**Abstract**

**Background/Objectives:** The review techniques for obtaining of 111 In and preparation of indium [111In] chloride, experimental results feasibility study and peculiarity for 111In obtaining for irradiations natCd and enriched 111Cd targets is presented. **Methods/Statistical analysis:** Some methods for obtaining 111In by means of nat Ag (α, xn) reaction with α particles from 16 to 30 MeV. However the yield 111In in this reaction in several times lesser, than in reaction 111Cd (p, n)111In. Moreover impurity nuclide 109In are resulted in 107Ag (α, 2n) reaction, that takes target cooling within 36 hours before separation 111In. All measured to the present time cross-sections of the reactions to obtain 111In are accumulated in database IAEA. **Findings:** It was shown, that technical production rate of 111In no less then 627 MBq/h can be provided with using 120 cm cyclotron P7M of Tomsk Polytechnic University. To increase production rate it needs to increase technical yield 111In in the target under irradiation, under its separation from the target and synthesise RPP. **Applications/Improvements:** 111In is interesting for radionuclide therapies of oncological diseases because it emits Auger electrons having a high linear energy transfer (LET), compared with LET α-particles.

**Keywords:** Cadmium, Cyclotron, Peculiarities, Radioisotopes, Radio Pharmaceutical Preparations

### 1. Introduction

Radio pharmaceutical preparations (RPP) with nuclide 111In (T_{1/2} = 2,807 d, E_{γ} = 171,28 кэВ (90,24 %) and 245,39 кэВ (94,0 %) are among widely used in nuclear medicine. 111In apply for labelling of cellular components of blood, monoclonal antibodies, detection of pathologies of a myocardium, localisation of abscesses of a cystitis of kidneys, radio immunoglobulin therapy, visualisation of a swellings, tumours in oncology and in some other areas. 111In is interesting for radionuclide therapies of oncological diseases because it emits Auger electrons having a high linear energy transfer (LET), compared with LET α-particles.

As a chemical element has 8 stable isotopes: 106Cd(1,25 %), 108Cd(0,89 %), 110Cd(12,49 %), 111Cd(12,80 %), 112Cd(24,13 %), 113Cd(12,22 %), 114Cd(28,73 %), 116Cd(7,49 %).

It is possible to obtain 111In by means of reactions:

\[
^{112}\text{Sn}(p, 2n)^{111}\text{Sb} \rightarrow \text{EC, } \beta^+ \rightarrow ^{111}\text{In}, \quad ^{110}\text{Cd}(\text{He3}, 2n)^{111}\text{Sn} \rightarrow \text{EC, } \beta^+ \rightarrow ^{111}\text{In}.
\]

Maximal yields of 111In are provided in direct reactions: 111Cd (p, n)111In and 111Cd(d, 2n)111In. Few isotopes of indium are resulted when cadmium irradiated by means of 11 MeV protons: 111In in reaction 111Cd(p, n); 113mIn (T_{1/2} = 1,66 h); 114In (T_{1/2} = 71,9 s); 114mIn (T_{1/2} = 49,5 d); 115mIn (T_{1/2} = 4,87 h). Practically, single radioisotope 114mIn influences on a radionuclide purity 111In. Other radioisotopes have small time of a life.

Development of methods of obtaining and radiochemical separation 111In has been begun since the late forties years. The problem of obtaining and separation 111In without the carrier for commercial delivery has been stated in 1955 for the first time in framework of the joint program of the Leningrad State University (USSR) and Oak Ridge National Laboratory (ORNL) (USA). 15 MeV deuterons, of cyclotron Y-120 and a cadmium target were used in this work. Method co sedimentation with Fe (OH)₃, and extraction by isopropyl ether were used.
for $^{111}$In extraction from the target. The thick target yield $^{111}$In has been measured as $18 \pm 12$ μCi/μA•h. In 1967 in clinic Sloan Kettering Institute for Cancer Research in New York production $^{111}$In for medicine have been started using of natural cadmium target using 15 MeV protons of compact cyclotron. $^{114}$Cd impurity was as 3%.

Measurements of excitation functions of nuclear reactions induced proton irradiation of enriched $^{109}$Cd and $^{112}$Cd targets $^{20-22}$ and the reactions induced $^4$He in silver target $^{23-24}$ have been allowed to evaluate possibilities of using these reactions for production $^{111}$In in commercial scales. Yield $^{111}$In equal $515 \pm 60$ μCi/μA•h ($19.5 \pm 2.2$ MBq/μA•h) from a thick target of $^{112}$CdO ($^{111}$Cd > 96.5 %) at 16 MeV proton irradiation have been determined $^{25}$. While enriched $^{111}$Cd is used impurity of $^{114}$mCd is minimised. Excitation function and thick target yields $^{111}$In in reactions $^{113,114}$Cd (p, xn)$^{111}$In for in protons from 3 to 63 MeV have been measured $^{26}$. Yield $^{111}$In in reactions $^{113}$Cd (p, 3n)$^{111}$In and $^{114}$Cd (p, 4n)$^{111}$In for protons 42 MeV were 1140 and 880 μCi/μA•h with accuracy ± 20 %, and the impurity $^{114}$In$^{111}$In equal 0.27 and 1.5 μCi/μA•h for targets $^{113}$Cd and $^{114}$Cd accordingly. Cross-sections reactions with various Cd isotopes for obtaining $^{111}$In have been studied $^{27-29}$.

It is necessary to notice, that there are some methods for obtaining $^{111}$In by means of $^{108}$Ag(a, xn) reaction with α particles from 16 to 30 MeV $^{30}$. However the yield $^{111}$In in this reaction in several times lesser, than in reaction $^{111}$Cd (p, n)$^{111}$In. Moreover impurity nuclide $^{109}$In are resulted in $^{107}$Ag (a, 2n) reaction, that takes target cooling within 36 hours before separation $^{111}$In. All measured to the present time cross-sections of the reactions to obtain $^{111}$In are accumulated in database IAEA $^{29}$.

2. Theoretic Estimations of 111 in Obtaining using 120 cm Cyclotron.

Activity of obtained radionuclide after charged particles bombardment of a target is determined by the equation (1)$^{31}$:

$$A = n \frac{(1 - e^{-\sigma})}{\int_{E_{th}}^{E} \frac{\sigma(E)}{dE} dE}$$

(1)

where: $A$ - activity of a radionuclide, $c$; $n = \frac{N}{M}$ - number of nuclei in 1 g of a target, $N_A$ - an Avogadro number, $M$ - atomic weight, atomic units; $I$ - intensity of charged particles, $c$; $\lambda$ - α decay constant, $\lambda = \frac{ln2}{T_{1/2}}$, $c$; $T_{1/2}$ - a half-life time, $t$ - irradiation time; $\sigma(E)$ - cross-section of the reaction for particle with energy $E$, cm$^2$; $dE/dx$ - LET, MeVcm$^2$/g; $E_{th}$, $E_{out}$ - energy of particles at entrance and at leaving of the target accordingly, MeV. For thick target $E_{out}$ is equal to reaction threshold. Yield of radionuclide is being increased with increasing of irradiation time approaching to saturation value.

To obtain maximum yield it takes choose target thickness $d$ by equation (2):

$$d = (R(E_{th}) - R(E_{out})) \sin \vartheta$$

(2)

where: $R(E_{th}) = R(E_{out})$ - range in target material of proton with energy $E_{th}$, $R(E_{th}) = R(E_{out})$ - range of the protons with energy of threshold $E_{th}$; $\vartheta$ - angle between a surface of a target and a beam.

Range of protons in metallic Cd is presented in Figure 1. Using Eq. 2 it is possible to determine necessary $^{111}$Cd target mass for given proton energies $E_{th}$ and $E_{out}$, and beam cross section area. For example, for proton with initial energy 11 MeV, energy of a threshold $^{111}$Cd(p,n) reaction of 1.6 MeV and $\vartheta = 6^\circ$ it takes thickness of metal $^{111}$Cd target 0.032 g/cm$^2$ (37 μm). If the beam area on the target is 8 cm$^2$ it takes 0.032 \cdot 8 = 0.256 g $^{111}$Cd. As protons are accelerated up to 11 MeV using the cyclotron of Tomsk Polytechnic University $^{111}$Cd (p, n)$^{111}$In reaction has been chosen for $^{111}$In manufacture.

It is necessary to notice, that internal proton beam current in cyclotron chamber at least in 2 times larger than in extracted beam and energy of particles in beam could be easily changed by means of changing radius of target. Energy of protons $E_p(r)$ in cyclotron is determined be orbit radius $r$, cm and frequency of electric field - $f$, MHz by equation (3)$^{32-33}$:

$$E_p(r) = 2.05 \times 10^{-11} f r^2$$

(3)

If we use activity of saturation $A_2$ by a current 1 μA at end of bombardment (EOB) for thick target in $^{111}$Cd (p, n)$^{111}$In reaction evaluated $^{29}$, we may evaluate activity $^{111}$In EOB A after irradiation by current $i$ [μA], during time $t$ [hour] for the target containing $\rho$ isotope abundance of $^{111}$Cd be Equation 4:

$$A = i^* A_2 (1 - e^{-\lambda t})$$

(4)
where: \( \lambda = \frac{\ln 2}{T_{1/2}} = \frac{0.693}{2.807 \times 24} = 0.010829 \text{h}^{-1} \) – decay constant for 111In.

Figure 1. Range of protons in metal cadmium.

For example, for a target from metal cadmium (100 %, \(^{111}\text{Cd}\)) irradiated by protons with energy 10.5 MeV \( A_2 \) is equal 2183 MBq/μA \(^3\). Theoretical possible activity \( A^{(111}\text{In}) \), for beam current \( i = 60 \mu\text{A} \) in cyclotron P7M TPU, in dependence of irradiation time \( t \) for target from enriched cadmium \(^{111}\text{Cd} \, (95.92 \pm 0.06\%) \) and natural cadmium \(^{111}\text{Cd}, 12.8\% \) is presented in Table 1.

Table 1. Expected activity 111In EOB at an irradiation of a target a beam of protons 60 μA

| t, h | \( A^{(111}\text{In}), \text{MBq, for} \) enriched Cd: \(^{111}\text{Cd}, \) (95.92±0.06%) | \( A^{(111}\text{In}), \text{MBq, for} \) natural Cd: \(^{111}\text{Cd}, 12.8\%, \) |
|------|-------------------------------------------------|-------------------------------------------------|
| 5    | 6439                                            | 859                                             |
| 10   | 13442                                           | 1793                                            |
| 15   | 18836                                           | 2513                                            |
| 20   | 24465                                           | 3264                                            |
| 25   | 29797                                           | 3976                                            |

It follows from Table 2 that to obtain enough for applications activity \(^{111}\text{In}\) there needs to use target of enriched isotope \(^{111}\text{Cd} \, (95.92 \pm 0.06\%) \).

3. Facility for Target Irradiation on Internal Cyclotron Beam

Target in cyclotron used to be irradiated by extracted beam or by internal one in accelerating chamber \(^3\). The choice what kind of irradiation to apply depends on available charged particles in the beam (charged positively or negatively), technical characteristics of a cyclotron and device for a target irradiation. Irradiation of target in cyclotron accelerating chamber is preferably used to avoid positive particles beam losses under extraction. There are devices for target irradiation in P7M cyclotron, both with using extracted and internal beam. Ion source of the cyclotron with additional rod for target irradiation on internal beam is presented in Figure 2. Under irradiation of a target it needs to provide:

- An irradiation of the target which are on a head of a rod, by means of tangential beam of protons.
- Heat removal from the target, by cooling by water of an underside.
- Measurement of beam current on the target.

Figure 2. (a) A source of protons in cyclotron P7M, (b) with an additional rod with head for deposition Cd target on copper support with golden layer.
Distilled water at rate 10 l/min, 8 bar was used to cool target head. The copper support, covered thin golden layer with deposited cadmium was fastened to the target head by pins and nuts. Cadmium deposited on support surface by means of cadmium melting. In compare with galvanic deposition melting provides deposit well defined amount of enrich metal Cd on the target. Cadmium surface was carefully polished, washed and dried. After irradiation a source of ions take off from the cyclotron chamber and place on a table (the Figure 2а), target support was separated from the head and was transported to radiochemical laboratory for separation $^{111}$In.

4. The Experiments on Obtaining $^{111}$In on Cyclotron P7M

4.1 Target of natural cadmium
The target was made of 330 mg natural cadmium that has been deposited on support surface by melting of 20 x 0,5 mm Cd foil. Target has been placed in cyclotron chamber on 52 cm radius. Energy of protons is equal 11,2 MeV for that target position and 14,197 MHz frequency of accelerating field. Beam was stroke to the target surface at 6°. Beam current on the target was 40 μA. Irradiation time - 20 minutes. The beam charge at bombarding radiation is equal 13,3 μAh$^{13-15}$. After irradiation cadmium target has been disssolved in 8M HBr acid. Total activity $^{111}$In of the solution was 26,3 MBq EOB. Activity EOB another In radioisotopes were: $^{114}$In - 4 %, $^{115}$In - 12 % of $^{111}$In activity. In recalculation on a target enriched to it is possible to expect that activity $^{111}$In EOB for such target will be equal 197,5 MBq. Technical yield of $^{111}$In for 96 % on $^{111}$Cd target was evaluated as 197,5 MBq /13,3 μAh = 14,8 MBq/μAh.

4.2 Target of Enriched by $^{111}$Cd Cadmium
The target was made of cadmium enriched to (95,92±0,06%) $^{111}$Cd and deposited on support by melting. The target was placed on pathway of internal beam in the cyclotron to manufacture $^{111}$In
Proton beam current was 45-50 μA, bombardment time was 1 h.
Data for experimental obtaining of $^{111}$In in 3 independent experimental runs are given in Table 2.

Maximum technical yield of $^{111}$In is equal 627 MBq/h (12,5 MBq/μAh).

Table 2. Experimental obtaining of 111In by means of irradiation 95,92% 111Cd targets

| № bombarding radiations | Mass of cadmium, 95,92% $^{111}$Cd, g | Current of a beam of protons, μA | Irradiation time, h | Activity (EOB) $^{111}$In, MBq |
|-------------------------|--------------------------------------|---------------------------------|---------------------|-------------------------------|
| 1                       | 0,335                                | 45                              | 1                   | 462,4                         |
| 2                       | 0,345                                | 45                              | 1                   | 238,5                         |
| 3                       | 0,350                                | 50                              | 1                   | 627,0                         |

These preliminary results can be used for prediction $^{111}$In obtaining. For example, to have 7 GBq it takes to irradiate target by 50 μA proton beam for about 11,2 hours. It is necessary to notice that there is a possibility to increase $^{111}$In production rate due to adjustment of target position and rising beam current.

5. Conclusion
The review techniques for obtaining of $^{111}$In and preparation of indium $[^{111}\text{In}]$ chloride, experimental results feasibility study and peculiarity for $^{111}$In obtaining for irradiations $^{nat}$Cd and enriched $^{111}$Cd targets is presented. It was shown, that technical production rate of $^{111}$In no less then 627 MBq/h can be provided with using 120 cm cyclotron P7M of Tomsk Polytechnic University.

To increase production rate it needs to increase technical yield $^{111}$In in the target under irradiation, under its separation from the target and synthesise RPP.

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