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Computation Study of Radioisotopes Gallium-68 (^{68}Ga) Production using Long-lived & High Activity methods

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Abstract: *Radioisotopes used for gamma-ray-based diagnostics have the main problem that imaging resolution quality. Gallium-68 is a positron (β$^+$) emitting radioisotope that has better imaging resolution than gamma-based radioisotopes. Gallium-68 (^{68}Ga) can be produced by irradiating natural gallium or zinc-68 enriched as a target with protons in an accelerator facility. Indonesia has planned to build a cyclotron type accelerator that operates in 13 MeV proton energy and 50 µA proton beam who has initials named DECY-13. Before it was commissioned for radioisotopes production purpose that was must conduct a preliminary study to determine ^{68}Ga optimum irradiation time and properties, one of which was the monte carlo computation method using PHITS v3.24 software. Simulations were begun by irradiating proton with natural gallium target for 25 days with 2 days cooling and zinc-68 enriched for 120 minutes with cooling 10 minutes. The results at EOB of the long-lived process using the ^{nat}Ga target obtained total radioactivity of 189.42 MBq (5.12 mCi).The total radioactivity result of high activity process which used ^{68}Zn enriched as target was 268.6 GBq (7.259 Ci). the radioactivity was compared with another accelerator, that the long-lived process was too small and uneconomical to done, but the high activity process was feasible to produce. The results of this research expected will be considered as a feasibility study for the 68Ga production process in Indonesia in the future.*

INTRODUCTION

Gallium-68 was the radioisotope that was first reported successfully made in 1937 by Bothe and Gentner by irradiating gallium. (1). Since discovered, much research has been focused on the application of 68Ga, the first published medical application of ^{68}Ga was in the early 1960s to trace tumors in the brain (2). Since then, many applications of gallium-68 have been developed for various diseases.

Table 1. various application of Gallium-68

Ligand	Diagnostic Application
^{68}Ga-PSMA (3)	Prostate Cancer
^{68}Ga -ABY-025 (4)	Metastatic Breast Cancer
^{68}Ga -NOTA-MSA (5)	Atherosclerosis
^{68}Ga -NOTA-PRGD2 (6)	Lung Cancer
^{68}Ga -NOTA-AE105 (7)	Invasive Cancer Phenotype

Until now, Indonesia still relies on imports to fulfill the ^{68}Ga radioisotope demand. To reduce imports, BATAN build a cyclotron type accelerator with initial name DECY-13 (Development of Experimental Cyclotron in Yogyakarta-13 MeV) which was used to produce radioisotopes ^{18}F but able to produced ^{68}Ga. The decy-13 can accelerate protons to an energy of 13 MeV with 50 µA proton beam (8). To prepare the production process when the accelerator has been commissioned, it was necessary to conduct a preliminary study for the process. The computational simulation of the production process using the Monte Carlo method was one way that can be used for this study.

Galium-68 was a positron/ β+ emitting radioisotope which has 2 commonly used methods for its production. First, the long-live process that uses the target gallium in its natural

or enriched form. The second was a high activity process that used zinc-68 enriched as a target.
Long-live radioisotope ^{68}Ga stored at equipment called generator ^{68}Ge/^{68}Ga that has nuclear reaction mechanism :

$$p + {}^{69}Ga \longrightarrow 2n + {}^{68}Ge \xrightarrow{Electron\ Capture} {}^{68}Ga$$

From the reaction above, it can be seen that germanium-68 was an intermediate product that has a half-life of 271 days or is more familiarly called the parent radioisotope. ^{68}Ge as a parent radioisotope will decay to ^{68}Ga as a daughter radioisotope which has a half-life faster than the parent of 67.72 minutes. this makes it suitable to make as generators for long-term use (9). The disadvantage of this method that was the radioactivity obtained was small (10).

The production of ^{68}Ga that was used Zinc-68 enriched as a target can obtain high radioactivity which was can generate smoother imagine on diagnostic purpose. (11), but the extraction from another radionuclides impurity hard to be done (12). The reaction mechanism was :

$$p + {}^{68}Zn \longrightarrow {}^{68}Ge + n$$

Table 2. production facility of gallium-68 in world

Accelerator location	Targets	Proton Energy (MeV)	Product Activity (GBq)	Ref
iThemba Laboratories, South Africa	Gallium metals in Nb	36	16.6	(13)
Los Alamos National Laboratory, USA	Gallium in Nb	60	70	(14)
Institute of Nuclear Physics, Kazakhstan	Gallium metals in Nb	30	12.4	(15)

Galium-68 (^{68}Ga) was used for the imaging process using the application of an annihilation reaction between a positron and an electron which produces 2 photons forming an angle of 180° ± 0.25° (opposite) with both photons energies of 511 keV which is read by a Positron emission tomography (PET) (16). The positron emitted by gallium-68 has a characteristic energy of1077.35 keV (3%), 1883.09 keV (0.138%), 805.75 keV (0.084%) and 1260.97 keV (0.083%) (17). Gallium-68 radioisotope solution obtained from generator ^{68}Ge/^{68}Ga nor direct activation from ^{68}Zn which has the final chemical form as [^{68}Ga]$GaCl_{3(aq)}$. [^{68}Ga]$GaCl_3$ solution has a chemical property such as : colorless, pH on a range of 1 – 2,3 and found Fe(III) and Zn(II) as impurities (9).

Monte Carlo was a probabilistic-based simulation method by randomly distributing the generated number in an area. Because the bombardment process between proton particles and the target on the accelerator is probabilistic/opportunity, the Monte Carlo simulation was able to use, one of which was used the PHITS program (18). PHITS (Particle and Heavy Ion Transport code System) was a general purpose Monte Carlo particle transport simulation code developed under collaboration between JAEA, RIST, KEK and several other institutes that can be downloaded as freeware after registration accepted, the latest PHITS version was 3.24 (19). The output of PHITS simulation was statistical information on the probability of proton and target interactions. it was will be processed with the DCHAIN program algorithm already installed in PHITS which will produce output in the form of radioactivity from gallium-68 (20).

EXPERIMENTAL SECTION

Target Materials

Natural gallium metal was used as irradiation target material that was produced long-lived radioisotopes. It's density value is 5.91 gr/cm^3 at solid state with orthorhombic crystalline structure (21). It's chemical composition can see in table 3 below.

Table 3. gallium composition and isotopes abundance

Materials	Content	Reff
Gallium (^{nat}Ga)	99,9980%	(22)
Isotopes abundance :		
Gallium-69 (^{69}Ga)	60,1%	(23)
Gallium-71 (^{71}Ga)	39,9%	(23)
Trace Elements :		
Zinc (^{nat}Zn)	0,0001%	(22)
Lead (^{nat}Pb)	0,0001%	(22)
Aluminium (^{nat}Al)	0,0012%	(22)
Copper (^{nat}Cu)	0,0001%	(22)
Vanadium (^{nat}V)	0,0005%	(22)

Gallium metal was put into the target chamber which has a diameter of ϕ = 2 cm. The target was covered with Niobium foil with 5 grams mass of gallium used (15)(24).

For short-lived high activity radioisotope, enriched Zinc-68 was used which has a density of 7,133 gr/cm^3 with hexagonal crystalline structure (25). Its chemical composition can see in table below:

Table 4. Zinc isotopes abundance

Materials	Content	Reff
Zinc-68 (^{68}Zn)	99,26%	(26)
Zinc-64 (^{64}Zn)	0,01%	(26)
Zinc-66 (^{66}Zn)	0,1%	(26)
Zinc-67 (^{67}Zn)	0,61%	(26)
Zinc-70 (^{70}Zn)	0,02%	(26)

The target put in target chamber with 300 mg mass(11). The foil as a cover using materials such as havar, aluminum, niobium and titanium with a thickness between 25 to 50 µm (24).

Irradiation

The initial energy of the proton was 13 MeV, its will be reduced after interacted with 2 foil of niobium thick 30 µm and 5 mm of helium as a cooling medium before meets the target. The actual energies can be determined using formula (1) and (2).

$$E_{Final} = E_{Initial} - (E_{1st\ Foil\ out} + E_{Helium\ out} + E_{2nd\ Foil\ out}) \quad (1)$$

$$E_{out} = E_{in} - \left[\left(\frac{dE}{\rho.dx}\right)\ x\ \rho\ x\ d\right] \quad (2)$$

where: $E = Proton\ Energy\ (MeV)$

$\left(\frac{dE}{\rho.dx}\right) = proton\ stoping\ power\ (MeV.cm^2.g^{-1})$

$\rho = Material\ density\ (g.cm^{-3})$

$d = Thickness\ (cm)$

The real thickness of the target was chosen after calculating the maximum range of protons after hits the target. For safety reasons, the minimum thickness of the target must be slightly longer than the maximum range of protons, so that proton can't through the chamber. The maximum range is calculated by the formula (3) and then compared with the initial target thickness.

$$t = \frac{M}{\rho.\pi\ .r^2} \quad (3)$$

where: $t = Target\ thickness(cm)$

$M = Material\ mass\ (grams)$

$\rho = Material\ density\ (g.cm^{-3})$

$r = Radius\ (cm)$

The long of irradiation time begins by following the reference, which is 10-20 days for the long-lived process and 120 minutes for the high-activity process. for the long-lived process, a cooling time after irradiation will be added which was 2 days and for high radioactivity was 10 minutes cooling time that was to remove the short-lived radioisotope that was formed. Simulation of the irradiation process will use the PHITS program which will produce a file in the form of collision statistics between the target and the proton. Then the file is processed with the DCHAIN algorithm which is already included in PHITS to calculate the activity of the product and the decayed results radioisotopes.

RESULTS AND DISCUSSION

The result of this research was presented into four categories, namely Irradiation Energy, Irradiation Process, Irradiation Result and Comparation with experiment.

Irradiation Energy

Stopping power has been simulated using SRIM program from 10 KeV into 100 MeV proton energy. The result can be seen in figure below :

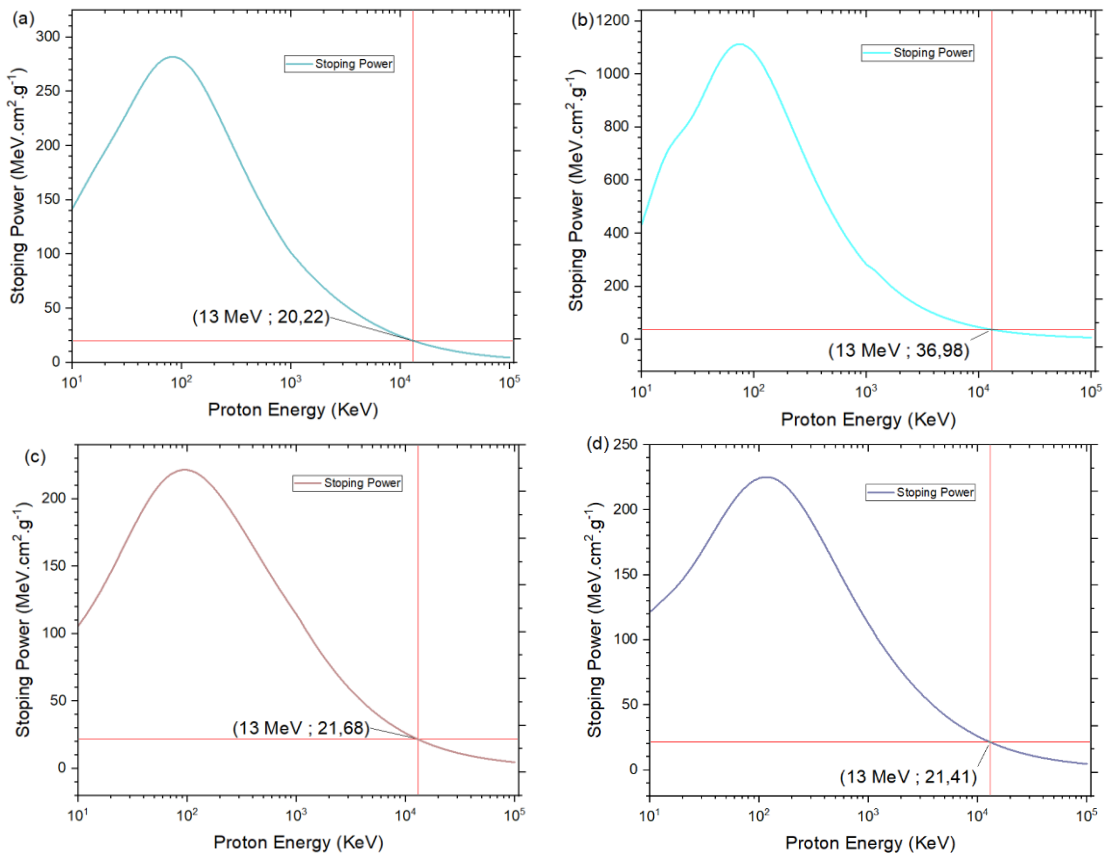

Figure 1. Stopping power of 10 KeV to 100 MeV proton on : (a) Niobium, (b) Helium, (c) Natural Gallium, (d) Zinc-68 enriched

The proton degradation energy and proton maximum through-thickness were calculated using proton stopping value above that was used to determining actual proton energy and target thickness.

Table 5. Real Proton energy after interaction with target chamber parts

Materials	Stopping power (MeV.cm^{-2}.g^{-1})	Density (g.cm^{-3})	Thick (cm)	Proton Energy (MeV)	
				in	out
1st Niobium Foil	20.22	8.57	2.50x10^{-3}	13	12.57
Helium	36.98	1.66x 10^{-4}	0.5	12.57	12.56
2nd Niobium Foil	20.22	8.57	2.50x10^{-3}	12.56	12.13

Actual proton energy that hitting the target after being reduced by interaction with part of targets chamber was 12.13 MeV. the long-lived process was recommended to increase the irradiation time for maximized the radioactivity result. Meanwhile, the target actual thickness, the following results are obtained:

Table 6. Thick validation of targets material

Materials	Proton Energy (MeV)	Stopping power (MeV.cm^{-2}.g^{-1})	Density (g.cm^{-3})	Max thickness (cm)	Initial Thick (cm)
Naturals gallium	12.13	21.68	5.91	0.094674	0.269
Zinc-68	12.13	21.41	7.13	0.079431	0.013

The natural gallium thickness was thicker than the proton maximum through-thickness which was in the safety range for the irradiation process, But the zinc-68 thick was shorter and didn't on the safety range. Due to the price of Zinc-68 enriched being too expensive (27) and there were manufacturers who accept custom sizes (28), the diameter of the target was reduced from 10 mm to 4 mm which resulting in 0.084 cm as a new thickness that was thicker than the maximum proton through-thickness. its diameter reduction must also be accompanied by a reduction in the proton beam diameter which must be focused with a quadrupole magnet (29). This thickness value will also be validated when performing the simulation which is discussed in the next subchapter.

Irradiation Process

the first simulation was started using the number of particles (N) 1000 and number of iteration (X) 100 which resulted in the distribution of the relative error as follows:

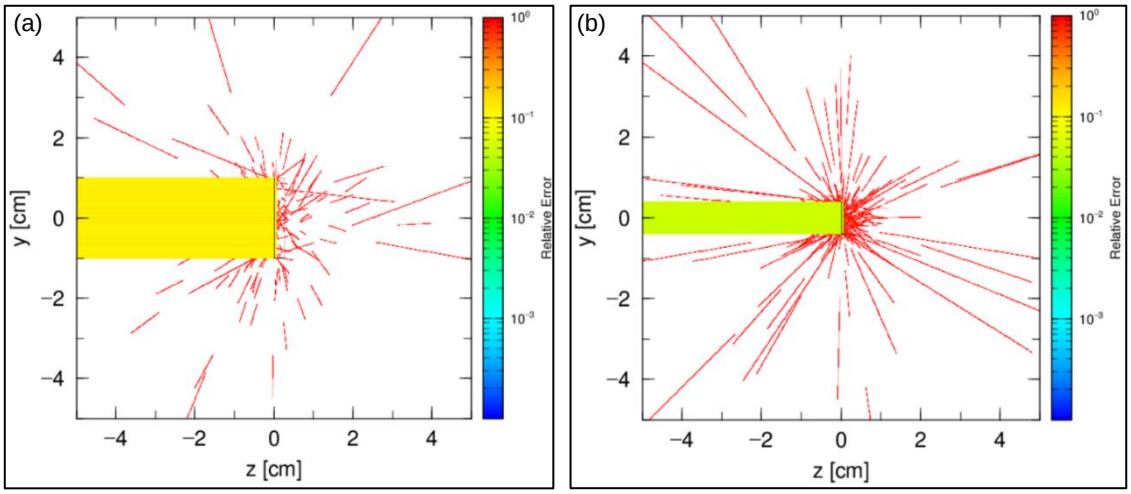

Figure 2. Relative error map in YZ axis for : (a) long-lived process, (b) High Activity process

The relative error was confident to be accepted if lower than 5% (30) however, the simulation result was bigger. Thus, the next simulation must be using a larger number of particles (N) and a number of iteration (X). the result of simulation that used some increased N and X showed in figure 3.

The continuation simulation has been found satisfactory results. increasing the particle number and iteration will significantly reduce the relative error. However, lots of iterations used will make the simulation time longer and computational cost expensive (31). Increasing iterations from 1000 to 10000 cause a high increase in time-consuming and an insignificant decrease in error (31), therefore the use of an iteration value of 1000 was considered very good for this simulation.

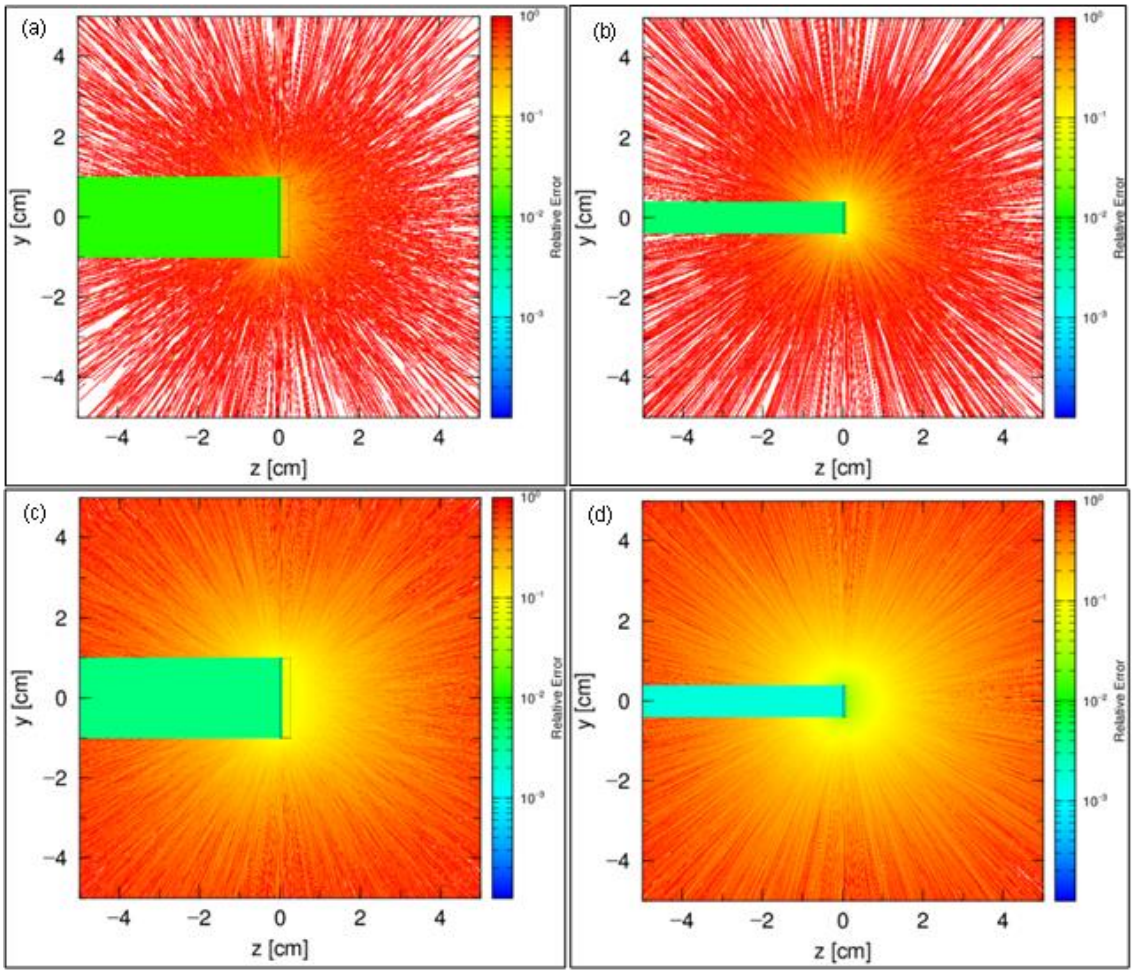

Figure 3. Relative error map in YZ axis with number = 10000 & iteration = 1000 for : (a) long lived process, (b) High Activity process ; and number = 30000 & iteration = 3000 for : (c) long lived process, (d) High Activity process

Irradiation Result

The simulation for the long-lived process was used 25 days irradiation with 2 days cooling. The result of the simulation showed in figure 4, 5, and 6.

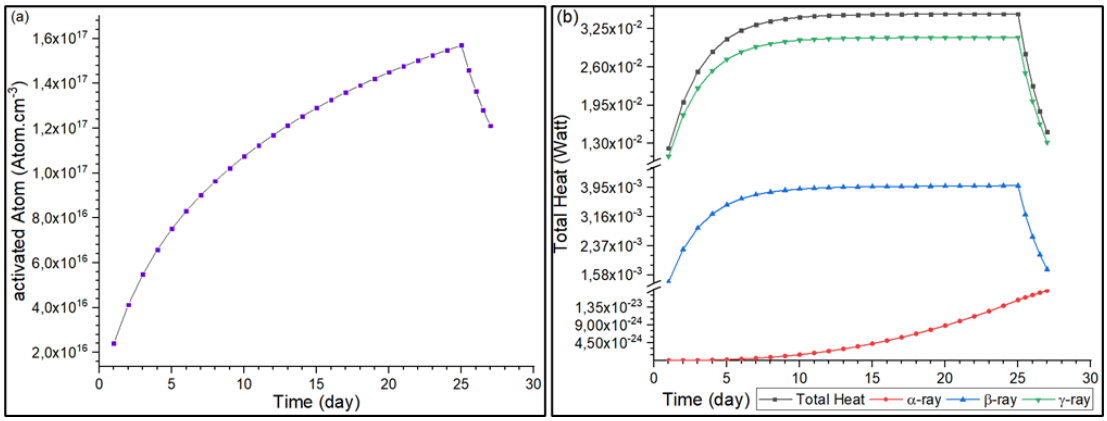

Figure 4. graph of long-lived process for (a) Activated atom and (b) Heat produced

On the 25th irradiation day or usually named end of bombardment (EOB) that found total activated atoms was $1.57x10^{17}$ atoms.cm^{-3} ($\pm 2.46x10^{15}$). the process conducted heat amount $3.50x10^{-2}$ Watt (Joule.s^{-1}) that obtained from alpha-ray decay was $1.53x10^{-23}$ W, beta-ray decay was $4.00x10^{-3}$ W and gamma-ray decay was $3.10x10^{-2}$ W. The heat conducted will be cooled by the cooling water fluid at the back of the target chamber. The radioactivity obtained during the process was shown in the figure below:

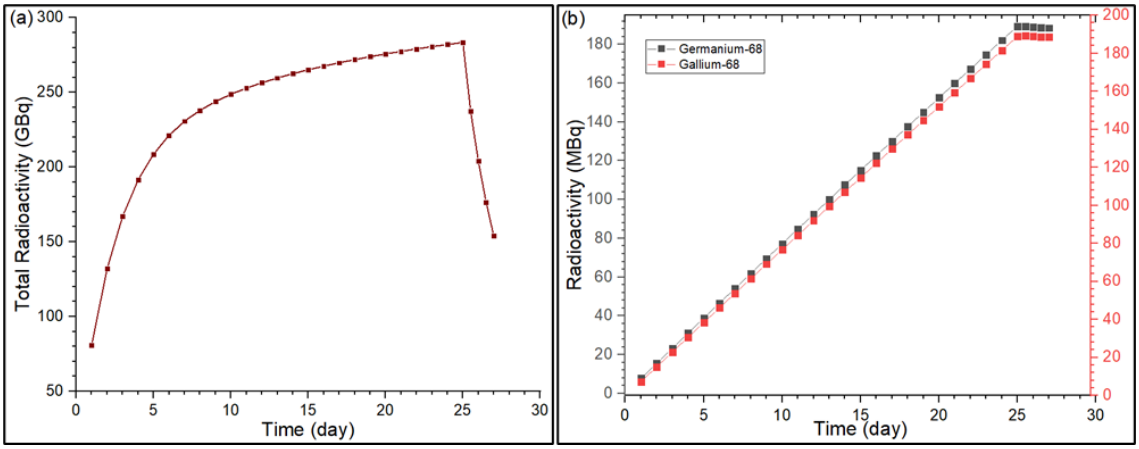

Figure 5. graph of long-lived process for (a) Total Radioactivity; and (b) ^{68}Ge/^{68}Ga Radioactivity

Total highest Radioactivity obtained at EOB was 283.36 GBq and reduced 46% after 2 days cooling into 153.91 GBq, It proves that many short-lived radioisotopes have decayed such as ^{69}Ge and ^{67}Ga that was safe for the next production steps (9). The activity on the 10th day shown in figure 5(a) has been sloping, this was because the target was near its saturation point. if the saturation time of irradiation has been exceeded, increasing the irradiation time will not increase the target radioactivity. However, in figure 5(b) the activity of germanium-68 increased continuously, that was because the saturation time of the activation reaction usually occurs up to 8 times the half-life (32) which needs to validate its exact value with experimental data. the half-life of germanium-68 was 271 which causes it not saturated on 25 days irradiation. The length of irradiation time must be adjusted to the desired radioactivity and the irradiation cost of the accelerator used. Meanwhile, for 25 days of irradiation, was obtained germanium-68 with a radioactivity of 189.42 MBq/5.12 mCi. For activity data obtained at intervals of 1–60 days, it can be seen in the graph below:

Table 7. Radioactivity of ^{68}Ge/^{68}Ga (mCi) from long-lived process in several times

Day	0	10	20	30	40	50
1	0.211	2.293	4.322	6.300	8.226	10.104
2	0.422	2.499	4.522	6.495	8.416	10.289
3	0.632	2.703	4.722	6.689	8.606	10.474
4	0.841	2.908	4.921	6.883	8.795	10.658
5	1.050	3.111	5.119	7.076	8.983	10.842
6	1.259	3.314	5.317	7.269	9.171	11.025
7	1.467	3.517	5.515	7.462	9.359	11.208
8	1.674	3.719	5.712	7.654	9.546	11.390
9	1.881	3.921	5.908	7.845	9.732	11.572
10	2.088	4.122	6.104	8.036	9.919	11.753

gamma-ray emission during the irradiation process was presented at figure 6 :

The gamma-ray dose-rate that in photon form was emitted 230.22 mSv.m^2.h^{-1} at EOB and reduced 58% into 97.59 mSv.m^2.h^{-1} At end of cooling. The total flux of gamma-ray obtained $1.55x10^{11}$ source.s^{-1} has $4.10x10^{10}$ source.s^{-1} with energy 511 keV which was identic characteristic with photon from positron and electron annihilation reaction.

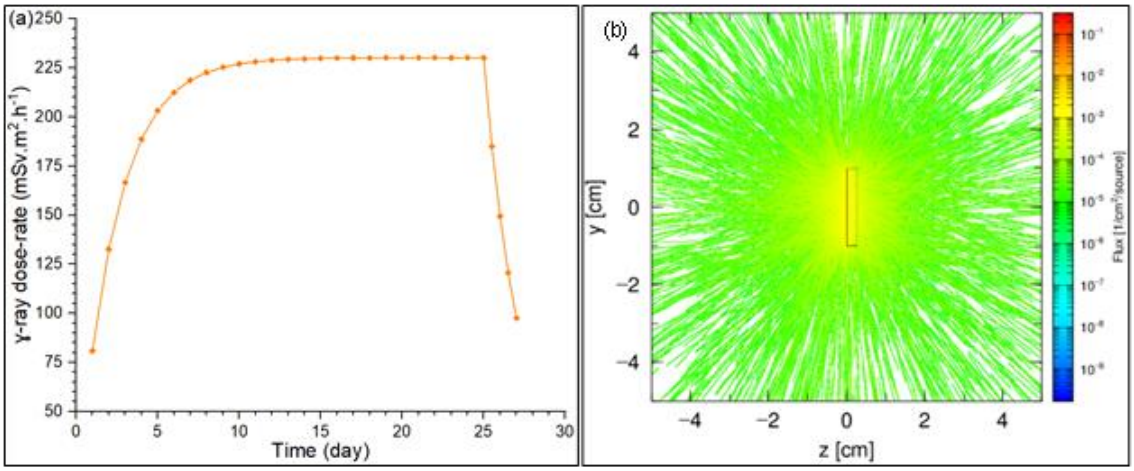

Figure 6. graph of long-lived process for (a) ɣ-ray dose-rate; and (b) photon distribution map in YZ

During the long-lived process found a total of 149 isotopes of the product containing 95 stable isotopes and 54 radioisotopes. Top 5 result of stable isotopes and radioisotope after 2 day cooling can seen in table 8 below :

Table 8. Top 5 stable isotope product from long-lived process (arranged by atom concentration)

Stable Isotopes	Concentration [atoms/cc]
Gallium-69	3.07×10^{22}
Gallium-71	2.04×10^{22}
Aluminium-27	6.13×10^{17}
Vanadium-51	2.55×10^{17}
Germanium-71	1.22×10^{17}

Table 9. Top 5 radioisotope product from long-lived process (arranged by radioactivity)

Radioisotopes	Radioactivity [atoms/cc]	Concentration [atoms/cc]
Germanium-69	1.75×10^{16}	8.63×10^{10}
Germanium-71	9.59×10^{16}	6.73×10^{10}
Gallium-68	1.10×10^{12}	1.88×10^{8}
Germanium-68	6.36×10^{15}	1.88×10^{8}
Gallium-72	2.92×10^{11}	3.98×10^{6}

The high activity process was irradiated 120 minute long with 10 minute cooling time that was obtained result shown in figure 7, 8, and 9.

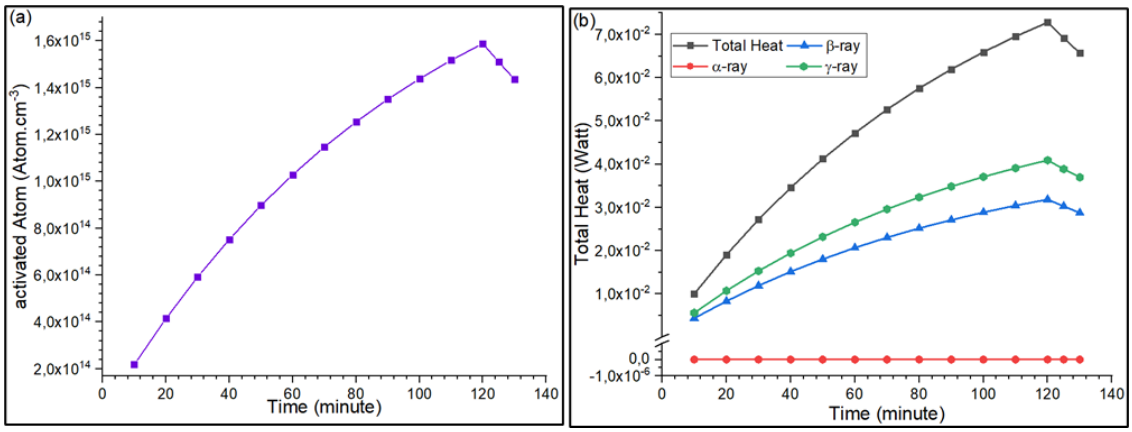

Figure 7. graph of high activity process for (a) Activated atom and (b) Heat produced

Amount of 1.59×10^{15} atoms.cm^{-3} ($\pm 1.44 \times 10^{13}$) was activated by irradiation for 120 minutes. The total heat conducted was 7.28×10^{-2} Watt (Joule.s^{-1}) with contribution from beta-ray decay was 3.19×10^{-2} W and gamma-ray decay was 4.09×10^{-2} W the alpha-ray decay does not occur during the irradiation process so it doesn't contribute to the heat conducted. The radioactivity generated during the irradiation process of producing a dose that was shown in the figure 8 below:

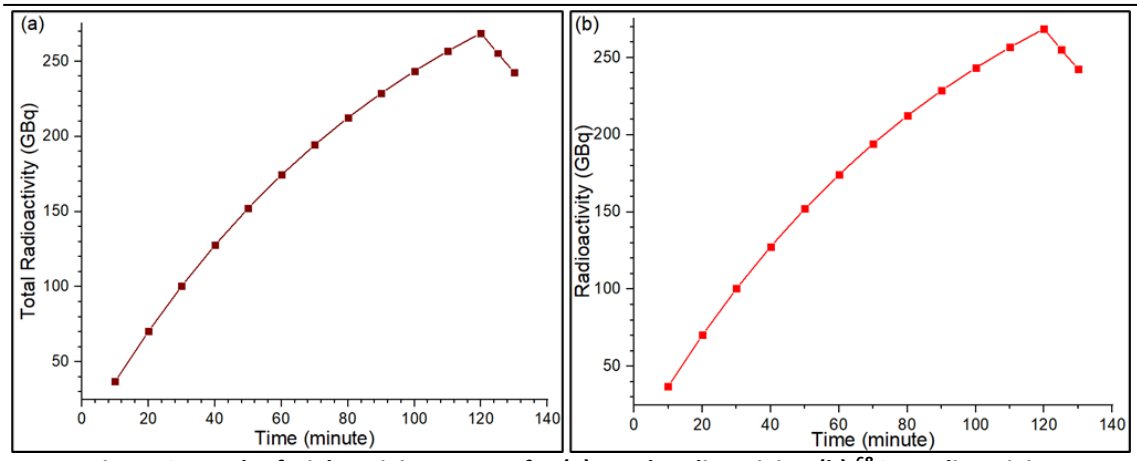

Figure 8. graph of High activity process for (a) Total Radioactivity; (b) ^{68}Ga Radioactivity

Radioactivity of gallium-68 at EOB was 268.6 GBq (7.259 Ci) from 268.72 GBq (7.263 Ci) total radioactivity earned or 99.96%. it was reduced to 242.5 GBq (6.553 Ci) after 10 minutes of cooling.

The production ^{68}Ga process from irradiation of ^{68}Zn resulted high radionuclide purity with 1.5-2 time of half life irradiation times (33). Activity data obtained at intervals of 10 – 240 minutes of irradiation can be seen in the graph below:

Table 10. Radioactivity of ^{68}Ga (mCi) from high activity process in several times

Time [Minute]	Activity [Ci]	Time [Minute]	Activity [Ci]
10	0.999	130	7.552
20	1.900	140	7.816
30	2.714	150	8.054
40	3.449	160	8.269
50	4.112	170	8.463
60	4.711	180	8.639
70	5.251	190	8.797
80	5.739	200	8.939
90	6.179	210	9.069
100	6.577	220	9.185
110	6.935	230	9.290
120	7.259	240	9.385

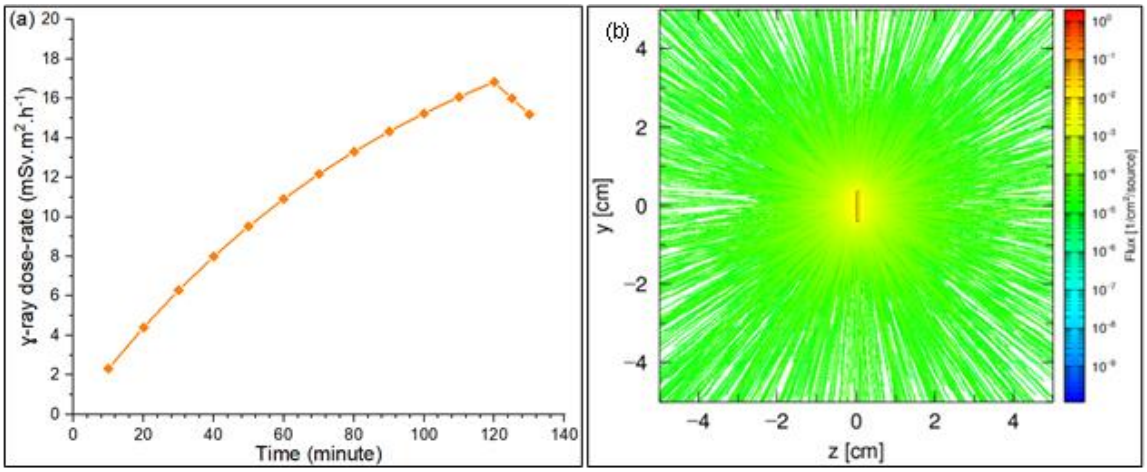

Figure 9. graph of high activity process for (a) ɣ-ray dose-rate; and (b) photon distribution map in YZ

On minute 120th was obtained total ɣ-ray dose-rate was 16.8 $mSv.m^2.h^{-1}$ with contribution from ^{68}Ga 16.8 $mSv.m^2.h^{-1}$ (99.64%). After cooling total dose reduced to 15.2 $mSv.m^2.h^{-1}$. at EOC total gamma-ray flux $4.41x10^{11}$ $source.s^{-1}$ contain $4.39x10^{11}$ $source.s^{-1}$ flux from annihilation reaction or 98,15%.

At end of cooling High activity process was founded 69 isotopes, top 5 from 30 stable isotopes and 39 radioisotopes were presented in table 7 & 8 below:

Table 11. Top 5 stable isotopes product from high activity process (arranged by atom concentration)

Stable Isotopes	Concentration [atoms/cc]
Zinc-68	$5.20x10^{22}$
Zinc-67	$3.20x10^{20}$
Zinc-66	$5.24x10^{19}$
Zinc-70	$1.05x10^{19}$
Zinc-64	$5.24x10^{18}$

Table 12. Top 5 radioisotopes product from high activity process (arranged by radioactivity)

Radioisotopes	Radioactivity [atoms/cc]	Concentration [atoms/cc]
Germanium-68	$2.42x10^{11}$	$1.42x10^{15}$
Germanium-70	$4.41x10^{7}$	$8.07x10^{10}$
Germanium-67	$3.23x10^{7}$	$1.31x10^{13}$
Germanium-66	$2.10x10^{7}$	$1.03x10^{12}$
Zinc-69	$5.14x10^{6}$	$2.50x10^{10}$

Comparation with other experiment

The yield of long-lived process and high activity process obtained at EOB were compared with other available yield data from another accelerator site that showed in table 13 and 14.

Table 13. Comparison activity and yield of long-lived process with another accelerator site

Accelerator location	Energy (MeV)	Time (hour)	Beam (μA)	EOB activity (GBq)	Yield (Ci/A.hour)
iThemba Laboratories, South Africa (13)	2-34	-	65	-	15.1
Los Alamos National Laboratory, USA (14)	60	492	125	70	32
Institut de Physique Nucléaire Orsay, France (34)	20	45	-	-	9.2
Current simulation	13	600	50	0.189	0.171

Table 14. Comparison activity and yield of high activity process with another accelerator site

Accelerator location	Energy (MeV)	Time (Minute)	Beam (μA)	EOB activity (GBq)	Yield (mBq/A.h)
University Hospital "S.Orsola – Malpighi", Italy (35)	16.5	32	46	3.5	142.66
Department of Radiology, Mayo Clinic, USA (36)	14	30	20	1.93	192.50
Department of Oncology, University of Alberta, Canada (37)	12.5	73	30	37.5	1027.40
Current simulation	13	120	50	268.6	2686.00

After comparing the results obtained with another accelerators, it can be concluded that the activity and yield of long-lived process predictions for DECY-13 was too small and uneconomical to done, that was because the proton energy and proton beam used were not as large as other accelerators. However, for the high activity process, the activity and yield obtained were similar with other sites, which causes the high activity process to be feasible to be produced using DECY-13.

CONCLUSION

From the research simulations, the DECY-13 cyclotron can be used for the production of the radioisotope gallium-68 which will be very useful for nuclear medicine and molecular imaging. Long-lived process was produced 0.189

GBq, but it was too low and not economic. 2 hours irradiation with 10 minutes cooling time on Hight activity process was produced 269 GBq radioactivity and it was possible to done. However, it's radioactivity was radioactivity at End of bombardment (EOB) that was reduced after purification which usually used resin column. Future works need to be researched in actual condition using this paper as a reference to find out deviations from the actual situation.

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