DEVELOPMENTAL WORK ON ECONOMIC PRODUCTION OF HIGH AND LOW SPECIFIC ACTIVITY ^{64}CU – SUITABLE FOR PRECLINICAL STUDIES USING ACCELERATOR NEUTRONS

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Abstract

^{64}Cu is a theranostic radioisotope which is generating interest in the field of PET imaging and planning of therapy. Several radiochemical and pre-clinical studies need to be carried out to establish suitability and stability of new ^{64}Cu radiopharmaceuticals. However, obtaining ^{64}Cu is an expensive process as it is typically available via proton irradiation of enriched ^{64}Ni in a medical cyclotron. The paper investigates an economical method of obtaining ^{64}Cu with activity levels suitable for research scale production / radiochemical experiments utilizing accelerator neutrons. Natural foils of Cu and Zn were irradiated in the neutron field produced during the irradiation of ^{18}O, in the routine production of ^{18}F via the ^{18}O(p,n)^{18}F route in a medical cyclotron. Evaluation of yields of ^{64}Cu and radionuclidic impurities were determined by the quantification of the photo-peaks by off-line gamma -ray spectrometry. No carrier added ^{64}Cu was separated from the irradiated zinc by solvent extraction with high radionuclidic purity and separation yields of > 90%. The average yields of low specific activity and high specific activity ^{64}Cu at the end of bombardment was 455 and 861 Bq/g*microampere*h respectively.

1. INTRODUCTION

^{64}Cu has generated interest in the field of PET imaging and planning of therapy [1], as it decays by three different routes, namely, electron capture, β− and β+ decay. Its half-life of 12.8 h also makes it suitable for versatile applications.

The utility of reactor produced low specific activity (LSA) ^{64}Cu produced via ^{63}Cu(n,γ)^{64}Cu reaction and its use in the form of [^{64}Cu]$CuCl_2$ as a radiopharmaceutical for PET imaging of prostate cancer and glioblastoma patients have been demonstrated [2]. However the utilization of ^{64}Cu is mostly limited to studies, sourcing no carrier added high specific activity (HSA) ^{64}Cu, produced via the ^{64}Ni(p, n)^{64}Cu route in a medical cyclotron [3] . ^{64}Ni has a natural abundance of < 1 %. An enriched ^{64}Ni target is required to produce ^{64}Cu, increasing the cost of the radiochemical and pre-clinical studies that need to be carried out to establish suitability and stability of new ^{64}Cu radiopharmaceuticals.

Radiochemical studies and uptake studies performed on mice use activity of the order of only a few hundred microcuries [4, 5] This study investigates the potential of an economical method for research scale production of ^{64}Cu utilizing accelerator neutrons produced in the routine irradiation of ^{18}O in a medical cyclotron.

2. MATERIALS AND METHODS

2.1 Neutron Source and Irradiation parameters

The study was carried out in the medical cyclotron facility of PETtrace-800 cyclotron at the Radiation Medicine Centre, Mumbai, India. The cyclotron accelerates protons and deuterons to fixed energies of 16.5 MeV and 8.4 MeV respectively. The six target assemblies of liquid and gaseous targets (Fig 1), enables production of ^{13}N, ^{15}O, ^{11}C and ^{18}F. However, to meet current demands of nuclear medicine centres, the cyclotron is used for regular production of only the ^{18}F isotope in 12 - 15 irradiations per week. The ^{18}F routine production is carried out via the $^{18}O(p,n)^{18}F$ route in the liquid target irradiation system. ^{18}F produced is converted to [^{18}F] radiopharmaceuticals - [^{18}F] FDG, [^{18}F] FET, [^{18}F] FLT and [^{18}F] NaF, as per the requirement. The Table 1 illustrates the features of the cyclotron and target irradiation system. Natural foils of Cu, and Zn, were irradiated in the neutron field. The proton beam current was set at 55 microamperes.

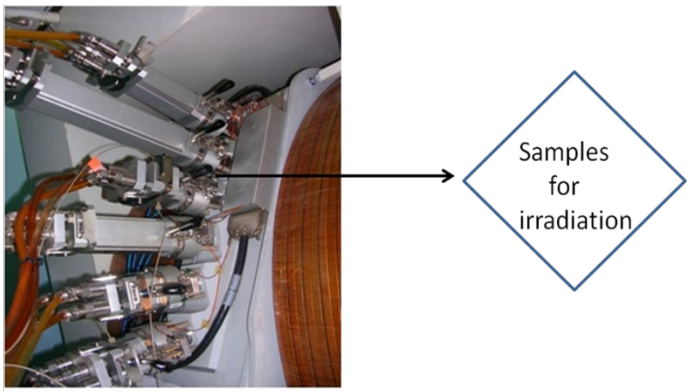

FIG. 1: Target irradiation systems in the Medical Cyclotron facility and experimental setup for irradiation

TABLE 1: Features of the Cyclotron and target irradiation system

Cyclotron	PETtrace 800
Proton energy	16.5 MeV (Fixed)
Beam Current (H^-)	1 – 75 μA (Variable)
Liquid target irradiation system	Target- $H_2{}^{18}O$ water ^{18}O enrichment - 98% Volume - 2.4 mL Cavity- Ag

2.1. Evaluation of the yield of ^{64}Cu and radionuclidic impurities

Radioactivity levels of ^{64}Cu and other radioisotopes co-produced were determined by the quantification of photo-peaks by off-line gamma-ray spectrometry [6]. The γ-ray counting of radionuclides was performed using a pre-calibrated HPGe detector coupled to a PC based 4K channel analyzer. The energy and efficiency calibration of the detector system was carried out using a standard ^{152}Eu source. Radioactivity levels of ^{64}Cu and of the radionuclidic impurities ^{65}Zn, ^{69m}Zn were determined by the quantification of the photo-peak counts of the 1345.8 keV, 1115.5 keV, 438.6 keV γ-lines respectively. Co-produced ^{67}Cu was quantified by the 184.6 keV γ-line. Spectroscopy software, Interwinner 7 was used for the analysis.

2.2. Separation of ^{64}Cu from irradiated zinc

The irradiated zinc was dissolved in concentrated hydrochloric acid and evaporated to dryness. No carrier added ^{64}Cu was separated from the irradiated zinc via solvent extraction [6-8]. Solvent extraction with dithizone (diphenylthiocarbazone) dissolved in CCl_4, a water immiscible medium was carried out. The Fig 2 shows the

schematic of the radiochemical separation process. The separation yields were determined by measuring the ^{64}Cu activity before and after the separation.

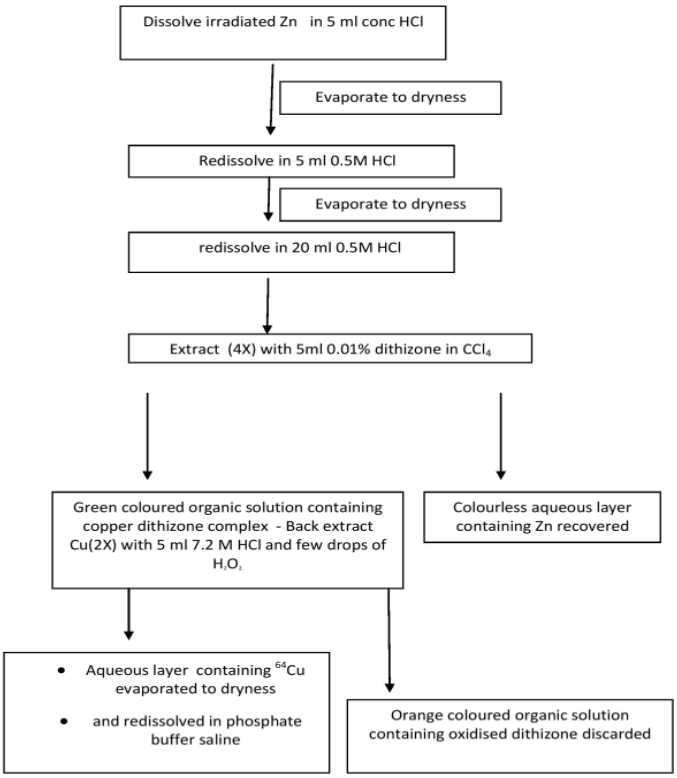

FIG. 2: Schematic of the radiochemical separation process

3. RESULTS AND DISCUSSION

3.3. Neutron Source

Neutron generators, cyclotrons and electron linear accelerators that could be used as a Compact Accelerator Based Neutron Source (CANS) are available as 'commercial off the shelf' varieties [9,10]. The accelerator neutrons produced via the $^{18}O(p,n)^{18}F$ route range from thermal to fast [11]. The unfolded neutron spectrum is shown in Fig 3 [11]. The neutron flux is anisotropic to the incoming proton beam.

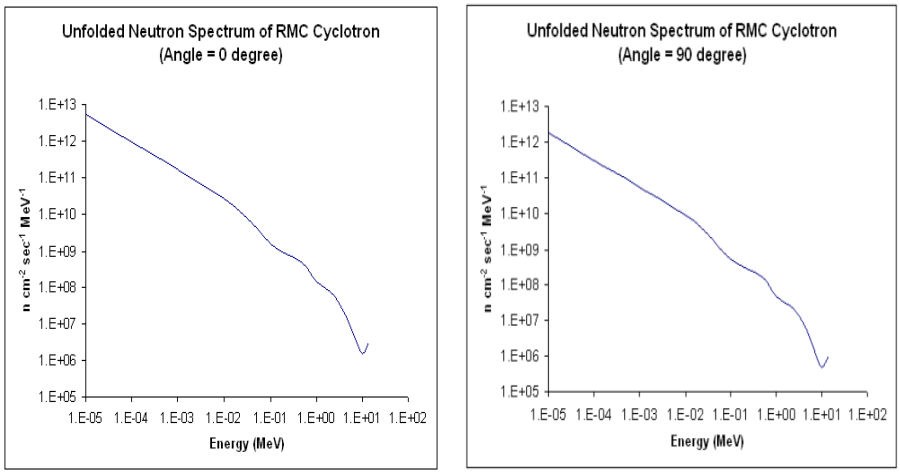

FIG. 3: Unfolded neutron spectrum [11]

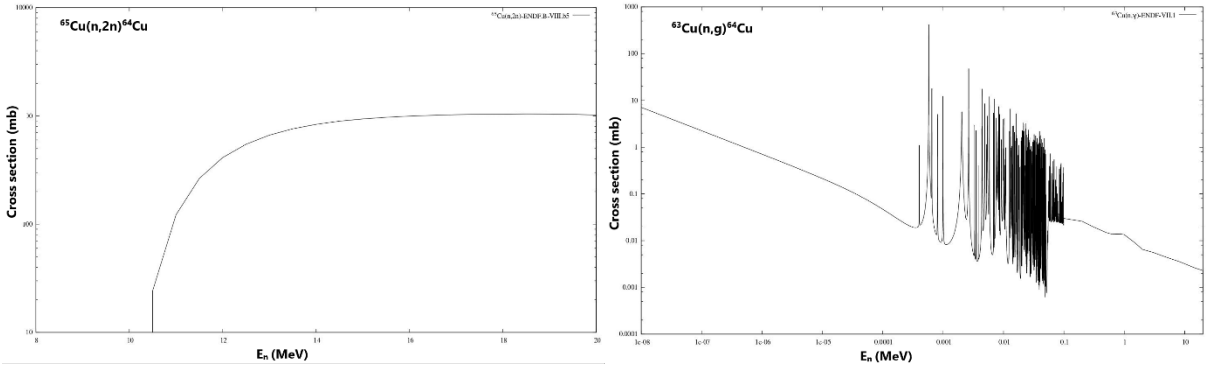

FIG 4: Excitation function of ^{65}Cu(n,2n)^{64}Cu and ^{63}Cu(n,g)^{64}Cu

3.4. LSA ^{64}Cu

Correlating the neutron spectrum (Fig 3) and the excitation functions of ^{64}Cu produced via ^{65}Cu(n,2n)^{64}Cu and ^{63}Cu(n,g)^{64}Cu (Fig 4), it can be inferred that LSA ^{64}Cu is formed via a dual route ^{65}Cu(n,2n)^{64}Cu + ^{63}Cu(n,g)^{64}Cu in the irradiated natural Cu foil. The Table 2 shows that the average cumulative activity of LSA ^{64}Cu produced is 455 ± 26 Bq/g*microampere*h at the end of bombardment (EOB).

TABLE 2: YIELDS OF LOW SPECIFIC ACTIVITY ^{64}Cu AT EOB

Irradiation time (h)	Target and weight (g)	^{64}Cu (Bq/ g*microampere*h)
1.1	Cu (0.02)	431
1.2	Cu (0.022)	483
1.1	Cu (0.02)	452

3.5. HSA ^{64}Cu

The radionuclides ^{64}Cu, ^{67}Cu, ^{65}Zn and ^{69m}Zn co-produced via the various (n,x) routes [6] were identified via gamma spectrometry of the irradiated Zn foil. As seen from Table 3, the average yields of high specific activity ^{64}Cu is 861 ± 15 Bq/g*microampere*h at EOB. The level of co-produced ^{67}Cu was 3 orders less than the ^{64}Cu produced at EOB. The ^{64}Cu and ^{67}Cu coproduced are inseparable and the ratio of ^{67}Cu/^{64}Cu post EOB increases due to the differences in their half-lives (Fig 5). The radioisotopes ^{64}Cu and ^{67}Cu are a theranostic pair and ^{64}Cu can be used as a tracer to study the uptake of ^{67}Cu, as the biological behaviour of these isotopes *in vivo* is expected to be equivalent.

TABLE 3: YIELDS OF HIGH SPECIFIC ACTIVITY ^{64}Cu AT EOB

Irradiation time (h)	Target and weight (g)	^{64}Cu (Bq/ g*microampere*h)
1.1	Zn (0.026)	879
1.2	Zn (2.1)	851
1.1	Zn (2.1)	855

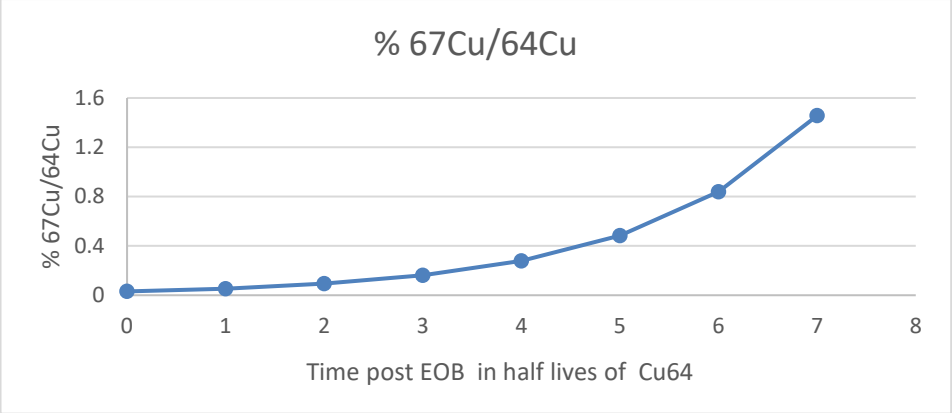

FIG 5: % ^{67}Cu/^{64}Cu post EOB

3.6. Separation of ^{64,67}Cu from irradiated Zn

The solvent extraction method is based on the selective extraction of Cu dithizonate into an organic solvent from a dilute acidic solution of the Zn target and back extraction of Cu into the aqueous phase. Dithizone is selective for Cu in the pH range 2–5, and for Zn in the pH range 6.5–9.5. The Fig 6 shows that the radionuclide impurities ^{65}Zn and ^{69m}Zn are not detected in the separated ^{64}Cu, indicating achievement of high radionuclidic purity. Shielding out the thermal neutrons will help in reducing the levels of coproduced ^{65}Zn, enabling easier handling of the irradiated Zn targets. High separation yields of > 90%, with high radionuclidic purity and good reproducibility was achieved.

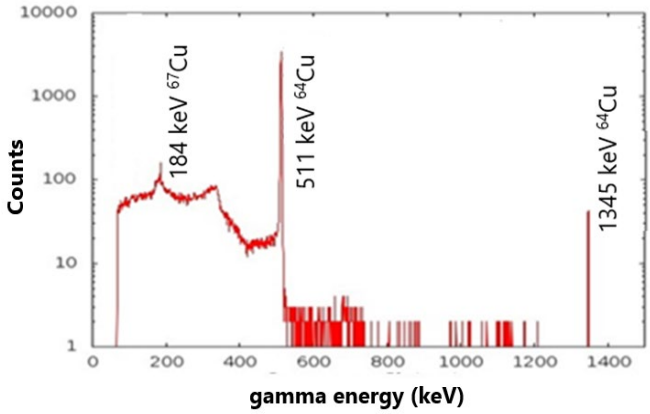

FIG 6: Gamma spectrometry of separated ^{64,67}Cu from the irradiated Zn foil

4. CONCLUSION

In this paper, we demonstrate an economical method of obtaining low and high specific activity ^{64}Cu via accelerator neutron bombardment of natural Cu and Zn. LSA ^{64}Cu is produced via a dual route ^{65}Cu(n,2n)^{64}Cu + ^{63}Cu(n,g)^{64}Cu in the irradiated natural Cu foil. Separation yields of > 90% of HSA ^{64}Cu inseparable from ^{67}Cu was obtained from the irradiated natural Zn foil. The potential use of a cocktail of mixed isotopes of the same element with different decays and energies may improve the therapeutic effect and is an interesting consideration to explore.

The growth and spread of medical cyclotrons is taking place across the globe, providing potential avenues for research scale production of ^{64}Cu via the accelerator neutrons. Utilization of these secondary neutrons requires no extra capital investment and holds promise for research scale production of other medically useful radioisotopes via various (n,x) reactions [12], without interrupting the regular production and supply of ^{18}F-radiopharmaceuticals.

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