

PRODUCTION OF ^{67}Ga AT THE OSLO CYCLOTRON

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Abstract

A method for production of ^{67}Ga at the Oslo Cyclotron is described. The method is based on the nuclear reaction $^{68}\text{Zn}(p,2n)^{67}\text{Ga}$. The target is natural zinc metal of thickness 1.3 mm fixed by a thin alloy layer to a copper disc for efficient cooling during irradiation. By applying a beam of 29 MeV protons, a maximum production yield of $\sim 1.8 \text{ mCi}/\mu\text{Ah}$ was obtained. By demanding a contamination level of $^{66}\text{Ga} \leq 1\%$, the "useful" yield after a decaytime of 88 h is $\sim 0.8 \text{ mCi}/\mu\text{Ah}$.

Gallium has been separated carrierfree from the zinc matrix by cation exchange from 7.5 M hydrochloric acid solutions and prepared as a citrate complex at pH 5.5. After sterile filtering, autoclavation, pyrogene testing and analysis for iron and zinc, the ^{67}Ga -radiopharmaceutical has been applied in human investigations at the Ullevål hospital in Oslo.

INTRODUCTION

In 1949 reactor produced radioisotopes of gallium were for the first time considered and evaluated for possible medical applications¹⁾. When gallium-lactate containing ^{72}Ga as a tracer was injected in animals, a certain deposition in bones was found to take place.

In order to overcome the disadvantages of ^{72}Ga such as low specific activity and short half-life, the idea of using carrierfree ^{67}Ga was introduced. This was obtained in 1953. Gallium produced by proton bombardment of natural zinc was prepared as a citrate complex and used in animal experiments²⁾. However, these experiments showed less bone uptake than the previous ones. Not until 16 years later it was realized that carrierfree gallium is sequestered by the plasma, and enhanced bone deposition will not be seen until the plasma is saturated with gallium³⁾.

During these experiments the same group accidentally observed that ^{67}Ga -citrate concentrates in soft tissue tumors⁴⁾. This discovery marked the start of a new development of radiogallium in nuclear medicine, and ^{67}Ga -citrate has later been recognized and gained reputation as a soft tissue tumor localizing agent (for more detailed information see ref. 5) and refs therein). Its physical half-life of 78.26 h and its decay by pure EC followed by the main γ -ray energies of 93.3, 184.5 and 300.2 keV makes it suitable for in-vivo use, and it is readily detected by commercial gamma-cameras.

Today, ^{67}Ga is produced regularly by different methods at several accelerator facilities throughout the world. The present article describes the production technique developed at the Oslo cyclotron.

PRODUCTION METHODS

At the particle energies available at small cyclotrons carrierfree ^{67}Ga may be obtained by: a) proton bombardment of natural or enriched zinc, b) deuteron bombardment of natural or enriched zinc, c) alpha-particle bombardment of copper, d) ^3He bombardment of copper and e) indirectly by alpha-particle bombardment of natural or enriched zinc. The main nuclear reactions involved are listed in table 1 together with some results reported in the literature.

TABLE 1. REPORTED PRODUCTION METHODS FOR ^{67}Ga WITH A SMALL CYCLOTRON

NUCLEAR REACTION	TARGET TYPE	TARGET THICKNESS mg/cm^2 (mm)	BEAM ENERGY MeV	BEAM CURRENT μA	PRODUCTION YIELD $\text{MBq}/\mu\text{Ah}$ ($\mu\text{Ci}/\mu\text{Ah}$)	REFERENCES
$^{68}\text{Zn}(p,2n)^{67}\text{Ga}$	Nat. Zn, 99.99%, electrolysed on Ag	140-240 (0.2-0.33)	21	235	12.6 (340)	6)
$^{68}\text{Zn}(p,2n)^{67}\text{Ga}$	Flattened Zn-tube	140(0.2)	21	350	15.9 (430)	6)
$^{68}\text{Zn}(p,2n)^{67}\text{Ga}$	Enriched ^{68}Zn , 98.46%, electroplated on Ni(Cu)	135(0.19)	22	350	46.3 (1250)	7)
$^{68}\text{Zn}(p,2n)^{67}\text{Ga}$	Nat. Zn electroplated on Cu	-	22	-	20.4 (550)	8)
$^{68}\text{Zn}(p,2n)^{67}\text{Ga}$	Nat. Zn or enriched ^{68}Zn electrolysed on Au(Cu)	200(0.3)	21	30-40	20.4-22.2 (550-660)	9)
$^{66}\text{Zn}(d,n)^{67}\text{Ga}$ $^{67}\text{Zn}(d,2n)^{67}\text{Ga}$	Nat. Zn	-	16	-	12.8 (350)	10)

Table 1 continues:

$^{66}\text{Zn}(d,n)^{67}\text{Ga}$ $^{67}\text{Zn}(d,2n)^{67}\text{Ga}$	Nat. Zn electroplated on Ag(Cu)	50(0.075)	8	200	1.1 (30)	11)
$^{66}\text{Zn}(d,n)^{67}\text{Ga}$ $^{67}\text{Zn}(d,2n)^{67}\text{Ga}$	Nat. Zn melted onto Cu	70(0.1)	16	200	10.2 (275)	12)
$^{66}\text{Zn}(d,n)^{67}\text{Ga}$ $^{67}\text{Zn}(d,2n)^{67}\text{Ga}$	Nat. Zn foil folded, ZnO powder	30(0.04)	8	2	1.2 (33)	13)
$^{66}\text{Zn}(d,n)^{67}\text{Ga}$ $^{67}\text{Zn}(d,2n)^{67}\text{Ga}$	Nat. Zn soldered onto Cu	70-140 (0.1-0.2)	14	150	7.6 (205)	14)
$^{66}\text{Zn}(d,n)^{67}\text{Ga}$ $^{67}\text{Zn}(d,2n)^{67}\text{Ga}$	Nat. Zn electroplated onto Cu	93(0.13)?	16	600	12.6 (340)	15)
$^{66}\text{Zn}(d,n)^{67}\text{Ga}$	Enriched ^{66}Zn , 90%, electroplated onto Cu	93(0.13)?	16	600	35.0 (950)	15)
$^{63}\text{Cu}(\alpha,\gamma)^{67}\text{Ga}$ $^{65}\text{Cu}(\alpha,2n)^{67}\text{Ga}$	Nat. Cu plate	2670(3)	30	500	5.9 (160)	16)
$^{65}\text{Cu}(^3\text{He},n)^{67}\text{Ga}$	Nat. Cu	-	23	-	0.04 (1.1)	11)

Table 1 continues:

$^{64}\text{Zn}(\alpha, p)^{67}\text{Ga}$	Nat. Zn, folded foil,	30(0.04)	19	20	2.9 (77.5)	13)
$^{64}\text{Zn}(\alpha, n)^{67}\text{Ga} \rightarrow$	ZnO powder					
β^+	^{67}Ga					
$^{64}\text{Zn}(\alpha, p)^{67}\text{Ga}$	Nat. Zn, stacked foils	195(0.27)	25	0.5	6.1 (165)	17)
$^{64}\text{Zn}(\alpha, n)^{67}\text{Ga} \rightarrow$						
β^+	^{67}Ga					

The accelerator installed in our laboratory is a Scanditronix MC-35 cyclotron which can deliver variable particle energies with maximum values of 35 MeV protons and alpha-particles, 18 MeV deuterons and 47 MeV ^3He -ions. Since the irradiations have to be performed in the extracted beam, the maximum obtainable beam currents are generally below 50 μA .

On the basis of the literature results listed in table 1, the capabilities of our cyclotron and some initial irradiations of alpha-particles on natural copper, we finally decided to develop a ^{67}Ga production technique based on proton irradiation of natural zinc.

OPTIMIZATION OF EXPERIMENTAL CONDITIONS

When irradiating natural zinc with protons in order to produce ^{67}Ga , an unavoidable contaminant is ^{66}Ga ($t_{1/2} = 9.5$ h). It decays by β^+ -emission followed by high-energy γ -ray emission which may expose the patient to higher radiation dose and obscure the gamma-camera pictures.

In order to optimize the experimental conditions with respect to high ^{67}Ga content and low ^{66}Ga contamination, the production yield for these two isotopes were determined as a function of the proton bombarding energy by irradiating a stack of 15 zinc foils. The foil thickness was 0.1 mm (71.4 mg/cm²) and the purity was 99.95%. The energy of the extracted protons was 29 MeV, the mean proton current 0.2 μA and the irradiation time 5 min. In order to determine the absolute amount of ^{66}Ga and ^{67}Ga the foils were allowed to cool for about 24 hours, and then counted individually on a γ -ray spectroscopy system composed of a Ge(Li)-detector and a computerized multichannel analyzer.

The yields from the foil experiments were normalized to 1 h irradiation time and 1 μA beam current. The normalized yield for the individual foils are given in fig. 1, and the integrated yields in foil stacks composed of 1,2,3,...,15 foils are illustrated in fig. 3.

In order to reduce the contamination level of ^{66}Ga below a preselected value before administration to the patients, a decay time of the sample

is necessary. Based on the results from the foil experiments this decay time was calculated as a function of the applied target thickness. Irradiation times of 1 h and 3 h were supposed, and the contamination levels selected were 1% and 0.1% (defined as the ratio of the activity of ^{66}Ga to ^{67}Ga). The results are illustrated in fig. 2. The data from the foil experiments allow similar curves to be constructed for other bombarding energies between 15 and 29 MeV.

It may be useful to know the maximum obtainable yield when one of these contamination levels has to be kept. The curves in fig. 2 have been applied to calculate these yields as a function of the target thickness for 29 MeV bombarding energy. The results are illustrated in fig. 3. The upper curve, corresponding to the yield at the end of irradiation, levels off towards higher target thickness. The lower two reaches a maximum with a subsequent decrease in the yield and the target thickness of 1.3 mm with a bombarding energy of 29 MeV.

The average bombarding energy for each single foil in the experiment may be calculated by the procedure for stopping power calculations described in ref. 18. Then the information inherent in each of the curves of fig. 3 may be expressed in illustrative curves like those given in fig. 4. Having a particular maximum proton energy available, one may read off the optimum target thickness. For a particular target thickness the optimum proton energy may be found.

TARGETRY

The zinc targets which have been used in experiments described in the literature, may be divided into three groups: those composed of zinc oxide powder, those of metallic zinc without a substrate and those of metallic zinc on a substrate. Columns 2 and 3 in table 1 contain some concentrated information on various target types, and column 7 gives the corresponding references. The listed target thicknesses range from 0.04 to 0.33 mm. Obviously, a target with a desired homogeneous thickness of 1.3 mm is not difficult to produce if an oxide target or a metallic target without a substrate can be applied. However, the use of zinc oxide powder was not desirable due to the contamination danger inherent in the handling process. Moreover, the planned design of the irradiation

chamber supposed the target to be placed as a window to the beam tube vacuum system with direct water cooling (pressure 3 bar) applied to the window backside. Uncertainties to whether a zinc plate of thickness 1.3 mm would sustain this pressure during bombardment, made us decide that the zinc target should have a mechanically strong substrate with good thermal conductivity. A copper substrate was chosen because it meets these two requirements and because it, due to its low cost, may be dispensed after use.

In order to attain an efficient cooling, the mechanical contact between the two metals should be good, and the zinc should not flake off or be distorted during irradiation. Various ways of producing the target have been tested including electrolysis, evaporation, gluing and melting.

The electrolysis experiments were performed both from sulphuric acid solutions by the procedure described by Koehler¹⁹⁾ and from hydrochloric acid solutions according to Hampel²⁰⁾. The bath temperature could be kept constant at various values, and electrolysis series with different current fluxes were accomplished. None of the procedures were fully successful. It appeared difficult to avoid grain or thread growing with increasing zinc thickness. This effect leads to metal porosity with possible liquid inclusions. A zinc thickness of 0.6 mm showed a porosity of 8%. This target was subject to a test irradiation with 10 μ A 27 MeV protons. The zinc layer was deformed by blisters. Besides, the zinc adherence to the copper substrate was relatively poor. The best results were obtained if, during the initial phase of the electrolysis, a rather weak current density was applied. The time for preparing a 0.6 mm target thickness (after machining the zinc layer to a plain surface) were several hours, and the bath had to be frequently watched in order to remove the zinc "beards" whenever necessary. Accordingly, electrolysis were judged to be impractical for our purpose.

The evaporation experiments of zinc onto a copper surface were carried out using a commercial vacuum evaporating apparatus. The zinc was contained in a tantalum vessel with an evaporating orifice which could be varied in size. The vessel was heated ohmically and the copper plate placed above the orifice at variable distances. The desired thickness of 1.3 mm covering the required 4-5 cm² target area could easily be ob-

tained. However, the zinc layer adhered poorly to the copper, and had a tendency to flake off during the following machining of the surface. Besides, it was practically impossible to avoid a zinc layer onto other surfaces in the vacuum clock, resulting in current-leading bridges on electrical insulators, break-down of vacuum gauges and a thorough and lengthy cleaning process after each target preparation.

A single test was also made to glue a zinc disc onto the copper plate with an epoxy-based glue (Araldite). After a short irradiation period the zinc layer was etched away with hydrochloric acid, and, as might be expected, a black layer of carbonized material appeared close to the center of the beam. Hence, during extended irradiations the cooling would probably be insufficient, and the method was discarded.

Melting of zinc onto a copper surface appeared to be the most successful method. In order to achieve a thin alloying layer at the contact surfaces the copper plate must be heated, and the temperature carefully controlled. The final designs of the target and the apparatus made to perform the controlled melting of the zinc, are illustrated in fig. 5. A 2 mm thick zinc disc of diameter 25 mm is placed into the 1.3 mm deep circular cavity of a 40 mm squared 2 mm thick copper plate. The zinc surface has been prepared by mechanical polishing, and the copper surface by etching in warm dilute nitric acid with subsequent rinsing in distilled water and ethanol. The copper plate is mounted into a brass chamber and the zinc covered with a thin stainless steel foil. Mechanical pressure is applied to the zinc disc by means of the screw piston. This ensures good mechanical contact between the zinc and the copper. A thermocouple mounted in mechanical contact with the copper plate indicates the temperature. The chamber is then slowly heated in a small ceramic laboratory oven until 420 °C is reached (The melting point of zinc is 419.4 °C). The heat is then immediately turned off. The chamber is removed from the oven and allowed to reach room temperature. During the entire heating and cooling period the chamber is flushed continuously with nitrogen. After cooling the steel foil is torn off the zinc layer, and the surface is machined to the appropriate target thickness. The zinc is thus fixed firmly to the copper through a thin alloy layer at the contact surfaces.

THE PRODUCTION APPARATUS

Although the maximum proton energy is about 35 MeV, a practical limit is approximately 30 MeV when high beam current is desired. The beam is extracted through a 10 m linear beam tube into the irradiation area. The end of the beam tube with the target chamber is schematically illustrated in fig. 6, and the target mechanism is shown with more details in fig. 7. The square formed target plate is loaded manually by dropping it into position onto the loading spring which ensures a proper positioning. The target is fixed firmly by turning the backplate into a semilocked position. The vacuum and water systems are thereby sealed by "o"-ring tightnings, and the water cooling is applied directly on the backside of the target plate.

The target mechanism is surrounded by a 20 cm thick neutron shield made of a solid suspension of boric acid in paraffin (44% by weight of boric acid, melting point of the paraffin 54-56 °C). This shield reduces the neutron flux by a factor of 5-10. The shield is mounted on a movable support illustrated in fig. 8.

After irradiation the entire handling procedure is executed remotely. The cooling water is turned off and remaining water removed from the target backside by compressed air. The target chamber is ventilated. The target mechanism is opened by a pneumatic cylinder (fig. 7). The target is then automatically released and guided by the transfer channel directly into a stainless steel box situated in the middle of a cylindrical lead container (fig. 8 and 9). The transfer channel is then slid away by means of an electrical motor, and the lid is placed on the container by means of an electrically driven tackle. The lid for the inner steel box is fixed to the outer lid by a small permanent magnet, and is automatically snapped onto the box. An "o"-ring tightening on the lid prevents humidity from penetrating into the box and activity from leaking out. After the top lid is fixed by screws, the irradiated target is ready for the 25 km transport to The Isotope Laboratories, IFE, Kjeller, for chemical processing.

CHEMICAL SEPARATION OF GALLIUM AND PREPARATION OF A RADIOPHARMACEUTICAL

The final product, the radiopharmaceutical, is wanted in the form of a ^{67}Ga -citrate complex in an isotonic saline solution. The solution must contain minimum amount of zinc. The iron amount must also be kept at a lowest possible value because there are recent indications that iron-citrate inhibits the uptake of ^{67}Ga in tumors²¹⁾. Hence, we are faced with the problem of separating tracer amounts of ^{66}Ga from the target material zinc and from microamounts of iron which is present as a contaminant in the target material.

Chemical separation procedures reported in the literature are mainly based on solvent extraction and ion exchange. The main procedures are a). solvent extraction with isopropyl ether from strong hydrochloric acid solutions²²⁾, b). solvent extraction with methyl isobutyl ketone from a 2 M hydrochloric acid solution containing 1 M sulphate¹⁴⁾, c). solvent extraction with 4-methyl-2-pentatone from a 5 M hydrochloric acid solution, a stripping with water and a subsequent anion exchange step⁶⁾, d). cation exchange from strong hydrochloric acid solutions¹⁰⁾, and e). adsorption on alumina from a hydrochloric acid solution containing nitrate at pH 2.5²³⁾.

All the five procedures contain steps to decontaminate the solution for possible iron content, and for all of them acceptable removal of the target material zinc is reported. When considering their applicability two factors were of importance: the processing laboratory wanted to avoid the involvement of volatile organic materials which when mixed with air ultimately might produce explosive conditions, and the procedure should be as simple as possible and keep the involvement of man to a minimum. Procedure d. was judged to meet these requirements best, and was chosen as a starting point for further studies.

Each step in the procedure has been tested several times under realistic conditions, and parameters like acidity, the dimensions of the ion exchange column, elution rate, elution volume etc. have been varied. Detailed results from these investigations will not be given here. This discussion will be restricted to a few specific comments on selected points followed by a description of the final procedure.

It has been found^{24,25)} by chromatographic methods that hydrolysis of gallium occurs to a significant degree when increasing the pH above 6. Although the ^{67}Ga biodistribution has been reported to be largely unaffected in the pH-range 6-10, it is probably advantageous for storing purposes to reduce the pH of the final citrate solution below 6 in order to avoid a strong hydrolysis. Commercial suppliers deliver their product at a pH ~ 5.5-7.0.

The buffered isotonic saline solution may be prepared at different pH-values by varying the amount of citric acid and sodiumcitrate, keeping the total citrate concentration at 1.53 mg/ml. This is equivalent to the recommendation of the company New England Nuclear²⁶⁾, NEN, which is one of the great suppliers of ^{67}Ga . The relation between the three parameters has been determined by measuring the pH-value in solutions of NaCl, Na-citrate and citric acid demanding an osmotic pressure corresponding to normal isotonic salt water (7 mg/ml of NaCl), and the constant citrate concentration of 1.53 mg/ml. The results are illustrated in fig. 10.

The main separation principle, sorbtion of radiogallium on a cation exchanger from strong hydrochloric acid solutions, constitute in fact a chemical problem. When increasing the HCl concentration one would ultimately expect the formation of GaCl_4^- which should not be fixed on a cation exchange column. The opposite is indeed the case. The overall distribution coefficient has been found to increase above 5-6 M HCl. This behaviour has previously been noticed by other investigators²⁷⁾, but no explanation of this unexpected deviation has, to the authors' knowledge, so far advanced. This problem may be the subject for a future study.

The final procedure slightly modified from the one described in ref. 10 consists of the following steps:

1. Prepare a column of the cation exchange resin DOWEX 50x8, 200-400 mesh (column length 10 cm, diameter 0.5 cm), preequilibrated in conc. HCl. Prepare at room temperature a saturated solution of NaI in conc. HCl.

2. Dissolve the zinc target in 25 ml of this solution and add another 5 ml after the end of reaction. The I^- reduces any $Fe(III)$ present to $Fe(II)$. The final solution has an acidity of $[H^+] = 7.5 M$.
3. Percolate the solution through the column at a speed of 2.5 ml/min. $Ga(III)$ is fixed to the column while $Zn(II)$ and $Fe(II)$ run quantitatively through.
4. Wash the column with five separate portions of 5 ml of the NaI -solution to remove any traces of Zn and Fe , and subsequently with two portions of pure conc. HCl to remove traces of I^- .
5. Elute $Ga(III)$ with 20 ml $3M HCl$ at the same speed as mentioned previously.
6. Evaporate the solution containing $Ga(III)$ to dryness by letting a sterile air stream blow through the liquid under gentle and controlled heating ($50-60^\circ C$).
7. Cool down to room temperature and dissolve the residue in an isotonic saline solution containing citrate as a complexing agent for gallium. Use the curves of fig. 10.
8. Perform sterile filtering and autoclavation of the citrate solution and analyze the product for traces of Fe and Zn by atomic absorption.

A process equipment based on this procedure has been built inside a leadshielded fume hood at The Isotope Laboratories, IFE, Kjeller. The main principles are illustrated in fig. 11. The apparatus has been used in several full-scale test productions with good results. The procedure gives routinely > 80% chemical yield, and the contamination levels of Fe and Zn is below 2 ppm. It requires at present four to five hours of working time and human attention, but parts of it may easily be automated.

Our product at pH 5.5 has been pyrogentested and injected on mice with no negative reactions. This part was performed by personnel at IFE. The radiopharmaceutical has subsequently been used in human investigations at the Department of Nuclear Medicine, Ullevål Hospital, in Oslo.

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Figure Captions

- Fig. 1. The figure shows the depth distribution of ^{66}Ga and ^{67}Ga in a 1.5 mm thick target of natural zinc irradiated with 29 MeV protons. The depth resolution is 0.1 mm (one foil thickness). The results have been normalized to an irradiation time of one hour, and are expressed in mCi/ μAh .
- Fig. 2. The required decay time of the irradiated sample in order to reduce the contamination of ^{66}Ga below 1% (left axis) and 0.1% (right axis), respectively, as a function of the applied target thickness. The proton energy is 29 MeV. The results are illustrated for the two different and realistic irradiation times of 1 h and 3 h.
- Fig. 3. The upper curve shows the integrated production yield of ^{67}Ga after an irradiation time of one hour as a function of the target thickness, expressed in mCi/ μAh . This curve has in the two lower curves been converted to curves expressing the "useful" production yield taking into account the decaytime required to reduce the ^{66}Ga -contamination below 1% and 0.1%, respectively. The proton bombarding energy is 29 MeV.
- Fig. 4. The integral "useful" production yield of ^{67}Ga at 1% contamination level of ^{66}Ga as a function of the applied target thickness. The proton bombarding energy is parameter.
- Fig. 5. Cross section of the heating arrangement used for production of the zinc targets.
- Fig. 6. Principle layout of the proton beamline at the irradiation position.
- Fig. 7. The target-holding mechanism shown in the semilocked (a.) and the open (b.) position.

Fig. 8. Sketch of the apparatus for production of ^{67}Ga .

Fig. 9. The container used for transport of the irradiated zinc target between the Cyclotron laboratory and the Isotope laboratory, Kjeller. The wall thickness of the lead container is at minimum 10 cm.

Fig. 10. The pH-value as a function of the concentrations of citric acid and Na_3 -citrate, keeping the total citrate concentration at 1.53 mg/ml.

Fig. 11. Principle layout of the chemical processing apparatus built for the production of the ^{67}Ga -citrate radiopharmaceutical.

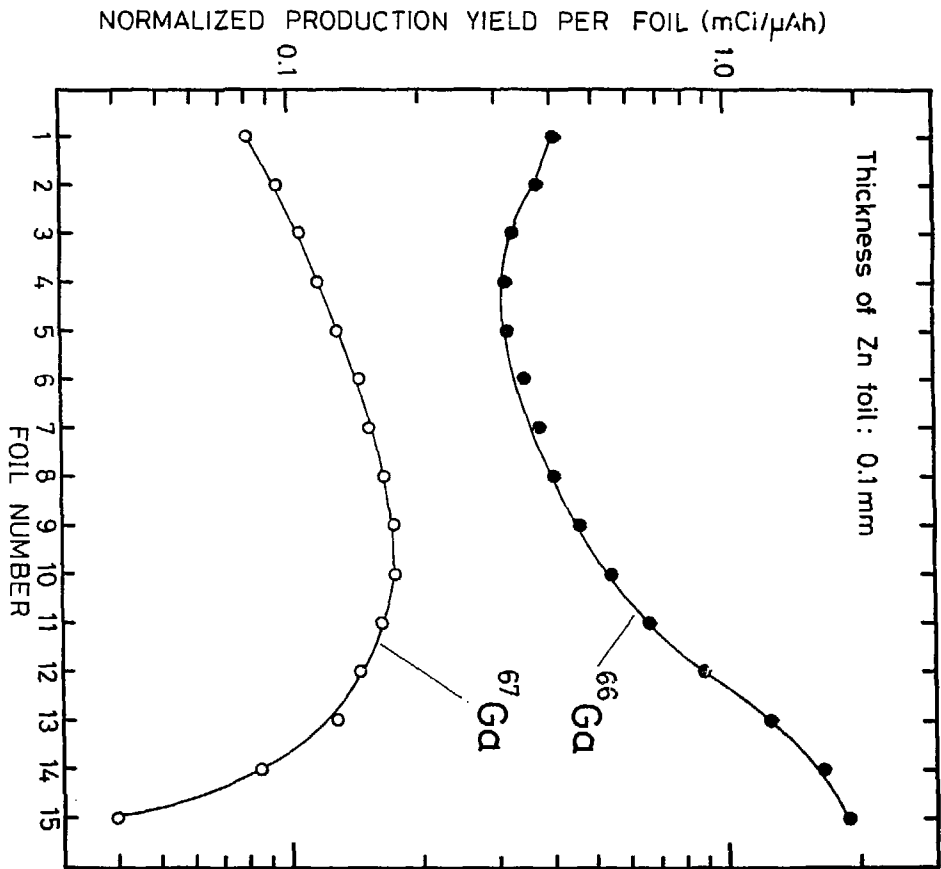


Fig. 1

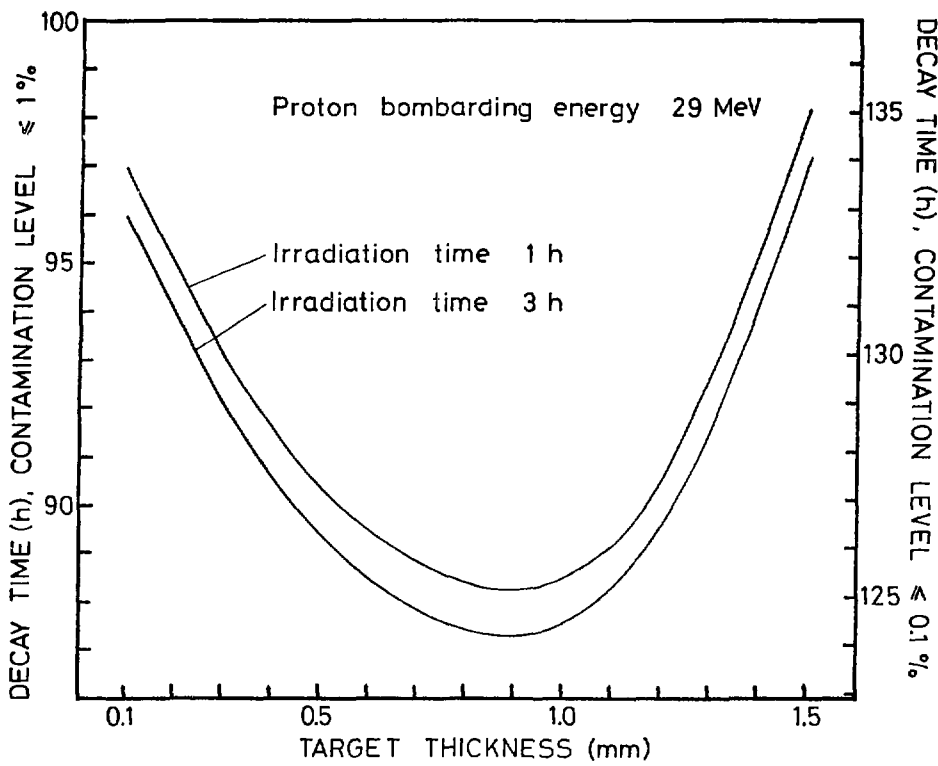


Fig.2

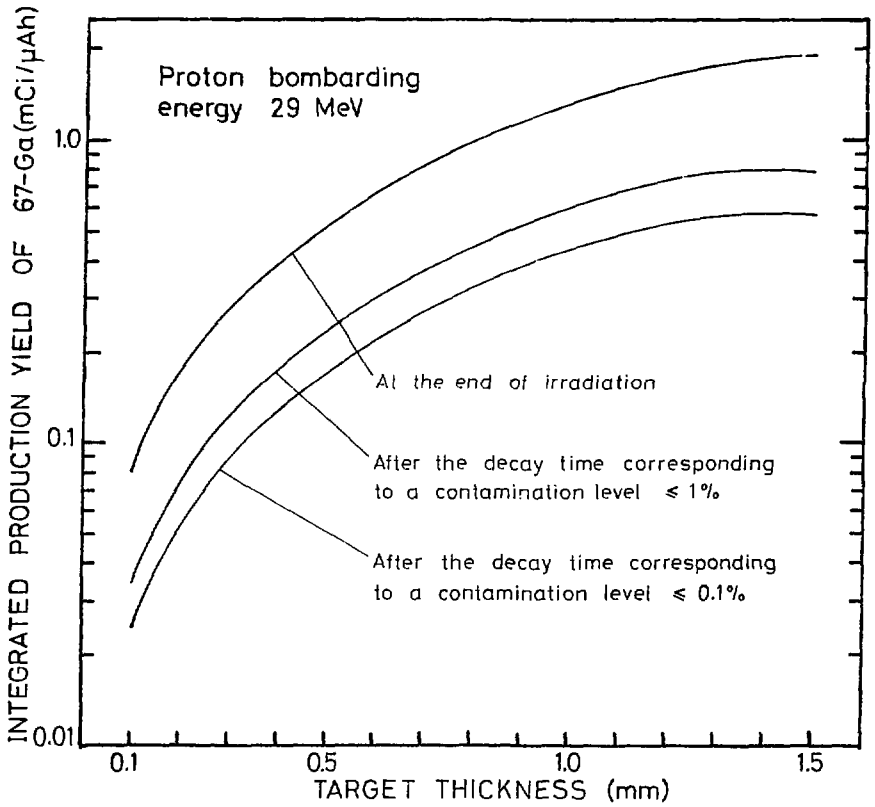


Fig. 3

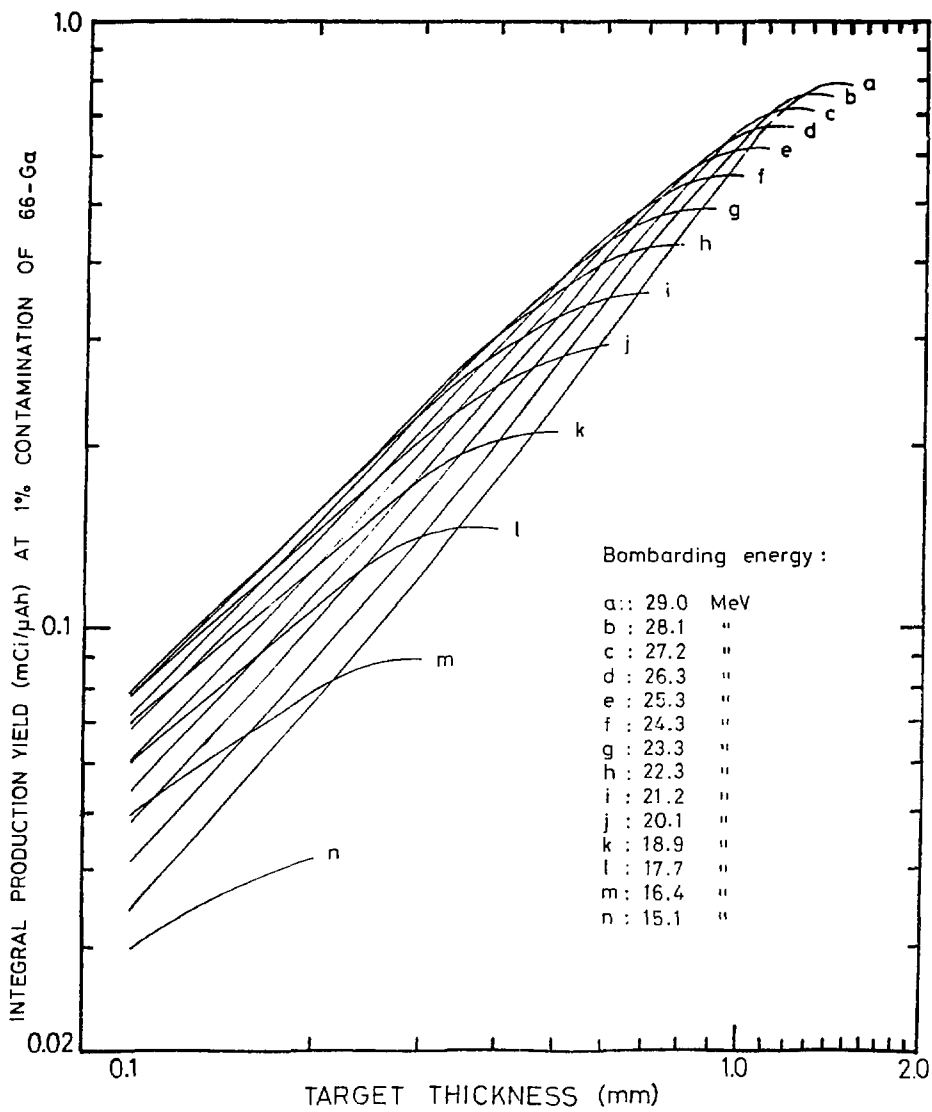


Fig.4

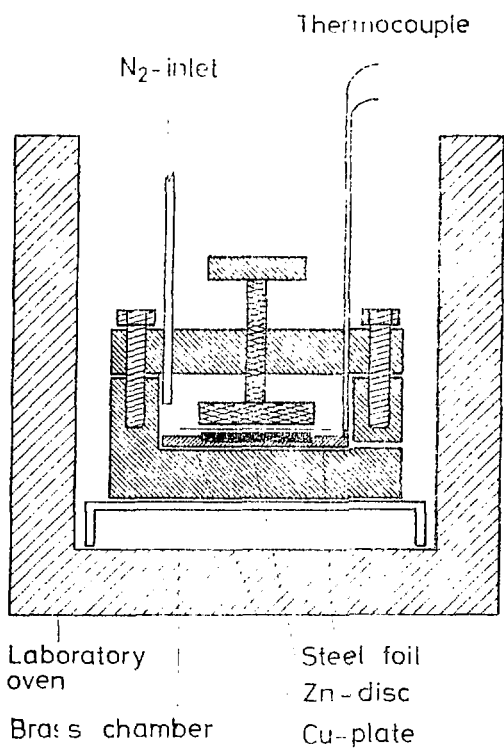


Fig. 5

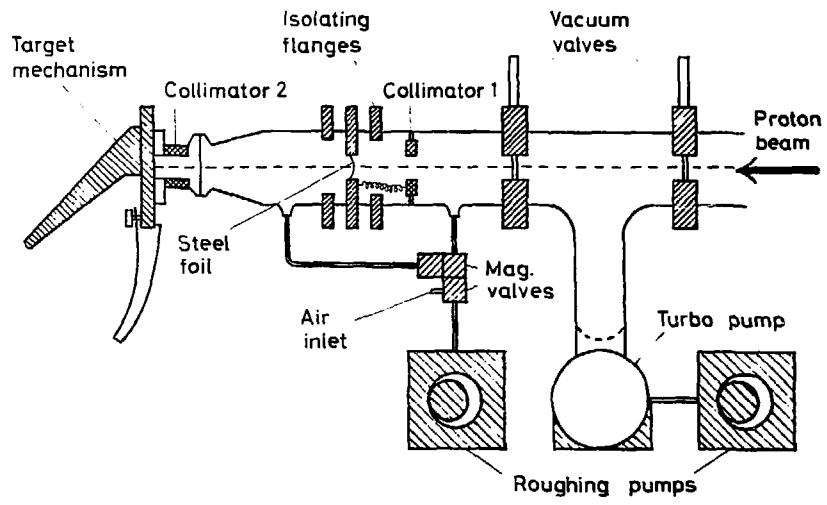


Fig. 6

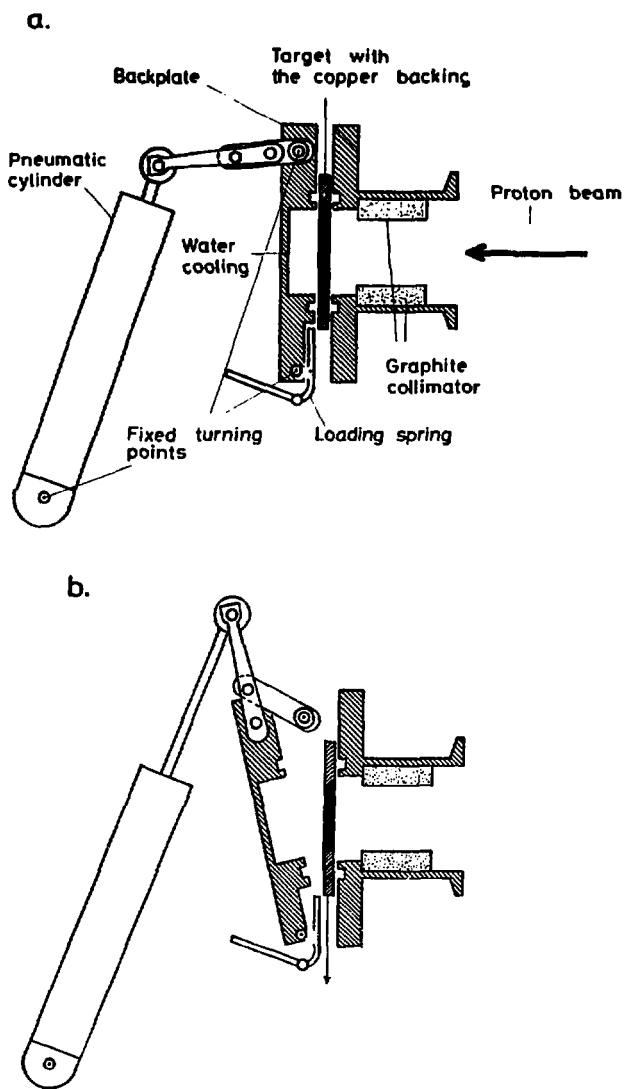


Fig. 7

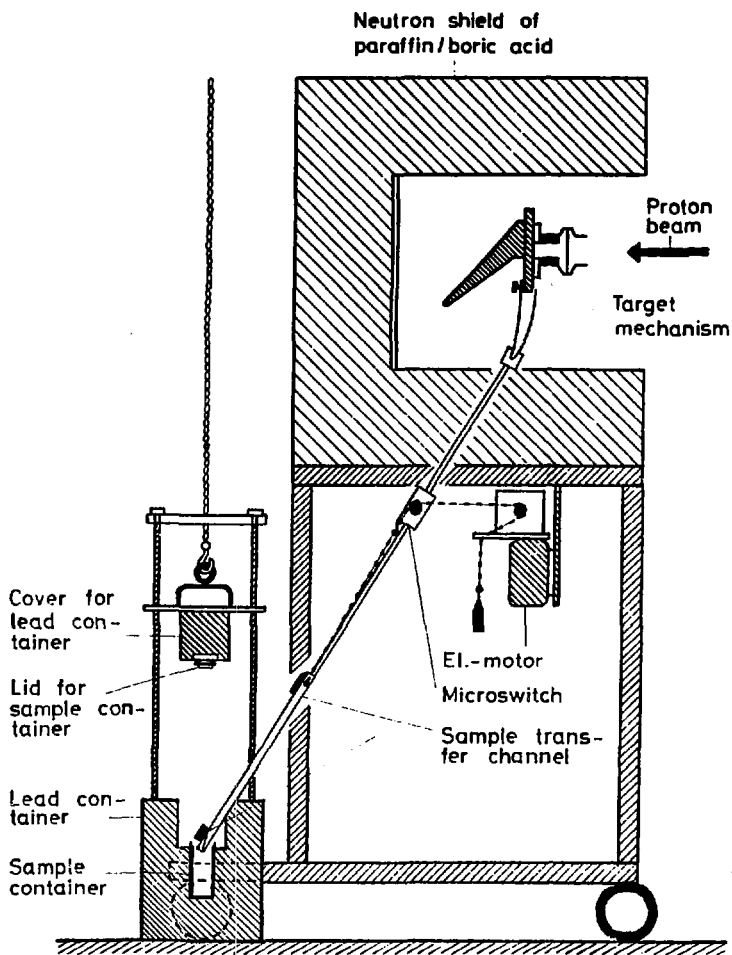


Fig. 8

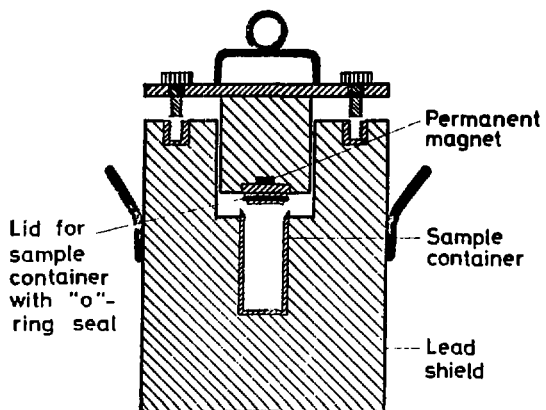
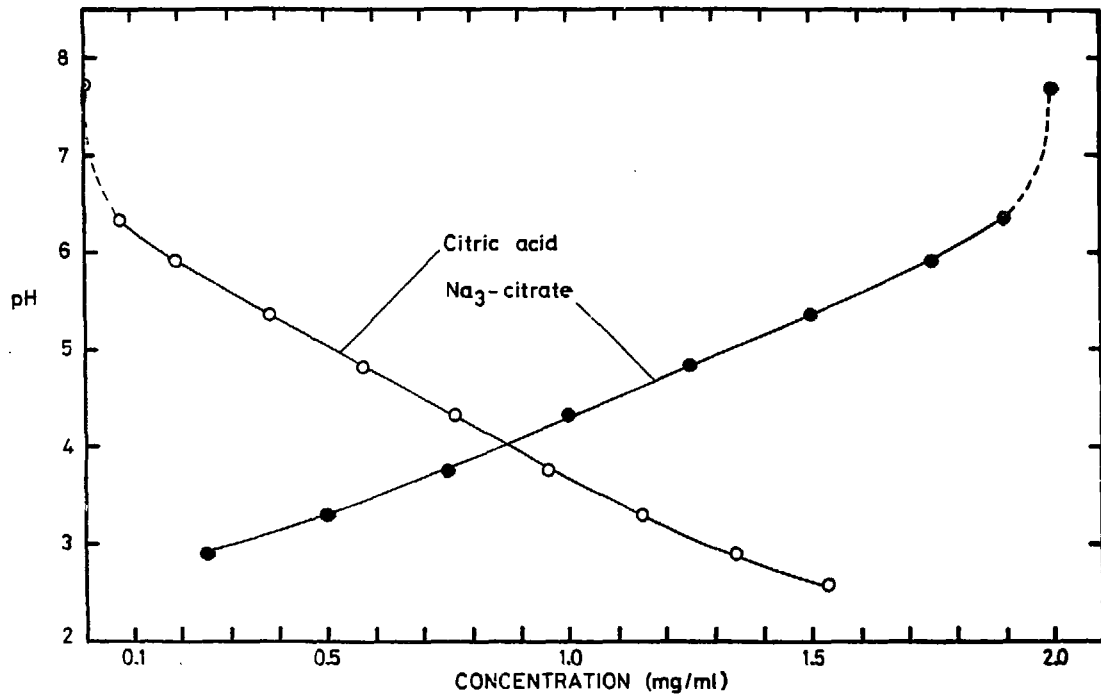


Fig. 9

Fig.10



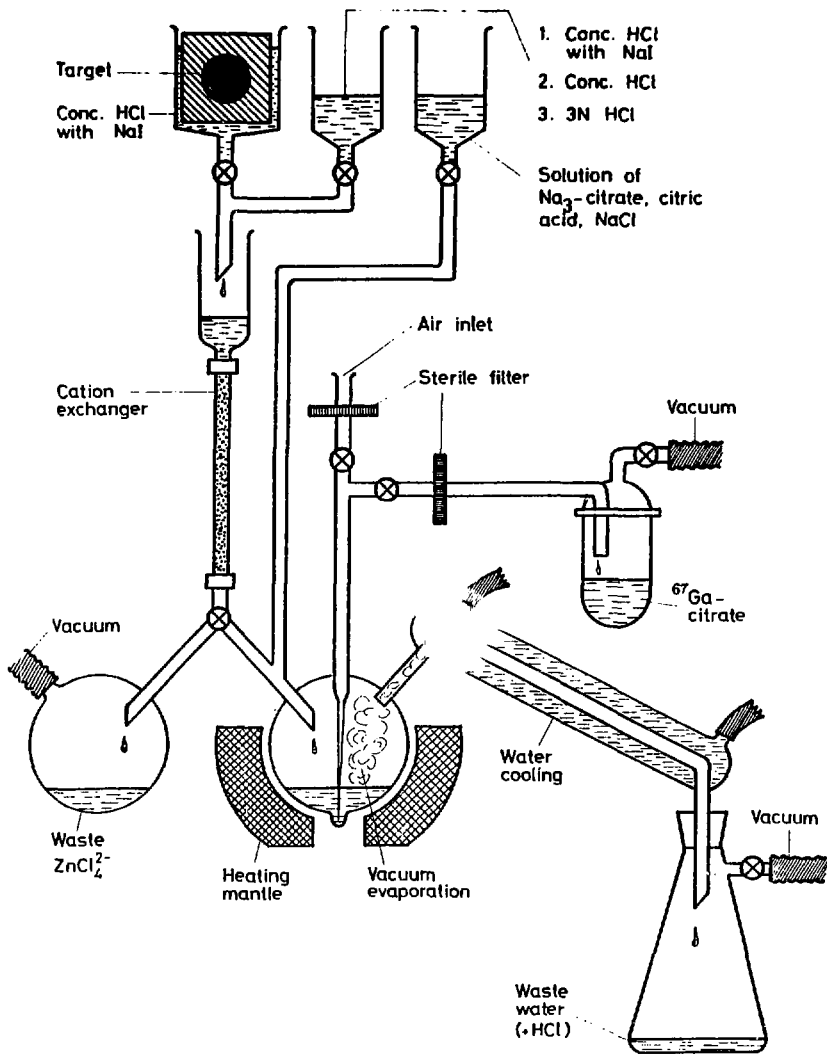


Fig.11