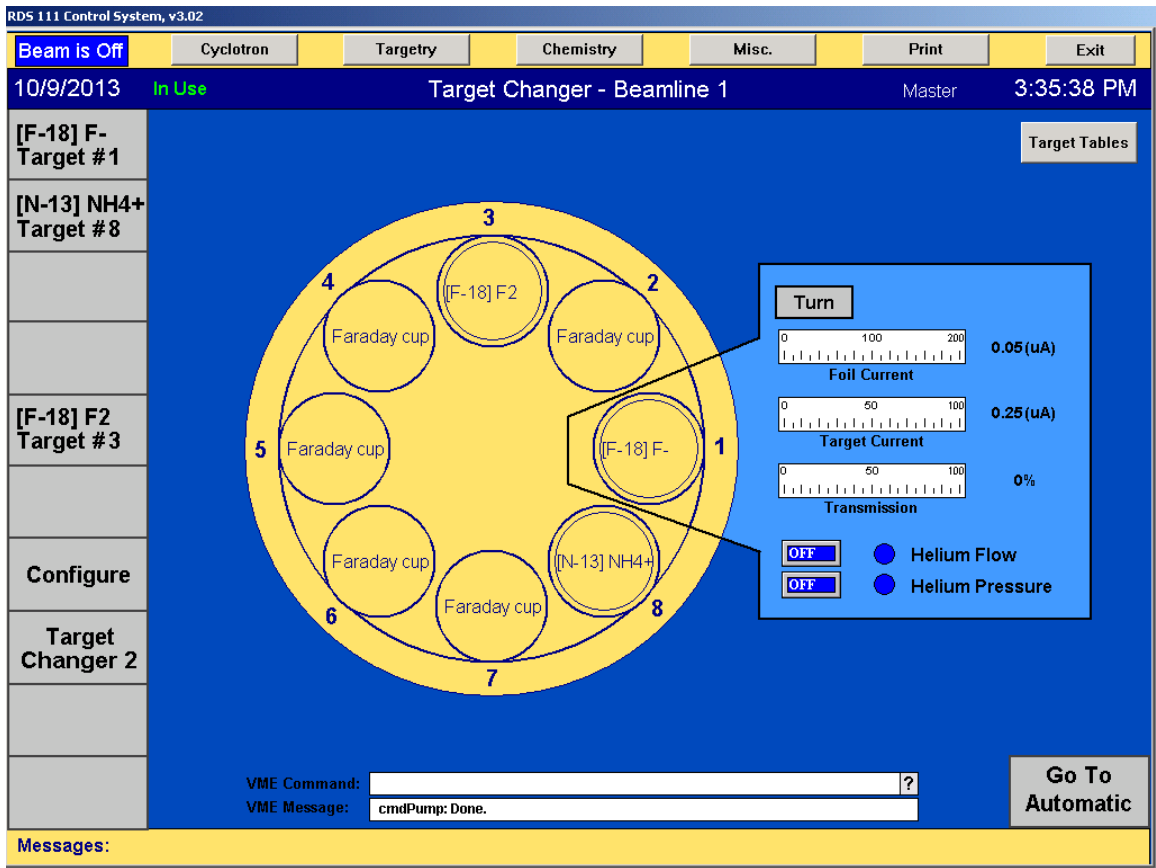


Figure 2.17: Schematic diagram of target changer (Courtesy Siemens Ltd)

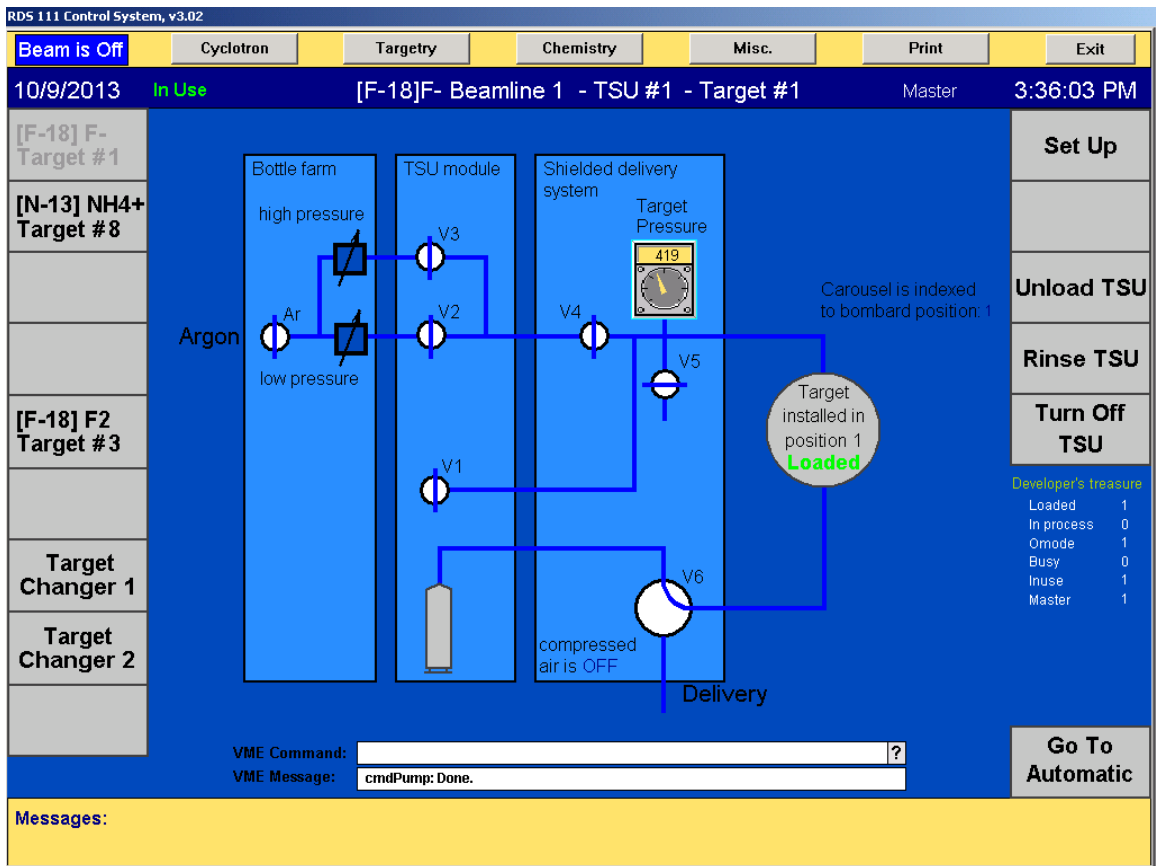


Figure 2.18: Loading parameter of F-18 Target (Courtesy Siemens Ltd)

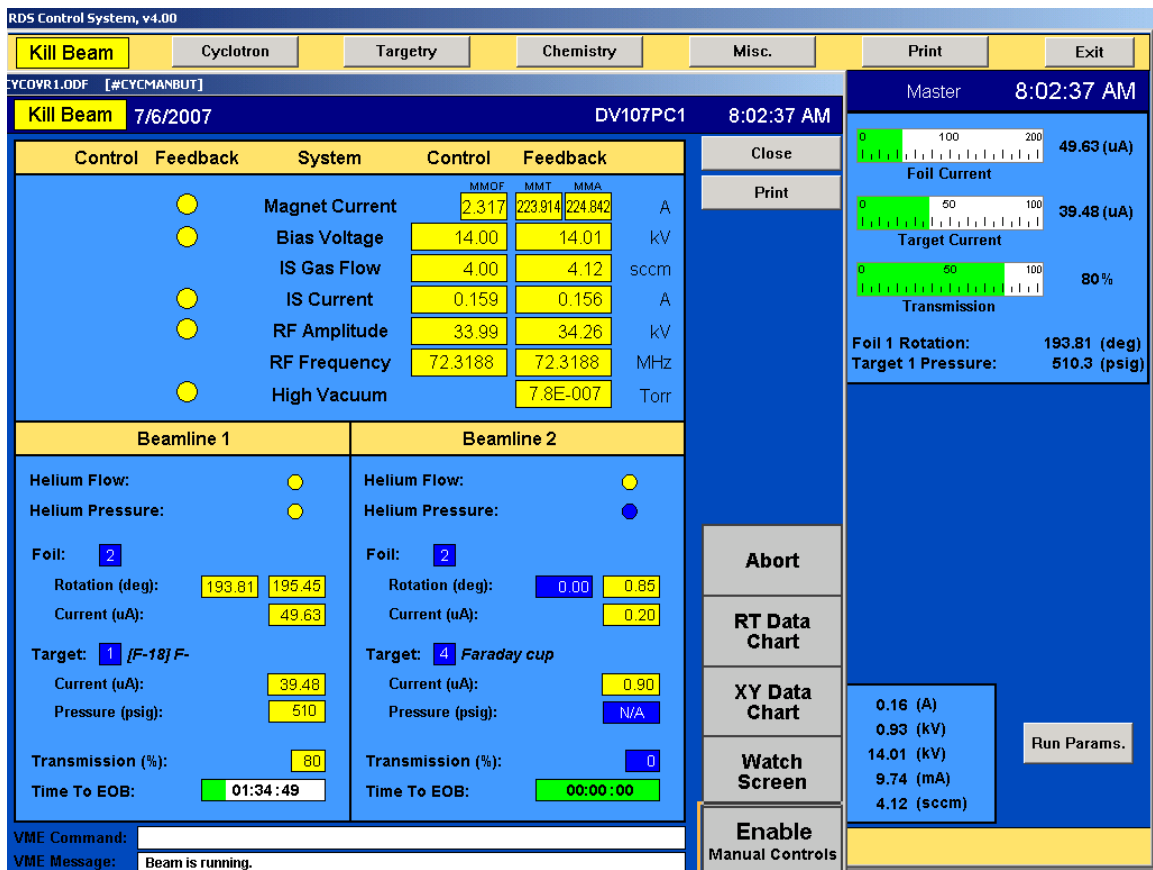


Figure 2.19: Schematic diagram parameters of automatic bombardment (Courtesy Siemens Ltd)

## 2.10.4 IMPORTANT POINTS TO BE FOLLOWED

Some small but very important point should use before cyclotron operations-

1. Rinse the target before and after the bombardment.
2. Check exhaust creating negative pressure or not.
3. Water cooling is proper or not.
4. Pressure of gas cylinders are OK or not.

Maximum duration of bombardment time 150 minutes. We can increase the bombardment time up to 210 minutes. We cannot increase bombardment time more than 210 minutes, because of saturation yield. This is useful in commercial setup. But for

running the cyclotron so long there are lots of parameters have to check. Among them water chiller temperature, helium cooling are the most sensitive parameter for optimum performance. There is a monthly maintenance of Water chiller by chiller engineers. For helium cooling there is a regularly check up of helium gas cylinder by operator and cyclotron engineer during monthly maintenance. In our setup we have silver target, if we do not believe these parameters and increase the time of the bombardment silver knock off takes place. Silver knock off is process in which, silver from silver target coming out with  $^{18}\text{F}$  transfer during transfer as we are using silver target. It will damage the target and influence the  $^{18}\text{F}$ -FDG synthesis too. This silver coming from cyclotron will cause for low yield of FDG. The cyclotron facility that is using onsite  $^{18}\text{F}$ -FDG generally bombarding less than two hours.

The vacuum level is created by three to four diffusion pumps and one mechanical pump. The number of diffusion pump depends on the brand and model of the cyclotron. The mechanical pump created vacuum level up to  $10^{-3}$  Torr. But we need about  $10^{-7}$  Torr, so we needed an additional vacuum creating device. For that manufacturer used multiple diffusion pumps. In this model of cyclotron we have the alternative of two side bombardment. That is called beam line one and beam line two. In each beam line, one bottle of  $^{18}\text{O}$  water for target loading and one bottle of  $^{16}\text{O}$  for target rinse are placed. The total numbers of water bottles are four. Lots of time it is found that vacuum window blown and target window rupture found simultaneously. Vacuum window cannot blow alone. If there is a vacuum window blown, we have to take immediate action to prevent the diffusion pump and mechanical pump. For that we have to remove the polytube from bottles of water. If don't do this immediate the vacuum rupture. The all water from bottles will get inside the vacuum system i.e. within the mechanical pump and diffusion pumps. Because inside the cyclotron tanks the vacuum level was  $10^{-7}$  Torr and suddenly vacuum break through a vacuum window and target window. So cyclotron tank will suck

the air and water through all possible paths. There are only two paths available one is through vacuum window and target window path and another is through water bottles path. As explained after vacuum break water will go within the vacuum system and vacuum will not be generated and cyclotron system will down for three days.

## 2.11 OPTIMIZATION OF THE IRRADIATION PARAMETRES OF MEDICAL CYCLOTRON FOR MAXIMUM YIELD

**Table 2.10: Bombardment parameter with respect to yield**

Sl. No.	DCBOP ( $\mu$ A)	Beamline	No. of Bombardment	Beam current	F-18 unload	F-18 after rinse	Duration of bombardment	Trap	Residue	FDG
1	289	2	72	36	719	802	35	780	8	482
2	254	2	73	36	988	1101	55	1100	13	562
3	104	2	74	36	1115	1222	60	1220	15	666
4	253	2	75	36	785	870	40	850	10	420
5	131	2	76	35	1010	1110	55	950	7	Fail
6	117	2	77	35	555	623	30	580	10	291
7	Manual	2	78	36	485	610	40	600	11	250
8	Manual	1	1	36	205	790	50	780	5	Fail
9	Manual	1	7	37	717	994	38	570	8	Fail
10	262	1	8	37	1130	1201	80	1180	11	746
11	272	1	9	37	903	980	60	970	8	260
12	Manual	1	14	38	801	888	50	850	6	109
13	Manual	1	15	39	981	1065	60	1064	8	582
14	339	1	20	40	776	892	55	850	9	533
15	333	1	22	40	650	757	40	490	12	Fail
16	334	1	23	40	795	908	50	820	14	Fail
17	314	1	25	37	835	950	57	880	12	424
18	300	1	26	39	628	728	45	640	7	354
19	320	1	27	37	963	1092	70	1000	9	579
20	313	2	1	37	831	1098	55	1050	8	Fail
21	314	2	2	37	657	777	30	770	5	385
22	317	2	3	37	1092	1282	60	1180	10	731
23	320	2	4	38	885	1045	45	1010	5	668
24	316	2	5	38	430	577	25	510	5	366
25	311	2	6	38	1075	1325	60	1290	7	756
26	325	2	7	38	821	1023	45	1020	8	636

Sl. No.	DCBOP (µA)	Beamline	No. of Bombardment	Beam current	F-18 unload	F-18 after rinse	Duration of bombardment	Trap	Residue	FDG
27	319	2	8	38	604	880	45	860	7	506
28	320	2	9	38	872	1054	45	980	6	484
29	320	2	10	38	913	1005	40	990	13	527
30	Manual	2	11	30	199	234	15	220	2	114
31	284	2	12	38	1317	1523	70	1450	12	947
32	296	2	13	38	1144	1444	66	1180	10	727
33	298	2	14	38	1145	1415	69	1140	13	Fail
34	301	2	15	38	649	808	33	700	9	153
35	301	2	16	38	977	1102	48	1010	7	452
36	303	2	17	38	1223	1491	72	1450	9	650
37	310	2	18	38	817	1053	50	1010	10	483
38	305	2	19	38	1287	1402	70	1180	10	736
39	302	2	20	38	926	1173	55	1120	9	215
40	Manual	2	21	33	209	308	15	280	3	140
41	305	2	22	38	1030	1240	60	1220	9	746
42	295	2	23	38	782	1007	49	880	8	615
43	283	2	24	38	1148	1390	64	1260	8	780
44	397	2	25	38	758	878	40	850	8	437
45	324	2	26	38	680	808	38	810	6	517
46	303	2	27	38	715	878	40	770	7	530
47	298	2	28	38	470	585	25	530	4	327
48	290	2	29	38	677	880	40	800	10	498
49	380	2	30	38	640	854	40	800	3	456
50	302	2	31	38	812	1034	50	880	13	354
51	301	2	32	38	890	1160	60	Fail	Fail	Fail
52	291	2	33	38	797	1040	50	840	152	204
53	281	2	34	38	404	551	24	490	5	204
54	307	2	35	38	700	893	41	440	63	Fail
55	270	2	36	38	550	743	33	630	6	Fail
56	263	2	37	38	732	1004	50	920	11	412
57	265	2	38	38	1142	1510	87	1300	16	830
58	279	2	39	38	1012	1299	67	1090	12	740
59	265	2	40	38	400		20	350	8	230
60	280	2	41	38	880	1210	67	1080	12	790
61	266	2	42	37	650		30	520	6	361
62	280	2	43	37	947		45	800	10	547
63	272	2	44	37	994		45	840	12	606
64	268	2	45	37	710		30	580	8	240
Average	290.561404			37.453125	806.78125	992.6440678	48.09375	877.0476	11.87302	488.1111

### **2.11.1 DISCUSSIONS**

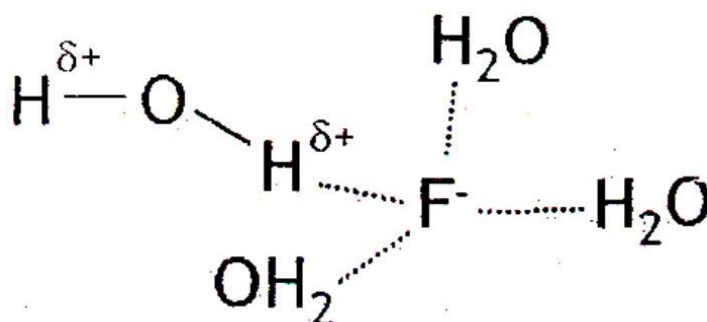
Seven types of different bombardment parameters of the cyclotron were observed. The names of those parameters are direct current beam on post, number of bombardment, beam lines, beam current,  $^{18}\text{F}$  yields, duration of bombardment and rinsed with  $^{16}\text{O}$  water. Sixty four batches of the run were observed. All the parameters are shown in table 10. As indicated in table 10, there is no relation between DC beam on post and yield. DC beam on post is just an indicator of cyclotron initialization. If the DC beam on post is less than  $250\ \mu\text{A}$ , the cyclotron will not initialize, and then we have to do manual bombardment or rectify the problem. As clearly shown table 10, if the target gets older its yield will fall. At Table 10, serial number 1 has bombardment number 72 and bombardment time is 35 minutes the yield was 802 mCi. At table serial number 7 has bombardment number 78, bombardment time is 40 minutes and yield was 610 mCi. The second example is serial number 9 has bombardment number 7, bombardment time 38 minutes and yield 994 mCi. When target older i.e. 27<sup>th</sup> bombardment the bombardment time is 70 minutes and yield was 1092 mCi only. The next parameter is the beam current. This is also called target current. We have observed from  $30\ \mu\text{A}$  to  $40\ \mu\text{A}$ . We started our bombardment from  $30\ \mu\text{A}$ . The number of bombardment is 11, the bombardment time is 15 minutes and yield was 234 mCi. When we increase the beam current from  $30$  to  $33\ \mu\text{A}$ , then the number of bombardment is 21, the bombardment time is 15 minutes and yield was 308 mCi. In the following step we tried on  $35\ \mu\text{A}$ , the number of bombardment is 77, bombardment time is 30 minutes and yield was 623 mCi. We bombarded on  $36\ \mu\text{A}$ , the number of bombardment was 72, the duration of bombardment was 35 minutes and the yield was 802 mCi. On  $37\ \mu\text{A}$  the yield was 650 mCi and its bombardment time was 30 minutes and its bombardment number was 42.

### 2.11.2 REACTIVITY OF FLUORIDE

In this form fluoride ion will not be reactive to label the precursor and thus has to be prepared accordingly to satisfy these requirements:-

1. It must be in solution (soluble)
2. It must be anhydrous ( no water , since water inhibits its reactivity)
3. It must be reactive, i.e. its reactivity must possibly not be suppressed due to components, other than water.

But in this work, rinse option used, because by using rinse option there is increase in valuable amount of activity. The minimum activity difference between  $^{18}\text{F}$  unloads and  $^{18}\text{F}$  after rinse was 35 mCi, in the serial number 30. Where we have bombarded 15 minutes only and activity increases from 199 to 234 mCi. This was manual bombarded. The maximum activity difference between  $^{18}\text{F}$  unloads and  $^{18}\text{F}$  after rinse is 595 mCi, in the serial number 8. Where we have bombarded 50 minutes only and activity increases from 205-790 mCi. This was again a manual bombardment. That signifies the minimum activity increase after rinse was 35 mCi and the maximum activity increase was 595. The mean difference between  $^{18}\text{F}$  unloads and  $^{18}\text{F}$  after rinse was 186 mCi. This was a significant amount of activity.



**Figure 2.20: Picture of  $^{18}\text{F}$  surrounded by water molecules in aqueous media courtesy by S. W. Pennycuik.**

To make  $^{18}\text{F}$  ion anhydrous, we have to get rid of water ( $^{16}\text{O}$  water). We could manage it simply boiling this water off, in that case we would lose it, or we are taking advantage of trap and release technique to capture  $^{18}\text{F}$  ions and getting them separated from water. The trap and release method is based upon ion exchange. After being properly activated, specially formulated Resins trap  $^{18}\text{F}$  ions, while  $^{16}\text{O}$  water goes through the resin column and into collection vial. To release  $^{18}\text{F}$  ion from the trap and release column, it can be flushed with a water solution (very small amount i.e. 0.125 ml per run) of potassium carbonate ( $\text{K}_2\text{CO}_3$ ). As a result, negative  $^{18}\text{F}$  ions (anions) are displaced from resin with another anion carbonate ions ( $\text{CO}_3^{-2}$ ), which settle on the column.

### ***2.11.3 ADVANTAGES OF THE TECHNIQUE***

There are several advantages of this technique:-

1.  $^{18}\text{O}$  water is also saved and recycling
2. Metal ions that comes from cyclotron target get trapped by column (this is particularly visible in the case of a silver target). After potassium carbonate flush they form metal carbonate that is not soluble in water and remain trapped on the column. That is why the trap and release column often becomes grayish after the potassium carbonate flush.

### ***2.11.4 FREQUENCY OF THE PARTS CHANGE IN THE CYCLOTRON***

Apart from parameters there are also lots of things that can improve the yield. If some parts of cyclotron get faulty or working improperly then we have to change that part immediately. This is an engineer's responsibility to change the parts of cyclotron within the stipulated time period. Here the inventory of a small number of parts and there instance period:

1. Change/ultrasonic clean the v-vial every Monday.

2. Inline check valve – monthly.
3. Change the delivery line every month.
4. Target rebuild within three months.
5. Peakmani fold maintenance –quarterly.
6. Ion source rebuild six months.

### **2.11.5 YIELD OF $^{18}\text{F}$**

There are few more points that improve the yield of  $^{18}\text{F}$ . These points are mostly related with operational aspects

1. Rinse before and after the target.
2. Fill the water tank of water chiller inside the cyclotron room by water make up switch because water was evaporate by filaments of Diffusion pump. If water level was not proper DP filament may get faulty and cyclotron will down.
3. Target beam alignment should be proper.
4. Target cooling by helium pressure and water cooling should be properly so that it will cool the target during bombardment which is provides optimum performance for the production of  $^{18}\text{F}$ .
5. Change the  $^{18}\text{O}$  water every time when  $^{18}\text{O}$  vial is empty.
6. Purity of  $^{18}\text{O}$  water. Minimum 95 % acceptable. If we increase the percentage of  $^{18}\text{O}$  water enrichment then yield will increase. Purity of 97%, 98% or 99 % are available by manufacturer.

It was noted that automatic bombardment had always more yield than manual bombardment. This is because in automatic bombardment each and every parameter will set automatically for maximum output. But in case of manual bombardment whatever value we put will reflect and give feedback, either it is its best value or not

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*Chapter 3*

*Synthesis of  $^{18}\text{F}$ -FDG*

## CHAPTER 3: SYNTHESIS OF $^{18}\text{F}$ -FDG

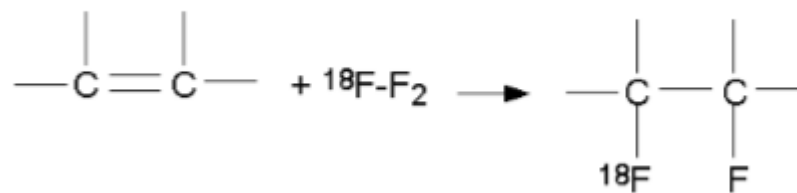
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### 3.1 SYNTHESIS OF $^{18}\text{F}$ -FDG

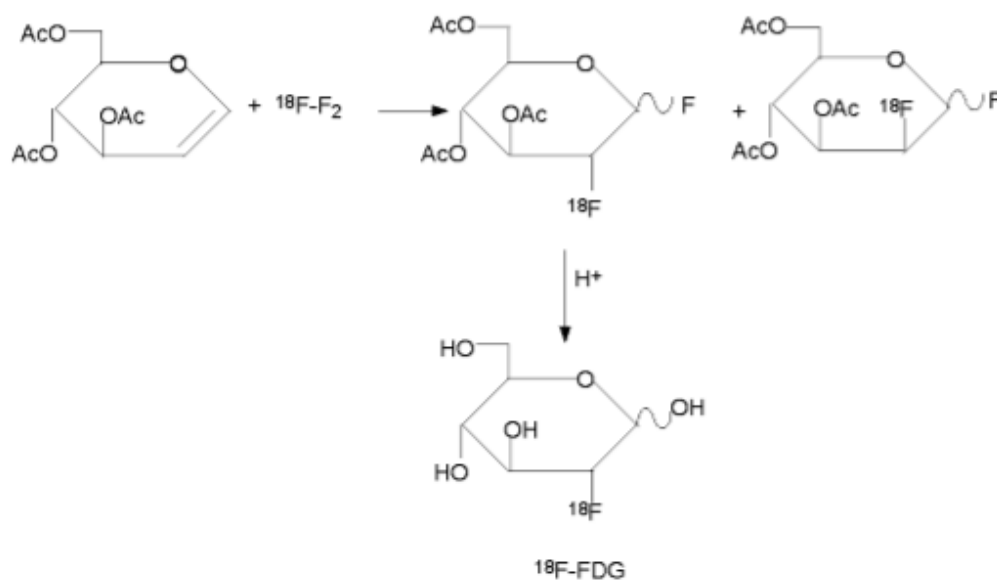
$^{18}\text{F}$ -FDG synthesized at the place where medical cyclotron is installed. It is synthesized by radiochemistry module. The appropriate place for radiochemistry module is just behind the cyclotron wall. The synthesis of  $^{18}\text{F}$ -FDG is mainly described by two methods. One is Electrophilic Fluorination and second is Nucleophilic Fluorination (1). Each method is described below one by one.

#### 3.1.1 ELECTROPHILIC FLUORINATION

$^{18}\text{F}$ -FDG is an analogue of glucose in which the hydroxyl group situated on the 2 number carbon of a glucose molecule, which is replaced during synthesis by a fluoride atom. Like glucose,  $^{18}\text{F}$  during the synthesis of  $^{18}\text{F}$ -FDG is fluoride atom replaced the triflate ion from the position of 2 number carbon of mannose which is an analogue of glucose (2). Like glucose,  $^{18}\text{F}$ -FDG is also taken up into living cells by facilitated transport after that it is phosphorylated by hexokinase. However unlike glucose,  $^{18}\text{F}$ -FDG cannot undergo further metabolism in the living cell because the hydroxyl group present at the 2 number carbon is a requirement for the process (3-4). The first synthesis of  $^{18}\text{F}$ -FDG was completed by electrophilic fluorination in Brookhaven National Laboratory in 1976. In this reaction 3, 4, 6-tri-O-acetyl-D-glucal chemical was used as a precursor. In electrophilic fluorination the addition of fluorine molecule diagonally to a double bond, results in a difluoro derivative of the parent compound. Difluoro-mannose derivatives also produced with difluoro-glucose derivatives in a ratio of 3:1 when glucal was reacting with  $^{18}\text{F}$ -F<sub>2</sub>. The total synthesis time and yield of this process was 120 minutes and 8 percentages (5).



**Figure 3.1: Electrophilic Fluorination courtesy by S Yu BIIJ**



**Figure 3.2: Synthesis of  ${}^{18}\text{F-FDG}$  by Electrophilic Fluorination courtesy by S Yu BIIJ.**

The above mentioned method was collaborated with hospital of the University of Pennsylvania. Here first  ${}^{18}\text{F-FDG}$  trial in human was done by Abbash Allavi. The major bring to light of this process was the utilize of acetylhypofluorite (5).

The main restriction of electrophilic fluorination was that only 50% was stable fluorine which produced during bombardment of gaseous fluorine. So out of total only

50% of radioactive F<sub>2</sub> molecules were integrated into the precursors. The maintenance and operation of a neon target is very difficult and tedious (6-7).

### **3.1.2 NUCLEOPHILIC FLUORINATION**

After numerous attempts, nucleophilic substitution methods build up for the synthesis of <sup>18</sup>F-FDG (8-12). In 1986 by Hamacher et al. who had used Kryptofix 222TM as a medium (13). The consistent yield was over 50% and the reaction time was reduced up to 50 minutes. Nucleophilic substitution reaction 2 linking the adding up of a nucleophilic fragment into a fragment with a departing group. Nucleophilic molecules are highly negatively charged molecule and leaving groups are electron drawing group attached to the parent fragment throughout an unbalanced chemical bond.

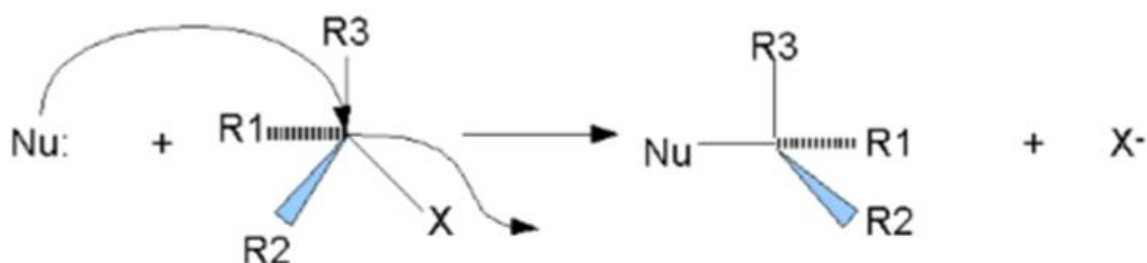
The nucleophilic molecule has a more attraction towards the relatively electron lacking position in the parent molecule created by the electron pulling leaving group. By this the nucleophilic fragment makes a covalent bond with the parent fragment and substituted the leaving group. After this inversion of molecules occurs in which stereo-configuration of the parent molecule is also altered. In the synthesis of <sup>18</sup>F-FDG, <sup>18</sup>F ion is the nucleophile i.e. electron rich. The precursor used in this synthesis is mannose triflate. In mannose triflate the 1,3,4,6 position carbons of a mannose molecule are protected with an acetyl molecule and triflate is the departure cluster at the 2 number carbons. In the reaction Kryptofix 222TM work as a catalyst and acetonitrile as solvent, <sup>18</sup>F ion reacts with mannose triflate at 2 number of carbon, at the same time as the triflate group leaves the protected mannose molecule to form <sup>18</sup>F-FDG.

### **3.2 STEPS OF SYNTHESIS OF <sup>18</sup>F-FDG**

The steps of synthesis of <sup>18</sup>F-FDG are discussed below (14-16):

### 3.2.1 REMOVAL OF FLUORIDE ION FROM $^{18}\text{O}$ -WATER

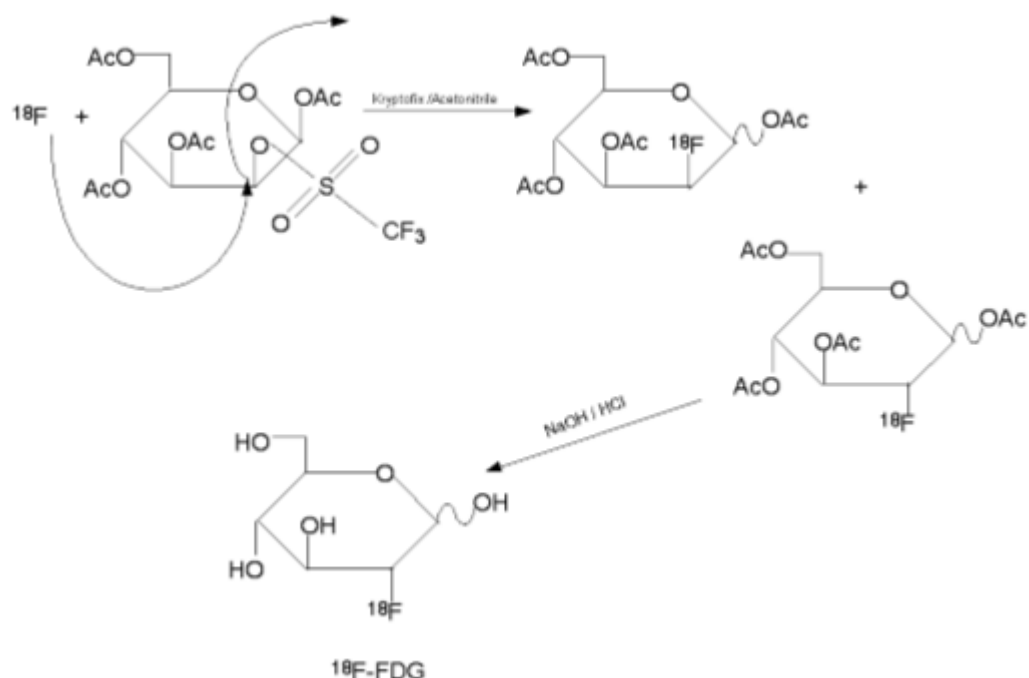
The hydration energy of fluorine is very high, so water is not an appropriate solvent in this synthesis from  $^{18}\text{F}$ . Acetonitrile (IUPAC name of methyl cyanide) used as polar aprotic solvent in an  $\text{S}_{\text{N}}2$  nucleophilic substitution reaction. The production of  $^{18}\text{F}$  takes place by  $^{18}\text{O}$  (p, n)  $^{18}\text{F}$  reaction, should be carried out under anhydrous conditions. To obtain this we use a light QMA cartridge. The  $^{18}\text{F}$  trapped via an ion-exchange effect and permissible the  $^{18}\text{O}$  water to stream through. The trapped  $^{18}\text{F}$  is then eluted with stock solution (Kryptofix and potassium carbonate solution. Kryptofix 222 TM is a cyclic crown which binds the potassium ion, preventing the formation of  $^{18}\text{F}\text{-KF}$ , which forms a cage like arrangement. Potassium will go up against ion of  $^{18}\text{F}$  to improve its reactivity but does not interfere with the synthesis process.



**Figure 3.3: Nucleophilic substitution: Nu = nucleophilic molecule, X = leaving group courtesy by S Yu BIIJ**

### 3.2.2 EVAPORATION OF RESIDUAL $^{18}\text{O}$ WATER

$^{18}\text{F}$  is eluted into reaction vessel from QMA, it is essential to evaporate any residual water from the solution. The main advantage of using acetonitrile is due to the formation of an azeotropic mixture with water. In this the boiling point of mixture lesser than the acetonitrile. So during evaporation it removes any residual  $^{18}\text{O}$  water escaped into the reaction vessel together with the  $^{18}\text{F}$ .



**Figure 3.4: Synthesis of  $^{18}\text{F}$ -FDG by nucleophilic substitution courtesy by S Yu BILJ**

### ***3.2.3 ADDITION OF MANNOSE TRIFLATE WITH THE $^{18}\text{F}$ WITH ACETONITRILE***

This is the most important step of the  $^{18}\text{F}$ -FDG synthesis. The precursor is added to the  $^{18}\text{F}$  after the evaporation residual water. The choice of precursor determines the effortlessness of preparation, effortlessness of producing the ultimate result, consistency and yield. Mannose is most commonly used as a precursor molecule for synthesis of  $^{18}\text{F}$ -FDG worldwide. Its structure is similar to FDG, except with a triflate group at the 2 numbers of carbon place and acetyl groups at 1,3,4,6 places of carbons via ester bonds, which can be eagerly broken down at an elevated or lesser pH. The fluorination will not happen at these positions because acetyl groups guard the hydroxyl groups.  $^{18}\text{F}$  ion comes up to the mannose triflate at the 2 number of carbon of mannose triflate, simultaneously the triflate group leaves the protected mannose molecule to form  $^{18}\text{F}$ -

FDG. After the nucleophilic substitution reaction of the triflate group by F-18, the acetyl groups are easily removed by hydrolysis leading to the formation of  $^{18}\text{F}$ -FDG.

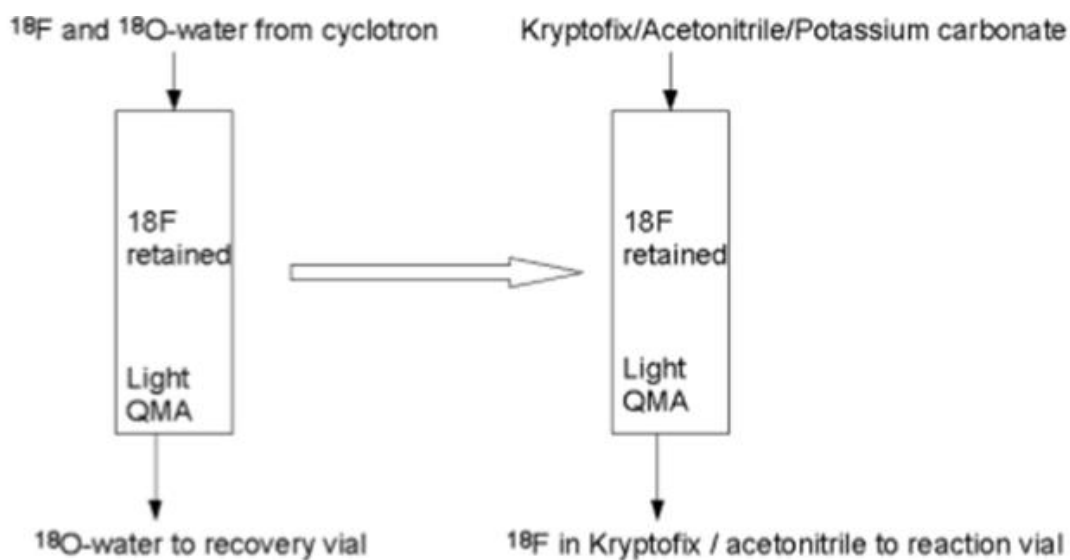


Figure 3.5: (a) Retention of  $^{18}\text{F}$ -FDG in light QMA ion exchange column; (b) elution of  $^{18}\text{F}$  from light QMA ion exchange column courtesy by S Yu BIIJ

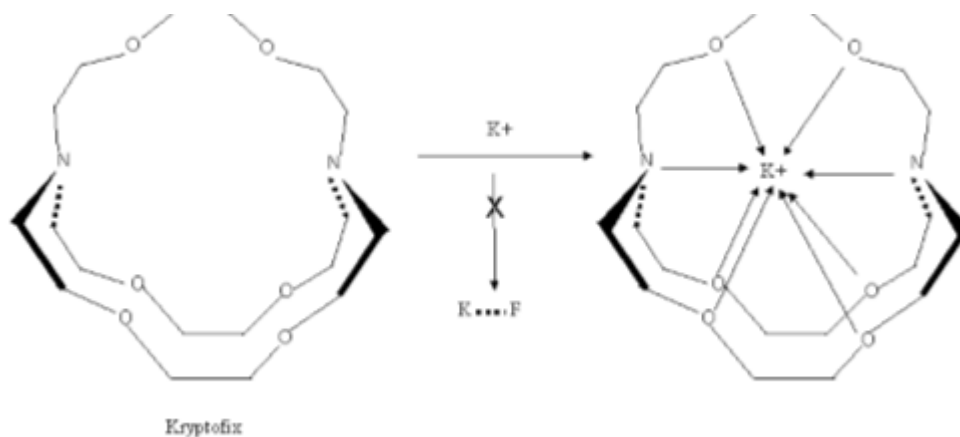


Figure 3.6: Kryptofix 222 TM and  $\text{K}^+$  courtesy by S Yu BIIJ

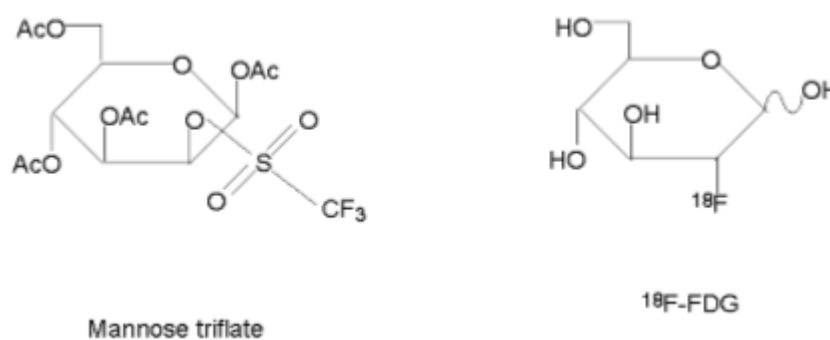


Figure 3.7: Structures of mannose triflate and  $^{18}\text{F}$ -FDG courtesy by S Yu BIIJ

### **3.2.4 HYDROLYSIS**

To eliminate the defensive acetyl groups on the 1,3,4,6 position carbons hydrolysis takes place. It can be done by two ways basic and acid hydrolysis. Acid hydrolysis takes place by hydrochloric acid and base hydrolysis takes place by sodium hydroxide. In acid hydrolysis longer time and higher temperature required. In basic hydrolysis it is faster and takes place at room temperature.

### **3.2.5 PURIFICATION OF THE $^{18}\text{F}$ -FDG PRODUCT**

This is the final stage of synthesis of  $^{18}\text{F}$ -FDG. The anion exchange column is prepared by using AG50 and AG11. Around 1.5 mg resin of AG50 and 3 mg of AG11 per column is used. AG50 is the cation exchange resin used to remove  $\text{K}^+$  /K222 complexes and AG11 is ion retardation resin used to neutralize the acid. The Alumina cartridge is used to remove unreacted  $^{18}\text{F}$ . Last one C-18 bonded silica cartridge is used to remove intermediate product of FDG (Acetylated  $^{18}\text{F}$ -FDG). The crude FDG purified after passing through this purification column.

### **3.3 QUALITY CONTROL OF $^{18}\text{F}$ -FDG**

Since we are going to inject the produced  $^{18}\text{F}$ -FDG to the human being so quality control is mandatory. In Indian context various pharmacopoeia are applicable which includes the USP (United state of Pharmacopeia), BP (British Pharmacopeia), EP (European Pharmacopeia, etc. In United State (US) FDA (Food and Drug Administration) has also published an outline Chemistry, Manufacturing and Controls (CMC) document concerning  $^{18}\text{F}$ -FDG. It should be noted that the quality control requirements of  $^{18}\text{F}$ -FDG differ among these references (17-20).

### **3.3.1 CHARACTER**

It is first seen by visual inspection of the  $^{18}\text{F}$ -FDG direct in the product vial. The product should be observed behind adequate shielding.  $^{18}\text{F}$ -FDG product should be clear and colorless (21).

### **3.3.2. IDENTITY**

Gamma spectrum or determine the half life are two tools which helps to know the radionuclidic identity However, the energy of Photon 0.511 MeV and the sum of the peak at 1.022 MeV are ordinary features to positron emitters. Therefore, obtaining a gamma spectrum may not be sufficient in confirmation about the presence of  $^{18}\text{F}$  (21).

### **3.3.3 HALF LIFE**

Measurement of the half-life can be done by doing the same examination in the same dose calibrator at two or more time points. Lots of quality control expert has established that a minimum of 10 min is necessary. To check the half-life of produced activity is a more reliable method to confirm the presence of  $^{18}\text{F}$  (21).

### **3.3.4 RADIOCHEMICAL IDENTITY**

In BP, the radiochemical identity can be confirmed either by High Performance liquid Chromatography or Thin Layer Chromatography. To test the  $^{18}\text{F}$ -FDG, the TLC stationary phase is TLC-SG (Thin Layer Chromatography-Silica Gel) and the mobile phase is acetonitrile: water (95%:5% v/v). The Rf (Relative Front) of the  $^{18}\text{F}$ -FDG, free  $^{18}\text{F}$ -, and acetylated  $^{18}\text{F}$ -FDG are about 0.45, 0.0 and 0.8 to 0.95 respectively. The spot size should be about 1  $\mu\text{L}$ . It should be dried and placed above the mobile phase level (21).

### **3.3.5 pH**

The pH value of produced radiopharmaceuticals should be as close to pH of blood. It should be noted that the pH paper used should be verified with normal pH buffers, show a colour alter for each 0.5 pH unit, and the pH value calculated by means of pH paper is only an approximation. So pH meter is more reliable (21).

### **3.3.6 CHEMICAL PURITY**

The chemical purity of FDG and 2-chloro-deoxyglucose (this is applicable for acid hydrolysis only) are determined by HPLC. We used a Carbopac™ column with good results. As NaOH absorbs carbon dioxide on or after air with good grace, it should be protected from air, kept in plastic items and newly primed. The Carbopac™ column is also very sensitive to carbonate ions. The test of presence of Kryptofix involves spotting the drop of sample and the reference normal solution on a TLC-SG plate and then developing in a methanol and ammonia mixture (9:1 ratio). The developed plate is then exposed to vapour of iodine. The reference solution spot colour is darker than test solution spot colour. According to the literature, this TLC method is not very reliable. The spots can be indistinct (22).

### **3.3.7 RADIONUCLIDIC PURITY**

According to BP doing gamma spectrum and half-life measurement are two methods to determine the radionuclidic purity of an  $^{18}\text{F}$ -FDG. Measurement of half-life is only verify the being there of  $^{18}\text{F}$ . It does not disclose the percentage purity of the  $^{18}\text{F}$ . The additional precise technique is to get a gamma spectrum with a multi-channel analyzer after confirmation of  $^{18}\text{F}$  by measuring its half-life. The BP allows the  $^{18}\text{F}$ -FDG to be released before the completion of this test (21).

### **3.3.8 RADIOCHEMICAL PURITY**

According to BP HPLC technique and TLC technique both are the applicable for the purpose of radiochemical purity.

### **3.3.9 STERILITY**

Sterility is tested by incubating the test model with both Soybean Casein Digest Medium and Fluid Thioglycollate standard for 14 days at 37°C. SCDM is a culture media for aerobic microorganisms and fungi while FTM is a media for anaerobic microorganisms. The “reference bacteria” is incubating in SCDM and FTM.

### **3.3.10 BACTERIAL ENDOTOXINS (LAL TEST)**

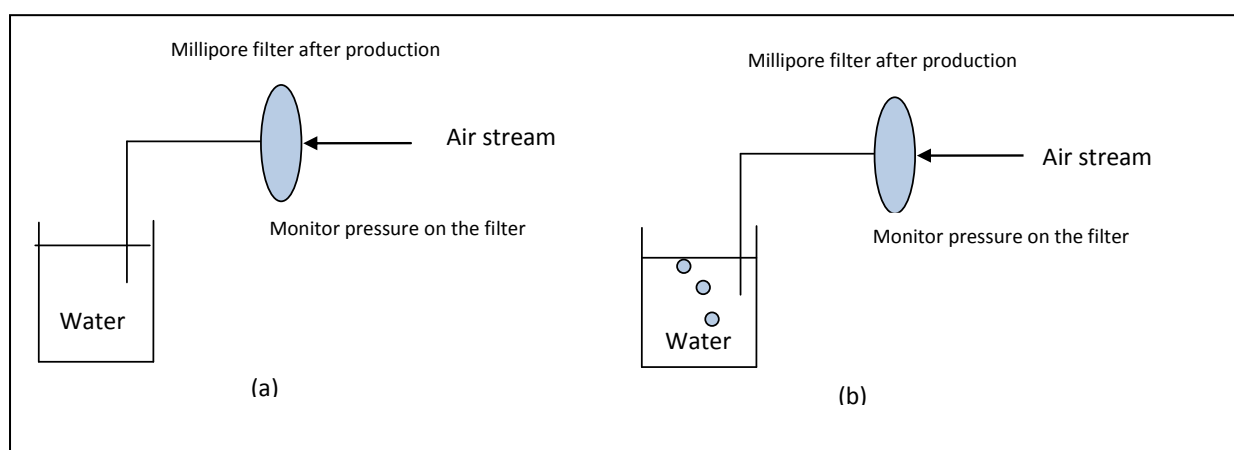
With the help of gel-clot technique bacterial endotoxins level is commonly tested. In this technique lysate of amoebocytes from horseshoe crab used, *Limulus Polyphemus*. Most commercially available endotoxin testing kits need an incubation period of 20 to 60 minutes. Therefore, it is improbable that the test can be done before dispatch of the radiopharmaceuticals (23-24).

For this test we also use Charles River Portable Test System (PTS) reader. The PTS provides quantitative LAL test results in about 15min with a simple, one button operation and can be used for a wide range of application. Results are displayed on the screen and can be printed or downloaded for reporting and trending. It measures the endotoxin level which is used. The PTS<sup>TM</sup> (Portable Test System Trade Mark) uses LAL Kinetics chromogenic that determines a color strength that is straight related to endotoxin concentration in radiopharmaceuticals. Each cartridge contains a precise amount of LAL reagent, chromogenic substrate and control standard endotoxin (CSE).

The cartridge is manufactured according to rigid quality control procedures promoting test accuracy, consistency and product stability.

### 3.3.11 FILTER MEMBRANE INTEGRITY TEST

Lots of laboratories have also included this test as one of their regular quality control tests of  $^{18}\text{F}$ -FDG. Since the  $^{18}\text{F}$ -FDG is released and injected into patients before the result of sterility results are obtainable, there is practically no guarantee of the product sterility.



**Figure 3.8: (a) Filter membrane is intact, no air passes through the membrane, no air bubble in water; (b) Filter membrane is broken or at bubble point, air passes through the membrane, air bubble in water. The bubble point should be higher than or equal to maximum pressure listed in the specification of the filter courtesy by S Yu BIJ.**

## 3.4 OPTIMIZATION THE SYNTHESIS PARAMETERS OF POSITRON EMITTING FLOURO-DEOXY GLUCOSE IN CYCLOTRON FACILITY

**Table 3.1: Showing the percentage of yield of FDG of original method and our modified method without decay.**

SI No	OLD METHOD %	NEW METHOD %
1	54.9	68
2	53.4	67.9

<b>SI No</b>	<b>OLD METHOD %</b>	<b>NEW METHOD %</b>
3	56	67.4
4	56.1	65.4
5	54.8	67
6	57.1	69
7	53	59
8	56.6	68.4
9	55.9	68.3
10	58.2	69.3
11	58.3	67.4
12	57.6	69.4
13	59	70
14	61	72
15	60	71.5
16	61.3	70.4
17	60.9	70.3
18	59.6	70.2
19	58.8	70.2
20	59.2	69.3
21	51	59.3
22	56	69.2
23	58.9	68.3
24	53.4	63.2
25	57.9	65.3
26	56.6	68.6
27	58.9	67.3
28	56.8	65.3
29	60.1	71.3
30	60.2	78.3
31	59.8	64.3

<b>SI No</b>	<b>OLD METHOD %</b>	<b>NEW METHOD %</b>
32	58.9	67.8
33	59.5	69.3
34	58.6	68.3
35	59.3	65.3
36	58.5	67.4
37	57.8	64.9
38	60.3	67.2
39	63.4	69.4
40	61	69.1
41	62	71.2
42	60.1	75.2
43	60.6	71.1
44	49	62
45	50.5	63.4
46	57	69.2
47	58.5	65.8
48	57.9	67.5
49	58.7	66.6
50	59.7	76.1
51	61.2	67.4
52	62	65.5
53	54.7	65.8
54	56.3	63.4
55	61.2	65.6
56	59.6	64
57	54.9	65.4
58	58.8	63
59	57.9	68
60	55	59

<b>SI No</b>	<b>OLD METHOD %</b>	<b>NEW METHOD %</b>
61	57	61
62	61	67
63	59.1	65
64	56.9	61.8
65	57.6	67.4
66	58.5	71.4
67	59.5	73.4
68	54.7	67.2
69	56.5	72
70	61	75
71	61	62.2
72	59.9	65.3
73	57.9	62.3
74	56.3	61.2
75	58.8	69.2
76	56.8	69.3
77	57.4	65.6
78	57.2	67.3
79	59.1	68.9
80	59	65.8
81	59.1	70.4
82	58.8	70
83	58.9	70.5
84	59.5	71.2
85	58	70.1
86	60	72.3
87	58.8	68.2
88	59.5	71.2
89	58.4	69.8

<b>SI No</b>	<b>OLD METHOD %</b>	<b>NEW METHOD %</b>
90	58.2	69.1
91	59.4	70
92	59.7	69
93	59.1	68.1
94	57	67
95	57.3	63.9
96	59.3	64.6
97	58.5	65.2
98	59.3	67
99	59.3	66
100	60.1	66.9
Average	58.176	67.635

**Table 3.2: Showing the Synthesis Time FDG of original method and our modified method in minutes.**

<b>Sl No.</b>	<b>OLD METHOD</b>	<b>NEWMETHOD</b>
1	47.3	38.1
2	46.2	39.1
3	48.2	38.2
4	45.2	39
5	50.1	38.8
6	48.1	37
7	52.3	39.8
8	48.2	37.8
9	47.5	38.5
10	46.2	38.1
11	47.3	38.3
12	48.8	37.2
13	49.1	35.2
14	45.8	34.7
15	47.7	34.5
16	47.2	35
17	45.5	35.4
18	46.6	35.7
19	47.3	36.2
20	46.2	36.4
21	47.2	37.2
22	45.8	37.1
23	46.2	35.2
24	55.06	36.2
25	57.6	37.3
26	52.4	38.1
27	51.6	37.8
28	50.2	36.5
29	48.6	37.2
30	47.2	36.4

<b>SI No.</b>	<b>OLD METHOD</b>	<b>NEWMETHOD</b>
31	46.8	39.1
32	45.8	35.3
33	44.9	36.9
34	45.8	36.1
35	46.2	35.1
36	45.3	35.7
37	46.2	34.9
38	45.9	36.1
39	46.1	35.7
40	45.9	37.3
41	47.1	37.5
42	45.7	37.9
43	46.5	37.7
44	46.2	37.1
45	44.4	36.5
46	45.3	36.7
47	44.7	36.9
48	45	36.4
49	46.3	36.6
50	47.2	36.8
51	44.7	36.1
52	45.9	36.9
53	46.1	36.3
54	45.6	36.5
55	46	35.5
56	45.4	35
57	43	35.6
58	45	36
59	45.3	37
60	46.2	35.1
61	47.1	38
62	46.9	34

<b>SI No.</b>	<b>OLD METHOD</b>	<b>NEWMETHOD</b>
63	46	34.4
64	44.7	35
65	44.9	34.9
66	45.6	35.7
67	45.1	36.8
68	44.9	38.9
69	45	40.4
70	46	39.2
71	46.3	38.2
72	45.8	38.3
73	38.3	37.6
74	45.2	36.7
75	45.1	36.3
76	45.8	37.1
77	45.2	38.1
78	45.6	37.4
79	45.1	38.4
80	46.3	37.3
81	46.3	36.4
82	44.7	35.7
83	46.2	35.9
84	45.2	36.2
85	45.6	36.9
86	45.2	36.6
87	45.6	36.8
88	45.2	37.6
89	45.3	37.8
90	45.1	37.7
91	45.6	38.9
92	45.2	35.6
93	45.4	35.1
94	45.7	34.6

SI No.	OLD METHOD	NEWMETHOD
95	45.7	35.5
96	46	37.3
97	44.9	35.9
98	45.3	36
99	44	36.8
100	44.1	35.4
<b>Average</b>	<b>46.3436</b>	<b>36.757</b>

### ***3.4.1 DISCUSSION***

We have to start up the synthesis program before the arrival of  $^{18}\text{F}$  from medical cyclotron, so that there was conditioning of the heater block of the radiochemistry explorer  $^{18}\text{F}$ -FDG4 module. This will help to the heater block performs exactly same as prescribed in the company manual. Heater block will cut off its temperature at the right time owing to which there is no delay heating, so it increases the yield of  $^{18}\text{F}$ -FDG. It also prevents charring of reaction vessels due to overheating by heater block. If charring takes place synthesis will give out and no  $^{18}\text{F}$ -FDG is produced.

As observed in table 1, the minimum, maximum and average synthesis yield of  $^{18}\text{F}$ -FDG was 49 %, 63.3 % and 58.176 % respectively by old method. But in new method the minimum, maximum and average synthesis yield of  $^{18}\text{F}$ -FDG was 59 %, 78.3 % and 67.635 % respectively. This data was obtained from 100 synthesis of  $^{18}\text{F}$ -FDG. So average increases in yield of  $^{18}\text{F}$ -FDG were about 9.459 % by new method.

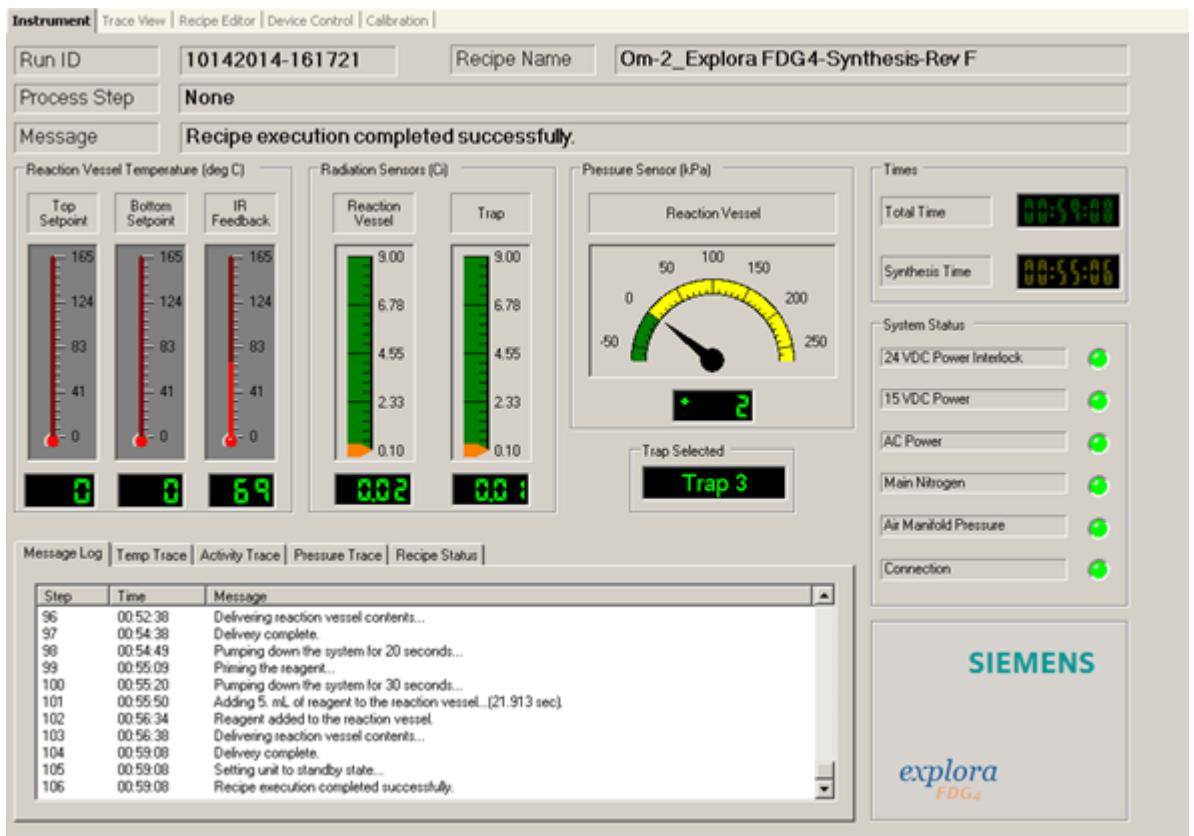


Figure 3.9: Showing the synthesis time of  $^{18}\text{F}$ -FDG

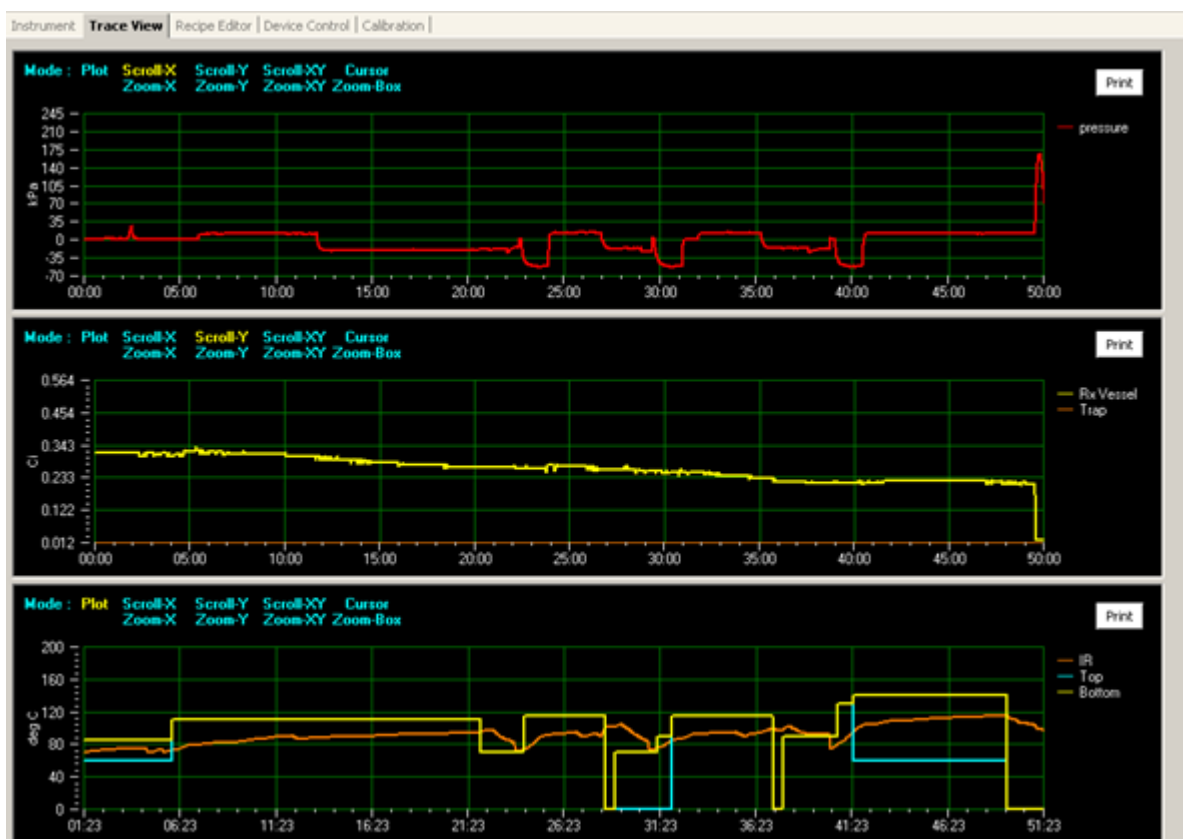


Figure 3.10: Showing the synthesis time of  $^{18}\text{F}$ -FDG

### **3.4.2 BENEFITS OF NEW PROTOCOL**

As observed in table 2, the minimum, maximum and average synthesis time of  $^{18}\text{F}$ -FDG was 38.3 minutes, 57.6 minutes and 46.34 minutes respectively by old method. But in new method the minimum, maximum and average synthesis time of  $^{18}\text{F}$ -FDG was 34.0 minutes, 40.4 minutes, 36.75 minutes respectively. This data was obtained by 100 synthesis of  $^{18}\text{F}$ -FDG. So the average difference in synthesis time of  $^{18}\text{F}$ -FDG was about 9.59 minutes by new method.

So by adopting the new method we had decreases synthesis time as well as also increase the yield of  $^{18}\text{F}$ -FDG. It is also decreases the chemical consumption as compared to the original protocol.

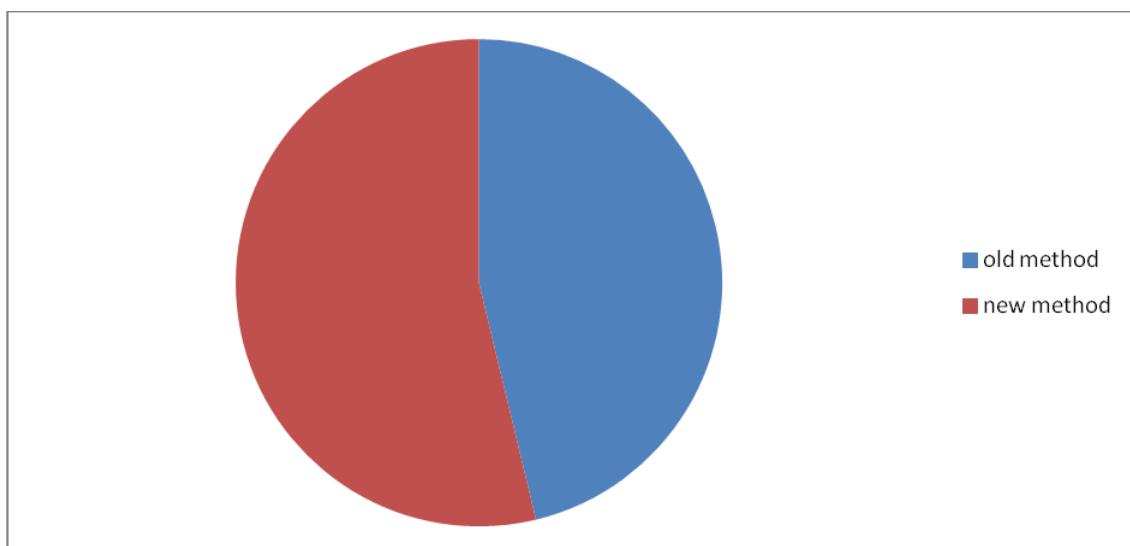
In company manual the standard synthesis time for good run is around 45-50 minutes, but in our new protocol the synthesis time is about 34-40 minutes. So in the new protocol there is decrease in time of more or less 10 minutes.

As described above, this protocol is very useful in various ways. The most important thing for this protocol is the quantity of water coming from cyclotron is very less. For removal of water in original protocol there are three steps available, at QMA, at first evaporation and at the second evaporation of  $^{18}\text{F}$ -FDG synthesis respectively. But in the new protocol we have removed the second evaporation.

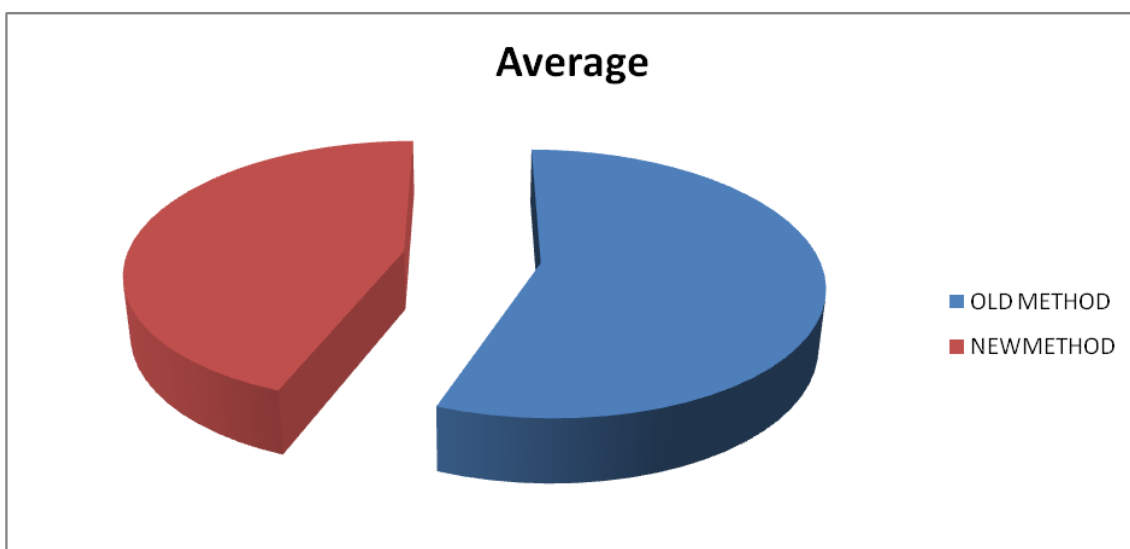
For adopt the new protocol the charging of QMA (Quaternary ammonium anion exchange-Sep-Pak column) is very significant. For charging of QMA 10 ml of 0.5 M Potassium carbonate solution is required. To prepare 0.5 M Potassium carbonate solution completely dissolving 6.9 gm in 100 ml water. After dissolving of Potassium carbonate in 100 ml water and wait for 10 minutes, and then that it mix up completely by Vertex Mixture and becomes a transparent solution from milky solution. To activate QMA

cartridge pass 10 ml of 0.5 M Potassium carbonate solution followed by 10 ml of air and 10 ml sterile water. Then push 10 ml of air 5 times or dry with a stream of nitrogen to remove any possible liquid content.

The first evaporation is called azeotropic distillation. Acetonitrile is a extensive organic solvent and water form a binary (two component) azeotrope. Acetonitrile boils at 81.6° C and water boils at 100° C. The mixture forms an azeotrope which boils at 76.1° C. The components of an azeotrope cannot be separated by simple distillation since they boil off together.



**Figure 3.11: Showing the yield  $^{18}\text{F}$ -FDG by both methods**



**Figure 3.12: Showing the synthesis time of  $^{18}\text{F}$ -FDG by both methods**

### 3.4.3 PREPARATION OF CHEMICALS

Preparation of chemicals is very crucial for the synthesis of  $^{18}\text{F}$ -FDG. All chemicals were prepared in aseptic, bacterial and germ free condition. At Our setup we prepared all chemicals in the Laminar Flow Hood, in which infrared light was applied. Before the use of laminar flow hood we spray 70 % ethanol in it, this will help to take out or kill all microorganisms. Preparation of Mannose Triflate is very easy, only it is prepared in sterile condition.

Preparation of K222 is very important. It is checked that the solution is clear and colorless. It should not cloudy or milky. Regarding preparation of K222, type of septa is very significant, one can't use any kind of septa. The new supplier gave us different kinds of septa. After using these septa the K222 solution became brown. After a week of experiment and experience, we found those the septa were faulty. Hence do not change the brand of septa.



**Figure 3.13: Colour of septa Changes when we use bad quality of septa**

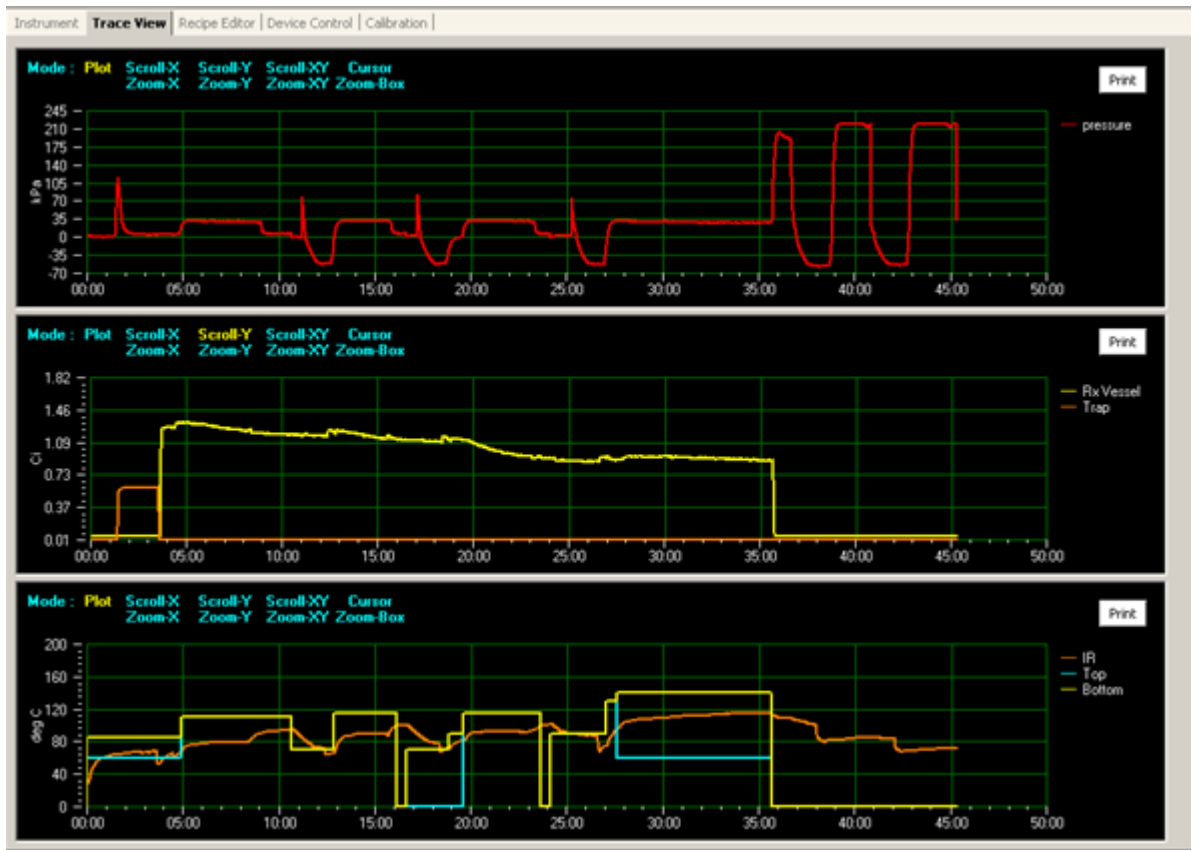


Figure 3.14: Original graph of original protocol



Figure 3.15: Graph of our modified method

### 3.4.4 IMPORTANT OBSERVATION

Few minor aspects regarding the operations of Explora  $^{18}\text{F}$ -FDG 4 Radiochemistry module for synthesis of FDG in our new protocol

1. First open the door of Explora  $^{18}\text{F}$ -FDG 4 radiochemistry module and empty the waste vial to minimize the radiation level and to maintain an optimum vacuum level during synthesis.
2. Removal of used QMA, and used purification column set to minimize the radiation level.
3. Then check the Radiation level of Explora, if radiation level was high, then get rid of the causes of radiation exposure level.
4. Check the start up procedure, it will determine the functioning status of all valve. If any trouble arises, it can be solve the problem within the stipulated time frame.
5. Check the working condition of Charcoal filter, if charcoal filter will not works the radiation would be very high during synthesis of FDG.
6. Sometimes it is found that operator missed to charge the cartridge i.e. QMA. So remember to charge QMA, C-18 and Alumina. If QMA not charged it will not trap the  $^{18}\text{F}$  and synthesis will not move further. If C-18 and Alumina will not charge it will not absorb the possible impurities.
7. Ensure the working condition of the Radiation detector.
8. During every change of chemical, need to change the septa and spikes, and also check the spike. If any rubber part inserts to the spike, then remove this rubber part otherwise liquid does not go through these septa. It will result in failure of synthesis of FDG.

9. Check the working condition of Exhaust, delivery tube and purification column.
  
10. To check patency of deliver line and purification column, simply turn over the command of 3 ml water push. It will reassure that purification column and delivery tube were working fine.

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## *Chapter 4*

# *Radiation Environment Around a Medical Cyclotron*

# **CHAPTER 4: RADIATION ENVIRONMENT AROUND A MEDICAL CYCLOTRON**

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## **4.1 GENERAL INFORMATION**

The beginning of positron emission tomography (PET) into clinical imaging has led to a sturdy boost in the figure of medical cyclotrons globally (1). At present time, around 20 cyclotrons are in functional in India. The competent authority in India, AERB made regulatory inspections before approving the facility for routine operation. Over the last few years, there has been continuous increase in the number of cyclotrons installed (2). The cyclotrons are use to make  $^{18}\text{F}$ -FDG, whichever for own use at the center or for distribution to other PET centers. There are lots of commercial distributors those produce  $^{18}\text{F}$ -FDG and distribute to PET centers in their vicinity or those centre situated far away from the Medical Cyclotron facility by aircraft.

## **4.2 RADIATION SAFETY ASPECTS IN CYCLOTRON FACILITY**

In a cyclotron centre, the radiation safety requirements to be more firm matter due to piercing gamma radiation and elevated specific gamma ray constant of positron emitters. The radiation safety issues in a cyclotron-PET facility and conventional nuclear medicine facility are much different from each other because of penetrating 511 KeV gamma photons, very high secondary neutrons and specific gamma ray constant of positron emitters from the cyclotron .The occupational workers in a cyclotron-PET facility have tougher work practice. All positron emitters having considerably higher specific gamma ray constant than conventional isotopes. The radiation survey in a cyclotron facility is very important in radiation safety aspects and it will also assist in enlightening work practice of workers (3-7).

### 4.3 SPECIFIC GAMMA RAY CONSTANT

Table 4.1: Specific gamma ray constant of  $^{18}\text{F}$ ,  $^{99\text{m}}\text{Tc}$  and  $^{131}\text{I}$

Radioisotopes	Specific Gamma Ray Constant (mrem/hr/mCi)
$^{99\text{m}}\text{Tc}$	$1.2 \times 10^{-1}$
$^{131}\text{I}$	$2.82 \times 10^{-1}$
$^{18}\text{F}$	$6.92 \times 10^{-1}$

### 4.4 REQUIREMENTS OF RADIATION SAFETY

The operator's console must be outside the cyclotron vault. There is need to strict radiation safety even though the availability of cyclotron and radiochemistry laboratories adequate shielding, occupational workers remain unsure about radiation exposure from positron emitter's radioisotopes. For producing of large amount of activity in medical cyclotrons facility effective radiation shielding is compulsory (8).

### 4.5 TYPES OF RADIATIONS EMITTED BY OPERATION OF CYCLOTRON

During operation cyclotron there are two types of radiation emitted, one is positrons and other is neutrons. The neutrons slow down by shielding and very few are reflected back toward the cyclotron, activated the cyclotron components. Some of gamma and neutron radiations escape to the outside the shielding, may produce external exposure to the working personnel. So with sufficient shielding around cyclotron the radiation arises can be reduced to negligibly low levels for radiation safety aspects (9).

## 4.6 RADIATION SURVEY

Still after the adequate shielding, it is mandatory by AERB to assess the radiation levels inside and outside of the cyclotron during operation of cyclotron. This helps to keep the radiation exposure within limits. So routine survey of radiation during and after the cyclotron operation is an important part of overall radiation safety aspects in the cyclotron facility (10).

## 4.7 DECAY OF $^{18}\text{F}$

It is necessary to know about the physical decay of  $^{18}\text{F}$ , so that we can handle accordingly. Physical decay chart for  $^{18}\text{F}$  is given below in the table form.

**Table 4.2: Physical decay chart for  $^{18}\text{F}$ .**

Minutes	Fraction remaining
0	1.00
10	0.938
15	0.909
30	0.826
60	0.683
110	0.500
220	0.250
440	0.060

## 4.8 RADIATION SURVEILLANCE

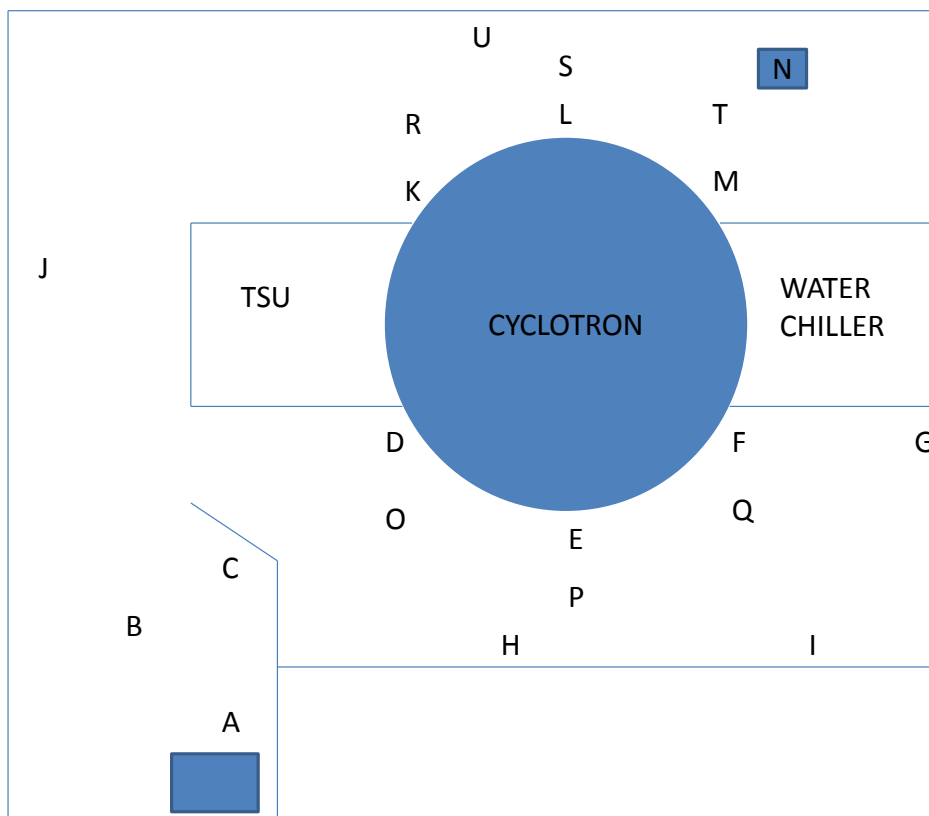
The radiation levels in the cyclotron and radiochemistry laboratory to access the radiation safety aspects of the facility were monitored. The radiation exposure rate was also measured in the facility at various locations before bombardment, during

bombardment and after bombardment in the cyclotron room and its surroundings and in the radiochemistry laboratory before, during and after  $^{18}\text{F}$ - FDG Synthesis. The radiation levels in the cyclotron and radiochemistry laboratory should be within prescribed limits with safe work practice (8, 11-12).

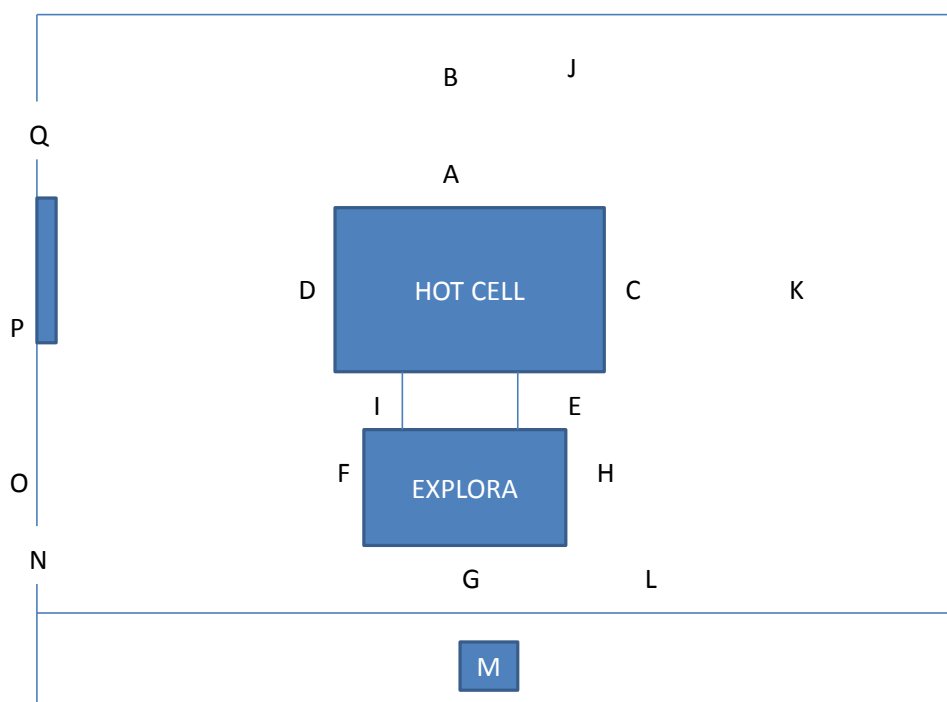
#### *4.7.1 METHOD OF SURVEILLANCE*

The gamma ray exposure rate levels in the cyclotron room and radiochemistry laboratory were monitored by portable and calibrated RAM GAM-1 model of survey meter from Rotem Industries, Israel. 190N Victoreen portable neutron survey meter from Fluke Biomedical, Ohio, and USA, was used to check the secondary neutrons in the region of the cyclotron. The radiation monitoring in the environs of cyclotron was done at definite locations (point A to X) in the cyclotron and (point A to W) in radiochemistry lab. (Figure 1 and Figure 2) shows the layout of cyclotron room with points of measurements for radiation survey. Point A at the entrance of the cyclotron area, points B through E were located inside the cyclotron room at 1 meter from the shell of cyclotron shield and points F all the way through I were located on the inner wall of the cyclotron room on the beam line one side. When the second beam line (BL2) was used, point B through E and point F through I were considered on the further side of the cyclotron room at respective locations. The radiation survey for gamma rays and the neutrons were monitored at the above said points before, during and immediately after the cyclotron production runs. During cyclotron run, the entry gate is locked to avoid any unauthorized entry; furthermore, there is a beam 'ON' display for warning. Radiation survey was also completed at the opening of the exhaust systems of both cyclotron and radiochemistry laboratory (13-15).

## 4.9 LAY OUT DIAGRAM



**Figure 4.1: Schematic diagram of Cyclotron Lay out**



**Figure 4.2: Schematic diagram of Radiochemistry laboratory Lay out**

**Table 4.3: Various points of Medical cyclotron where plan to do radiation surveillance**

<b>Location</b>	<b>Name of Location</b>
A	Master Computer
B	Entrance
C	Maze wall
D	Near TSU on the surface wall of shield BL 1 side
E	Near BL 1 on the surface wall of shield
F	Near water cooler assembly on the surface of wall of shield BL 1 side
G	on the room wall near water chiller pipe
H	on the room wall BL1 side
I	on the room wall BL1 side
J	on the room wall near TSU
K	Near TSU on the surface wall of Shield BL 2 side
L	Near BL 2 on the surface wall of Shield
M	Near water cooler assembly on the surface of wall of shield BL 2 side
N	on the PIT
O	1 meter from D
P	1 meter from E
Q	1 meter from F'
R	1 meter from K'
S	1 meter from L
T	1 meter from M
U	on the room wall BL2 side
V	Exhaust inlet on Exhaust Plant on the roof
W	Exhaust outlet on Exhaust Plant on the roof
X	1 meter from point W

**Table 4.4: Various points of Radiochemistry room where plan to do radiation surveillance**

<b>Location</b>	<b>Name of Locations</b>
A	centre of glass window of Hot cell
B	near dose calibrator below hot cell
C	left side of Hot cell above one meter
D	Right side of Hot cell dose calibrator side
E	left side of delivery line between Hot cell and Explora box
F	Right side of Explora box
G	Front side of Explora box
H	Left side of Explora box
I	Right side of delivery line between Hot cell and Explora box
J	Above the delivery line on the floor just front of Hot Cell
K	one meter from point C
L	Corner of Slab (slab situated one meter in front of Explora box)
M	Explora computer
N	Entrance door 2
O	In the Corridor just beside Explora box behind the concrete wall
P	In the Corridor just behind Glass window
Q	Entrance door 1
R	Exhaust pipe passing through Room on the roof
S	Inlet of Exhaust on Exhaust Plant on the roof
T	outlet of Exhaust on Exhaust Plant
U	one meter from point T
V	Behind the L- Bench
W	1 meter from the TLC Scanner

#### 4.10 CYCLOTRON AND RADIOCHEMISTRY READINGS

The three versions in case of cyclotron include before the bombardment, during the bombardment and after the bombardment of cyclotron run. The three versions in the case radiochemistry room are before synthesis during synthesis and after synthesis. As all three reading of each point taken in a single day. All the readings were taken in mR/hour formats. Here, twenty five readings were taken of each period and each point three readings were conducted before, during and afterwards. The layout of cyclotron it is showing that the different regions where radiation survey conceded. The details of the exposure around a medical cyclotron and radiochemistry area using of survey measures are presented below in tabulated form. The various points of cyclotron were mentioned in Table 5 and 6 and radiochemistry room is mentioned in Table 7.

**Table 4.5: Exposure rate of Gamma ray in mR/hr at deferent point during bombardment of cyclotron for production of F-18**

SI No.	Points	Minimum Value	Maximum Value	Average value
1	A	0	0.03	0.018
2	B	0.01	0.09	0.07
3	C	0.05	0.82	0.546
4	D	0.04	15.7	6.147
5	E	0.04	5.05	1.609
6	F	0.05	12.88	5.47
7	G	0.32	1.96	0.984
8	H	0.07	1.3	0.536
9	I	0.06	1.09	0.55
10	J	0.45	8.17	2.06
11	K	0.75	26	12.02
12	L	0.12	5.82	2.83

SI No.	Points	Minimum Value	Maximum Value	Average value
13	M	2.23	15.9	9.94
14	N	0.73	26.8	7.60
15	O	2.13	8.05	5.05
16	P	0.05	9.37	1.50
17	Q	1.34	6.91	3.79
18	R	0.64	12.61	5.18
19	S	0.09	8.88	2.99
20	T	0.04	9.35	5.06
21	U	0.06	1.99	1.42
22	V	0.05	0.89	0.464
23	W	0.0	0.3	0.072
24	X	0.0	0.07	0.0304

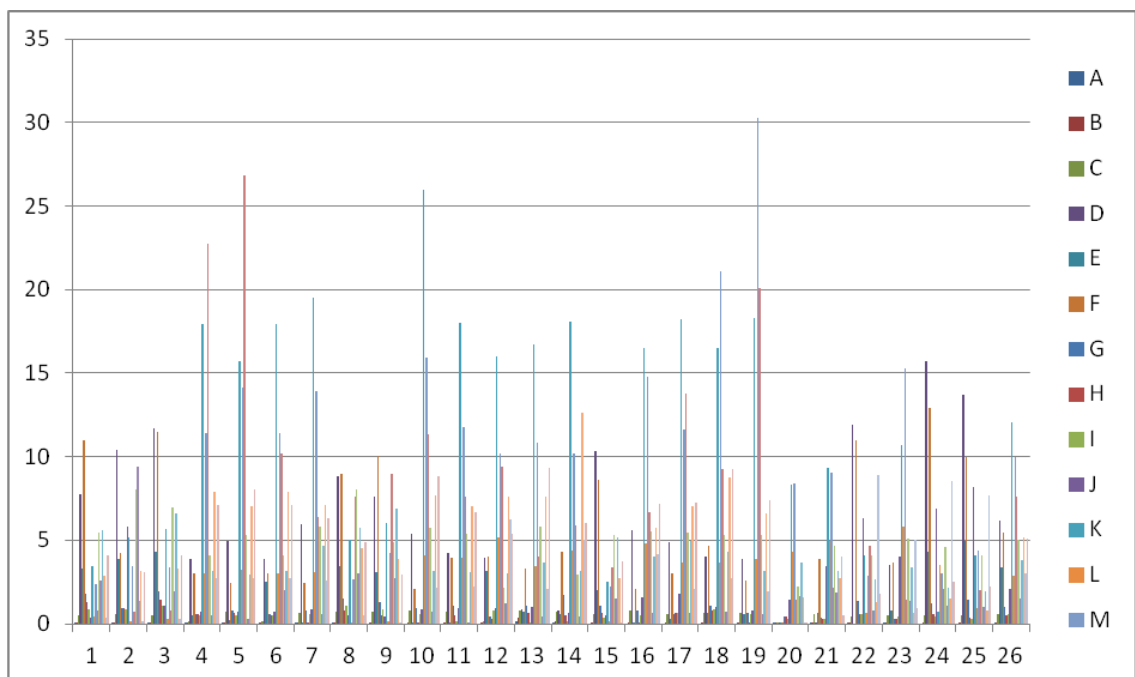
#### **4.11 MEASUREMENT OF GAMMA RAYS EXPOSURE RATE**

Before bombardment it was found that each and every point exposure levels were near to background level except Pit. The mean exposure level on the quarry was 7.61mR/hr. The maximum exposure level on the quarry was 26.8 mR/hour and minimum exposure level was 0.76 mR/hr. During bombardment it was found that there were ten points where radiation levels were high. Those points were D, F, K, M, N, O, Q, R, S and T. At point D, the average exposure level, maximum exposure level and minimum exposure level were 6.147, 15.7 and 0.04 mR/hr. At point F the average exposure level, maximum exposure level and minimum exposure level were 5.47, 12.88 and 0.05 mR/hr. At point K the average exposure level, maximum exposure level and minimum exposure level were 12.022, 19.5 and 0.75 mR/hr. At point M the average exposure level, maximum exposure level and minimum exposure level were 9.9496, 30.03 and 2.23 mR/hr. At point N the average exposure level, maximum exposure level and minimum exposure level were 7.6096, 20.1 and 0.73 mR/hr. At point O, the average exposure

level, maximum exposure level and minimum exposure level were 5.0508, 8.05 and 2.13 mR/hr. At point Q, the average exposure level, maximum exposure level and minimum exposure level were 3.791, 6.91 and 1.34 mR/hr. At point R the average exposure level, maximum exposure level and minimum exposure level were 5.1828, 12.61 and 0.64 mR/hr. At point S, the average exposure level, maximum exposure level and minimum exposure level were 2.9964, 8.88 and 0.04 mR/hr. At point T the average exposure level, maximum exposure level and minimum exposure level were 5.0664, 9.29 and 0.04 mR/hr.

The maximum exposure level was 30.03 and minimum exposure level was 0.00. The maximum exposure was recorded at M. It is located at near water cooler assembly on the surface of wall of shield BL 2 side. The minimum exposure was recorded at A. It is located at master computer.

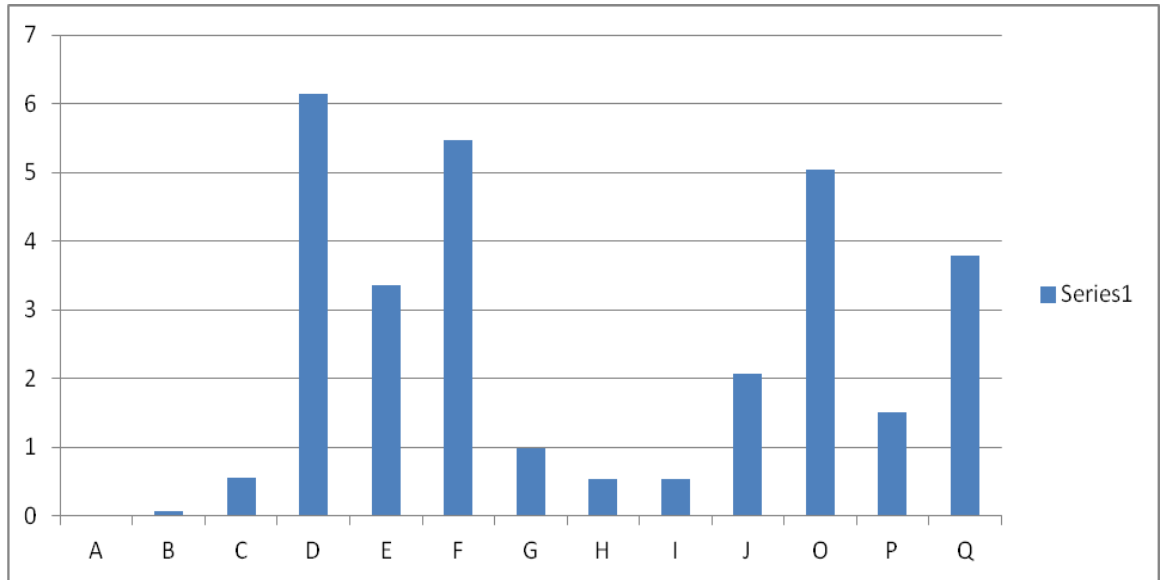
After bombardment it is found that each and every point reading was near to background level except Pit.



**Figure 4.3: Showing the radiation level inside the Cyclotron facility**

**Table 4.6: Radiation Level at beam line 1 side**

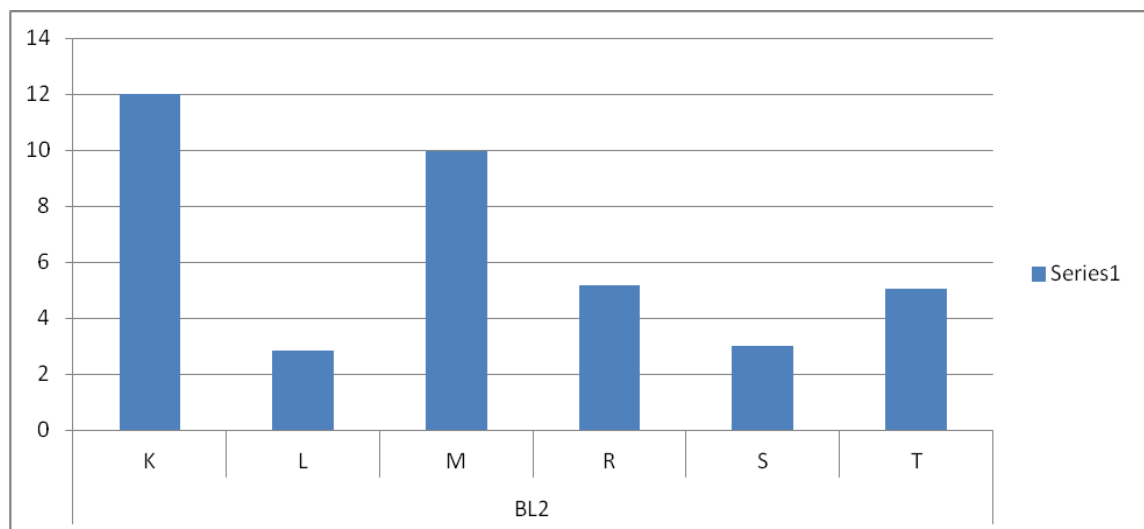
A	B	C	D	E	F	G	H	I	J	O	P	Q
0.0188	0.07	0.55	6.14	3.35	5.47	0.98	0.536	0.546	2.061	5.05	1.51	3.791



**Figure 4.4: Showing the radiation level inside the Cyclotron facility in BL 1**

**Table 4.7: Radiation Level at beam line 2 side**

K	L	M	R	S	T
12.02	2.838	9.9496	5.183	2.996	5.066



**Figure 4.5: Showing the radiation level inside the Cyclotron facility in BL 2**

**Table 4.8: Exposure rate of neutron in mR/hr at deferent point during bombardment of cyclotron for production of <sup>18</sup>F**

Sl No.	Point	Minimum Value	Maximum Value	Average Value
1	A	0.0	0.08	0.0144
2	B	0.01	0.1	0.0604
3	C	0.05	0.8	0.535
4	D	0.04	14.1	5.91
5	E	0.06	5	1.81
6	F	0.04	12.3	5.34
7	G	0.3	1.9	0.968
8	H	0.05	1.45	0.545
9	I	0.1	1.1	0.530
10	J	0.38	2.17	1.14
11	K	0.7	18.2	11.93
12	L	0.06	5.04	2.67
13	M	2.4	29	10.28
14	N	0.73	26.8	7.55
15	O	2.1	8.1	4.97
16	P	0.07	9.5	1.55
17	Q	1.4	6.6	3.82
18	R	0.7	13	5.40
19	S	0.03	9.1	3.13
20	T	0.04	9.5	5.20
21	U	0.12	1.5	0.90

#### **4.12 MEASUREMENT OF NEUTRON EXPOSURE RATE**

Before bombardment it was found that each and every point exposure levels were near to background level except Pit. The average exposure level on pit was 7.55 mR/hr. The maximum exposure level on pit was 26.8mR/hr and minimum exposure level was 0.73 mR/hr. During bombardment it was found that there were ten points where radiation levels were high. Those points were D, F, K, M, N, O, Q, R, S and T. At point D, the average exposure level, maximum exposure level and minimum exposure level were 5.91, 14.1 and 0.04 mR/hr. At point F the average exposure level, maximum exposure level and minimum exposure level were 5.34, 12.3 and 0.04 mR/hr. At point K the average exposure level, maximum exposure level and minimum exposure level were 11.93, 18.2 and 0.70 mR/hr. At point M the average exposure level, maximum exposure level and minimum exposure level were 10.28, 29.0 and 2.40 mR/hr. At point N the average exposure level, maximum exposure level and minimum exposure level were 7.55, 26.8 and 0.73 mR/hr. At point O, the average exposure level, maximum exposure level and minimum exposure level were 4.97, 8.10 and 2.10 mR/hr. At point Q, the average exposure level, maximum exposure level and minimum exposure level were 3.80, 6.60 and 1.40 mR/hr. At point R the average exposure level, maximum exposure level and minimum exposure level were 5.40, 13.0 and 0.70 mR/hr. At point S, the average exposure level, maximum exposure level and minimum exposure level were 3.13, 9.10 and 0.03 mR/hr. At point T the average exposure level, maximum exposure level and minimum exposure level were 5.20, 9.50 and 0.04 mR/hr.

The maximum exposure level was 30.03 and minimum exposure level was 0.00. The maximum exposure was recorded at M. It is located at near water cooler assembly on the surface of wall of shield BL 2 side. The minimum exposure was recorded at A. It is located at master computer.

After bombardment it is found that each and every point reading was near to background level except Pit.

**Table 4.9: Exposure rate of gamma ray in mR/hr at deferent point during synthesis of  $^{18}\text{F}$ -FDG in radiochemistry laboratory**

Sl. No.	Points	Minimum Value	Maximum Value	Average Value
1	A	0.0	0.67	0.092
2	B	0.0	7.44	0.768
3	C	0.0	4.5	0.32
4	D	0.0	1.71	0.36
5	E	0.01	7.68	5.35
6	F	0.0	1.76	0.32
7	G	0.0	2.5	0.41
8	H	0.0	0.91	0.16
9	I	0.0	26	2.98
10	J	0.0	41	5.44
11	K	0.0	1.05	0.147
12	L	0.0	1,02	0.104
13	M	0.0	0.73	0.07
14	N	0.0	0.83	0.099
15	O	0.0	0.71	0.090
16	P	0.0	0.45	0.088
17	Q	0.0	0.59	0.092
18	R	0.0	0.59	0.178
19	S	0.0	8.23	1.05
20	T	0.0	7	0.64
21	U	0.0	1.75	0.153
22	V	0.01	0.67	0.128
23	W	0.2	0.94	0.453

#### **4.13 RADIOCHEMISTRY LAB READINGS**

Before synthesis it was found that each and every point exposure levels were at background levels. During synthesis it was found that there were four points where radiation levels were high. Those points were E, I, J and S. At point E the average exposure level, maximum exposure level and minimum exposure level were 7.68 ,5.35 and 0.01mR/hr. At point I the average exposure level, maximum exposure level and minimum exposure level were 2.9838, 26.01 and 0.00 mR/hr. At point J the average exposure level, maximum exposure level and minimum exposure level were 5.4412, 41 and 0.00 mR/hr and at point S the average exposure level, maximum exposure level and minimum exposure level were 1.052, 8.23 and 0.00 mR/hr.

After synthesis it was found that each and every point reading was near to background level in the normal condition. Sometimes it was found that the charcoal filter of the Explora was malfunctioning, in this place the charcoal filter was not capable to absorb the produced radioactive during synthesis. So produced radioactivity was spread into all areas of radiochemistry lab. The spread radiation was detected by the radiation area monitor, radiation survey meter and pocket dosimeter or any one of them. The value of leakage radiation was 1-5 mR/hr. This value depends on the quantity of radioactivity present inside the Explora during synthesis.

The second region of high radiation level in the radiochemistry lab was due to malfunction of exhaust of this area. Due to this, Exhaust was not able to remove the produced radioactivity during synthesis. So all produced radioactivity was spread into all areas of radiochemistry lab. The value of leakage radiation was 1-2 mR/hr. This value again depends on the quantity of radioactivity present inside the Explora during synthesis.

We have centralized air-conditioner in our laboratory. So if there was a leakage in the radiation it was spread the entire radiochemistry lab. To prevent from this situation we had adopted a tremendous conclusion. We had just switched off the centralized AC and closed the door of radiochemistry room. And then the activity present in the radiochemistry lab remained inside the Explora room and it won't expel. By taking in this technique the remaining region of the radiochemistry lab was radiation free and other radiation worker of the radiochemistry lab was not affected by this radiation. So that they can execute their work without any interference.

#### 4.14 MINIMIZATION OF RADIATION DOSE TO STAFF AND ATTENDANT OF THE PATIENTS IN PET SCAN

**Table 4.10: Showing that exposure rate after patient's injection.**

	Radiation Exposure during injection (mR/hr)		Radiation exposure after injection (mR/hr)		Time expended with patients (Sec)		Remarks
Sl. No.	During FDG injection	After Water Push	At contact	at 1 meter	before injection	After injection	
1.	15	9	33.7	4.75	4	25	
2.	16	9	34.1	4.1	4	26	
3.	17	10	40	3.14	3	30	
4.	12	8	55.7	5.52	3	15	
5.	40	20	60	3.42	3	17	canula removal
6.	16.7	6	69.8	4.48	5	16	
7.	12	7	107	6.85	5	30	
8.	8.2	3.4	30	2.57	6	31	

9.	39	13	79	4.99	7	32	
10.	15	5.9	103	3.87	5	20	
11.	20	4.45	94.4	4.05	6	26	
12.	6.63	3.38	89.9	2.17	10	35	Pediatric pt
13.	15	7	91	5.67	7	27	sick pt
14.	19.2	9	45.6	4.57	4	15	
15.	22.4	7.7	81	6.29	15	17	on streture
16.	14.2	7.7	46.7	3.68	5	15	
17.	10.61	7.71	44.6	4.36	10	32	Old Pt
18.	21.8	6.8	53.6	3.38	3	14	
19.	15.5	7.3	27.1	3.1	5	20	New resident
20.	27	9	46	4	12	40	New resident
21.	34	11	61	4.71	12	29	
22.	31	7.2	34.2	4.7	10	15	
23.	37	9	63	4	14	12	New resident
24.	13	5	58.5	4.58	10	22	New resident
25.	27	11	23.9	3.58	12	35	New resident
26.	32	10	87	3.47	12	23	New resident
27.	25	10	41	3.11	10	21	New resident
28.	24	4.5	66	4.5	12	18	New resident
29.	25	4	21	2.1	10	16	New resident
30.	18	6	40.5	4.35	9	21	
31.	19.2	5	53.4	4.23	6	21	
<b>Average</b>	<b>20.91741</b>	<b>7.87225</b>	<b>57.47419355</b>	<b>4.13838</b>	<b>7.70967</b>	<b>23.09677</b>	

**Table 4.11: Showing that exposure rate after patient's scan finished.**

<b>Patient No.</b>	<b>Radiation exposure level at the distance of one meter during pt discharge (mR/hr)</b>
1.	1.28
2.	1.16
3.	3.10
4.	1.25
5.	2.70
6.	4.15
7.	5.29
8.	5.00
9.	2.58
10.	2.93
11.	2.61
12.	2.91
13.	5.10
14.	2.72
15.	1.31
16.	3.20
17.	1.21
18.	1.35
19.	5.25
20.	1.40
Average	2.825

#### **4.15 DISCUSSION**

Patients and their attendant were counseled regarding waiting areas and keeping distance before commencing the process. This helps minimize the radiation exposure

received to the Nuclear Medicine physician, technologist, attendant and surrounding people. Generally, instruction is passed on by Doctors or Technologist. The program line is formulated and guided by either by Medical Physicist or Radiation Safety Officer (RSO).

For this study 35 patients were taken. Three parameters were taken, the names of parameters are radiation exposure during injection (mR/hr), Radiation exposure after injection (mR/hr) and time expended with patients (Sec). These parameters were again split into two sections. Radiation Exposure during injection was divided in to two parts 1) During FDG injection and 2) After water push. Radiation exposure after injection was divided into two parts 1) At contact and 2) At 1 meter. Time expended with patients was divided into two parts 1) Before injection and 2) After injection.

The maximum radiation exposure during FDG injection was 40 mR/hr to the nuclear medicine physician. The minimum radiation exposure during FDG injection was 6.63 mR/hr to the nuclear medicine physician, This was a pediatric patient and the total activity for this patient was 2.2 mCi. The average radiation exposure during  $^{18}\text{F}$ -FDG injection was 20.91 mR/hr to the nuclear medicine physician.

The maximum radiation exposure after water push was 20 mR/hr to the nuclear medicine physician. The minimum radiation exposure after water push was 3.39 mR/hr. The typical radiation exposure after water push on was 7.88 mR/hr to the nuclear medicine physician.

The maximum radiation exposure after injection was at contact 107 mR/hr. The minimum radiation exposure after injection was at contact 21 mR/hr. The average radiation exposure after injection was at contact 57.47 mR/hr.

The maximum radiation exposure after injection was at 1 meter distance 6.85 mR/hr. The minimum radiation exposure after injection was at 1 meter distance 2.1 mR/hr. The average radiation exposure after injection was at 1 meter distance 4.13 mR/hr.

The maximum time spent with the patient by a nuclear medicine physician before injection was 15 seconds. This was the maximum time taken by a nuclear medicine physician for FDG injection. This patient was on the stretcher, old and sick. The minimum time spent with the patient by a nuclear medicine physician before injection was 3 seconds. The mean time spent with the patient by a nuclear medicine physician before injection was 7.70 seconds.

The maximum time spent with the patient by a nuclear medicine physician after injection was 40 seconds. This was the maximum time taken by a nuclear medicine physician after FDG injection with patients. This nuclear medicine physician was on training. Later this nuclear medicine physician has decreased his time of injection. The minimum time expended with the patient by a nuclear medicine physician after injection was 12 seconds. The mean time expended with the patient by a nuclear medicine physician after injection was 23.09 seconds.

Now we minimized the radiation dose received to the nuclear medicine physician by change the position of lead line carrier container (Injection of FDG placed in this box in the injection room), chair of canulation and injection chair.

At the time of canulation and injection, nuclear medicine physician were getting 6-7 mR/hr and 2 mR/hear from lead line carrier container due to four injections of 10 mCi of FDG placed. After discussion with the nuclear medicine physician they may suppose three stuffs

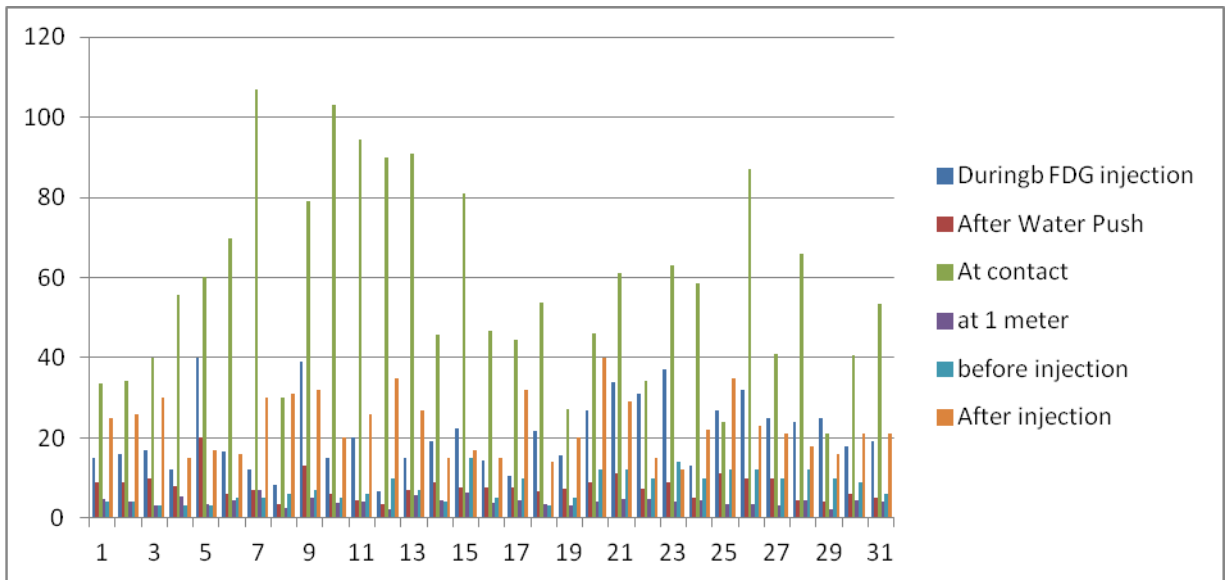
1. Canulate the patients before activity came in the injection room
2. Change the location of chair of canulation.
3. Change the position of the chair of FDG injection

It is likewise suggested that change the position of the lead line carrier container. After keep it even inside in the lift and nuclear medicine physician would like to inject, they can inject by taking doses from inside the elevator. Later switching place of canulation , the rate of exposure was 0.02 mR/hear from lead line carrier container due to  $^{18}\text{F}$ -FDG. The exposure rate at the injection place after change the place of the lead line carrier container was 0.35 mR/hear from lead line carrier container due to  $^{18}\text{F}$ -FDG.

It is found that before water wash the exposure rate was 10.07 mR/hr and after water wash the exposure rate was 7.15mR/hr.

The exposure rate behind the nuclear medicine physician was 0.33 mR/hr (when nuclear medicine physician was standing in the front of the patient).The exposure rate behind the nuclear medicine physician was 2.47mR/hr (when nuclear medicine physician was not standing in the front of the patient). So total absorb dose to the nuclear medicine physician was 2.14 mR/hr.

The actual dosage of an adult patient for  $^{18}\text{F}$ -FDG is 10 mCi. After injection patient have wait around 45-60 minutes in a cubical room. This room is called post injection waiting area. The scanning time for an adult was about 20 minutes. After scan patients have waited. And then that nuclear medicine physician can confirm that there is additional views are taken or not. If additional view required patients have to wait again 30 minutes to 3 hours. After finishing the scan the maximum radiation exposure level, minimum radiation exposure level and average radiation exposure level at 1 meter was 5.29, 1.16 and 2.82 mR/hr respectively.



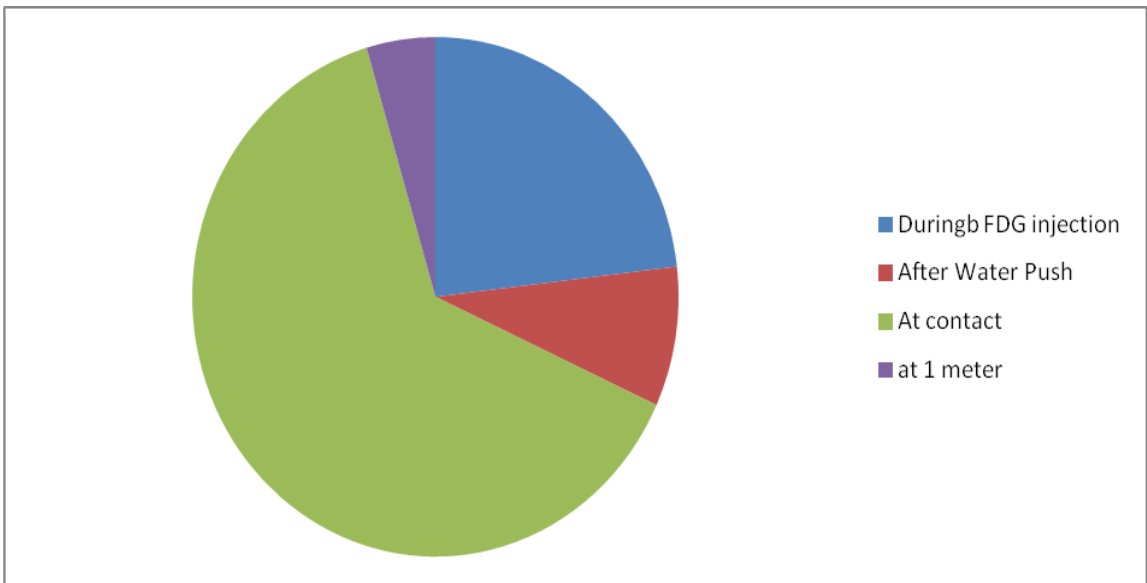
**Figure 4.6: Showing the radiation exposure level during injection of  $^{18}\text{F}$ -FDG to the patients**

**Table 4.12: Showing that exposure rate during injection of  $^{18}\text{F}$ -FDG to the patient.**

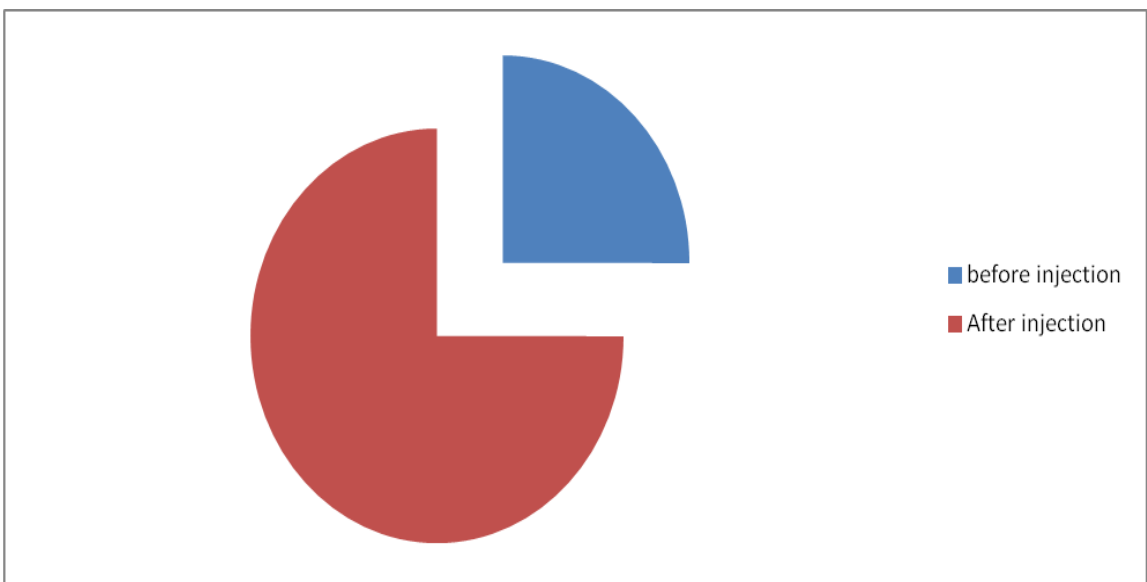
<b>During injection</b>	<b>FDG</b>	<b>After Water Push</b>	<b>At contact</b>	<b>at 1 meter</b>
648.44		244.04	1781.7	128.29

**Table 4.13: Showing the comparison of exposure rate between before injection and after injection of  $^{18}\text{F}$ -FDG to the patient.**

<b>before injection</b>	<b>After injection</b>
239	716



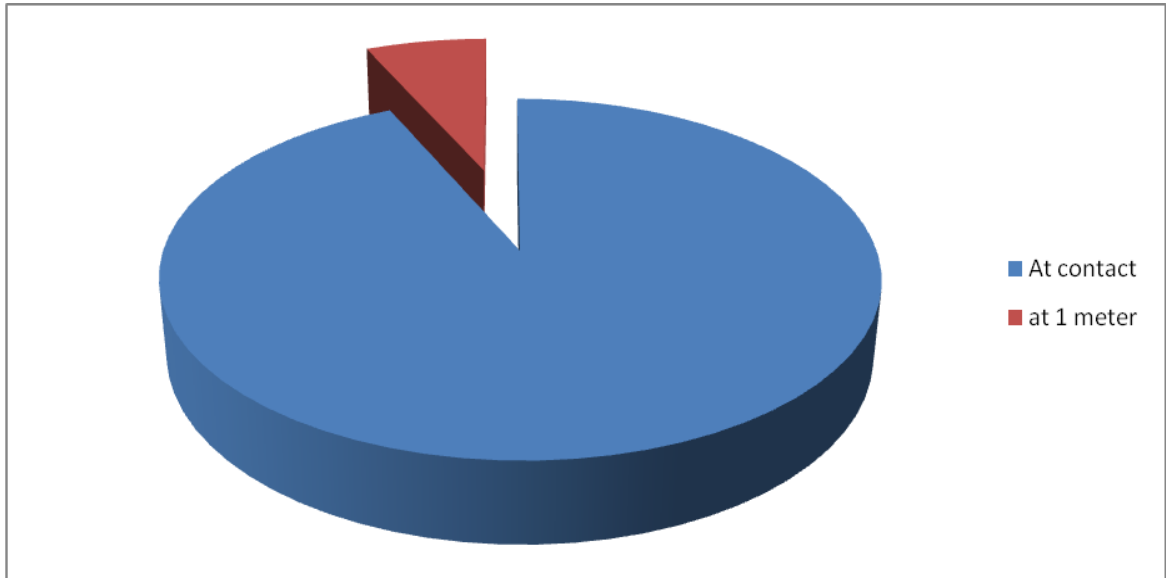
**Figure 4.7: Showing that exposure rate during injection of  $^{18}\text{F}$ -FDG to the patient.**



**Figure 4.8: Showing the exposure rate before injection and after injection of  $^{18}\text{F}$ -  
FDG**

**Table 14: Showing the exposure rate at contact and at a distance of Patients who injected  $^{18}\text{F}$ -FDG**

<b>At contact</b>	<b>at 1 meter</b>
1781.7	128.29



**Figure 4.9: Exposure rate at contact and at a distance of Patients who injected  $^{18}\text{F}$ -FDG**

#### **4.16 IMPORTANT OBSERVATIONS**

A list have been prepared after carefully observe the above mentioned parameters on 31 patients which will minimize the radiation dose to staff and attendant of the patients in PET scan

1. Nurse will canulate to the patients
2. Then nuclear medicine physician/technologist will put medicine to the patients through canula

3. Instructed to patients that after put medicine nobody will direct communicate to the patients (until unless there was no emergency) because after radioactive injection the patients will become source of radiation
4. If possible use CCTV camera and mike to instruct the patients
5. Patients have just follow the instructions
6. Patients have to remove all the metallic items like jewelry, key, metallic cloth, belt, valet, spectacle, hairpins, hairclip, coins, pen, money bag, safety pin etc.
7. Before injection patients attendant have to put 3 liter of water bottle or liquid
8. All above mention instruction have to finished before the bring injection in to the injection room
9. After injection patients have to wait 45 minute to 60 minutes for PET/CT scanning this is called waiting period
10. During this waiting period patients have to drink 2-3 liters of water or liquid and micturate
11. Patients micturate very much carefully so that urine should not drip on his /her clothes or body parts.
12. During scanning the patients instructed that they should not move on PET/CT table
13. Patients should keep off the unnecessary talk with Nuclear medicine physician or Technologist after injection
14. After scanning patients may need to consider some other scan so patients may rest sometimes after scanning.
15. If patients would like to ask something after injection it is recommended that patients ask question through their attendant or through mike.

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## *Chapter 5*

# *Conclusion & Future*

## *Scope*

# CHAPTER 5: CONCLUSION AND FUTURE SCOPE

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## 5.1 CONCLUSION

This chapter concludes and summarizes the thesis work. The directions and scope for further research in the area of medical cyclotron and  $^{18}\text{F}$ -FDG are also suggested.

The value of neutrons and gamma rays radiation inside the medical cyclotron are significant during operations of medical cyclotron. In this thesis, we have made systematic study before, during and after medical cyclotron bombardment and  $^{18}\text{F}$ -FDG synthesis. The interesting results of the present study can be separated into subsequent three parts:

First part (Chapter-2) covers the experimental techniques and methodology in which we improve our work practice in our scenario. Here we have optimized the working principle of medical cyclotron. We have optimized the environmental as well as equipment conditions. A significant improvement has been found after implementations of optimization the irradiation parameters of medical cyclotron. In this section ion source conditioning and method of manual bombardment are mentioned.

In the second part (Chapter 3), the synthesis of  $^{18}\text{F}$ -FDG has been studied. The influence of various parameters on yield was mentioned. The effect of optimization of synthesis parameter of synthesis of positron emitting  $^{18}\text{F}$ -FDG was implemented up to great extent. Preparation of all chemicals is very crucial. It must be prepared in aseptic condition, bacteria and germ free environment. In our new protocol there are lots of benefits discussed. Some of them are mentioned below

- Less time consumed
- Less chemical consumed

- Less decay of  $^{18}\text{F}$
- Yield increase
- Available of  $^{18}\text{F}$ -FDG earlier than before
- $^{18}\text{F}$ -FDG available for more patients

Third part (Chapter 4) deals with the radiation environment in the medical cyclotron facility and exposure rate from patients after  $^{18}\text{F}$ -FDG injection. The time spent by nuclear medicine physicians during injection period was also recorded for betterment of practices.

During operation of medical cyclotron the radiation level was very high. So during this time duration it is advisable that nobody can enter in to the cyclotron room. To prevent this we have interlock system in our medical cyclotron facility, if someone enters in the cyclotron room by mistake the bombardment of cyclotron immediately stop just after opening of the door of the cyclotron room. All though this is not possible because cyclotron operator will not allow anyone to enter in the cyclotron room as he is sitting in the front of the cyclotron monitor during the bombardment.

The exposure level of neutrons and gamma rays (ionizing radiation) on the outer wall of the Cyclotron room was measured at regular interval, It was found within the safe limit prescribed by competent authority i.e. AERB. Neutron only produced during cyclotron operations.

The exposure level during transfer of  $^{18}\text{F}$  from cyclotron to radiochemistry module i.e. Explora FDG 4 was found little high, so it was advisable to all staff of lab to not stand in between them.

During synthesis of  $^{18}\text{F}$ -FDG the radiation level was found within the safe limit prescribed by competent authority

The exposure level during the test of quality of product in quality control area was very less, as all work carried out behind the L-Bench.

The exposure rate during injection is high so the Nuclear Medicine Physicians administering the dose to patient should avoid standing very close to the patient as well as should spent the minimum time with the injected patients.

If they follow the radiation safety guideline approved by the competent authority (AERB), the radiation dose to the staff and Nuclear Medicine physicians would be within the permissible limits.

## **5.2 FUTURE SCOPE**

Medical cyclotron produces positron emitting radio nuclides. There are mainly five types of Positron emitting radionuclides to produced i.e. Fluorine- 18, Carbon-11, Nitrogen -13 and Fluorine- 18 Gas. Among them more than 95% Fluorine-18 is produced. Rest of the radionuclide would be mainly use for research purposes.

$^{18}\text{F}$  is used in clinical purpose due its half life and its uptake in the tissues of the body. From  $^{18}\text{F}$  there is a possibility to produce lots of radiopharmaceuticals, some of them mentioned below.

### **5.2.1 $^{18}\text{F}$ -FDG**

Fluorodeoxyglucose is the most frequently used PET radio radiopharmaceutical. It is used to measure the cellular metabolism. It may be used in the primary diagnosis as well as staging of various tumors like breast cancers, lymphomas, high grade neuroendocrine tumors and brain tumors, lung cancers, colon cancers. It could also be

used for the response assessment after chemo and radiotherapy in the patients and its uptake values have been incorporated in the PERCIST (PET Response Criterion in Solid Tumors) criterion. Apart from oncology it could also be utilized in the patients with pyrexia of unknown origin, inflammatory connective tissue disorders, vasculitis, dementias, parkinsonism, epilepsy etc.

### **5.2.2 <sup>18</sup>F-DOPA**

Fluorodopa is a radio labelled amino acid precursor. It is transported by neutral amino-acid transporter into the cells, where it is converted to fluorodopamine by dopa decarboxylase. Thus this agent allows evaluation of amino acid transport and peptide synthesis. It would be used for the evaluation of brain tumors and neuroendocrine tumors. It would be also used for the assessment of dopa metabolism in patients with Parkinsonism.

### **5.2.3 <sup>18</sup>F-MISO**

Fluoromisonidazole is a hypoxia imaging agent. It is reduced to nitrite radical inside the cell where it gets trapped, if oxygen does not exist to reoxidize and would be used in a variety of circumstances like in head and neck cancers, lung cancers and gliomas. This information about cellular hypoxia would be used for radiotherapy planning and for choosing drugs for chemotherapy.

### **5.2.4 <sup>18</sup>F-CHOLINE**

Fluorocholine is a phospholipid which is metabolized by the enzyme within the cells. It would be used for imaging of lipid metabolism inside the cells. It would be used in multitudes of disorders like prostate cancers, parathyroid tumors, gliomas, and lung cancers. It would provide good target to background ratios but false positives continue to be a problem.

### 5.2.5 <sup>18</sup>F-FLUOROTHYMIDINE

<sup>18</sup>F-Fluorothymidine is a nucleoside which is metabolized by thymidine kinase and gets incorporated into the DNA. It may be used to measure the DNA synthesis and thus assess the proliferative indices of various tumors. It would be utilized in brain tumors and breast cancers.

## LIST OF PUBLICATIONS

---

- Rajeev Kumar, Nishikant A Damle, Chandrasekhar Bal, Arun Malhotra, Madhavi Tripathi, Rakesh Kumar, Santosh Gupta, Rajendra G Sonkawade, Pankaj Gupta, 2013. “Extraction of residual  $^{18}\text{F}$ -fluoride for PET bone scan simultaneously with the synthesis of  $^{18}\text{F}$ -FDG using Explora synthesis module in single run of cyclotron with minimal radiation exposure”. J Nucl Med. 54 Supplement 2
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## LIST OF ABSTRACTS

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- Rajeev Kumar, Rajendra Sonkawade, Nishikant A. Damle, Madhavi Tripathi, Chandrasekhar Bal, Partha S. Chakraborty, Praveen Kumar. Synthesis of generator based  $^{68}\text{Ga}$  labeled PSMA by an automated module: Indian experience. Accepted at SNMMI Annual Meeting 2015, JUNE 6-10, 2015 Baltimore, USA
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- Rajeev Kumar, R G Sonkawade, 2012. “Radiation environment in and around PET Cyclotron facility”. International Conference on Radiation Environment-Assessment, Measurement & its Impact. Babasaheb Bhimrao Ambedkar University, Lucknow.

## **LIST OF CONFERENCES ATTENDED**

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- International Conference on Radiation Environment-Assessment, Measurement & its Impact, 12-14 April, 2012 at Babasaheb Bhimrao Ambedkar University, Lucknow.
- Second world Congress on  $^{68}\text{Ga}$  (Generator and Novel Radiopharmaceuticals), Molecular Imaging (PET/CT), Targeted Radionuclide therapy and Dosimetry: On the way to Personalized Medicine. 28<sup>th</sup> February to 2<sup>nd</sup> March 2013 at Department of Nuclear Medicine and PET PGIMER Chandigarh, India.
- Post Second world Congress on  $^{68}\text{Ga}$  workshop. 4-5<sup>th</sup> March 2013 at Institute of Nuclear Medicine and Allied Sciences, New Delhi, India.
- 53<sup>rd</sup> Annual meeting of Society of Nuclear Medicine, 6-10<sup>th</sup> June 2015 at Baltimore Maryland, USA, oral presentation.
- First National Meet of Nuclear Medicine Physicist Association of India. 27<sup>th</sup> March 2016 at All India Institute of Medical Sciences New Delhi.