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Production and quality control of ^{66}Ga as a PET radioisotope

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ABSTRACT

Background: ^{66}Ga ($t_{1/2}$=9.49 h, β^+: 4.153 MeV, γ: 511, 834, 1039, 2752 keV) has a wide range of applications in different fields of medical sciences. Production of ^{66}Ga became one of our main interests, according to its increasing applications in nuclear medicine, particularly in PET imaging.

Materials and Methods: ^{66}Zn (p,n)^{66}Ga reaction was determined as the best choice for the production of ^{66}Ga**,** according to the present facilities and conditions. The bombardment was performed by 15 MeV protons in Cyclone 30-IBA accelerator with a current intensity of 180 μA for 67 min. ALICE nuclear code and SRIM nuclear program were used to determine the optimum energy and target thickness. Targets were prepared by electroplating of ^{66}Zn (>95%) 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 used for the recovery of target material. Quality control of the product was carried out in two steps of chemical and radionuclidic purity control.

Results: The activity of ^{66}Ga was 2.41 Ci at the end of bombardment (E.O.B.) and the production yield was 12.04 mCi/μAh. The chemical separation yield was 93% and the yield of chemical recovery of the target material was 97%. Quality control tests showed a radionuclidic purity of more than 97% and the amounts of chemical impurities were in accordance with standard levels.

Discussion: Our production yield was comparable with previous reports given in the literature. The chemical separation method used in this research was simple and brought up acceptable results. So, this process can be considered as one of the best choices for the production of ^{66}Ga.
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Keywords: *^{66}Ga, ^{66}Zn production, cyclotron, chemical separation, quality control.*

INTRODUCTION

The three radioisotopes ^{66}Ga, ^{67}Ga and ^{68}Ga are well known and widely used in the field of nuclear medicine. $^{66}Ga^{3+}$ and $^{68}Ga^{3+}$ have been proposed for positron emission tomography (PET) imaging studies (Loe'h *et al.* 1980, Goethals *et al.* 1991, Jurisson *et al.* 1993, Daube-whitherspoon *et al.* 1997, Kowalski *et al.* 2003, Froidevaux *et al.* 2004, Velikyan *et al.* 2004, Griffiths *et al.* 2004, Rovainen *et al.* 2004). ^{66}Ga has been proposed for the study of some slow dynamic processes (such as lymphatic transport) by positron emission tomography (Goethals *et al.* 1987, 1988, Lewis *et al.* 2002), and for radioimmunotherapy by it's attachment to monoclonal antibodies (Zweit *et al*. 1987) in the detection and staging

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of tumors and other lesions after dosimetric studies using its high energy positrons (Goethals *et al.* 1990, Graham *et al.* 1997, Kairemo 1993) using end point energy of 4.2 MeV (Szelecsenyi *et al*. 1994). It has been shown that a ^{66}Ga-labeled somatostatin analogue, selectively targeted somatostatin receptor positive tumors, is a successful imaging agent (Ugur *et al.* 2002). ^{66}Ga has been used in the radiolabelling of blood cells (Ellis and Sharma 1999, Jalilian *et al.* 2003) and albumin colloids (Naganawa *et al.* 1977) for various diagnostic purposes. It has been reported for successful folate receptor targeting both *in vitro* and *in vivo* for clinical diagnostic imaging (Ke *et al*. 2003, Ke *et al.* 2004, Mathias *et al*. 2003). ^{66}Ga can also be used as a standard source for high energy calibration of Ge detectors (Molnar *et al.* 2002, Helmer *et al*. 2004, Baglin *et al*. 2002, Lloyd *et al.* 1968).

A brief summary of nuclear characteristics of ^{66}Ga and other gallium radioisotopes is given in table 1 (Wien 1966, Coté *et al*. 1966, Strauss and Lenkszus 1969, Phelps *et al.* 1970, Thakur 1977, Lederer and Shirley 1978, Zweit *et al.* 1987, Graham 1997, Kowalsky and Perry 1987, Firestone and *et al.* Shirley 1996, Szelecsenyi *et al.* 1994, Schmid *et al.* 1996, Najam *et al*. 1971)

Our recent studies on the preparation and tumor imaging properties of [^{67}Ga] bleomycin in normal and tumor-bearing mice showed a good tumor/blood and tumor/muscle ratio suggesting an appropriate diagnostic agent (Tabeie *et al.* 2003).

The aim of this study was to produce ^{66}Ga as a positron emitter for tumor imaging. Due to the interesting properties and increasing importance of positron emission tomography, the production and preparation of ^{66}Ga radioisotope is reported in the present paper.

MATERIALS AND METHODS

Production of ^{66}Ga was performed in the NRCAM 30 MeV cyclotron (Cyclone-30, IBA). Ion Beam Application department-NRCAM provided ^{66}Zn with a purity of more than 95%. Chemicals were purchased from Aldrich Chemical Company, Milwaukee, WI (USA) and Merck Company (Germany). Gamma spectroscopy was performed with a high purity germanium (HPGe) detector (model GC1020-7500SL) coupled with a Canberraä multichannel analyzer. Radionuclide purity was checked by the same detector. All calculations and counting were based on 1039 keV characteristic peak.

Table 1. Important nuclear characteristics for Ga isotopes.

Characteristic	**^{67}Ga**	**^{68}Ga**	**^{66}Ga**
γ Photon Energy(keV) and abundance (%)	93 (37%), 185 (20.4%), 300 (16.6%), 394 (4.64%)	511 (β^+) (178%), 1077 (3.0%)	511 (β^+) (114%), 834 (6.03%), 1039 (37.9%), 2752 (23.2%)
Electron (s) Energy (keV)	84, 92	1900 (β^+)	4153 (β^+)
Half Life	78 h	68 m	9.49 h
Decay Mode	EC to ^{67}Zn	10% EC to ^{65}Zn 90% β^+	43% EC to ^{66}Zn 57% β^+
Main Production Method	^{68}Zn (p,2n)^{67}Ga	^{68}Ge Daughter ^{66}Zn (α,2n)^{68}Ge	^{66}Zn (p, n)^{66}Ga
Natural Abundance of Target	(18%)	(28%)	(28%)
Contaminant	^{66}Ga, ^{65}Zn	^{68}Ge	^{65}Zn
Beam Energy (MeV)	12-22	12-22	6-15

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Selection of the proper reaction and energy

Various nuclear reactions that can be used for the production of ^{66}Ga are given in table 2 (Goethals *et al*. 1988, Szelecsenyi *et al.* 1991, Szelecsenyi *et al.* 1994, Tárkányi *et al.* 1990, Zweit *et al.* 1988, Steyn and Meyer 1973).

Table 2. Various nuclear reactions for the production of ^{66}Ga.

Nuclear Reaction	Useful Energy Range (MeV)	Natural Abundance (%)
^{66}Zn(p,n)^{66}Ga	6-15	27.9
^{67}Zn(p,2n)^{66}Ga	15-25	4.1
^{68}Zn(p,3n)^{66}Ga	20-30	18.8
^{63}Cu(α,n)^{66}Ga	15-25	69.2
^{66}Zn(d,2n)^{66}Ga	12-16	27.9

Our available reactions were restricted to ^{66}Zn (p,n)^{66}Ga, ^{67}Zn(p,2n)^{66}Ga and ^{68}Zn(p,3n) ^{66}Ga, since the only available particle accelerator could accelerate protons in the energy range of 15-30 MeV with a maximum current intensity of 200 microamperes. Among the above mentioned reactions, ^{66}Zn (p,n)^{66}Ga was selected according to its higher thick target yield (Szelecsenyi *et al.* 1998).

In order to determine the excitation function for ^{66}Zn (p,n)^{66}Ga reaction, ALICE nuclear code (Blann and Bislinghoff 1991) was run for the proton beam energy range of 3-30 MeV (figure 1). On the other hand, many different nuclides may be produced as a result of proton bombardment of ^{66}Zn in the energy range of 0-30 MeV, the most important of which are given in table 3. It can be concluded from table 3 that the most important impurity is ^{65}Ga, since it can not be separated from ^{66}Ga by chemical methods, and proton energy had to be below 15.2 MeV (threshold energy for ^{66}Zn (p,2n) ^{65}Ga reaction). The produced copper isotopes (^{62}Cu and ^{63}Cu) could easily be separated by chemical procedures.

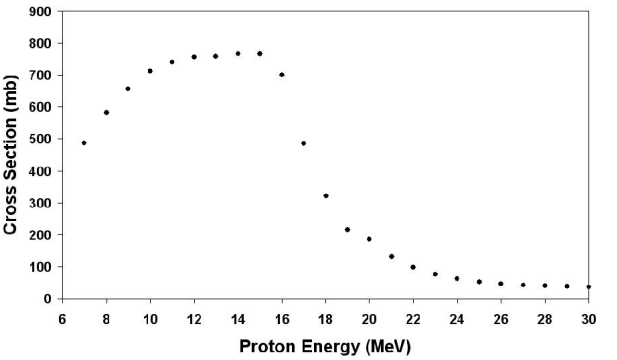


Figure 1. Results of ALICE code for ^{66}Zn (p,n)^{66}Ga reaction

Table 3. Main possible nuclear reactions during proton bombardment of ^{66}Zn (0-30 MeV).

Reaction	Half Life	Threshold Energy (MeV)
^{66}Zn(p,n)^{66}Ga	9.5 h	5.9
^{66}Zn(p,2n)^{65}Ga	15 min	15.2
^{66}Zn(p,α)^{63}Cu	Stable	0
^{66}Zn(p,nα)^{62}Cu	9.74 min	9.5
^{66}Zn(p,pn)^{65}Zn	244.3 d	13
^{66}Zn(p,p2n)^{64}Zn	Stable	19.5

^{65}Zn is the only radioactive impurity that can interfere with the target mass (^{66}Zn) in the recovery bulk during target rehabilitation. Thus, if proton energy is 15 MeV, there would just be a small amount of ^{65}Zn (figure 2) and no ^{65}Ga during the whole process.

Excitation function was calculated for ^{66}Zn (p,n) ^{65}Zn reaction using ALICE nuclear code. Our results were compared with the reported measurements of Szelecsenyi *et al.* (1998), Hermanne *et al.* (1992) and Levkovskij (1991). Figure 2 shows that results of ALICE code obtained in the present study are in accordance with previous experimental data and confirm that proton energies not exceeding 15 MeV are best for the production of ^{66}Ga with minimum amount of radioactive impurity. Proton energy

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was chosen 15 MeV in order to achieve the maximum possible production yield.

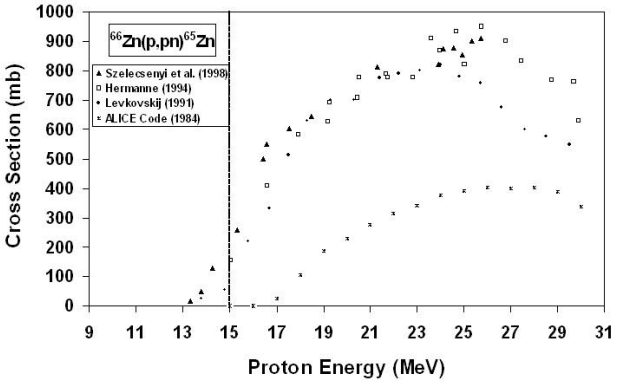


Figure 2. Excitation function for ^{66}Zn (p, pn) ^{65}Zn nuclear reaction.

Targetry

The method selected for targetry was electrodeposition of ^{66}Zn on a copper backing plate. The target was taken to the irradiation station and was placed at an angle of 6 degrees toward the proton beam in order to achieve higher production yield. The target was cooled by a flow of 18 ℃ distilled water with a rate of 50 lit/min.

The target had to be thick enough to reduce the energy of incident protons from 15 MeV to about 6 MeV because the optimum proton energy was 15 MeV and the threshold energy of the ^{66}Zn (p,n)^{66}Ga reaction was 5.9 MeV.

SRIM nuclear code (Ziegler *et al.* 2000) was run in order to determine the best target thickness in the above energy range. The results obtained from SRIM nuclear code are illustrated in figure 3.

It can be concluded from figure 3 that the best target thickness is 473 microns. But the target anglulation (6 degrees) reduces the required target thickness by 10 times. We only needed to electrodeposit a 47.3 micron zinc layer on the copper backing. To do so, ^{66}ZnO was dissolved in 0.05 N HCl to prepare a zinc cation-containing solution. The mass of zinc ions in the cell had to be twice as that of the electrodeposited layer. Hydrazin dihydrochloride (2 ml) was added to reduce the bath. Our electrodeposition cell conditions for preparation of thick target are given in table 4.

Electrodeposition in these conditions resulted in a 50 micron zinc layer on the copper backing.

Table 4. 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	**50 min**

Radiochemical Separation

Several methods have been introduced for the separation of gallium from zinc and copper. Liquid-liquid extraction (LLX) with trioctylamine (TOA) can only separate trace amounts of gallium, zinc and copper (Lahiri *et al*. 1997). Ion exchange chromatography and electrolysis method is complex, time

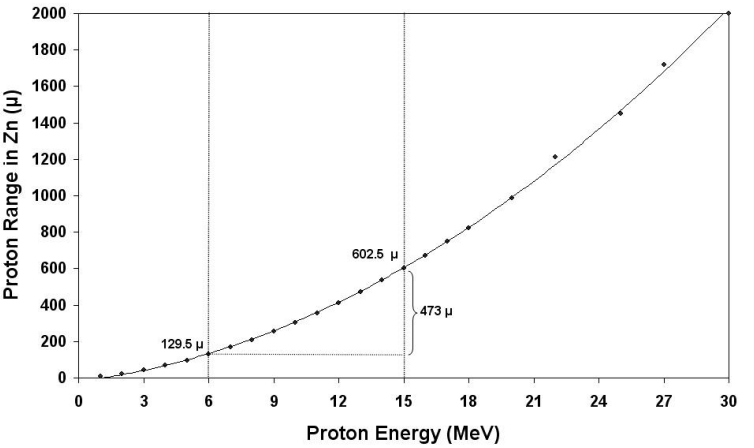


Figure 3. The optimum target thickness according to SRIM program.

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consuming and expensive (Schwarzbach *et al*. 1995). Ion exchange chromatography and solvent extraction method is difficult and time consuming (Dasgupta *et al.* 1991). The method used in this research was a combination of ion exchange chromatography and liquid-liquid extraction methods.

After the target bombardment process, chemical separation was carried out in no-carrier-added form. The irradiated target was dissolved by 10 N HCl (15 ml, H_2O_2 added), and the solution was passed through a cation exchange resin (Dowex 50 W×8, 200-400 mesh, H^+ form) (h:10 cm, Ø:1 cm) which had been pre-treated by passing 25 ml of 9 N HCl. The column was then washed by 25 ml of 9 N HCl with a rate of 1 ml/min to remove copper and zinc ion contents and ^{66}Ga remained on the column. Then ^{66}Ga cations were washed out by 20 ml of 4 N HCl. Finally, solvent-solvent extraction method was used to achieve a higher purity of ^{66}Ga. For this purpose, 10 N HCl (20 ml) was added to the 4N eluent in order to obtain the optimum normality to extract ^{66}Ga ions. Isopropyl ether was used to extract ^{66}Ga from the aqueous phase (2 times). Nitrogen bubbling was used for 10 minutes to mix the aqueous and organic phases.

The mixed organic phases were back-extracted using 12.5 ml of 0.05 N HCl. The resulting high-purity [^{66}Ga] $GaCl_3$ solution was directly used for the labeling step. Schematic diagram of the separation process of carrier-free ^{66}Ga from zinc and copper is given in figure 4.

Recovery process

After the separation of ^{66}Ga from zinc and copper, it was preferred to find a method for the recovery of ^{66}Zn (target material), because it is very expensive. The solution previously gathered in the recovery bulk was heated, almost to dryness, and the remainder was dissolved in 6 N HCl. This solution was loaded on an anion exchange chromatography AG 1×8 column (100-200 mesh, Cl^- form, 25 cm high, 1.5 cm Ø) preconditioned with 25 ml of distilled water

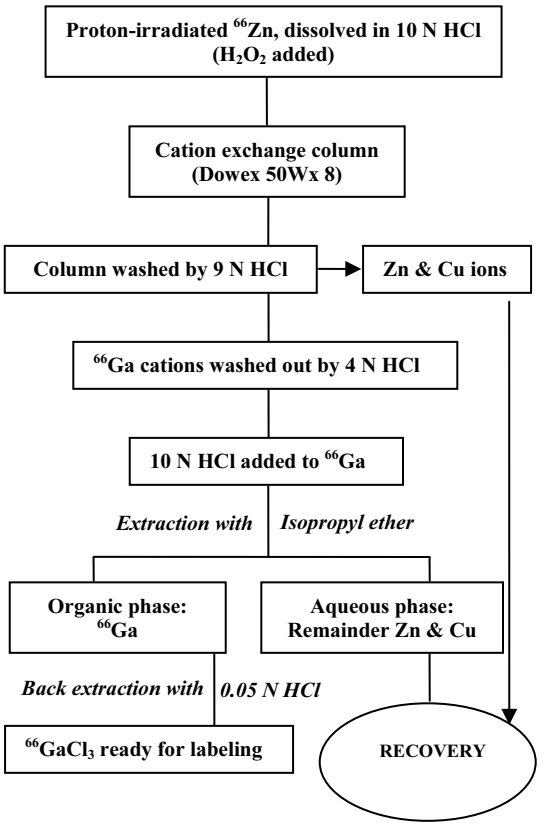


Figure 4. Flow chart of ^{66}Ga separation.

and 100 ml of 6 N HCl. The loading rate was 2 ml/min. Copper was washed off the column by 50 ml of 2 N HCl with a rate of 2 ml/min. Then ^{66}Zn was separated by washing the column with 150 ml of 0.05 N HCl.

Quality control of the final product

Quality control of the product was performed in two steps: radionuclidic purity control by gamma spectroscopy using an HPGe detector, and chemical purity control by high resolution colorimetric assays.

RESULTS

^{66}Ga was produced by 15 MeV proton bombardments of an electroplated enriched 0.036 g/cm^2 ^{66}Zn-target at the angle of 6 degrees in a 30 MeV cyclotron (Cyclone-30, IBA). The target was bombarded with a current intensity of 180 μA for 67 min (200 μAh). The resultant activity

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of ^{66}Ga was 2.41 Ci at the end of bombardment (E.O.B.) and the production thick target yield was 12.04 mCi/μAh which was comparable with the data given in the literature (Barrandon *et al.* 1975, Little and Lagunas-Solar 1983, Tárkányi *et al.* 1990, Kopeckỳ 1990, Bonardi 1988, Dmitriev 1986, Nagame *et al.* 1978, Nortier *et al*. 1991, Intrator *et al*. 1981).

The chemical separation process was based on a no-carrier-added method and obtained ^{66}Ga in [^{66}Ga] $GaCl_3$ form. The chemical separation yield (93%) was obtained by activity measurement before and after chemical processing. The resultant activity after chemical separation process was 2.24 Ci. Concentration of the final product was 56 mCi/ml. The whole chemical processing step took about 3 hours. The target (^{66}Zn) recovery process took about 4 hours with a yield of 97%.

Quality control of the product was performed in two steps:

Radionuclide purity: The gamma spectroscopy of the final sample was carried out by a HPGe detector and showed a radio-nuclide purity higher than 97% showing the presence of 511, 834 and 1039 keV gamma energies, all of which originated from ^{66}Ga (figure 5).

Chemical purity: The presence of copper and zinc cations were checked by high resolution colorimetric assays. The formation of colored dithizone metal complexes demonstrated that the zinc and copper cation concentrations were far below the internationally accepted limits (less than 1.5 ppm zinc and 0.75 ppm copper cations in our assay compared to USP limits: 5 ppm for each).

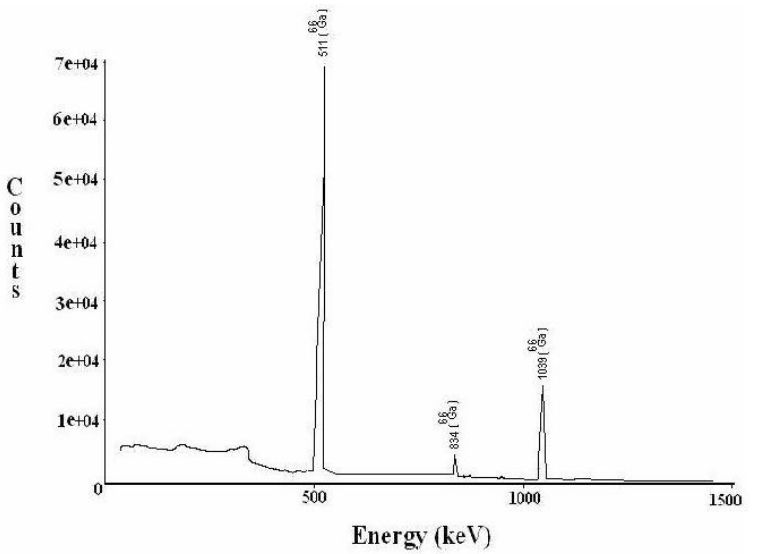


Figure 5. Gamma spectroscopy scheme of the final [^{66}Ga]$GaCl_3$.

DISCUSSION

According to ^{66}Ga increasing medical was considered as one of our high priorities, application, it's production. Results of our calculations for excitation function using ALICE code for the determination of proton beam energy was compared with the previously reported measurements of Hille *et al.* (1972), Little and Lagunas-Solar (1983), Szelecsenyi *et al.* (1998), Hermanne *et al.* (1992), Levkovskij (1991), Howe (1958) and Tárkányi *et al.* (1990). The results are shown in figure 6 which shows that ALICE code calculations are in good agreement with the experimental data given in the literature.

The activity of ^{66}Ga produced at the NRCAM was high enough to be used in different fields of study. Comparison of the production yield with the data given in the literature, showed a good agreement. The results are illustrated in figure 7.

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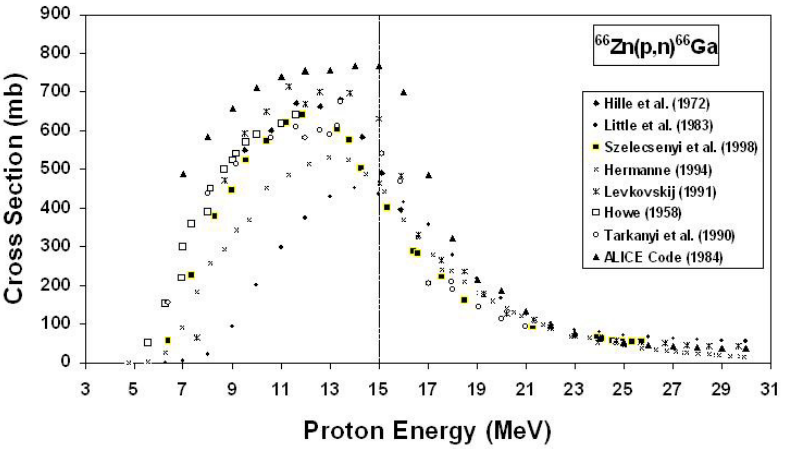


Figure 6. Excitation function for ^{66}Zn (p,n)^{66}Ga nuclear reaction.

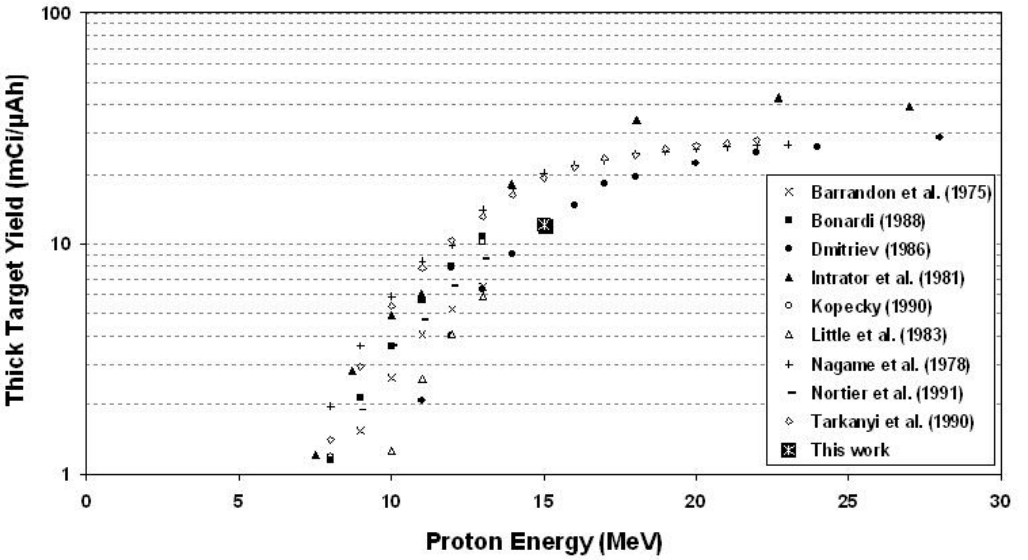


Figure 7. Comparison of the result with the previous data given in the literature.

Quality control procedures showed satisfactory results and the chemical processing of the product was so efficient that the resultant [^{66}Ga] $GaCl_3$ (in 0.05 N HCl) could directly be sent for labeling.

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