

MEDICAL RADIOISOTOPES PRODUCTION AT TR-19 CYCLOTRON FROM IFIN-HH

Radu-Anton LEONTE¹, Dana NICULAE², Liviu Ștefan CRĂCIUN³,
Gheorghe CĂTA-DANIL⁴

A new cyclotron and a radiopharmaceutical laboratory for radioisotope production and multi-disciplinary research have recently become operational in IFIN-HH. The variable energy of TR-19 cyclotron meets the optimal range for production of commonly used radioisotopes in PET imaging, as well as some research isotopes. In this paper are presented the modalities to obtain the radioisotopes via cyclotron irradiation, with focus on obtaining ^{99m}Tc and ^{68}Ga . Specific technical aspects and the advantages of the proposed methods are discussed. It is shown that the cyclotron route represents a feasible alternative for production of ^{99m}Tc and ^{68}Ga to the current method of generator, widely considered as a standard.

Keywords: radioisotopes, cyclotron, ^{99m}Tc , ^{68}Ga , ^{18}F , PET

1. Introduction

The constant progress in the radioactivity field, along with the evolution of the nuclear reactions research, led to increased development for production of radioisotopes [1]. The route of obtaining artificial radioisotopes by irradiation of various types of targets at the cyclotrons represents an important modality for producing them. The range of radioisotopes obtained in this way is wide and depends both on the targets characteristics and technical parameters of the cyclotrons. All radioisotopes used in nuclear medicine are artificial isotopes. Worldwide, most of the radioisotopes employed in medical applications are produced at nuclear reactors, but another significant part of them can be obtained only by irradiation at cyclotron or similar particle accelerators [2]. In nuclear medicine the radioactive isotopes are employed both in the diagnosis and treatment of diseases. Due to the short half-life of the radioisotopes used for medical imaging (ranging from minutes to few days), preclinical and clinical studies should take place in the proximity of their production place [3].

¹ PhD student, Faculty of Applied Sciences, University POLITEHNICA of Bucharest, Romania, and Radiopharmaceuticals Research Centre, Horia Hulubei National Institute for R&D in Physics and Nuclear Engineering, Romania, e-mail: radu.leonte@nipne.ro

² Head of department, Radiopharmaceuticals Research Centre, Horia Hulubei National Institute for R&D in Physics and Nuclear Engineering, Romania, e-mail: dana.niculae@nipne.ro

³ Senior Researcher, Radiopharmaceuticals Research Centre, Horia Hulubei National Institute for R&D in Physics and Nuclear Engineering, Romania, e-mail: cliviu@nipne.ro

⁴ Professor, Department of Physics, University POLITEHNICA of Bucharest, Romania, e-mail: cata-danil@physics.pub.ro

A new cyclotron and a laboratory for radioisotope production and multi-disciplinary research are operational in IFIN-HH since 2012, being part of the Radiopharmaceuticals Research Centre. The core of the entire centre is the TR-19 cyclotron (manufactured by Advanced Cyclotron Systems, Inc. - Canada). The mission of this centre is to produce radioisotopes for medical use, as well as other research isotopes. More details on this centre are given in reference [4]. In this paper are presented the modalities to obtain the radioisotopes of medical interest via cyclotron irradiation using this machine, with focus on obtaining ^{99m}Tc and ^{68}Ga . Although widely considered a standard in obtaining these two radioisotopes the current method of radioisotope generator has a couple of drawbacks which can be surpassed by using the cyclotron route. The specific technical aspects and the advantages of the proposed methods are discussed, showing up that TR-19 represents a feasible alternative for routine production of ^{99m}Tc and ^{68}Ga .

2. TR-19 cyclotron

TR-19 is a variable energy, negative ions cyclotron for the production of commonly used PET (Positron Emission Tomography) radioisotopes, as well as other research isotopes. It is a versatile machine, designed to operate in dual beam, by using simultaneous flow of protons into two diametrically opposed extraction ports, to irradiate liquid, solid and gaseous targets. Irradiations can be performed simultaneously on two targets placed in the two irradiation stations. Each irradiation station is independently adjustable on the two extraction ports which can accommodate up to four reaction chambers on one extraction port and two external beam lines on the second extraction port, which can be switched remotely. The cyclotron accelerates negative hydrogen ions (H^-), on a vertically arranged plane. The beam is extracted by inserting the extraction probe at a certain radius to the centre of the trajectory of the accelerated ions, correlated with the needed energy. Stripping the negative ions (H^-) is performed by passing the beam through a very thin pyrolytic carbon foil placed at the extremity of the extraction probe. The stripper foil has the role to separate the electrons from the H^- ions. After stripping, the original negatively charged particle will become positively charged (H^+), consisting only of protons, and the beam will be deflected at 90° . In this way the protons are directed to the extraction ports, then out to the appropriate target. The energy of the extracted proton beam is in the 14-19 MeV range, with a maximum current of $300 \mu\text{A}$. The extraction of multiple beams is accomplished by inserting the extraction probes to different depths, so the first stripper foil only intercept part of the beam, allowing the remainder to continue its acceleration to the next one. Thus, are possible to obtain not only two simultaneous beams, but also beams of different energies and intensities in ratios from 1:100 to 1:1. The ion source of TR-19 is external, this feature providing the

advantage of “zero dose” routine maintenance of ion source and extraction system. On one side the beam is collimated through the target selector mounted on gimbals and moving in both the X and Y directions to accommodate targetry for radioisotope production. On the opposite side it is equipped with a specifically conceived 6 m long external beam line, ending in a separate bunker for research activities. Due to this configuration, the machine can provide beams for routine production of radioisotopes used in PET imaging as well as for radiochemistry and radiopharmacy developments, novel detector testing, radiation biophysics and radioprotection. More technical details on TR-19 cyclotron can be found in ref. [5].

3. Radioisotopes to be produced at TR-19 cyclotron

Being designed to provide accelerated protons with energies from 14 to 19 MeV, TR-19 cyclotron can be utilised for the production of commonly used PET radioisotopes ^{18}F , ^{11}C , ^{13}N , and ^{15}O , as well for other medical radioisotopes, historically produced by other techniques ($^{99\text{m}}\text{Tc}$ and ^{68}Ga). Further on, different reactions induced by TR-19 accelerated protons leading to the radioisotopes of interest are presented. For each radioisotope, relevant experimental values of the production cross-section have been extracted from the nuclear database (Experimental Nuclear Reaction Data – EXFOR, hosted by International Atomic Energy Agency) [6] and discussed in relation with TR-19 characteristics. We have considered only the protons induced reactions, since this is the type of accelerated particle in the existing configuration of TR-19.

Once the radioisotopes have been produced, they start to decay. The production of the radioisotopes and their decay are two simultaneous processes, characterised by different rates. The activity of the irradiated material at a certain moment after starting the bombardment is given by the difference between the generating and decay rates. For a thin target and a monoenergetic beam, the process is governed by the activation law [7]:

$$\Lambda = IN\sigma(1 - e^{-\lambda t}) \quad (1)$$

where:

Λ – is the activity of the radionuclide at time t ;

I – is the flux of the incident beam, measured in number of particles/($\text{cm}^2 \times \text{s}$);

N – is the number of target atoms;

σ – is the cross-section of the nuclear reaction for the radioisotope formation, measured in cm^2 ;

t – is the duration of bombardment, measured in s ;

λ – is the decay constant of the radionuclide, measured in s^{-1} .

Thus, the amount of radioactivity produced during irradiation depends strongly upon the duration of irradiation as number of half-lives of the radioisotope passed from the start of the bombardment (see Fig. 1). The $(1 - e^{-\lambda t})$

term is called the “saturation factor”, which approaches to unit after 6-7 half-lives, where the activity is more than 96% of the saturation value.

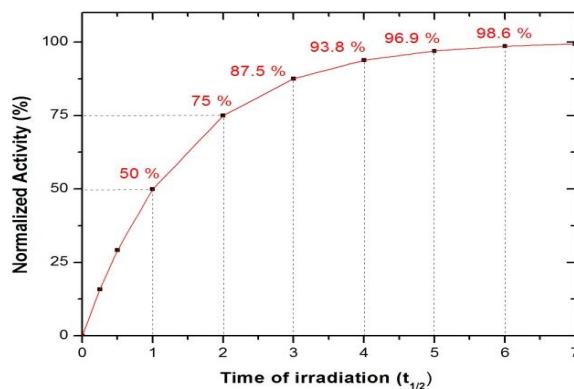


Fig. 1. The activity saturation curve of a cyclotron produced radionuclide; $t_{1/2}$ is the half-life of the radionuclide and normalised activity is the ratio between Λ and the saturation value

From Fig. 1 can be observed that after an irradiation duration equal to one half-life of the radioisotope, 50% of the saturation activity can be produced, and after 3 half-lives the gain in activity is negligible. Along with the duration of bombardment, the possible competitive nuclear reactions increase the content of radionuclidian impurities. Because the radionuclidian impurities are usually difficult to be separated from the main radioisotope, it is desired to keep the impurities content as low as possible. For these reasons, in practice, the bombardment time should be chosen taking into consideration the optimum between the final activity, the radionuclidian purity of the reaction mixture and the cost of irradiation itself, and usually ranges between 0.25 and 5 half-lives of the radioisotope of interest.

3.1. Fluorine-18 (half-life: 109.8 min)

^{18}F is the most used radioisotope in PET imaging [3], having chemical properties suitable for labelling a large number of biological active molecules. Depending on the nature of the biological vector, it is proper to investigate a large number of organs and pathologies. It could be produced by irradiating liquid or gaseous targets, but water target are preferred. The main nuclear reaction for obtaining ^{18}F at TR-19 cyclotron is $^{18}\text{O}(\text{p}, \text{n})^{18}\text{F}$, but it is accompanied by other competitive reactions: $^{16}\text{O}(\text{p}, 2\text{n})^{15}\text{N}$ and $^{17}\text{O}(\text{p}, \text{n})^{17}\text{F}$ which leads to undesired radionuclidian impurity (^{15}N and ^{17}F , respectively). In order to avoid the competitive reactions that involve ^{16}O and ^{17}O , the water used as target should have a high content of ^{18}O . The abundance of ^{18}O in nature is 0.205% [8], thus the necessity of enrichment of the water used as target. Typically ^{18}O enriched water with more than 95% ^{18}O is the minimum required, but usually a higher enrichment grade (98%) is preferred. Nuclear reactions cross-sections are important ingredients in defining the working parameters of radioisotopes production. In

Fig. 2 are presented the dependence of cross-section and saturation yield, as functions of protons energy, based on EXFOR database.

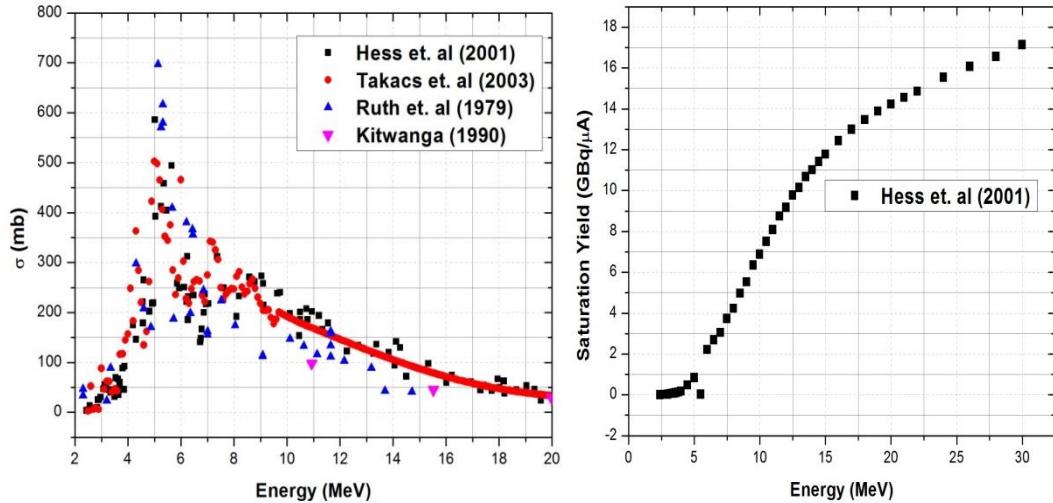


Fig. 2. Experimental excitation functions (left) and saturation yield (right) of $^{18}\text{O}(\text{p}, \text{n})^{18}\text{F}$ nuclear reaction (data are taken from EXFOR database)

Fig. 2 shows that, for an ideal thin target, decreasing the beam energy from 16 to about 5 MeV lead to a factor of 10 increase in cross-section. Thus, although technically difficult, degrading the beam energy seems to provide a high enhancement in the rate production of the radioisotope. In real working conditions, the targets are thick, therefore the beam energy degradation is done by the target itself. The reaction chamber material is an important issue for the radionuclidic impurities content of the radioactive product. Historically, for many years, the most widely used material for the reaction chamber was silver [1] due to its high thermal conductivity. During the bombardment, ^{109}Cd radionuclidic impurities might be generated through $^{109}\text{Ag}(\text{p}, \text{n}\gamma)^{109}\text{Cd}$ reaction. To avoid this, target chamber is made up of platinum passivated silver which eliminates the formation of silver colloids, too. More recently, due to the low level of radionuclidic impurities generated during irradiation, niobium is used with success [1]. Due to the high reactivity of the generated fluorine, high chemical resistance is also required. The vacuum isolation of the reaction chamber is done with Havar alloy foils that are used as separating window between the target body and vacuum chamber. Havar is a cobalt-based alloy that provides very high strength at high temperatures, has excellent corrosion resistance and is non-magnetic. It can withstand the high pressure differentials and also temperatures developed at target bombardment with protons. The drawback of this material is the activation products that are produced in the foils from the primary proton beam and secondary radiations, usually long-lived radionuclides. Some of these

by-products pass in the irradiated water and contaminate the reaction mixture. This leads to the necessity of further using of suitable separation techniques in order to keep the radionuclidic impurities present in the final product under the accepted limits. In order to lower the generated impurities, niobium-sputtered Havar foils are used. Table 1 describes the Havar foil main activated elements and their generated impurities during irradiation [9].

Table 1
Composition of Havar foils and generated impurities at irradiation with protons [9]

Havar foil components (natural isotopic abundances)	Concentration (%)	Reaction channel	Generated impurities	Half-life
Cobalt (Co)	> 41	$^{59}\text{Co}(\text{n}, 2\text{n})^{58}\text{Co}$	^{58}Co	70.85 d
Iron (Fe)	20	$^{56}\text{Fe}(\text{p}, \text{n})^{56}\text{Co}$	^{56}Co	77.24 d
		$^{58}\text{Fe}(\text{p}, \text{n})^{58}\text{Co}$	^{58}Co	70.85 d
		$^{54}\text{Fe}(\text{n}, \alpha)^{51}\text{Cr}$	^{51}Cr	27.70 d
		$^{54}\text{Fe}(\text{n}, \text{p})^{54}\text{Mn}$	^{54}Mn	312.19 d
Chromium (Cr)	>19	$^{52}\text{Cr}(\text{p}, \text{n})^{52}\text{Mn}$	^{52}Mn	5.59 d
		$^{54}\text{Cr}(\text{p}, \text{n})^{54}\text{Mn}$	^{54}Mn	312.19 d
		$^{52}\text{Cr}(\text{n}, 2\text{n})^{51}\text{Cr}$	^{51}Cr	27.70 d
Nickel (Ni)	~13	$^{58}\text{Ni}(\text{p}, \text{d})^{57}\text{Ni}$	^{57}Ni	35.90 h
		$^{60}\text{Ni}(\text{p}, \alpha)^{57}\text{Co}$	^{57}Co	271.80 d
		$^{58}\text{Ni}(\text{p}, 2\text{p})^{57}\text{Co}$	^{57}Co	271.80 d
Tungsten (W)	>2	$^{182}\text{W}(\text{p}, \text{n})^{182}\text{Re}$	^{182}Re	2.66 d
		$^{183}\text{W}(\text{p}, \text{n})^{183}\text{Re}$	^{183}Re	69.40 d
		$^{184}\text{W}(\text{p}, \text{n})^{184}\text{Re}$	^{184}Re	38.20 d
		$^{186}\text{W}(\text{p}, \text{n})^{186}\text{Re}$	^{186}Re	3.72 d
Manganese (Mn)	>1.8	$^{55}\text{Mn}(\text{n}, 2\text{n})^{54}\text{Mn}$	^{54}Mn	312.19 d
Molybdenum (Mo)	0.9	$^{95}\text{Mo}(\text{p}, \text{n})^{95\text{m}}\text{Tc}$	$^{95\text{m}}\text{Tc}$	61.00 d
		$^{96}\text{Mo}(\text{p}, 2\text{n})^{95\text{m}}\text{Tc}$	$^{95\text{m}}\text{Tc}$	61.00 d
		$^{96}\text{Mo}(\text{p}, \text{n})^{96}\text{Tc}$	^{96}Tc	4.28 d

The above table clearly shows that all impurities originating from Havar foil are characterised by half-lives ranging from 2 to more than 300 days, which is to be avoided as long as that means an unintended and long exposure of the surrounding tissue.

3.2. PET radioisotopes of the organogenic elements: ^{11}C , ^{13}N , ^{15}O

Along with ^{18}F , the most used PET radioisotopes are the radioactive isotopes of the organogenic elements, namely: ^{11}C , ^{13}N and ^{15}O , which are short-lived (with half-lives of 20.4 min, 10 min, and 2 min, respectively) and need to be produced in proximity of the nuclear medical unit, usually on-site. The main advantage of these radioisotopes is that the tracers are usually analogues of biological molecules, and thus present a close-to-natural behaviour after administration, providing a good representation of biological processes [10]. The most commonly used method of ^{11}C production is the $^{14}\text{N}(\text{p}, \alpha)^{11}\text{C}$ nuclear reaction, when ^{14}N gas target is bombarded with protons. Depending on the

chemical form intended to be obtained, pure nitrogen gas should be mixed with traces of oxygen (in order to obtain ^{11}CO and $^{11}\text{CO}_2$), or with hydrogen (to obtain ^{11}CN further hydrolysed to $^{11}\text{CH}_4$).

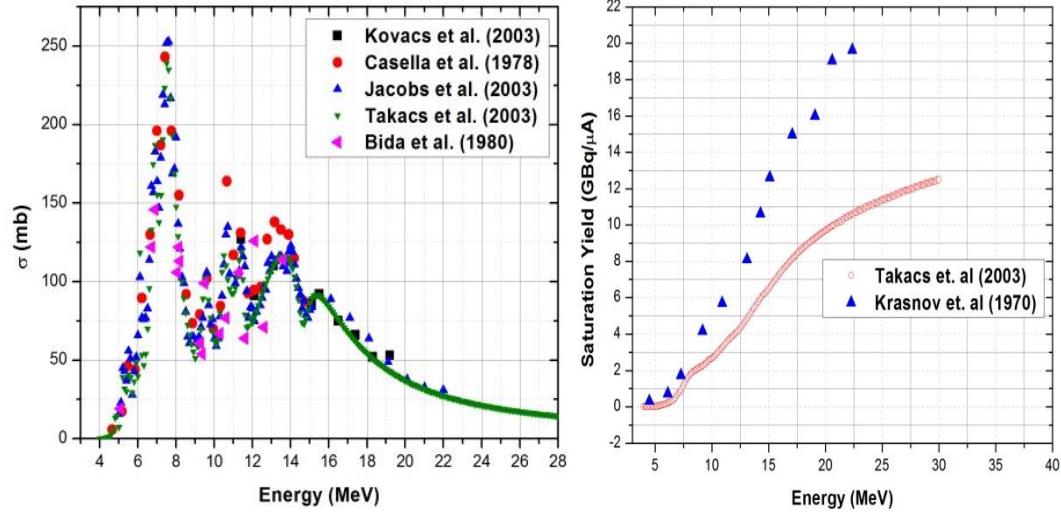


Fig. 3. Experimental excitation function (left) and saturation yield (right) of $^{14}\text{N}(\text{p}, \alpha)^{11}\text{C}$ reaction (data are taken from EXFOR database)

Although solid (Al_4C_3) or gaseous (CH_4) targets can be used to obtain ^{13}N , the most common method uses the liquid target consisting of ultrapure ^{16}O -water which undergoes the $^{16}\text{O}(\text{p}, \alpha)^{13}\text{N}$ nuclear reaction.

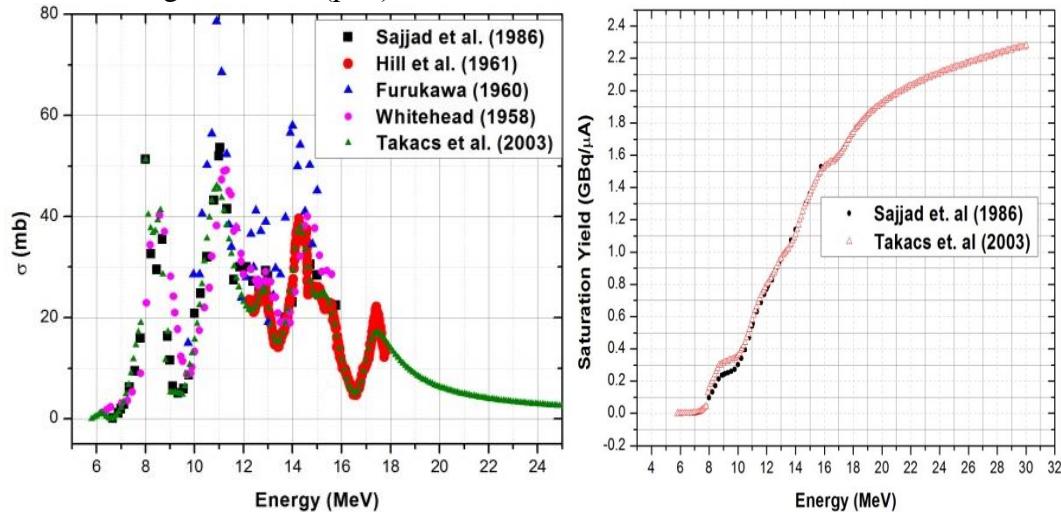


Fig. 4. Experimental excitation function (left) and saturation yield (right) of $^{16}\text{O}(\text{p}, \alpha)^{13}\text{N}$ reaction (data are taken from EXFOR database)

A mixture of nitrates, nitrites, ammonia, and hydroxylamine is obtained. Further on the nitrates and nitrites are separated and then reduced to the desired form of $^{13}\text{NH}_3$.

^{15}O can be obtained by irradiation of gaseous nitrogen through the $^{15}\text{N}(\text{p}, \text{n})^{15}\text{O}$ nuclear reaction.

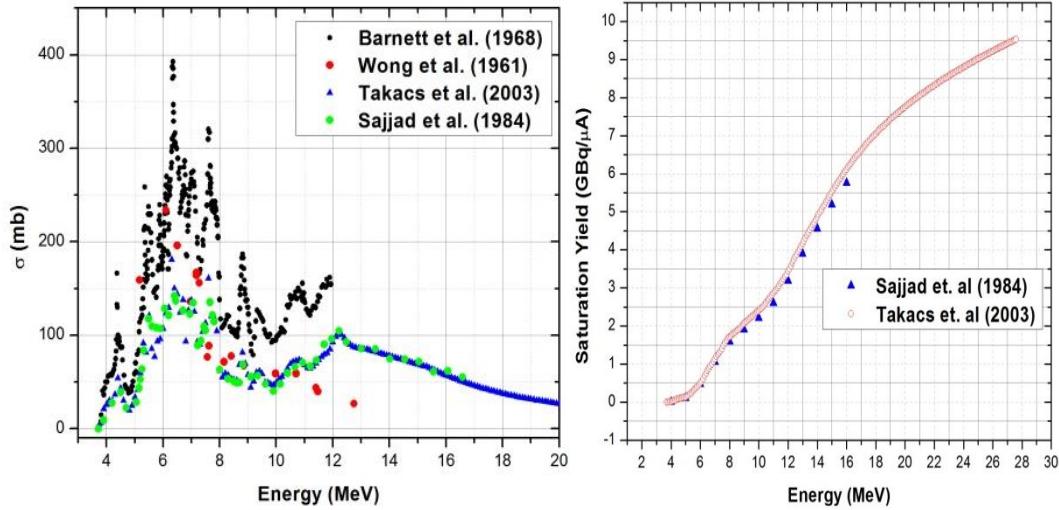


Fig. 5. Experimental excitation function (left) and saturation yield (right) of $^{15}\text{N}(\text{p}, \text{n})^{15}\text{O}$ reaction (data are taken from EXFOR database)

As shown in Figs. 3, 4, and 5, the maximum values of the main nuclear reactions cross-section are in the range of energies inferior to the working range of TR-19. Therefore, for a thin target, in all three cases a smaller energy is suitable for increasing the cross-section. But, again, the real thick targets produce this downshifting in energy.

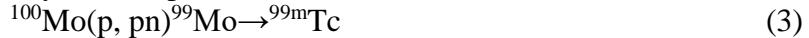
3.3 Technetium-99m (half-life: 6.0 h)

Unlike the other radioisotopes discussed in this paper, $^{99\text{m}}\text{Tc}$ is utilised in SPECT (Single Photon Emission Tomography). According to IAEA statistics, technetium-99m is used in approximately 85% of all nuclear medicine diagnostic imaging procedures worldwide, being overall the most widely used radioisotope in all nuclear medicine procedures today [11]. The classical method of obtaining $^{99\text{m}}\text{Tc}$ for medical use is the $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ generator, but there is a significant disadvantage of this classical method as long as it involves the fission of ^{235}U in nuclear reactors for obtaining the parent radioisotope, ^{99}Mo . As of beginning of 2008, more than 90% of the available ^{99}Mo was produced in only 5 nuclear reactors operating worldwide. A supply crisis of ^{99}Mo started in 2008 due to scheduled and accidental shutdown of these reactors [12]. Therefore, it is vital to find other feasible methods for production of $^{99\text{m}}\text{Tc}$ in sufficient quantities. Cyclotron production through the nuclear reaction $^{100}\text{Mo}(\text{p}, 2\text{n})^{99\text{m}}\text{Tc}$ is an alternative method to the nuclear fission. The natural occurring molybdenum is a mix of seven isotopes, with ^{100}Mo having a 9.74% natural abundance [8].

The main reaction of direct obtaining at cyclotron is:



but it is accompanied by the competitive reactions:



Taking into consideration the fluence of secondary neutrons, the following nuclear reaction also occurs:



For targets made of natural molybdenum, the following nuclear reactions have to be considered:



The final yield of the direct obtaining of $^{99\text{m}}\text{Tc}$ is highly dependent on the isotopic composition of the target, only ^{100}Mo undergoing the nuclear reaction for production of $^{99\text{m}}\text{Tc}$. The other six isotopes of technetium consist in impurities source for the final product of irradiation, therefore using targets highly enriched in ^{100}Mo is required.

The highest cross-section for production of $^{99\text{m}}\text{Tc}$ by the (p, 2n) reaction on ^{100}Mo lies between 12 MeV and 18 MeV, making TR-19 cyclotron very suitable for this purpose. As can be observed from Fig. 6, the peak of the cross-section is ~ 300 mb, corresponding to an energy of ~ 17 MeV. Especially thin targets are very suitable for the energy range of TR-19, as long as they can be irradiated without a significant attenuation effect due to the target thickness. At this energy other long-lived radionuclidian impurities are expected to be found. Their exit reaction channels are listed in Table 2.

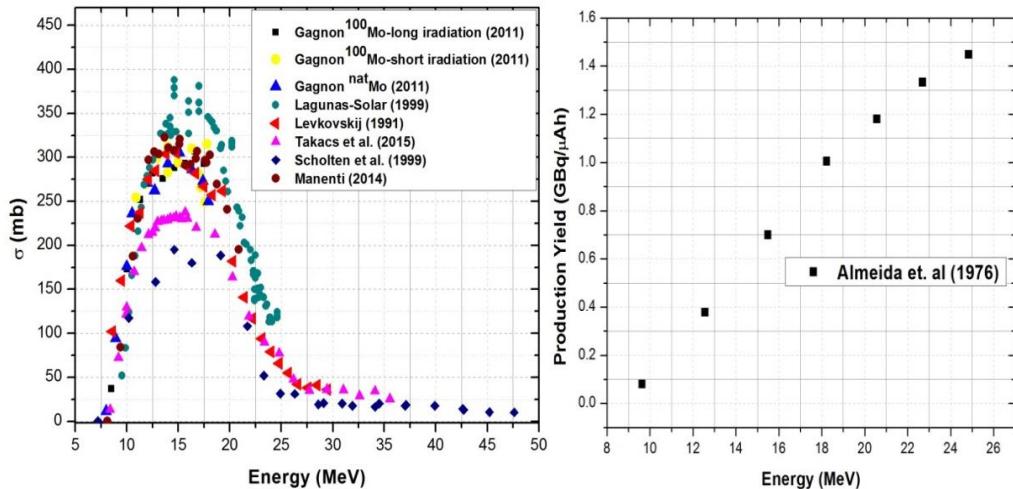


Fig. 6. Experimental excitation function (left) and saturation yield (right) of $^{100}\text{Mo}(\text{p}, 2\text{n})^{99\text{m}}\text{Tc}$ nuclear reaction (data are taken from EXFOR database)

Table 2
The opened reaction channels and the main radioisotopes impurities produced at 17 MeV irradiation energy of nat Mo solid target [13]

Reaction channels	$E_{threshold}$ (MeV)	Generated impurities	Half-life
$^{94}\text{Mo}(\text{p}, 2\text{n})$	13.807	$^{93}\text{Tc} / ^{93m}\text{Tc}$	2.75 h / 43.5 min
$^{94}\text{Mo}(\text{p}, \text{n})$	5.092	$^{94}\text{Tc} / ^{94m}\text{Tc}$	4.88h / 51.9 min
$^{95}\text{Mo}(\text{p}, 2\text{n})$	12.539		
$^{95}\text{Mo}(\text{p}, \text{n})$	2.499	$^{95}\text{Tc} / ^{95m}\text{Tc}$	20 h / 61 d
$^{96}\text{Mo}(\text{p}, 2\text{n})$	11.749		
$^{96}\text{Mo}(\text{p}, \text{n})$	3.795	$^{96}\text{Tc} / ^{96m}\text{Tc}$	4.28 d / 51.5 min
$^{97}\text{Mo}(\text{p}, 2\text{n})$	10.687		
$^{97}\text{Mo}(\text{p}, \text{n})$	1.114	$^{97}\text{Tc} / ^{97m}\text{Tc}$	2.6×10^6 y / 91 d
$^{98}\text{Mo}(\text{p}, 2\text{n})$	9.846		
$^{100}\text{Mo}(\text{p}, \text{d})$	6.126	^{99}Mo	2.7 d
$^{94}\text{Mo}(\text{p}, ^3\text{He})$	9.707	$^{92}\text{Nb} / ^{92m}\text{Nb}$	16 y / 10 d
$^{96}\text{Mo}(\text{p}, 2\text{p})$	9.395		
$^{97}\text{Mo}(\text{p}, ^3\text{He})$	8.488	$^{95}\text{Nb} / ^{95m}\text{Nb}$	3.6 d / 86.6 h
$^{97}\text{Mo}(\text{p}, 2\text{p})$	9.322		
$^{98}\text{Mo}(\text{p}, ^3\text{He})$	10.255	^{96}Nb	23.35 h
$^{100}\text{Mo}(\text{p}, \text{an})$	3.826		
$^{97}\text{Mo}(\text{p}, 2\text{p})$	9.896	$^{97}\text{Nb} / ^{97m}\text{Nb}$	72 min / 52.7 s

The targets for ^{99m}Tc production consist of molybdenum deposited on a copper support. Molybdenum can be in the form of powder pressed at high pressure on the copper support, or as a layer deposited on a copper plate. Powder-type targets are manufactured by pressing ^{100}Mo powder (purity higher than 99%) in the supporting copper disks. The layer should remain thin enough (220-250 μm), in order to allow the interaction with the proton beam in the entire volume of the target. The copper (oxygen free, purity 99.997%) is preferred as support material due to its high thermal conductivity requested to quickly dissipate the heat generated during irradiation. The temperature of the target must be maintained below the volatilization temperature of MoO_3 or of any Tc oxides that may be generated during irradiation. This is done by water cooling of the copper support.

3.4 Gallium-68 (half-life: 67.8 min)

The classical way to produce ^{68}Ga is the $^{68}\text{Ge}/^{68}\text{Ga}$ generator [14]. Compared to other methods for production of radioisotopes (namely reactors and accelerators), the generators require less space and have less demands in terms of radioactive safety and implied resources (both materials and humans). However, there are a couple of drawbacks of the generator method, such as limited life time of about 6 to 8 months, a continuously decreasing activity and a very limited number of patients (2 to 4, depending of the available activity of the generator) which can be investigated daily with ^{68}Ga -labelled compounds, due to the short half-life. The limited activity and the short half-life make the $^{68}\text{Ge}/^{68}\text{Ga}$ generators

usable only “on-site”. The cyclotron method of obtaining ^{68}Ga surpasses these drawbacks and offers the possibility to investigate daily as many patients as is permitted by the nuclear imaging facility, with much higher specific activity and without a decrease of the available activity during the year. Moreover, the higher specific activity available at cyclotrons brings the possibility to serve multiple medical centres.

The main nuclear reaction is:



and it is accompanied by the following competitive ones:



According to existing data, in order to take full benefit of the related excitation function and to minimize undesired radionuclide impurities formation, the incident proton energy should be in the range of 8-14 MeV [15]. From the experimental data of $^{68}\text{Zn}(\text{p}, \text{n})^{68}\text{Ga}$ reaction cross-section measurements, illustrated in Fig. 7, can be observed that at 11 MeV, the cross-section reaches a maximum value of ~ 850 mb. Because the TR-19 cyclotron uses variable extraction energy between 14 MeV and 19 MeV, the energy to be chosen in TR-19 case is 14 MeV.

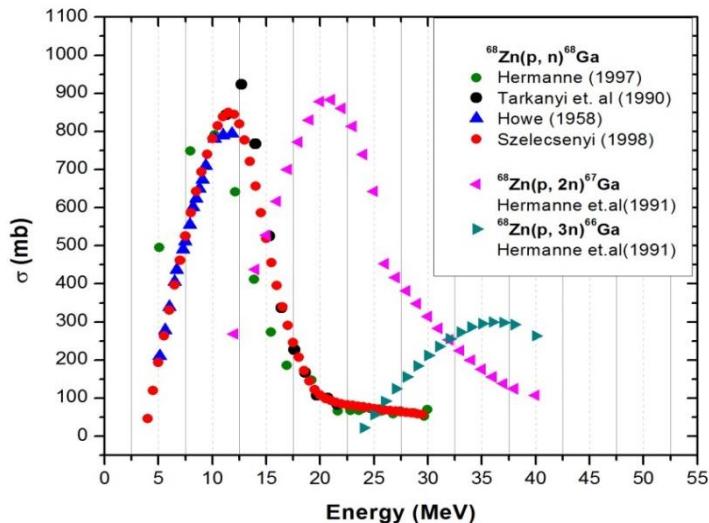


Fig. 7. Experimental excitation functions of $^{68}\text{Zn}(\text{p}, \text{n})^{68}\text{Ga}$, $^{68}\text{Zn}(\text{p}, 2\text{n})^{67}\text{Ga}$ and $^{68}\text{Zn}(\text{p}, 3\text{n})^{66}\text{Ga}$ reactions (data are taken from EXFOR database)

From Fig. 7 can be observed that at this energy, we expect to find ^{67}Ga ($t_{1/2} = 3.2$ d), obtained by the competing nuclear reaction $^{68}\text{Zn}(\text{p}, 2\text{n})^{67}\text{Ga}$. The irradiation energies higher than 14 MeV would increase the amount of ^{67}Ga with respect to the desired ^{68}Ga radioisotope. The ^{68}Ga cross-section decreases at energies higher than 14 MeV, while ^{67}Ga cross-section increases, reaching its

maximum at \sim 21 MeV. ^{66}Ga production exceeds the TR-19 available irradiation energy window, therefore its production will not be taken into consideration. Other metallic impurities which are isotopic stable, such as ^{68}Zn and ^{65}Cu , can be separated during purification steps. Again, beam energy degradation appears to be highly beneficial in terms of main reaction rate. A value of 11 MeV, practically doubles the cross-section compared to 14 MeV. In the same time, the cross-section of the competitive reaction would decrease three times, providing a lower content of ^{67}Ga in the final product. The thick real targets are effective in this energy downshift. Because the production yield is dependent on the isotope abundance of the target nuclide, over 97% ^{68}Zn enriched target materials will be used. In case of solid targets the metallic ^{68}Zn is electroplated onto copper substrate. The theoretical yield according to literature is about 5.73 GBq/ μAh and 5.69 GBq/ μAh for an ideal target thickness of 41 μm [15].

Regarding the target type used for obtaining ^{68}Ga at cyclotron via the $^{68}\text{Zn}(\text{p},\text{n})^{68}\text{Ga}$ nuclear reaction, there are two approaches. Both of them require specific target preparation and separation after irradiation. First approach uses a solid target, consisting in enriched ^{68}Zn (97% purity) electrodeposited on Cu support [16]. The second approach uses the liquid target, isotopically enriched (>99%) 1.7M solution of $\text{Zn}(\text{NO}_3)_2$ in 0.2M HNO_3 [17]. For a beam energy of 14-15 MeV, the solid type target allowed a production yield \sim 25 times higher in terms of activity/irradiation current than the case of the liquid target. Following the near future technical developments, the appropriate method will be implemented at TR-19.

4. Conclusions

The most commonly used PET radioisotopes (^{18}F and the organogenic ones: ^{11}C , ^{13}N and ^{15}O) can be successfully produced at TR-19 cyclotron which presents proper characteristics for this purpose. In the case of ^{18}F , ^{11}C , ^{13}N , ^{15}O and ^{68}Ga , the experimental excitation functions indicate that higher cross-sections could be achieved by degrading the energy of the proton beam. However, due to the thickness of the targets involved in radioisotopes production, the incident beam energy is downshifted, reaching the peak values of the excitation function inside the target material. In the energy working range of TR-19 cyclotron, the diagrams of the saturation yields show an increasing yield when the energy of the bombarding protons is increasing. Considering all those aspects, the energy range of TR-19 is suitable for the radioisotopes discussed in this work.

Direct obtaining at TR-19 cyclotron of the most used radioisotope in the nuclear medicine, namely $^{99\text{m}}\text{Tc}$, is a feasible alternative route and represents a solution to the current shortage of ^{99}Mo [18]. Obtaining of ^{68}Ga at cyclotron is possible, and also a degradation of the energy can increase the desired nuclear

cross-section, overall yield and improve the radionuclidic purity by lowering the content of ^{67}Ga .

Along with the classical PET radioisotopes the cyclotron route represents a feasible alternative for production of $^{99\text{m}}\text{Tc}$ and ^{68}Ga to the current method of generator, widely considered as a standard. It brings in the same time the advantage of larger activity available, independent of the parent isotope regeneration time. That helps to increase the number of patients investigated daily.

In order to optimize the production of a specific radionuclide, the following aspects must be taken into account: the threshold energy for the desired nuclear reaction, the energy where the maximum yield occurs, the competitive reactions and their threshold energies, the chemical and the physical form of the target, the material of the reaction chamber and the ease of separation of desired radioisotope from the target.

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R E F E R E N C E S

- [1]. IAEA, Cyclotron Produced Radionuclides: Physical Characteristics and Production Methods, International Atomic Energy Agency, Vienna, 2009
- [2]. IAEA, Cyclotron Produced Radionuclides: Principles and Practice, International Atomic Energy Agency, Vienna, 2009
- [3]. European Commission, Preliminary Report on Supply of Radioisotopes for Medical Use and Current Developments in Nuclear Medicine, Luxembourg, 2009, http://ec.europa.eu/euratom/docs/2009_radioisotopes_report_en.pdf
- [4]. I. Ursu, L. Crăciun, D. Niculae, N.V. Zamfir - The Radiopharmaceuticals Research Center (CCR) of IFIN-HH at Start, Rom. Journ. Phys., **vol. 58**, nos. 9–10, July 2013, pp. 1327–1336
- [5]. <http://www.advancedcyclotron.com/cyclotron-solutions/tr19>
- [6]. <https://www-nds.iaea.org/exfor/exfor.htm>
- [7]. Gopal B. Saha, Physics and Radiobiology of Nuclear Medicine, fourth edition, Springer, New York, 2013
- [8]. <http://www.ciaaw.org/isotopic-abundances.htm>
- [9]. D. Ferguson, P. Orr, J. Gillanders, G. Corrigan, C. Marshall, Measurement of long lived radioactive impurities retained in the disposable cassettes on the Tracerlab MX system during the production of $[^{18}\text{F}]$ FDG, Applied Radiation and Isotopes, **vol. 69**, no. 10, October 2011, pp. 1479–1485
- [10]. Gopal B. Saha, Basics of PET Imaging, second edition, Springer, New York, 2010
- [11]. IAEA, Non-HEU Production Technologies for Molybdenum-99 and Technetium-99m, International Atomic Energy Agency, Vienna 2013

- [12]. <http://www.euronuclear.org/1-information/news/medical-isotope-crisis.htm>
- [13]. *Ondřej Lebeda, Erik J. van Lier, Jan Štursa, Jan Ráliš, Alexander Zyuzin*, Assessment of radionuclidic impurities in cyclotron produced ^{99m}Tc , Nuclear Medicine and Biology, **vol. 39**, no. 8, 2012, pp. 1286–1291
- [14]. *Irina Velikyan*, ^{68}Ga -Based Radiopharmaceuticals: Production and Application Relationship, in Molecules, **vol. 20**, no. 7, July 2015, pp. 12913–12943
- [15]. *Mahdi Sadeghi, Tayeb Kakavand, Leila Mokhtari, Zohreh Gholamzadeh*, Determination of ^{68}Ga production parameters by different reactions using ALICE and TALYS codes, Pramana Journal of Physics, **vol. 72**, no. 2, February 2009, pp. 335–341
- [16]. *Mahdi Sadeghi, Tayeb Kakavand, Saeed Rajabifar, Leila Mokhtari, Ali Rahimi-Nezhad*, Cyclotron production of ^{68}Ga via proton-induced reaction on ^{68}Zn target, Nukleonika, **vol. 54**, no. 1, 2009, pp. 25–28
- [17]. *Mukesh K Pandey, John F Byrne, Huailei Jiang, Alan B Packard, Timothy R DeGrado*, Cyclotron production of ^{68}Ga via the $^{68}\text{Zn}(\text{p}, \text{n})^{68}\text{Ga}$ reaction in aqueous solution, Am J Nucl Med Mol Imaging, **vol. 4**, no. 4, June 2014, pp. 303–310
- [18]. <https://www.oecd-nea.org/med-radio/reports/Med-Radio-99Mo-Prod-Tech.pdf>