Separation of Radiocopper $^{64/67}$Cu from the Matrix of Neutron-Irradiated Natural Zinc Applicable for ^{64}Cu Production

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ABSTRACT

Radioisotope ^{64}Cu is a promising radiometallic-isotope for molecular-targeted-radiopharmaceuticals. Having a half-life of 12.70 hours and emitting β^+-radiation ($E_{\beta+}$ = 0.6531 MeV) as well as β^-ray ($E_{\beta-}$ = 0.5787 MeV), it is widely used in the form of biomedical-substrate-radiopharmaceutical for positron emission tomography (PET) diagnosis and simultaneously for targeted radiotherapy of cancer. The potential needs on the availability of ^{64}Cu-labeled pharmaceuticals for domestic nuclear medicine hospitals lead to a necessity for the local production of carrier-free ^{64}Cu using BATAN's G.A. Siwabessy reactor because of the technical and economical constraints in the production using BATAN's cyclotron. The presented work is accordingly to study whether the radioisotope ^{64}Cu can be produced and separated from the matrix of post-neutron-irradiated-natural zinc. This study is expected can be further improved and implemented in production technology of carrier-free ^{64}Cu based on ^{64}Zn (n,p) ^{64}Cu nuclear reaction exploiting the fast neutron fraction among the major thermal fraction due to unavailability of fast-neutron-irradiation facility in the BATAN's G.A. Siwabessy reactor. The solution of post-neutron-irradiated-natural zinc in 1M acetic acid was loaded into Chelex-100 cation exchanger resin column to pass out the Zn/Zn* fraction whereas the Cu* fraction which remained in the column was then eluted out from the column by using 1.5 M HCl and loaded into the second column containing Dowex-1X8 anion exchanger resin. The second column was then eluted with 0.5 M HCl. The collected eluate was expected to be zinc-free Cu* fraction. It was observed from the half-life and the γ-spectrometric analysis that radioactive copper-^{64}Cu containing ^{67}Cu was produced by neutron activation on the natural Zn-foil target and can be separated from the target matrix by the presented two-steps-column-chromatographic separation technique. The radioactivity measurement showed that wrapping the Zn target with cadmium foil increased the activity of radioactive copper and, thus, the Cu*/Zn*-ratio.

INTRODUCTION

Turning out attention to the development of molecular-targeted-radiopharmaceuticals, researches on production of metal radionuclides emitting both β^-(negatron) and β^+(positron) are incited to provide suitable radioisotope for diagnostic and therapeutic radiopharmaceuticals. Among the promising radiometalic-isotopes being reported is radiocopper-^{64}Cu [1] which decays by various ways *i.e.* positron decay (17.86%, $E_{\beta+}$ = 0.6531 MeV) followed by emission of γ-annihilation radiation (E_γ = 0.511 MeV), negatron

decay (39.0%, $E_{\beta-}$ = 0.5787 MeV), electron capture (43.075 %) and internal conversion (0.475%) [2,3] emitting a higher energy of γ-ray (E_γ = 1.34579 MeV) that is often not appeared clearly on the presentation of its γ-ray spectra because the intensity is very low.

Having a half-life of 12.7 hours, the ^{64}Cu is suitable to label biomedical substrates with slow biological up-take kinetics such as peptide and antibody monoclonal compounds. As a β^+-emitter, ^{64}Cu is used in positron emission tomography (PET) diagnostics giving an easier radiation dose estimation when compared to the shorter half-life PET nuclides such as ^{18}F ($t_{1/2}$ = 110 min) and ^{11}C ($t_{1/2}$ = 20 min) [4]. As a β^--emitter, it can be simultaneously used for targeted

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radiotherapy of cancer [1]. Many researches leading to the application of various ^{64}Cu-labeled radiopharmaceuticals for both medical diagnosis and therapy have been reported [5-9]. An extensive review on the chelation chemistry of copper and its role in copper radiopharmaceutical (specifically ^{64}Cu-radiopharmaceuticals) has also been available [10]. In Indonesia, however, the application of ^{64}Cu-radiopharmaceuticals can not be offered yet because of the lack of capability on the production technology of carrier-free [64]Cu [11].

This radioisotope can be produced from both nuclear reactor and cyclotron. In a research nuclear reactor such as BATAN's G.A. Siwabessy reactor in Serpong, the radiocopper-^{64}Cu can be produced by means of simple (n,γ)-nuclear reaction using high-enriched [63]Cu target , but by this nuclear reaction type the radioactive product can not be separated from its stable isotope in the target matrix. Accordingly, the specific activity of the product will be relatively low and mostly unsatisfactory to be used for medical purposes. The (n,p)-based nuclear reaction using high-enriched [64]Zn target is an alternative way to produce ^{64}Cu from nuclear reactor giving carrier-free (high specific activity) product [12]. This nuclear reaction needs fast neutron beams but there is no irradiation facility using fast neutron fraction available in the G.A. Siwabessy reactor. The bombardment of thermal neutron on the [64]Zn target will mainly produce radioisotope [65]Zn ($t_{1/2}$ = 244 days, E_γ = 1.115 MeV). If natural Zn is used as target, based on the composition of natural isotopic abundance of Zn [13,14], other radioactive Zn will also be produced ([69]Zn, [69m]Zn, [71]Zn and [71m]Zn), but their half-lives are very short as compared to the [65]Zn. The nuclear reaction based on proton activation in the BATAN's cyclotron in Serpong is accordingly important to be considered as a choice to produce carrier-free radioactive copper-^{64}Cu, but it still has big constraints related to either technical or economical consideration. The nuclear reaction of [68]Zn $(p,\alpha n)$ [64]Cu needs proton beam energy of more than 30 MeV [15] which can not be achieved by the BATAN's cyclotron machine, so technically it can not be performed in BATAN. In other side, the nuclear reaction of [64]Ni (p,n) [64]Cu [11,16-18] requiring less than 25 MeV of proton beam energy can be technically performed but the high-enriched [64]Ni is very expensive (about $ 18/mg in 2007) [10], due to its very low natural abundance, which is only 0.9256% [19], so it is still difficult to be implemented by the reason of economy.

Because of the potential needs on the availability of ^{64}Cu-labeled pharmaceuticals for domestic nuclear medicine hospitals, the local production of carrier-free ^{64}Cu using BATAN's G.A. Siwabessy reactor becomes a necessity. Among the neutron beams in the G.A. Siwabessy reactor, the existing fast neutron fraction might be probable to be exploited for irradiating the Zn-target while the thermal neutron fraction is prevented to bombard the target. This prevention is expected can be carried out by means of wrapping the target with cadmium foil or placing the target in a boron-irradiation tube.

The presented work is aimed, therefore, to study whether the carrier-free ^{64}Cu can be produced in G.A. Siwabessy reactor and, if so, to gain technical procedure for the separation of the resulting ^{64}Cu from the matrix of neutron-irradiated Zn-target. By the economical consideration, the presented work is performed using natural Zn-target instead of the high-enriched [64]Zn, and cadmium foil wrap instead of boron-irradiation tube. The presented works were expected can be further improved and implemented in [64]Cu- production technology based on [64]Zn (n,p) ^{64}Cu nuclear reaction.

EXPERIMENTAL METHODS

Materials and equipments

The natural Zn-target foil having purity of 99.9% (from Sigma-Aldrich) was put ready in small pieces form. Quartz tubes of irradiation grade used as irradiation tubes, as well as inner and outer capsules for irradiation which were made of high-purity aluminium, were produced by local company. Foil of natural cadmium (Cd-foil) having purity of 99.99 % (from Sigma-Aldrich) was used as wrapper for the quartz tube containing the Zn-target. Two types of ion exchanger resins, *i.e.* Chelex-100 (100 – 200 mesh) cation exchanger and Dowex-1X8 (200 – 400 mesh) anion exchanger (both from Bio-Rad Richmond) were used for chromatographic separation using glass column ($\varnothing$ 10 mm, h 200 mm) made by local company. The chemical materials used as mobile phase in column-chromatographic separation or as solvent were pro analysis grade (from E. Merck) and diluted as necessary using demineralized water (aqua DM) from water purification facility in Multi Purposes Reactor Center, BATAN, Serpong.

The target-contained-quartz tubes were closed by acetylene-glass welder, whereas the inner irradiation capsules were closed by argon-welding machine Super Tic 180. The welding result was then leak-tested by means of bubble test using vacuum pump Varian DD-20. A well-type

dose calibrator (Atom Lab) was used for radioactivity measurement. A γ-spectrometer system equipped with multi channels analyser (Canberra 1000) and HP-Ge detector of Canberra Industries was used for radionuclidic analysis. The system was calibrated using a set of standard-sealed-sources comprising [133]Ba (302.85 and 356.01 keV), [137]Cs (661.64 keV) and [60]Co (1,173.23 and 1,332.51 keV) from Du Pont [11].

Target preparation and post-irradiation treatment

An approximately 500 mg of natural Zn-target pieces were placed in quartz tube which was then closed by acetylene-glass welding and then wrapped using cadmium foil. The wrapping target was then placed into inner irradiation capsule which was then closed by argon-welding. After passing the leak-bubble test, the inner irradiation capsule was put into the outer capsule and this set of target was then sent to G.A. Siwabessy reactor to be irradiated at the CIP (central irradiation position). An unwrapped target was treated similarly as comparator.

The post-irradiated target was transported into the receiving hot cell and kept for several hours before further processing in order to allow the decay of the short-lived radioisotope produced. The quartz tube was brought out from the irradiation capsule and the Cd-foil wrap, and broken at the tip to transfer its content into a 100 mL glass beaker. The irradiated Zn was then dissolved in concentrate HCl (5 mL). The resulting solution was heated to dryness, and then the residue was re-dissolved with 1 M acetic acid solution (4.5 - 5 mL). The resulting solution was labelled as Bulk Solution.

Column preparation and radionuclidic separation

Two glass columns containing Chelex-100 cation resin and Dowex-1X8 anion resin respectively were prepared. Each column was filled with about 6 ml of resin-bed volume (7.5 cm of height) and conditioned with 1 M acetic acid (pH = ~ 2.7) for the cation exchanger column and with 1 M HCl for the anion exchanger column. The radionuclidic separation procedure was a two-steps-chromatographic column technique adopted from the method reported by Zinn, *et al.* [12]. A volume of 3 mL of Bulk Solution was cited and loaded into the Chelex-100 column and passed out the column

into a Bottle-A. The column was washed with 15 mL of 1 M acetic acid solution and then with 3 mL of water. All the eluate-washings were assumed as Zn/Zn*-fraction (the asterisk "*" indicates radioactive species) and collected in Bottle-A. The Chelex-100 cation exchanger column was then eluted with 10 mL of 1.5 M HCl solution to pass off the raw-Cu*-fraction from the column which was separately collected into a Bottle-B.

The content of the Bottle-B was loaded into the Dowex-1X8 anion exchanger column and passed out the column into a Bottle-C followed with washing the Dowex-1X8 column using 10 mL of 0.5 M HCl . The eluate was collected and combined in the Bottle-C and assumed as pure-Cu*-fraction. The whole column chromatographic separation is shown in Fig. 1.
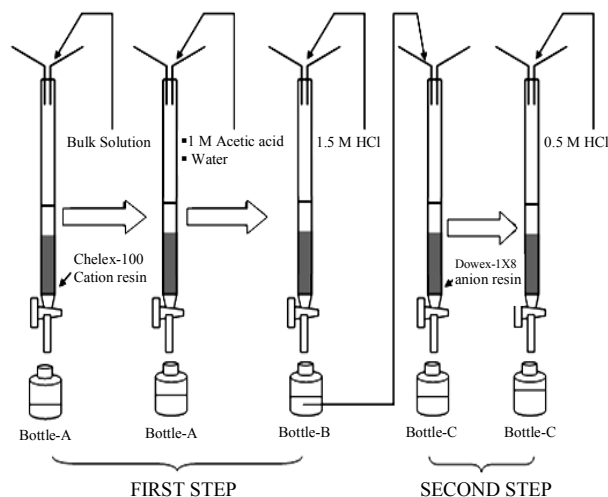

Fig. 1. Separation procedure using two steps of chromatographic column.

Radioactivity analysis

The radioactivity analysis comprised direct measurement of radioactivity, γ-ray spectrometry and half-life determination. The measurement of radioactivity was carried out directly using a well-type dose calibrator. For the γ-ray spectrometry, a 5 – 20 μL of sample was pipetted out, spotted and adsorbed on a 2-cm-diameter filter paper. The filter paper was dried and put into a small plastic bag and then counted by using calibrated γ-spectrometer to gain the γ-ray spectra. The half-life of the Cu* sample was determined by repeated measurement of its radioactivity and

plotting the results as a function of decay time. The resulting decay curve was compared to theoretical calculation using a half-life value of 12.70 hours [13].

RESULTS AND DISCUSSION

Naturally occurring zinc (Zn) is composed of five stable isotopes : ^{64}Zn, ^{66}Zn, ^{67}Zn, ^{68}Zn and ^{70}Zn with ^{64}Zn being the most abundant [18]. Their natural abundance, (n,γ) and (n,p)-nuclear reactions and products are shown in Table 1.

Table 1. Natural abundance of Zn-isotopes and their (n,γ) and (n,p)-nuclear reactions.

ISOTOPE AND ABUNDANCE	NUCLEAR REACTIONS AND PRODUCTS [(n,γ) and (n,p)]				
	Nuclear reaction	Cross section (×10^{-3} barn)	t$_{1/2}$ of product[13]	Important γ-rays	
				E$_\gamma$ (MeV)	Intensity (%)[13]
^{64}Zn (48.63 %)[13,14]	^{64}Zn (n,γ) ^{65}Zn	790[14] 787[20]	244.26 d	1.1155 0.511	50.60 3 (annihilation)[24]
	^{64}Zn (n,p) ^{64}Cu	37.4[21]	12.70 h	0.511 1.346	36 (annihilation)[25] 0.473
^{66}Zn (27.90 %)[13,14]	^{66}Zn (n,γ) ^{67}Zn	620[14] 618[20]	stable	--	--
	^{66}Zn (n,p) ^{66}Cu	0.775[22]	5.12 min	1.039	9
^{67}Zn (4.10 %)[13,14]	^{67}Zn (n,γ) ^{68}Zn	7500[14] 7472[20]	stable	--	--
	^{67}Zn (n,p) ^{67}Cu	1.37[21]	61.83 h	0.1846	48.7
^{68}Zn (18.75 %)[13,14]	^{68}Zn (n,γ) ^{69}Zn	1000[14] 1066[20]	56.4 min	318.71	0.0012
	^{68}Zn (n,γ) ^{69m}Zn	72[14]	13.76 h	0.4386	94.77
	^{68}Zn (n,p) ^{68}Cu	0.0154[23]	31.10 s	1.077	64
	^{68}Zn (n,p) ^{68m}Cu	0.00369[23]	3.8 min	1.077	12
^{70}Zn (0.62 %)[13,14]	^{70}Zn (n,γ) ^{71}Zn	83[14] 92[20]	2.45 min	0.5116	32 (no annihilation)
	^{70}Zn (n,γ) ^{71m}Zn	8.7[14]	3.96 h	0.3863	93
	^{70}Zn (n,p) ^{70}Cu	No data	4.5 s	0.8849	54

It is shown from Table 1 that the (n,γ)-nuclear reaction on ^{NAT}Zn will produce 5 radioactive zinc species whereas the (n,p)-nuclear reaction will produce 6 radioactive copper species. The (n,α)-nuclear reaction will also happen producing radioactive nickel but the cross section is very small [21], so it is left out of consideration. Among the radioactive zinc and copper being mentioned in Table 1, ^{65}Zn, ^{69}Zn, ^{69m}Zn, ^{71m}Zn, ^{64}Cu and ^{67}Cu are important to be taken into consideration, whereas the others are less important because they have short half-lives and, so, almost none will be left by the end of the running experiments. Nevertheless, it can be seen in Fig. 2, the dissolved post-neutron-irradiated-natural zinc (the Bulk Solution) shows peaks energy of γ-rays at 438 keV (^{69m}Zn), 511 keV (annihilation of ^{65}Zn and ^{64}Cu) and 1,115 keV (^{65}Zn). The peaks energy of other γ-rays from ^{69}Zn, ^{71m}Zn, ^{64}Cu and ^{67}Cu are not visible because

their net areas are too small as compared to the existing main peaks due to either the intensity of the γ-ray or the cross section of the corresponding nuclear reaction is too low.
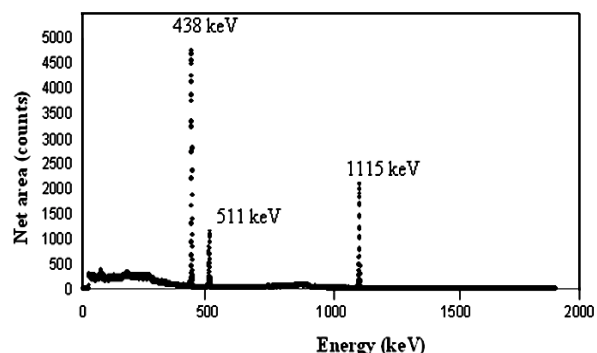
Fig. 2. Typical γ-spectrum of the dissolved post-neutron-irradiated-natural zinc (Bulk Solution).

The radionuclidic separation of the matrix in the dissolved post-irradiated target was then performed by means of two-steps chromatographic column using cation and anion exchanger resins successively [12]. The resulting fractions were collected in three receivers labeled as Bottle-A, Bottle-B and Bottle-C respectively as can be seen from Fig. 1 and Table 2.

Table 2. Radionuclidic separation system

FIRST COLUMN		SECOND COLUMN	
Type of resin : Chelex-100 cation exchanger Sample to be loaded : Bulk Solution		Type of resin : Dowex-1X8 anion exchanger Sample to be loaded : Fraction in Bottle-B	
Eluent	Resulting fraction	Eluent	Resulting fraction
1 M acetic acid	Bottle-A	None	Bottle-C
Water	Bottle-A (combined)		
1.5 M HCl	Bottle-B (loaded into the second column)	0.5 M HCl	Bottle-C (combined)

The γ-spectrometry analysis for the resulting fraction samples were then performed as similar to that for the Bulk Solution. The results were presented in Fig. 3, showing a typical γ-spectrum of the resulting fraction collected in Bottle-A, Bottle-B and Bottle-C successively.

Comparing to Fig. 2, it can be presumed that the Bottle-A (represented by Fig. 3(a)) contained Zn/Zn* fraction showing peaks position precisely similar to the Bulk Solution. It indicated that in the condition of weak acid (1 M acetic acid), the

Zn/Zn* fraction was mostly unbound by the cation exchanger resin. The intensity of the peak 511 keV, however, became to be lower indicating that the γ-annihilation of ^{64}Cu gave no more contribution as the ^{64}Cu/Cu* was retained in the column in the form of ^{64}Cu/Cu*$^{2+}$ cation. The peak 511 keV, thus, was expected coming from annihilation of ^{65}Zn [24].
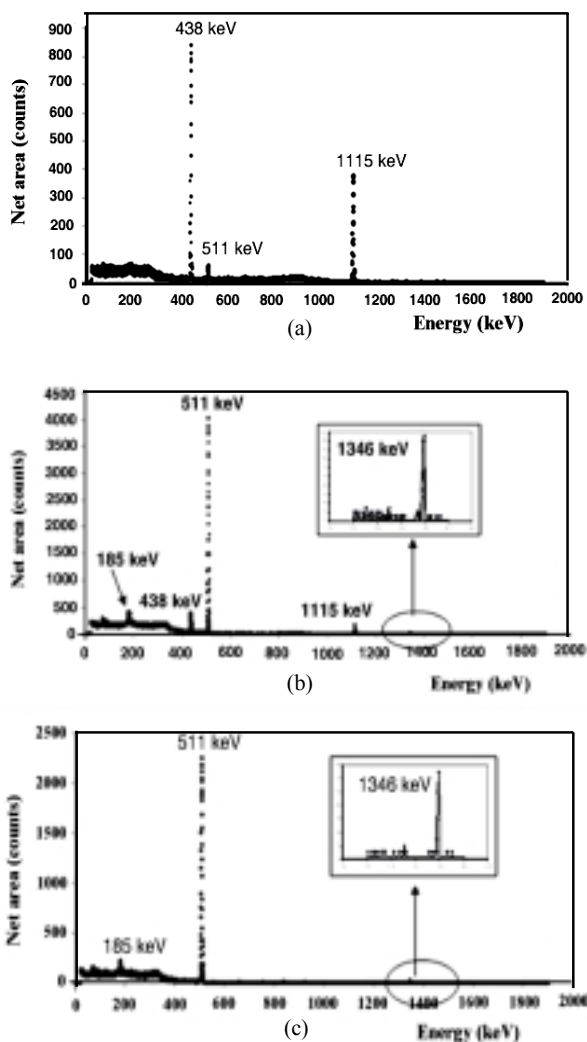

(a)

(b)

(c)

Fig. 3. Typical γ-spectrum of the separating fraction collected in Bottle-A (a), Bottle-B (b) and Bottle-C (c).

Comparing to Fig. 2, it can be presumed that the Bottle-A (represented by Fig. 3(a)) contained Zn/Zn* fraction showing peaks position precisely similar to the Bulk Solution. It indicated that in the condition of weak acid (1 M acetic acid), the Zn/Zn* fraction was mostly unbound by the cation exchanger resin. The intensity of the peak 511 keV, however, became to be lower indicating that the γ-annihilation of ^{64}Cu gave no more contribution as the ^{64}Cu/Cu* was retained in the column in the form of ^{64}Cu/Cu*$^{2+}$ cation. The peak 511 keV, thus, was expected coming from annihilation of ^{65}Zn [24].

Eluting the first chromatographic column using 1.5 M HCl released the retained Cu* fraction out of the column that was collected in the Bottle-B. This fraction showed a strong peak at 511 keV in accordance with the γ-annihilation of ^{64}Cu (Fig. 3(b)). The two strong peaks of Zn*, *i.e.* 438 keV (^{69m}Zn), and 1115 keV (^{65}Zn), were still appeared but with much lower intensities, indicating that a small part of Zn/Zn* was still in. A new peak was appeared at 185 keV in agree with the γ-ray emitted by ^{67}Cu, and a very small peak at 1346 keV, which can only be observed by partial magnification, was in agree with the γ-ray of ^{64}Cu [11]. The data explained that in the condition of 1.5 M HCl, the Cu* fraction was changed to anion complex Cu*Cl$_4^{2-}$ and passed out the column.

The Cu*-fraction, which contained a small part of Zn*, was then loaded into the second column containing anion exchanger resin, followed by elution with 0.5 M HCl. The resulting eluate showed no more peaks of Zn* but a strong peak at 511 keV in agree with the γ-annihilation of ^{64}Cu and a weaker one at 185 keV in agree with the γ-ray of ^{67}Cu (Fig. 3(c)). A very small peak at 1,346 keV was also observed by partial magnification agreeing with the γ-ray of ^{64}Cu. The data indicate that in the condition of 0.5 M HCl the Zn/Zn* fraction was in the form of Zn*Cl$_4^{2-}$ anion complex and retained in the anion exchanger column while the Cu* fraction was in the form of Cu*$^{2+}$ and passed out from the column. The observed data seemed to agree with the published data presented by Jentzsch and Frotsher showing anionic complexes of some elements in presence of various concentration of HCl [26] and met the report of Csicsovszki, *et al,* stating that zinc is to form negatively charged chloro-complex species even if the HCl concentration is relatively low [27].

The measurement of half-life is other important thing accompanying radiation spectrometry in order to determine a radionuclide. The Cu* fraction was accordingly subjected to this measurement by repeating the measurement of its activity. The decay curve was then prepared according to Equation-1 below :

$$\ln A(t) = \ln A(0) - \lambda.t \qquad \text{(Eq. 1)}$$

where A = radioactivity, λ = decay constant and t = decay time.

The resulting decay curve is presented in Fig. 4 as compared to theoretical line calculated using an internally-improved program [28] assuming that the half-life of ^{64}Cu was 12.7 hours. It can be seen that the decay curve of the resulting

Cu* fraction (curve-b) gave a linear relationship of ln A(t) vs. t. The slope and linearity coefficient value of this line were close by those of theoretical decay line (curve-a).
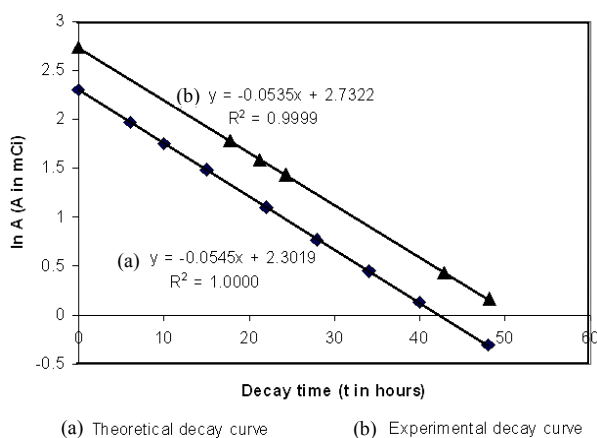
Fig. 4. Typical decay curve of Cu* fraction (b) as compared to theoretical curve assuming a half-life of 12.7 h (a).

Further calculation, however, gave a half-life value of 12.95 h, slightly higher than the assumed value (12.70 h), perhaps because the Cu* fraction contained also ^{67}Cu having a half-life of 61.83 h. The conformity of the obtained γ-ray energy and the half-life showed that the radioactive ^{64}Cu can be produced by neutron irradiation on natural Zn, as well as on high-enriched ^{64}Zn, in the BATAN's G.A. Siwabessy reactor and can be separated from the post-irradiated target by means of the presented chromatographic column method. The use of high-enriched ^{64}Zn target should be preferred, in term of product quality, because by using natural Zn-target the end product of ^{64}Cu was still contaminated by ^{67}Cu, even though the possibility of ^{67}Cu formation is too low if compared to that of ^{64}Cu.

Table 3. The effect of cadmium-foil wrap on the Cu*/Zn*-ratio.

NO	VARIABLES COMPARED	PROCESS-1	PROCESS-2	PROCESS-3
1	Weight of Zn target	0.533 g	0.500 g	0.504 g
2	Use of Cd-foil wrap	Yes	Yes	No
3	Irradiation time	96 hours	60.5 hours	86 hours
4	Total volume of post-irradiated target solution (Bulk Solution)	4.5 mL	4.5 mL	5 mL
5	Volume of the Bulk solution treated for separation	3 mL	3 mL	3 mL
6	Estimated radioactivity of Zn* at EOI[1]	99.45 mCi	58.92 mCi	84.30 mCi
7	Radioactivity of Cu* at EOI[2]	147.50 mCi	55.83 mCi	42.37 mCi
8	(Cu*/Zn*)-ratio at EOI [(7)/(6)]	1.58	0.95	0.51

REMARKS :
1). Calculated activity of the growing ^{65}Zn at the End of Irradiation (EOI) based on general formulation of : A = ϕ. σ. N. (1 − e $^{-λ.tir}$). using the data written in the irradiation form without considering the effect of the Cd-foil wrap.
2). Assuming as ^{64}Cu based on radioactivity measurement at the end of the separation process.

The application of cadmium-foil to wrap the Zn-target during the irradiation gave no significant effect to the separation or analytical procedures, but influenced the activity growth of the Cu* and, thus, the Cu*/Zn*-ratio as presented in Table 3. It can be seen from Table 3 the growth of the Cu* is larger in the Process-1 and the Process-2 (both were using Cd-foil wrap) as compared to the Process-3 (without Cd-foil wrap). In cases of Process-1 and Process-2, the thermal neutron beams were mostly absorbed by the Cd-foil as the Cd-element has a very high absorption for thermal neutron (σ = 2,450 barn) [29].

Accordingly, the ^{NAT}Zn (n,p) Cu* nuclear reaction performed by the unabsorbed fast neutron fraction was to be more dominant as compared to the case of Process-3, in which the ^{NAT}Zn (n,γ) Zn* nuclear reaction was to be more dominant. Consequently the activities of the Cu* and, thus, the Cu*/Zn*-ratios obtained from the two-former processes were higher than that from the third process. However, the radioactivity yields of both Zn* and Cu* might fluctuate significantly. It was suspected to be inflicted by irradiation parameters applied which, in general, varied from one irradiation cycle to another and, moreover, the parameters fluctuated during a cycle of irradiation. Such parameters included the change of reactor power and the deviation of the neutron flux from time to time. In the other side, the average value of neutron flux on a certain irradiation position is significantly influenced by the target burden at the other position that may be different from one process to another process [30].

CONCLUSION

Radioisotopes ^{64}Cu and ^{67}Cu were simultaneously produced by neutron irradiation on natural Zn target together with radioactive zinc. The radioactive copper could be separated successively, from the post-irradiated target matrix by two steps of ion exchange chromatography using cation and anion exchanger resins.

The presented procedures were applicable to provide carrier-free ^{64}Cu based on ^{64}Zn (n,p) ^{64}Cu as primary radioisotope used for diagnostic and therapeutic-molecular-targeted-radiopharmaceutical. The used of high-enriched ^{64}Zn target is preferred, in term of product quality, rather than the natural Zn.

Wrapping the Zn target by cadmium foil was able to diminish (n,γ)-nuclear reaction on the target

producing radioactive zinc and, in contrary, to increase the (n,p)-nuclear reaction producing radioactive copper. Nevertheless, the radioactivity yields might fluctuate due to the change on irradiation and reactor operation parameters.

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