Production and quality control of ^{66}Ga radionuclide

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Abstract The purpose of this study was to develop the required targetry and radiochemical methods for production of ^{66}Ga, according to its increasing applications in various fields of science. The ^{66}Zn(p,n)^{66}Ga reaction was selected as the best choice for the production of ^{66}Ga. The targets were bombarded with 15 MeV protons from cyclotron (IBA-Cyclone 30) at the Nuclear Research Center for Agriculture and Medicine (NRCAM) with a current of 180 μA for 67 min. ALICE and SRIM (Stopping and Range of Ions in Matter) nuclear codes were used to predict the optimum energy and target thickness. Targets were prepared by electroplating 95.73% enriched ^{66}Zn on a copper backing. Chemical processing was performed by a no-carrier-added method consisting of ion exchange chromatography and liquid-liquid extraction. Anion exchange chromatography was also used for the recovery of target material. Quality control of the product was carried out in two steps of chemical and radionuclide purity control. The activity of ^{66}Ga was 82.12 GBq at EOB and the production yield was 410.6 MBq/μAh. The radiochemical separation yield was 93% and the yield of chemical recovery of the target material was 97%. Quality control tests showed a radionuclide purity higher than 97% and the amounts of chemical impurities were in accordance with the United States Pharmacopoeiae levels.

Key words gallium-66 • cyclotron • radiochemical separation • target recovery

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Introduction

The two gallium radionuclides ^{67}Ga and ^{68}Ga are widely used in nuclear medicine. Gallium (administered mostly as gallium citrate) is a tumor seeking isotope for soft tissue tumors as well as bone seeking and dynamic studies.

Gallium-67 ($T_{1/2}$ = 78 h) emits gamma radiation with energies between 90 and 400 keV and is well suited for gamma camera scintigraphy. The reactions of protons and deuterons on zinc are the most suitable reactions leading to ^{67}Ga [47, 50, 53].

Gallium-68 is derived from the germanium radionuclide ^{68}Ge produced in the reaction ^{69}Ga(p,2n)^{68}Ge $\xrightarrow{\text{EC(100\%),271d}}$ ^{68}Ga $\xrightarrow{\beta^+(90\%),\text{EC}(10\%),1.14h}$ ^{68}Zn and is known as radionuclide generator ^{68}Ge → ^{68}Ga. Gallium-68 decays principally by positron emission and is used in conjunction with positron emission tomography (PET) scanners for imaging various organs and their physiological functions. This is an economical source of ^{68}Ga in hospitals not equipped with a cyclotron [50]. However, the short half-life of ^{68}Ga limits its use. The 1.14 h physical half-life of ^{68}Ga is too short for studying some slow dynamic processes by PET, requiring several hours.

The demand for long-lived positron emitting radionuclides has been increasing during the recent

years. In this regard, another gallium radionuclide, [66]Ga, with a half-life of 9.4 h seems to be a potentially useful label. However, physical characteristics of [66]Ga are far from an ideal radionuclide for PET imaging (β^+: 90–100%, low energy of positrons, no gamma rays). Gallium-66 decays in 56.5% by positron emission, the remainder by electron capture (EC). Energies of emitted positrons (expressed in MeV) have six components: 4.153 (51.2%), 1.84 (0.54%), 1.4 (0.1%), 0.935 (3.03%), 0.747 (0.97%) and 0.367 (0.82%). In addition to the annihilation photons, there are 61 photons associated with [66]Ga decay ranging from 0.291 to 4.806 MeV. Among them are five gamma lines with intensities higher than 3.5%: 0.834 (6.03%), 1.039 (37.9%), 2.190 (5.71%), 2.752 (23.2%), 4.296 (3.5%) and eight lines with intensities higher than 1% [5, 10, 41, 43, 45, 48, 58, 60]. The high energy of positrons and their long range (21 mm in water) result in lowering of spatial resolution and multi-line gamma rays tend to cause more coincidence events in detecting system of PET scanner. The above mentioned facts reduce the attractiveness of [66]Ga for use in imaging only, but strongly increase it when [66]Ga is used for radiotherapy [15]. The potential advantage of [66]Ga application is the possibility of PET imaging during therapy.

[66]Ga^{3+} and [68]Ga^{3+}, have been examined for PET imaging studies [7, 11, 14, 16, 25, 30, 36, 44, 57]. [66]Ga has been tested for the study of some slow dynamic processes (such as lymphatic transport) by PET [13, 33] and for radioimmunotherapy by attaching it to monoclonal antibodies [60] in the detection and staging of tumors and other lesions after dosimetric studies using its high energy positrons [12, 15, 26]. The use of [66]Ga-labeled somatostatin analogue as an imaging agent for somatostatin receptor positive tumors has also been reported [54]. [66]Ga has been examined for the radio-labeling of blood cells [9] and albumin colloids [40] for various diagnostic purposes. It has been reported for successful folate receptor targeting both *in vitro* and *in vivo* for clinical diagnostic imaging [27, 28, 37]. Gallium-66 can also be used as a gamma multi-line standard source for high energy calibration of Ge detectors [1, 17, 35, 38].

The significance of the positron emitting [66]Ga is increasing in research studies. The aim of this study was production of [66]Ga for the use in different fields of science. We hereby report the production and radiochemical processing of this radionuclide.

Experimental

Materials

High purity chemicals were purchased from Aldrich (Milwaukee, WI, USA) and Merck (Darmstadt, Germany) chemical companies. [66]Zn used as the target material (purity: 95.73%) was prepared at the Ion Beam Applications department of NRCAM. Irradiations were carried out with the focused external proton beam of the NRCAM cyclotron (IBA-Cyclone 30) of Atomic Energy Organization of Iran. Collimators in the beam tube limited the exposure area to a 1 cm diameter circle.

Chemical purity was controlled by differential-pulsed anodic stripping polarography using a Metrohm polarograph (model Polarecord) with an automatic controller E608. A gamma-ray spectrometer, consisting of a high purity germanium (HPGe) detector (model GC1020-7500SL) a PC-based 4096 channel analyzer (Canberra™ MCA) and associated electronics, was used for radionuclide purity control and activity measurement. All calculations and counting were based on the 1039.3 keV characteristic peak for [66]Ga.

Methods

Selection of the best nuclear reaction and particle energy

Various nuclear reactions can be used for the production of [66]Ga. It may be conveniently produced at a medium sized cyclotron by proton or deuteron bombardment of zinc isotopes or alpha bombardment of copper [13, 24, 47, 50–52].

In this study, reactions were actually limited to the [66]Zn(p,n)[66]Ga, [67]Zn(p,2n)[66]Ga and [68]Zn(p,3n)[66]Ga reactions, since high energy and high intensity deuteron or alpha beams are not available in the country yet, and our cyclotron can accelerate protons in the energy range of 15 to 30 MeV with a maximum current of 200 microamperes. Among the above mentioned reactions, the [66]Zn(p,n)[66]Ga reaction was selected owing to its high thick target yield and high purity [49].

The excitation function for the [66]Zn(p,n)[66]Ga reaction was calculated in this study, using the nuclear code ALICE-91 [3] for proton energy range from 3 to 30 MeV. These calculations were compared with collected experimental data (Fig. 1). A total of eleven published cross section data sets in the energy region considered were found in the literature [2, 18, 20–22, 29, 32, 34, 49, 50, 52].

As it can be seen in Fig. 1, model calculations predict correctly the place of maximum and the shape of excitation function but overestimate the values of cross sections. The experimental data indicate that the maximum cross section of $\sim$ 650 mb occurs at $Ep(\sigma_{max})$ $\sim$ 12 MeV.

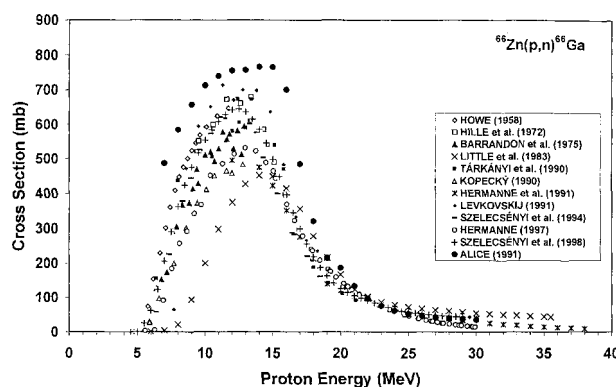The information concerning formation of undesired radionuclides (Ga, Zn and Cu) during 30 MeV proton

Fig. 1. Excitation function of the [66]Zn(p,n)[66]Ga reaction predicted by nuclear reaction model calculation (ALICE), compared with the available experimental data.

Table 1. Nuclear reaction Q-values, thresholds and products of the 30 MeV proton induced reactions on ^{64,66,67,68,70}Zn isotopes in the enriched ^{66}Zn

Zinc isotopes and their abundance in the enriched target [%]	Reactions	Q-value [MeV]	Threshold [MeV]	Half-life	Decay mode [%]
^{64}Zn (1.2%)	^{64}Zn(p,2n)^{63}Ga	−18.16406	18.45041	31.4 s	β$^+$(98.9), EC(1.1)
	^{64}Zn(p,n)^{64}Ga	−7.94722	8.07251	2.62 min	β$^+$(97.6), EC(2.4)
	^{64}Zn(p,γ)^{65}Ga	3.94238	0.00000	15 min	β$^+$(89.1), EC(10.9)
	^{64}Zn(p,nα)^{60}Cu	−10.86568	11.03697	23 min	β$^+$(88.0), EC(12)
	^{64}Zn(p,α)^{61}Cu	0.84410	0.00000	3.33 h	β$^+$(61.4), EC(38.6)
	^{64}Zn(p,pt)^{61}Cu	−18.96991	19.26897	3.33 h	β$^+$(61.4), EC(38.6)
	^{64}Zn(p,n^{3}He)^{61}Cu	−19.73368	20.04478	3.33 h	β$^+$(61.4), EC(38.6)
	^{64}Zn(p,pd)^{62}Cu	−16.34087	16.59847	9.74 min	β$^+$(97.2), EC(2.8)
	^{64}Zn(p,2pn)^{62}Cu	−18.56546	18.85814	9.74 min	β$^+$(97.2), EC(2.8)
	^{64}Zn(p,^{3}He)^{62}Cu	−10.84734	11.01834	9.74 min	β$^+$(97.2), EC(2.8)
	^{64}Zn(p,2p)^{63}Cu	−	−	stable	−
	^{64}Zn(p,t)^{62}Zn	−12.49311	12.69006	9.13 h	β$^+$(8.3), EC(91.7)
	^{64}Zn(p,nd)^{62}Zn	−18.75041	19.04600	9.13 h	β$^+$(8.3), EC(91.7)
	^{64}Zn(p,2np)^{62}Zn	−20.97500	21.30566	9.13 h	β$^+$(8.3), EC(91.7)
	^{64}Zn(p,d)^{63}Zn	−9.63707	9.78900	38.1 min	β$^+$(92.8), EC(7.2)
	^{64}Zn(p,np)^{63}Zn	−11.86166	12.04866	38.1 min	β$^+$(92.8), EC(7.2)
^{66}Zn (95.73%)	^{66}Zn(p,2n)^{65}Ga	−15.09719	15.32798	15 min	β$^+$(89.1), EC(10.9)
	^{66}Zn(p,n)^{66}Ga	−5.95740	6.04847	9.49 h	β$^+$(54.7), EC(45.3)
	^{66}Zn(p,γ)^{67}Ga	5.26939	0.00000	3.26 d	EC(100)
	^{66}Zn(p,nα)^{62}Cu	−9.30912	9.45143	9.74 min	β$^+$(97.2), EC(2.8)
	^{66}Zn(p,α)^{63}Cu	−	−	stable	−
	^{66}Zn(p,t)^{64}Zn	−	−	stable	−
	^{66}Zn(p,d)^{65}Zn	−8.83535	8.97041	244.26 d	β$^+$(1.4), EC(98.6)
	^{66}Zn(p,pn)^{65}Zn	−11.05994	11.22901	244.26 d	β$^+$(1.4), EC(98.6)
^{67}Zn (2.17%)	^{67}Zn(p,2n)^{66}Ga	−13.00964	13.20554	9.49 h	β$^+$(54.7), EC(45.3)
	^{67}Zn(p,n)^{67}Ga	−1.78285	1.80970	3.26 d	EC(100)
	^{67}Zn(p,nα)^{63}Cu	−	−	stable	−
	^{67}Zn(p,α)^{64}Cu	2.40771	0.00000	12.7 h	β$^-$(39), β$^+$(17.4), EC(43.6)
	^{67}Zn(p,^{3}He)^{65}Cu	−	−	stable	−
	^{67}Zn(p,2p)^{66}Cu	−8.91188	9.04608	5.1 min	β$^-$(100)
	^{67}Zn(p,t)^{65}Zn	−9.63028	9.77530	244.26 d	β$^+$(1.4), EC(98.6)
	^{67}Zn(p,pn)^{66}Zn	−	−	stable	−
^{68}Zn (0.97%)	^{68}Zn(p,3n)^{66}Ga	−23.20791	23.55225	9.49 h	β$^+$(54.7), EC(45.3)
	^{68}Zn(p,2n)^{67}Ga	−11.98112	12.15889	3.26 d	EC(100)
	^{68}Zn(p,n)^{68}Ga	−3.70348	3.75843	67.6 min	β$^+$(89), EC(11)
	^{68}Zn(p,γ)^{69}Ga	−	−	stable	−
	^{68}Zn(p,nα)^{64}Cu	−7.79056	7.90615	12.7 h	β$^-$(39), β$^+$(17.4), EC(43.6)
	^{68}Zn(p,α)^{65}Cu	−	−	stable	−
	^{68}Zn(p,^{3}He)^{66}Cu	−11.39203	11.56106	5.1 min	β$^-$(100)
	^{68}Zn(p,2p)^{67}Cu	−9.99292	10.14118	61.9 h	β$^-$(100)
	^{68}Zn(p,t)^{66}Zn	−	−	stable	−
^{70}Zn (0.01%)	^{70}Zn(p,3n)^{68}Ga	−19.40165	19.68129	67.6 min	β$^+$(89), EC(11)
	^{70}Zn(p,2n)^{69}Ga	−	−	stable	−
	^{70}Zn(p,n)^{70}Ga	−1.43709	1.45780	21.15 min	EC(100)
	^{70}Zn(p,nα)^{66}Cu	−6.51242	6.60628	5.1 min	β$^-$(100)
	^{70}Zn(p,α)^{67}Cu	2.60481	0.00000	61.9 h	β$^-$(100)
	^{70}Zn(p,2p)^{69}Cu	−11.10857	11.26868	3 min	β$^-$(100)
	^{70}Zn(p,t)^{68}Zn	−	−	stable	−
	^{70}Zn(p,d)^{69}Zn	−6.99130	7.09206	13.8 h	β$^-$(100)

Data extracted from T2-Nuclear Information Service, Los Alamos <http://t2.lanl.gov> and Nuclear Data Evaluation Lab. Korean Atomic Energy Research Institute <http://atom.kaeri.re.kr/ton/>.

bombardment of enriched ^{66}Zn targets are given in Table 1. We implemented ALICE code for calculation of the unknown excitation functions of reactions producing unwanted radionuclides (Fig. 2).

Preliminary information about the activities encountered in the activation of the 95.73% enriched ^{66}Zn sample by protons can be obtained from the analysis of Table 1. It can be concluded from Table 1 and Fig. 2 that the most important impurities are expected to be ^{65}Ga and ^{67}Ga, since they cannot be separated from ^{66}Ga by chemical methods. Therefore, proton energy had to be chosen below the threshold
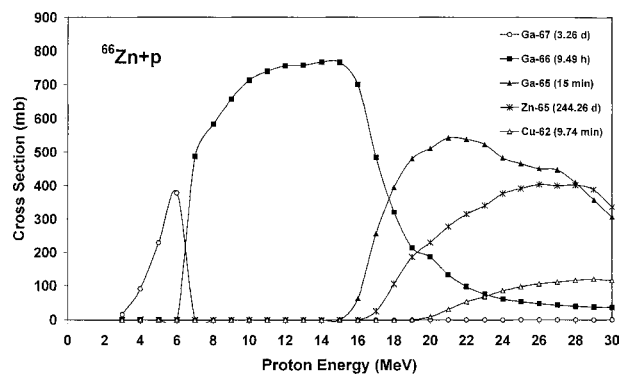
Fig. 2. Theoretical excitation functions for the formation of ^{65,66,67}Ga, ^{65}Zn and ^{62}Cu radionuclides during proton bombardment of ^{66}Zn using computer code ALICE.

energy for ^{66}Zn(p,2n)^{65}Ga reaction (i.e. 15.3 MeV) and above 7 MeV to avoid the ^{66}Zn(p,γn)^{67}Ga reaction. The produced copper and zinc isotopes (^{62,63}Cu, ^{64,65,66}Zn) can easily be separated by chemical processes.

The predominant reactions in the proton energy range of interest are (p,n) and (p,pn); although other reactions (with lower cross sections) with the emission of deuterons (d), tritons (t) and helium-4 (α) are also possible. The proton induced radioactive nuclides from 95.73% enriched ^{66}Zn and its isotopic contaminants (^{64,67,68,70}Zn) appearing in the zinc sample can be ^{66}Ga, but ^{64,65,67,68,70}Ga may also be produced. However, production of the undesired radiogalliums is negligible, due to the very low isotopic abundance of ^{64,67,68,70}Zn in the enriched target material.

^{65}Zn is the only radioactive impurity that can interfere with the target mass (^{66}Zn) in the recovery bulk during the target recovery process. As a result, if proton energy were 15 MeV, there would just be a small amount of ^{65}Zn and ^{65}Ga during the whole process (Fig. 2). Therefore, the incident proton beam energy was selected to be 15 MeV. According to the threshold energy for ^{66}Zn(p,n)^{66}Ga reaction, the beam energy inside the target thickness must be in the range of 15 to 7 MeV, in order to achieve the maximum possible production yield with minimum radionuclide impurity. The lower limit is chosen to minimize the production of ^{67}Ga.

Targetry

The method selected for targetry was electrodeposition of metallic ^{66}Zn on a copper backing plate. The target was fixed on a special shuttle and sent to the solid target room by a rabbit system. The shuttle is designed to place the target at an angle of 6 degrees toward the proton beam in order to achieve higher production yield due to the larger focal area and better heat transfer which enables the application of higher currents for target bombardment. The target was cooled by a flow of 18°C distilled water with a rate of 50 l/min. A schematic diagram of the irradiation chamber is given in Fig. 3.

The target had to be thick enough to reduce the energy of incident protons from 15 MeV to about 7 MeV. SRIM nuclear code (Stopping and Range of Ions in Matter) [59] was used to give the best target thickness
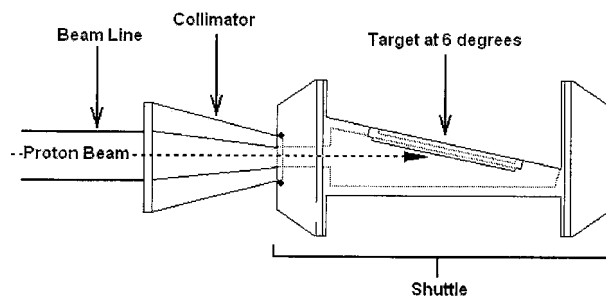

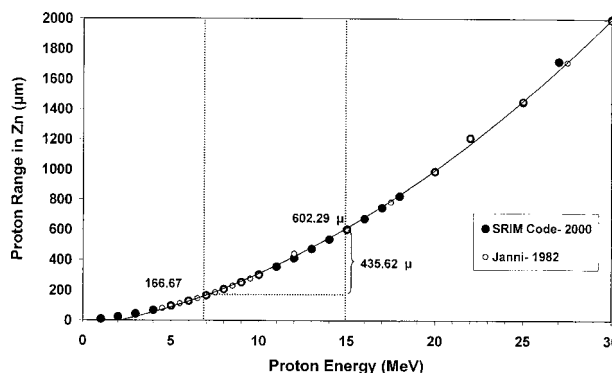**Fig. 3.** Schematic diagram of the irradiation chamber.

Fig. 4. Range-energy diagram for protons penetrating the zinc target using SRIM code and Janni's tables. Estimation of the target thickness is shown for the 15–7 MeV proton energy range.

in the above energy range. The required target thickness was also calculated using tables published by Janni [24].

Results of the two methods for proton range-energy in the target material were compared and proved to be in agreement with a relative difference of 0.01% (Fig. 4). Figure 4 shows that a 436 micron layer of ^{66}Zn is required to reduce the beam energy from 15 to 7 MeV.

The required target thickness is reduced by 10 times due to the target angle (6 degrees) in solid target design for IBA-Cyclone 30 cyclotrons. Therefore, a 43.6 micron layer of ^{66}Zn was enough for the production of ^{66}Ga with desirable efficiency. The method used for electro-deposition of zinc was based on the work reported by Hermanne *et al.* [19] with some modifications. For this purpose, 2.16 g of [^{66}Zn]ZnCl$_2$ was dissolved in 0.05 M HCl to prepare a zinc cation-containing solution. Hydrazine dihydrochloride (2 ml) was added as the reducing agent. The electrodeposition cell conditions are given in Table 2.

Table 2. Electrodeposition cell conditions

Cell volume	480 ml
pH	2.5–3
Current density	35 mA/cm^2
Anode material	platinum
Distance between the electrodes	3 cm
Stirrer frequency	800 RPM
Total electrodeposition time	45 min

Radiochemical separation

The target was bombarded with a current intensity of 180 μA of 15 MeV protons for 67 min (200 μAh).

Several methods have been introduced for the recovery of gallium from zinc and copper. Liquid-liquid extraction (LLX) with trioctylamine (TOA) can only separate trace amounts of gallium, zinc and copper [31]. Ion exchange chromatography alone is difficult and time consuming [6], and combining it with electrolysis is also complicated, time consuming and expensive [46]. The method used in this study, is a combination of ion exchange chromatography and liquid-liquid extraction.

After the target bombardment process, chemical separation was carried out in no-carrier-added form. The irradiated target was dissolved in 10 M HCl, and the solution was passed through a cation exchange resin (BioRad AG 50 W, 200–400 mesh, H$^+$ form) (h: 7 cm, Ø: 1.1 cm) which had been pretreated by passing 25 ml of 9 M HCl. The column was then washed by 25 ml of 9 M HCl with a rate of 1 ml/min to remove most of copper and zinc ion contents and ^{66}Ga remained on the column. Then, ^{66}Ga cations were washed out using 20 ml of 4 M HCl. Finally, the solvent-solvent extraction method was used to achieve a higher purity of ^{66}Ga. For this purpose, 10 M HCl (20 ml) was added to the 4 M effluent in order to obtain the optimum molarity to extract ^{66}Ga ions. Di-isopropyl ether was used to extract ^{66}Ga from the aqueous phase (2 times). Nitrogen bubbling was applied for 10 min to mix the aqueous and organic phases.
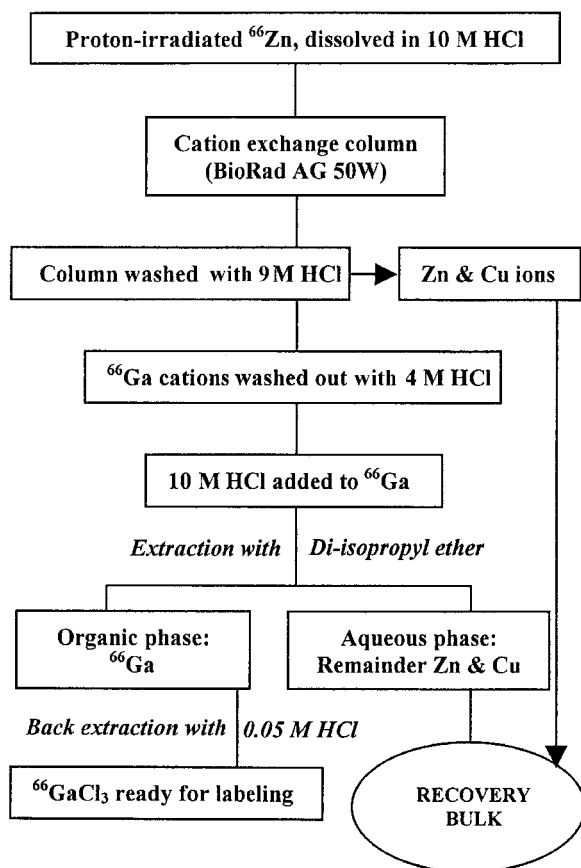

Fig. 5. Flow chart of ^{66}Ga separation.

The mixed organic phases were back-extracted using 12.5 ml of 0.05 M HCl. The resulting high-purity [^{66}Ga]GaCl$_3$ solution was sent for quality control. Schematic diagram of the separation process of carrier-free ^{66}Ga from zinc and copper is given in Fig. 5.

Recovery process

After the recovery of ^{66}Ga from zinc and copper, it was preferable to find a method for the recovery of ^{66}Zn (target material), due to its high price. The solution previously gathered in the recovery bulk was heated almost to dryness and the remainder was dissolved in 6 M HCl. This solution was loaded on an anion exchange chromatography AG 1X8 column (100–200 mesh, Cl$^-$ form, 25 cm high, 1.5 cm Ø) preconditioned with 25 ml of distilled water and 100 ml of 6 M HCl. The loading rate was 2 ml/min. Copper was washed out of the column by passage of 50 ml of 2 M HCl at a rate of 2 ml/min. ^{66}Zn was recovered by elution using 150 ml of 0.05 M HCl. This procedure is usually carried out six months after each bombardment, due to the production of a small amount of ^{65}Zn which originates from the ^{66}Zn(p,pn)^{65}Zn nuclear reaction.

Quality control

Quality control of the product was performed in two steps:
1. <u>Radionuclide purity control</u>. The radionuclide purity of radiogallium was ascertained by examining its gamma-ray spectrum using a calibrated high purity germanium detector (HPGe) coupled with a multi-channel analyzer. A few drops of the product was diluted and 10 ml of it was transferred to a 20 ml standard quartz vial and was filled with water and taken for gamma-ray spectrometry. The gamma rays were identified and the area under peaks were counted for 1000 seconds at a distance of 10 cm between the vial and the detector surface, so that the dead time loss was less than 5%.
2. <u>Chemical purity control</u>. This step was carried out to ensure that the amounts of zinc and copper ions resulting from the target material and backing in the final product are acceptable regarding internationally accepted limits [55, 56]. Chemical purity was checked by differential-pulsed anodic stripping polarography. The detection limit of our system was 0.1 ppm for both zinc and copper ions.

Results

Gallium-66 was produced by 15 MeV proton bombardment of an electroplated enriched 0.031 g/cm^2 ^{66}Zn-target, derived from the NRCAM cyclotron.

The target was irradiated with a 180 μA of 15 MeV external proton beam. The resultant activity of ^{66}Ga was 82.12 GBq at the end of bombardment and the thick target yield was 410.6 MBq/μAh.

The radiochemical separation process was based on a no-carrier-added method and obtained ^{66}Ga in the [^{66}Ga]GaCl$_3$ form. The radiochemical separation yield
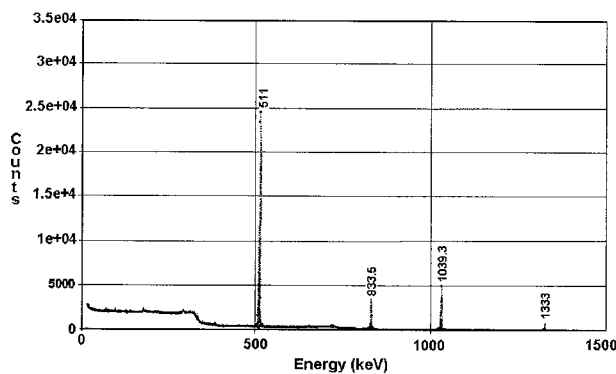
Fig. 6. The gamma-ray spectrum of the final [^{66}Ga]GaCl$_3$ sample (energies of gamma lines are given in keV).

(93%) was determined by activity measurements before and after radiochemical processing. The resultant activity after radiochemical separation process was 76.37 GBq. Radioactive concentration of the final product was 6.11 GBq/ml. The whole radiochemical processing step took about 3 h. The target recovery process took about 4 h with a yield of 97%.

Quality control of the product was performed in two steps:

1. <u>Radionuclide purity</u>. Gamma-ray spectroscopy of the final sample showed a radionuclide purity higher than 97.4% showing the presence of 511, 833.5, 1039.3 and 1333 keV gamma energies, all originating from ^{66}Ga (Fig. 6). The rest of activity (2.6%) was attributed to ^{67}Ga (2.1%) and ^{65}Ga (0.5%) due to the presence of ^{67}Ga and ^{65}Ga gamma-ray characteristic peaks.

2. <u>Chemical purity</u>. Polarography results showed the presence of 1.5 ppm copper and 0.8 ppm zinc ions in the final sample, both far below the USP limits, i.e. 5 ppm for copper [56] and 1 ppm for zinc [55].

Conclusion

Production of ^{66}Ga is one of our priorities, due to its increasing applications. The activity of ^{66}Ga produced at the NRCAM was desirable for the use in various scientific fields. Our production yield was in agreement with previously reported data. The results are illustrated in Fig. 7.
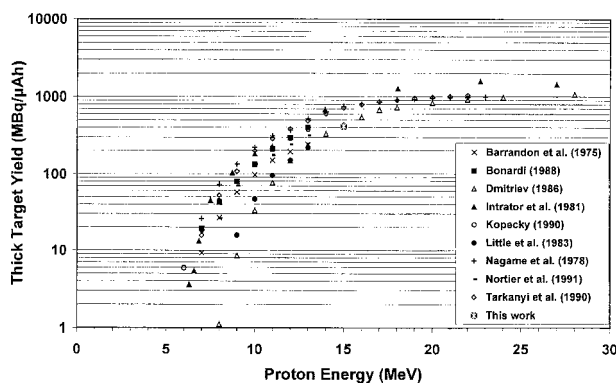

Fig. 7. Comparison of our experimental yield with the previous data given in the literature [2, 4, 8, 23, 29, 34, 39, 42, 52].

Quality control procedures gave satisfactory results and the chemical processing of the product was proved to be so efficient that the resultant [^{66}Ga]GaCl$_3$ (in 0.05 M HCl) was directly usable for labeling studies.

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