USE OF THE SCANDITRONIX MC 40 CYCLOTRON OF THE JRC (EC) FOR FDG PRODUCTION IN COMPLIANCE WITH THE EUROPEAN GMP

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Abstract

The Scanditronix MC40 Cyclotron of the Joint Research Centre (JRC) of the European Commission (Ispra site), installed in 1982, is used for materials research and for production of radioisotopes for medical applications (diagnosis and therapy). Regarding radioisotope production, the main ongoing projects are [^{18}F]Fludeoxyglucose (FDG) production in collaboration with Amersham Health (Italy) and studies of methods for production of ^{64}Cu [1], ^{211}At [2] and ^{225}Ac [3]. The present paper is focused on the use of MC 40 Cyclotron for routine FDG production in compliance with the European Good Manufacturing Practices (GMP) guidelines. The main components of the facility are described - the cyclotron, the target and the production and quality control laboratories.

INTRODUCTION

Labelled with the radiotracer ^{18}F (half-life 109.7 min), FDG is the most successful and widely used radiopharmaceutical for Positron Emission Tomography (PET). It is used mainly in oncology for cancer diagnosis, though its use cardiology and neurology is growing. In a collaboration between JRC (Institute for Health and Consumer Protection, European Commission) and Amersham Health (pharmaceutical group) an FDG production facility has been set-up in JRC laboratories (Ispra, Italy). The production is in compliance with the European Good Manufacturing Practices (GMP) [4] guidelines. Apart from the routine production, related training and accompanying research is carried out. For the routine production, JRC is responsible for supplying ^{18}F while Amersham Health is responsible for the FDG synthesis and distribution to hospitals. This has made FDG available as a radipharmaceutical product for the Lombardy and Piedmont regions in the north of Italy. The FDG production facility is located inside a controlled area of the cyclotron building (Fig. 1). It comprises the target for ^{18}F-Fluoride production, two automated FDG Synthesis modules and an automated dispensing unit. The FDG synthesis modules and the dispensing unit are installed in 3 separate hot cells. The quality control of the produced FDG is carried out according to the related monograph of the Europharmacopeia [5] in compliance with GMP guidelines.

Figure 1: JRC Cyclotron building

THE CYCLOTRON

The accelerator is a Scanditronix MC 40 model, which is variable energy and accelerates positive ions. It accelerates protons, deuterons, alphas and Helium-3 ion particles. The relevant characteristics of extracted beams are reported in Table 1 and Table 2.

Particle	Energy (min.-max.) (MeV)	Maximum Extracted Current (υA)
p	8 – 40	60
d	8 - 40	30
$^{4}He^{2+}$	8 - 53	30
$^{3}He^{2+}$	4 - 20	60

Table 1: Characteristics of the extracted beam of the JRC Cyclotron

The building of the facility is divided into a radiologically hot area for the cyclotron itself, the irradiation halls with seven beam lines and several laboratories, and a radiologically cold area for technical laboratories and offices.

The Italian Ministry of Health issued the licence for the Pharmaceutical Site. Concerning the Cyclotron validation, 2 parameters were taken into account for the licence - the radio frequency generator and the current measurement system need a periodic certified calibrations according to established Standard Operation Procedures (SOP), which are part of the quality system of the cyclotron.

Pole diameter	115 cm
Magnet weight	60 tons
Main coils Max. Curr.	850 A
Sectors	3
Hill gap	100 mm
Valley gap	180 mm
Max. magnetic field	2.1 Tesla
Extraction radius	50 cm
Trim coils	8
Harmonic coils	84 sets
RF cavities	2, lombda/4
Dees	2, 90 degrees
Beam aperture	20 mm
Tuning	Moving shorts/trim cap.
RF range	12.5 –27 MHz
Frequency stability	$< 10^{-6}$
Amplitude stability	$< 10^{-3}$
Max. Dee peak voltage	44 kV
Ion source	P.I.G. Type

Table 2: JRC Cyclotron characteristics

^{18}F PRODUCTION

The irradiation of $H_2{}^{18}O$ enriched water which yields ^{18}F is carried out on a dedicated beam line. ^{18}F is produced by the nuclear reaction

$$^{18}O(p,n)^{18}F$$

through a 16 MeV energy proton beam irradiating the target of ^{18}O enriched water. The target cavity is made of titanium, chosen for being chemically inert. The front face of the target through which the proton beam is transmitted to reach the enriched water has a thickness of 125 μm. It is irradiated with a beam of 18 mm diameter. The target is cooled with helium gas from the front side and water from the backside. The filling of the target with 1 ml of enriched water $H_2{}^{18}O$ is remotely controlled. Two hours irradiation with a current of 20 μA yields more than 74 GBq of ^{18}F, which is lower than the expected (theoretical) yield, but high enough to satisfy current requirements. A new target with an ultra high ^{18}F yield will be purchased to satisfy the increased FDG production necessary in the future.

^{18}F is a positron emitter, therefore causing the subsequent production of 511 keV gamma radiation. Its half-life is 109.7 min. Fig. 2 shows the ^{18}F target including all connections for cooling in place on the beam line.

^{18}F is a raw material for FDG synthesis, so therefore the quality of the starting product $H_2{}^{18}O$ must be validated. For this purpose several productions are carried out for the analysis of the purity of the ^{18}F in the irradiated enriched water. Each new lot of enriched water is analysed for ^{48}V impurities, which could be released from the body of the target. Several SOPs are approved and rigorously applied for the production of ^{18}F such as rinsing of the target body including the transfer line, the protocol for the production, and enriched water storage.

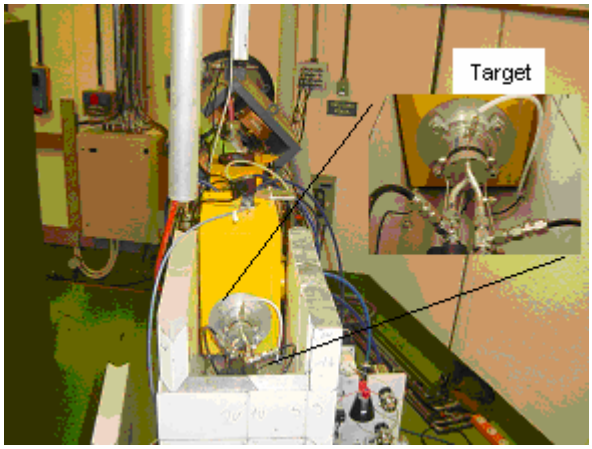

Figure 2: F-18 target in place on a beam line

FDG PRODUCTION LABOLATORIES

At the end of the cyclotron irradiation, the activated water is transferred with helium gas pressure to the synthesis module located in the production laboratory, which is C classified (compatible with Class 10000, Class M5.5 or Class ISO 7). A Teflon tube of 0.6 mm internal diameter and 25 m length is used for the transfer, which is remotely controlled. Although the transfer of the irradiated water takes less than a minute, the transfer line is shielded with 8 cm of lead to ensure the absorption of the 511 keV gamma radiation. The complete FDG production facility is located in a controlled area (radioprotection regulations) under reduced pressure with respect to the atmosphere. The Clean Room where the FDG is synthesised and sterilised is at a higher pressure with respect to other areas of the facility (pharmaceutical regulations). Three hot cells with dedicated ventilation are installed in the Clean Room and shielded with 8-cm thick lead. The hot cells contain two FDG synthesis modules and the FDG dispenser unit, which are fully controlled and monitored by computers. In the area dedicated to Quality Control all instruments and equipment are connected through a server.

FDG Synthesis

The use of two synthesis modules has several advantages:

- If a second FDG production run is needed the same day, a second module must be used to comply with radioprotection regulations.
- The two synthesis modules can be used alternately to reduce radiation exposure of the operators during the preparation of the product.
- The availability of two modules prevents any major interruption in FDG production if one of them is malfunctioning.

Figure 3: FDG Production laboratory

The synthesis of FDG is based on nucleophilic substitution with $^{18}F^-$, promoted by tetrabutylammonium (TBA) bicarbonate. The whole process for FDG synthesis can be summarised as follows:

- Collection of $^{18}F^-$ in an anion-exchanger
- Reaction with acetylated triflate in acetonitrile under phase transfer catalysis (TBA)
- Hydrolysation with HCl
- Purification by serial chromatography

The synthesis module is a closed system. All openings to the environment are closed either by septa or by sterile filters. Before a synthesis run the module is disinfected with Acetone and 70 % Ethanol and then dried. Between two syntheses the apparatus is hermetically closed. The FDG synthesis module ensures the recovery of the non-active ^{18}O enriched water. This water can be used for a further activation only if it is purified, distilled and possibly sterilised. For the present time, the recovered water is not re-used in this facility.

A synthesis cycle is accomplished in about 35 min. The preparation of the synthesis module does not exceed 15 min. After synthesis, the FDG is transferred to the dispensing unit by helium pressure. The yield of ^{18}F-FDG of high specific activity (10 Ci/μMol) is in the range of 50-60 % (not decay-corrected).

FDG Dispensing

The production facility is equipped with a dispensing unit in which a terminal sterilisation is performed. Up to 15 vials of FDG can be dispensed and sterilised in a single production run. The dispensing process is based on an aseptic dispensing under Class A air quality (laminar flow) and sterilisation in the final vials with steam at 134 ^oC for 3.5 min. The dispensing process lasts a maximum of 30 min depending on the number of vials to dispense. The FDG vials are put in lead containers inside the hot cell and then transferred through a pass through box in to the laboratory. The software of the synthesiser, dispenser and QC equipment are also designed according to GMP guidelines and all relevant parameters are recorded and stored and can be reviewed at any later time.

Quality Control

The Quality Control of the product is carried out according to the monograph of FDG of the European Pharmacopoeia where the specifications of the product as a radiopharmaceutical are presented. About 30 minutes are necessary for completion of those quality controls required for the release of the FDG. Radio nuclide, chemical and radiochemical purity controls are carried out. HPLCs, GC, TLC, pHmeter, and Activimeter are the main instruments used for the quality control. The biological quality controls of the produced FDG such as sterility and bacterial endotoxin level are sub-contracted to an external company. The FDG can be released before completion of the biological analysis.

CONCLUSION

After an extended period of setting up of laboratories, and of FDG production for testing and validation of the production facility, the JRC Scanditronix MC40 Cyclotron is successfully used for routine FDG production in compliance with the European GMP guidelines. The cyclotron is now running nearly every night for about 6 hours for ^{18}F production, and distribution of FDG to nearby hospitals and diagnostic centres has taken place since April 2004 without any significant interruption. This activity does not interfere with other research activities of the cyclotron that normally take place during daytime working hours.

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