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Medical Applications of Cyclotrons: The Status and Prospects in Egypt

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Abstract. Cyclotrons have been in regular use for medical radioisotopes production since about 1950. Cyclotrons from the point of view of chemists using them, can best be considered as devices providing a source of reagents, namely protons, deutrons, helium-3 and helium-4 which can bring about the nuclear reaction leading to the desired radionuclides. Many PET radiopharmaceuticals such as F-18 and C-11 could be produced by cyclotrons. The wide spread use of cyclotrons for radiopharmaceuticals production is still compromised by its high costs, compared with radiopharmaceuticals used for SPECT applications such as Tc-99m. In Egypt after cyclotron installation, much efforts will be needed by radiochemists to develop a research project concerning production of new PET and SPECT radiopharmaceuticals.

Introduction

Cyclotrons have been in regular use for medical radioisotope production since about 1950 [1]. However in the 1960's a real renaissance of the cyclotron for radionuclides production tookplace. With the application of Positron Emission Tomography (PET) and Single Photon Emission Tomography (SPECT) in nuclear medicine, an important era of cyclotron has been started for production of positron emitters and photon emitter radionuclides of potential use in nuclear medicine

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applications [2]. Most of the positron emitter nuclides are of short lived e.g. ^{11}C ($T_{1/2}$ 20.2 min.) which necessitate a cyclotron on site. Therefore the wide spread use of this technique is still compromised by its high cost. A complete installation of cyclotrons including whole-body camera, cyclotron and auxiliary equipments comes to at least USD 5-6 Million. Accompanying the installation of the first cyclotron an era of fast chemistry started for separation of the radioactive products, labeling of organic compounds, and biomedical evaluation using gas chromatography, high pressure liquid chromatography and thermochromatographic techniques [2].

(a) Production of PET radiopharmaceuticals

The PET technique is indeed attractive as it permits one to use radiolabelled and biologically active molecules with little or no structural change. Moreover a high resolution and improved sensitivity can be obtained with more precise quantitation, so that one ultimately acquires more functional information than by any other techniques about the nature of tissue function at the biochemical level. Of great importance in nuclear medicine is to produce PET radiopharmaceuticals with high specific activity to deliver highly localized tissue damage [3]. Development of a production process involves a study of several aspects such as nuclear data, energy of beam impinging on target, chemical separation processing and finally quality control of the produced radionuclide [1]. The cyclotron production of radionuclides leads in general to high specific activity products in spite of the large number of competing nuclear reactions [4]. The industry is trying very hard to convince workers in nuclear medicine that "the future of PET is already here". The production and sale of cyclotrons and PET cameras are now in the hands of large companies. Table (1) and (2) list some of the commonly used PET radiopharmaceuticals and their medical applications[5].

Table 1. PET radiopharmaceuticals requiring a cyclotron on site [3]

Radiopharmaceuticals	Application
^{11}C: $T_{1/2}$=20.4 min.	
^{13}C: $T_{1/2}$= 9.96 min	
^{15}O: $T_{1/2}$=2.04 min	
Available from automated system ("black box" or robot)	
^{11}CO	Cerebral + myocardial blood flow
$^{11}CO_2$	Cerebral blood flow
Acetate ^{11}C	Myocardial metabolism
Ammonia ^{13}N	Myocardial blood flow
$^{15}O_2$	Cerebral oxygen extraction + metabolism
$C^{15}O$	Cerebral + myocardial blood volume
$H_2{}^{15}O$	Cerebral + myocardial blood flow
Synthesized by radiochemist or robot	
Butanol ^{11}C	Cerebral blood flow
Methionine ^{11}C	Amino acid metabolism
Glucose ^{11}C	Cerebral glucose metabolism
N-methylspiperone C11	Dopamine receptor binding

Table 2. PET radiopharmaceuticals available without a cyclotron on site [3]

Radiopharmaceuticals	Application
Generator-based tracer agents	
-^{68}Ga agents	
($T_{1/2}$= 68.1 min; parent= ^{68}Ge:$T_{1/2}$= 288d)	
Citrate/transferrin ^{68}Ga	Plasma volume
^{68}Ga-EDTA	BBB + brain tumors
Macroaggregates ^{68}Ga	Lung perfusion
^{68}Ga-DTPA aerosols	Lung ventilation
^{68}Ga-EDTA	Kidney function
-^{82}Rb	
($T_{1/2}$= 26 min; parent= ^{82}Sr: $T_{1/2}$= 25.0 d)	
82Rb^{+}	Myocardial blood flow (K^{+} analogue)
-^{62}Cu	
($T_{1/2}$= 9.73 min; parent= ^{62}Zn: $T_{1/2}$= 9.2 h)	
^{62}Cu-PTSM	Brain + myocardial blood flow studies (chemical microsphere)
18 F agents	
($T_{1/2}$= 110.0 min)	
1. Available from automated system ("black box"or robot)	
Fluoride F 18	Skeletal studies
^{18}F-FDG	Cerebral glucose metabolism Myocardial glucose metabolism Tumor metabolism + response to therapy Differentiation of tumor, recurrence/ radiation necrosis
2. Synthesized by radiochemist or robot	
Fluorodopa F18	Dopa uptake studies
Spiperone ^{18}F	Dopamine receptor studies
N-methylspiperone ^{18}F	Dopamine receptor binding
16, -fluoro-17, -oestradiol F18	Oestrogen receptor binding
Uridine ^{18}F	Determination of cell proliferation and response to therapy

DTPA, Dimethylene triamine penta-acetic acid; EDTA, ethylene diamine tetra-acetic acid; BBB, blood brain barrier; PTSM, pyuvaldehyde bis (N^4-methylthiosemicarbone); FDG, fluorode oxyglucose.

(b) Production of SPECT radiopharmaceuticals

Many γ-ray emitting radionuclides have found applications in diagnostic nuclear medicine using either γ-cameras or in recent years Single Photon Emisson Computed Tomography (SPECT). Table 3 lists some of the commonly used SPECT radiopharmaceuticals and their routine methods of production which could be achieved using medium sized cyclotrons. It should be mentioned that the most commonly used radioisotope in nuclear medicine is ^{99m}Tc ($T_{1/2}$ = 6.0 h) produced using a nuclear reactor. Its widespread use is mainly based on its ideal nuclear properties for medical diagnosis and its convenient availability as a ^{99}Mo/ ^{99m}Tc generator.

Table 3. Routine methods of production of some commonly used photon emitters [2,4]

Radio-isotope	$T_{1/2}$	Mode of decay	Main γ-ray energy in KeV(%)	Production data		
				Nuclear process Ah	Energy range (MeV)	Thick target yield MBq (mCi)/ κ
^{67}Ga	3.26 d	EC (100)	93 (37) 185 (20)	^{68}Zn (p,2n)	26 → 18	185 (5)
^{111}In	2.8 d	EC (100)	173 (91) 247 (94)	^{112}Cd (p,2n)	25 → 18	166 (4.5)
^{123}I	13.2 h	EC (100)	159 (83)	^{123}Te (p,n) ^{124}Te (p,2n) ^{127}I (p,5n)^{123}Xea) ^{124}X (p,x)^{123}Xea)	14.5 → 10 26 → 23 65 → 45 29 → 23	137 (3.7) 392 (10.6) 777 (21)[b)] 414 (11.2)[b)]
^{201}Tl	3.06 d	EC (100)	69-82 (X-ray) 166 (10.2)	^{201}Tl (p,3n)^{201}Pbc)	28 → 20	18 (0.5)[d)]

a)^{123}Xe decays by EC (87%) and β^+ emission (13%) to ^{123}I.
b)This is ^{123}I yield expected from the decay of ^{123}Xe over an optimum time of about 7 h.
c) ^{201}Pb decay by EC (100%) to ^{201}Tl.
d)This is ^{201}Tl yield expected from the decay of ^{201}Pb over an optimum time of 32 h.

In our laboratory at Assiut University we have had since 1986 a collaboration with the Institute of Nnuclear Chemistry, KFA, J lich (Germany) concerning the preparation and characterization of small Tc-complexes for medical applications. More than 10 publications as an outcome of this collaboration have been published in the chemical literature and some of complexes could be of potential use in clinical studies [6]. Many of the accelerator produced γ-ray emitting radionuclides like ^{67}Ga, ^{111}In, ^{123}I and ^{201}Tl are also finding increasingly wide applications e.g. ^{67}Ga-citrate has been found to concentrate in certain viable primary and metastatic tumors as well as focal sites of infection, ^{111}In-oxine is proved for the labeling of leukocytes (white blood cells) which are used for lmaging sites of infection or inflammation and ^{201}Tl as the thallous ion is approved for use as a myocardial perfusion agent for assessing the integrity of the myocardium using stress and rest techinques. $^{210}Tl^+$ accumulates in viable myocardium via the Na-K-ATP ase pump, behaving as a K^+ mimic. Due to the less optimal nuclear properties of ^{201}Tl (73 h, 65-83 Kev X-ray) its replacement by a suitable ^{99m}Tc heart imaging agent is favorable [7,8].

After the installation of a cyclotron in Egypt a wealth of radioisotopes will be available in millicurie qauntities. Their applications in nuclear medicine should be one of the major aims of cyclotron installation in Egypt.We are in need to develop a research programme including a good collaboration between radiochemists, for the preparation of new PET and SPECT radiopharmaceuticals, and biochemists for their biomedical evaluation, and finally physicans for clinical application.

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التطبيقات الطبيّة للسيكلوترونات ، الحاضر والمستقبل في مصر

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(استلم في ١٤١٧/٩/٢٣ هـــ ، وقبل للنشر في ١٤١٨/٦/١١ هـــ)

ملخص البحـــث. يستخدم السيكلوترون في إنتاج النظائر المشعّة منـــذ عـــام ١٩٥٠ م. ومـــن وجهـــة نظـــر الكيميائيون، يعتبر السيكلوترون آلة لتقديم مصدر قذائف مثل البروتون ، الديوترون ،الهليوم-٣ والهليوم-٤ الـــتي بواسطتها يمكن إحداث التفاعل النووي اللازم لإنتاج النواة المشعّة المطلوبة. ونتيجة للتكلفة العاليـــة في اســـتعمال السيكلوترونات في إنتاج النظائر الطبية فإن إنتشارها محدوداً عكس النظائر الأخرى المستخدمة في الطب النـــووي والتي تعتمد في إنتاجها على مولّدات بسيطة التكلفة مثل التكنسيوم-٩٩ . وفي مصر ، بعد تجهيز الســـيكلوترون ، مطلوب جهود مكثفة من الكيميائيين لتطوير برنامج بحثي يختص بإنتاج نظائر طبية جديدة وتطبيقها على المستوى الطبّي والصيدلي.