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Standardization of ^{68}Ge-^{68}Ga using 4πβ(LS)-γ coincidence counting system for activity measurements

D.B. Kulkarni[a,*], Leena Joseph[a], R. Anuradha[a], M.S. Kulkarni[a], B.S. Tomar[b]

[a] Radiation Safety Systems Division, Bhabha Atomic Research Centre, Mumbai 400085, India
[b] Radioanalytical Chemistry Division, Bhabha Atomic Research Centre, Mumbai 400085, India

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ABSTRACT

^{68}Ga has great scope for use in future for positron emission tomography (PET) imaging due to its very fast blood clearance and fast target localization, even though at present ^{18}F is widely used. ^{68}Ge in equilibrium with ^{68}Ga (^{68}Ge-^{68}Ga) can also be used as a surrogate for ^{18}F calibration, as ^{18}F source standardization can be done at national metrology institute (NMI) but, these standards cannot be sent to nuclear medicine centers (NMCs) across India for calibration of isotope calibrators, due to the short half-life of ^{18}F (110 min). Providing ^{68}Ge-^{68}Ga standards to NMCs requires that first standardization must be carried out at NMI (BARC in India) to provide traceability to the measurements carried out at NMCs. In the present work, standardization of ^{68}Ge-^{68}Ga was carried out using 4πβ(LS)-γ coincidence counting system and CIEMAT/NIST efficiency tracing technique. The decay scheme correction factors for two gamma windows were calculated by Monte Carlo technique using general purpose code FLUKA. The activity concentration values were normalized by the activity concentration obtained by 4πβ(LS)-γ coincidence counting system using window-1. The final result reported to BIPM for 4πβ(LS)-γ coincidence counting was calculated by taking arithmetic mean of activity concentrations obtained for two gamma windows. The normalized activity concentration obtained by 4πβ(LS)-γ coincidence counting was 0.998 ± 0.005 and that obtained using CIEMAT/NIST efficiency tracing was 1.002 ± 0.007 which are in excellent agreement within uncertainty limits.

1. Introduction

Gallium-68 (^{68}Ga) is a positron emitting radionuclide used for clinical medicine since 1960 (Anger and Gottschalk, 1963), long before ^{18}F fluorodeoxyglucose (FDG) (Ido et al., 1978). The generators developed at that time produced ^{68}Ga in the form of ethylene-diamine-tetraacetic acid (EDTA) complex. This complex had to be first converted to Ga^{+3} cation before radiopharmaceutical preparation which made the process difficult, tedious and time consuming (Banerjee and Pomper, 2013). Because of these problems in radio-pharmaceutical preparation in the past, PET imaging based on ^{68}Ga was sidetracked in favor of new agents such as ^{99m}Tc for single photon emission computed tomography (SPECT) and ^{18}F for PET. In the recent past, direct elution of cationic ^{68}Ga with dilute acid (0.1 N HCl) has been reported by many researchers (Fani et al., 2008; Asti et al., 2008; Prata, 2012) and several ^{68}Ge/^{68}Ga generators are now commercially available. ^{68}Ga has the advantage of very fast blood clearance and fast target localization due of its pharmacokinetics and short physical half-life (68 min). Another advantage of ^{68}Ga is that it is in secular equilibrium with ^{68}Ge, which has a half-life of 270.95 days; hence, it can be used at places where medical cyclotrons which produce ^{18}F are not available.

The simplified decay scheme of ^{68}Ga in equilibrium with ^{68}Ge (^{68}Ge-^{68}Ga) (Grigorescu et al., 2004) is shown in Fig. 1. It can be seen that ^{68}Ge decays to ^{68}Ga by electron capture with 100% probability. ^{68}Ga decays by positron emission and electron capture. The most prominent decay is by positron emission, of which 87.94% is to ground state of ^{68}Zn and 1.2% is to 1077 keV excited state of ^{68}Zn. 8.71% of electron capture decay is to ground state and 1.79% to 1077 keV excited level of ^{68}Zn respectively. The electron capture events result in the emission of X-rays and Auger electrons with energies up to 10 keV. These Auger electrons and X-rays don't contribute to the isotope calibrator current. Thus current generated in an isotope calibrator during ^{68}Ge-^{68}Ga measurements is only due to annihilation photons with very little contribution from 1077 keV gamma photons of ^{68}Ga. The response of the isotope calibrator for ^{18}F is only due to annihilation photons. Thus isotope calibrator response of ^{68}Ge-^{68}Ga is similar to that of ^{18}F. Hence, ^{68}Ge in equilibrium with ^{68}Ga can be used as a surrogate

* Corresponding author.
E-mail address: devak@barc.gov.in (D.B. Kulkarni).

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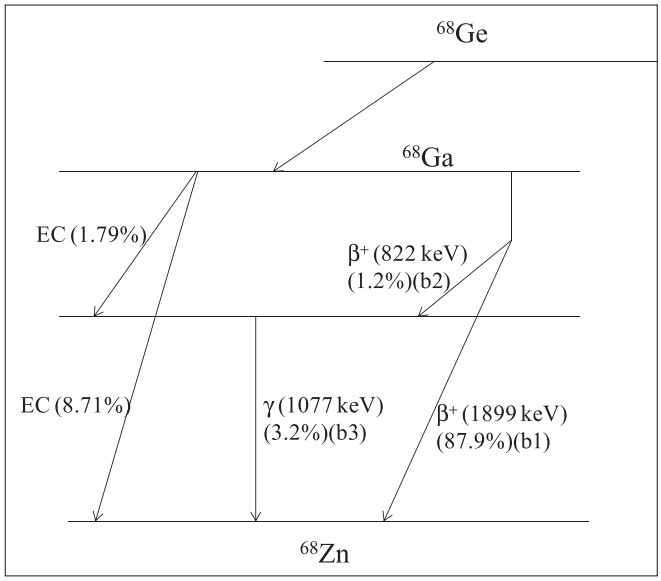

Fig. 1. Simplified decay scheme for ^{68}Ge-^{68}Ga.

for ^{18}F calibration at nuclear medicine centers, as providing ^{18}F standards to nuclear medicine centers (NMCs) across India for calibration of isotope calibrators is not possible due to its short half-life (110 min).

Accurate administration of radionuclide doses requires standards against which instrumentation used in the NMCs can be calibrated. To provide ^{68}Ge-^{68}Ga standards to NMCs, standardization must be carried out at National Metrology Institute (NMI) such as BARC so as to provide traceability to measurements carried out at NMCs. In order to establish equivalence of BARC standards with NMIs of other countries, BARC participated in Bureau International des Poids et Mesures (BIPM) organized international intercomparison of activity measurements for ^{68}Ge-^{68}Ga (CCRI(II)-K2.Ge-68) in 2015.

Many different methods can be used for standardization of ^{68}Ge (Zimmerman et al., 2008; Schönfeld et al., 1994; Grigorescu et al., 2004). Standardization using proportional counter based 4πβ-γ coincidence counting system involves the drying of sources, which results in the considerable loss of ^{68}Ge because of its volatility. Correction of the order of 20–26% was reported by Grigorescu et al. (2004). To avoid this large correction, standardization was carried out using liquid scintillation counter based 4πβ(LS)-γ coincidence counting system maintained as an absolute standard in the laboratory and CIEMAT/NIST efficiency tracing technique (Garcia-Toraño et al., 1991; Grau Malonda and Garcia-Toraño, 1982; Günther, 2002). The details of the standardization are presented in this paper.

2. Measurements

2.1. Source preparation

The sample for measurements was provided by NIST, USA, and contained 65 μg/g Ge^{+4} and Ga^{+3} in 0.5 N HCl. Two sources with weight 1010.492 mg and 2002.501 mg were prepared in injection glass (IG) vials for measurements in 4π gamma ion chamber (4π GIC), to evaluate the calibration factor for ^{68}Ge-^{68}Ga. The original solution was diluted with a dilution factor of 2.808942 using 0.5 N HCl. The diluted solution was used for the preparation of sources used for 4πβ(LS)-γ coincidence counting and CIEMAT/NIST efficiency tracing measurements. Seven sources were prepared in low potassium 20 ml glass liquid scintillation vials with 5 ml Ultima Gold scintillator for measurements in 4πβ(LS)-γ coincidence counting system. The amount of radioactive solution added was in the range of 24–26 mg. For measurements by CIEMAT/NIST efficiency tracing, seven sources with the radioactive solution in the range of 10–12 mg were also prepared in low potassium 20 ml glass liquid scintillation vials but with 15 ml Ultima Gold scintillator and 1 ml water, which is the standard geometry used by many NMIs. The ^{3}H standards traceable to NIST, USA, provided by Perkin Elmer along with the Packard TRI-CARB 2900 TR Liquid Scintillation Analyzer were used for CIEMAT/NIST efficiency tracing measurements. Blank samples with 5 ml Ultima Gold scintillator and 15 ml Ultima Gold scintillator +1 ml water were prepared in liquid scintillation vial for measurements with 4πβ(LS)-γ coincidence counting system and the CIEMAT/NIST method respectively.

2.2. 4πβ(LS)-γ coincidence counting measurements

The standardization was carried out by the efficiency extrapolation technique (EET) (Campion, 1959; Baerg, 1966, 1973), using the single vial single PMT 4πβ(LS)-γ coincidence counting system (Kulkarni et al., 2013). The positron counting efficiency (ε_β) for the sample was varied by chemical quenching using nitromethane, colour quenching using methyl red dye solution in Ultima Gold scintillator, and varying the EHT applied to the PMT anode (EHT variation). Four sources were measured by EHT variation and two sources each were measured by chemical quenching and colour quenching. The electron capture events in ^{68}Ge-^{68}Ga produce X-rays and Auger electrons with energies up to 10 keV. To avoid the contribution of electron capture events from ^{68}Ge-^{68}Ga, the lower level discriminator in beta channel was set to block all the pulses produced due to these events. Hence, the activity concentration measured is only due to positron emission of ^{68}Ga. In the gamma channel two gamma windows were set, one with 415–640 keV (window-1) to accept only 511 keV gamma photons and other greater than 415 keV (window-2) to accept 511 keV and 1077 keV photons. The coincidence equations (Grigorescu et al., 2004) used for two gamma windows are given by Eqs. (1) and (2) respectively. Y intercepts of the plots of $\left(\frac{N_\beta N_{\gamma 1}}{N_{c1}}\right)$ versus $\left(\frac{N_{\gamma 1}-N_{c1}}{N_{c1}}\right)$ and $\left(\frac{N_\beta N_{\gamma 2}}{N_{c2}}\right)$ versus $\left(\frac{N_{\gamma 2}-N_{c2}}{N_{c2}}\right)$ for two selected gamma windows are $N_0(b_1+b_2)\left[1+\frac{b_3}{b_1+b_2}\frac{\varepsilon^1_{\gamma 1077}}{2\varepsilon_\gamma}\right]$ (for window-1) and $N_0(b_1+b_2)\left[1+\frac{b_3}{b_1+b_2}\frac{\varepsilon^2_{\gamma 1077}}{2\varepsilon_\gamma}\right]$ (for window-2) respectively. The above said windows were set to check the validity of correction factors $\left[1+\frac{b_3}{b_1+b_2}\frac{\varepsilon^1_{\gamma 1077}}{2\varepsilon_\gamma}\right]$(for window-1) and $\left[1+\frac{b_3}{b_1+b_2}\frac{\varepsilon^2_{\gamma 1077}}{2\varepsilon_\gamma}\right]$ (for window-2) on final activity concentration. The second gamma window exaggerates the effect of 1077 keV gamma emission on measurements.

$$\frac{N_\beta N_\gamma}{N_{c1}N_0}{}^{1}=(b_1+\quad b_2)\left[1+\left(\frac{N_{\gamma 1}-N_{c1}}{N_{c1}}\right)\varepsilon_{\beta\gamma}\left(1-\frac{\varepsilon_{\gamma c}}{\varepsilon_\gamma}\right)\right]\left[1+\quad\frac{b_3}{b_1+b_2}\frac{\varepsilon^1_{\gamma\ 1077}}{2\varepsilon_\gamma}\right] \tag{1}$$

$$\frac{N_\beta N_{\gamma 2}}{N_{c2}N_0}=(b_1+\quad b_2)\left[1+\left(\frac{N_{\gamma 2}-N_{c2}}{N_{c2}}\right)\varepsilon_{\beta\gamma}\left(1-\frac{\varepsilon_{\gamma c}}{\varepsilon_\gamma}\right)\right]\left[1+\quad\frac{b_3}{b_1+b_2}\frac{\varepsilon^2_{\gamma\ 1077}}{2\varepsilon_\gamma}\right] \tag{2}$$

where,

Eq. (1) is for gamma window-1 i.e. 415–640 keV
Eq. (2) is for gamma window-2 i.e. greater than 415 keV.
b_1 and b_2 are branching ratios for positron emission (0.8794 and 0.012 respectively).
b_3 is the gamma abundance of 1077 keV gamma photons (0.032).
$\varepsilon_{\beta\gamma}$ is the efficiency of the liquid scintillation counter for 511 keV photons.
ε_γ is the full energy peak efficiency of the NaI(Tl) gamma detector for 511 keV photons.