



Verification of lithium formate monohydrate in 3D-printed container for electron paramagnetic resonance dosimetry in radiotherapy

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Abstract

The nondestructive dosimetry achieved with electron paramagnetic resonance (EPR) dosimetry facilitates repetitive recording by the same dosimeter to increase the reliability of data. In precedent studies, solid paraffin was needed as a binder material to make the lithium formate monohydrate (LFM) EPR dosimeter stable and nonfragile; however, its use complicates dosimetry. This study proposes a newly designed pure LFM EPR dosimeter created by inserting LFM into a 3D-printed container. Dosimetric characteristics of the LFM EPR dosimeter and container, such as reproducibility, linearity, energy dependence, and angular dependence, were evaluated and verified through a radiation therapy planning system (RTPS). The LFM EPR dosimeters were irradiated using a clinical linear accelerator. The EPR spectra of the dosimeters were acquired using a Bruker EMX EPR spectrometer. Through this study, it was confirmed that there is no tendency in the EPR response of the container based on irradiation dose or radiation energy. The results show that the LFM EPR dosimeters have a highly sensitive dose response with good linearity. The energy dependence across each photon and electron energy range seems to be negligible. Based on these results, LFM powder in a 3D-printed container is a suitable option for dosimetry of radiotherapy. Furthermore, the LFM EPR dosimeter has considerable potential for in vivo dosimetry and small-field dosimetry via additional experiments, owing to its small effective volume and highly sensitive dose response compared with a conventional dosimeter.

Keywords Electron paramagnetic resonance · Dosimetry · Lithium formate · Radiotherapy · 3D printer

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Introduction

Radiation dosimetry enhances the quality assurance (QA) of equipment, techniques, and treatments used in radiotherapy [1–3]. Advanced radiotherapy techniques, such as intensity-modulated radiation therapy (IMRT) and volumetric-modulated arc therapy (VMAT), require high precision and accuracy of QA equipment [4]. Several dosimetry systems are available, each with advantages and disadvantages compared with other systems. In particular, the thermoluminescence dosimeter (TLD) is a widely used solid-state dosimeter for determination of in vivo doses during external beam radiotherapy [5]. However, this requires complicated and prolonged annealing and is difficult to repeatedly readout [6, 7]. Meanwhile, electron paramagnetic resonance (EPR) dosimetry offers a non-destructive method and simple readout without an annealing process. Further, EPR dosimetry using alanine is recommended as a technique for standard dose assessment for the high doses used by the International Atomic Energy Agency (IAEA) [8]. Alanine has been used especially for in vivo dose estimates in radiotherapy [9, 10]. However, its accuracy is reduced for doses below 1 Gy, owing to its low sensitivity [11, 12]. Various compounds have been proposed for use in radiotherapy, and lithium formate monohydrate (LFM) is one of the most promising materials [13–15]. LFM is two to six times more sensitive than alanine [13]. In addition, the effective atomic number of LFM ($Z_{\text{eff}} = 7.3$) is closer to soft tissue ($Z_{\text{eff}} = 7.0$) than lithium fluoride ($Z_{\text{eff}} = 8.3$), which is the most widely used material for thermoluminescence dosimetry [15]. The density of single crystals of lithium formate monohydrate is reported to be approximately 1.48 g/cm^3 [16]. Thus, the probability of interaction of LFM with ionizing radiation is similar to that of tissue compared with lithium fluoride. Further, LFM has been evaluated to determine the fading signal under normal atmospheric conditions, something not observed for at least 28 days [13, 15, 17, 18].

In precedent studies, solid paraffin was needed as a binder material to make LFM EPR dosimeter stable and nonfragile, but its use complicates dosimetry [19]. The mass attenuation coefficients of paraffin differ considerably from those of lithium formate, as they are more than a factor of 2 lower at photon energies approximately 5–10 keV, approximately equal at 50 keV and increasing to a factor of 1.1 higher at 1 MeV [19]. In addition, the use of paraffin with a low dielectric constant affects the size of the LFM EPR dosimeter. The sample of higher dielectric constant increases the non-resonance absorption of the microwave energy, giving rise to losses in the EPR spectrometer sensitivity [20]. Therefore, an increase in the sample's dielectric constant requires that its diameter decrease. The

maximum size of the LFM EPR dosimeter with paraffin is 5 mm [20]. In addition, because the uncertainty depends on the homogeneity of the dosimeter batch, the combination of paraffin affects the accuracy of EPR dosimeter [21]. There are also concerns that the binder itself may generate a transient EPR signal, owing to radiation and/or thermal aging. This adds interference or noise to the EPR signal in different dose ranges [22, 23], and the limitations of paraffin binder can affect the accuracy of the radiation dosimetry.

These limitations of paraffin binder can affect the accuracy of the radiation dosimetry. We propose a binder-free LFM EPR dosimeter that is made into a 3D-printed insert to overcome the limitations of the paraffin binder. The container made from acrylic material, a widely available plastic that has been often used as a soft tissue-equivalent material because of its comparable attenuation coefficients in high-energy beams [24]. With a lithium formate density of 1.48 g/cm^3 close to density of 1.09 g/cm^3 of acryl, the dosimeter exhibits equivalent interaction close-to-water, so it does not induce rapid disturbances or discontinuities when inserted into a tissue equivalent phantom. However, since it is difficult to manufacture a container having a thickness of 1 mm according to a general acrylic processing procedure, containers have been manufactured using a 3D printer capable of more precise and delicate manufacture with a resolution of $100 \mu\text{m}$. The 3D-printed container has an EPR signal as a background signal in the process of hardening by irradiating with ultraviolet rays. Before manufacturing the LFM EPR dosimeter, we evaluated the dosimetric characteristics of the container based on the irradiated dose and energy because an increase in the EPR signal with the irradiated dose or radiation energy might cause it to affect the dose readout. In addition, the dosimetric characteristics of the LFM EPR dosimeter, including the reproducibility, linearity, energy dependence, and angular dependence, have been evaluated and verified using a radiation therapy planning system (RTPS). These experiments widen the knowledge of LFM EPR dosimetry and facilitate further study to extend dosimeter implementation and furthermore have significant potential for in vivo dosimetry and small field dosimetry.

Materials and methods

LFM EPR dosimeters

High-purity (98%) lithium formate monohydrate ($\text{CHLiO}_2 \cdot \text{H}_2\text{O}$) (LFM, Tokyo Chemical Industry Co., Ltd, Tokyo, Japan) was used. There was no mixing with a binder to avoid any possible contamination or contribution to the radiation-induced signal of LFM. The dosimeter container is a cylindrical pellet, as shown in Fig. 1, made by a 3D

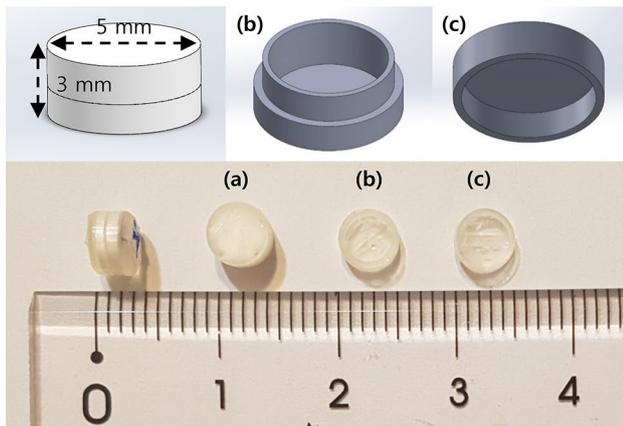


Fig. 1 Shape of the LFM EPR dosimeter. **a** LFM EPR dosimeter; **b**, **c** container

printer (Gprinter, Goo3D, Seong-nam, Korea), via digital light processing, and acrylic resin (density: 1.09 g/cm^3). The dosimeter container was used after drying for one day at $24 \pm 1 \text{ }^\circ\text{C}$ and $39 \pm 8\%$ relative humidity (rH). The $25 \pm 1 \text{ mg}$ of the ground LFM powder was added to the container. An X-ray image was taken to confirm that there is no air gap in the LFM EPR dosimeter. Eighty-four LFM EPR dosimeters were used. The tolerance in mass difference was less than $\pm 1 \text{ mg}$. All dosimeters were stored at $24 \pm 1 \text{ }^\circ\text{C}$ and $39 \pm 8\%$ rH.

EPR measurements

EPR spectra of all irradiated and unirradiated LFM EPR dosimeters and the 3D-printed container were acquired at room temperature using a Bruker EMX EPR spectrometer 3 days after irradiation. Before recording the EPR spectra, the spectrometer was warmed up for at least 1 h. The temperature and relative humidity in the laboratory during preparation, storage, and acquisition of EPR spectra were $24 \pm 1 \text{ }^\circ\text{C}$ and $39 \pm 8\%$ rH, respectively. For positional reproducibility, the LFM EPR dosimeter was placed in a Teflon tube with a length of 6 mm, width of 8 mm, and height of 110 mm. The EPR response of the LFM EPR dosimeter was acquired by applying a nominal microwave power of 20.02 mW, 3.0-mT sweep width, 1.2-mT modulation amplitude, and 10.23-ms conversion time. Preliminary experiments indicated that the best precision was achieved for measurements with a narrow sweep width (3 mT) without using an in-cavity reference, such as synthetic ruby or $\text{Mn}^{2+}/\text{MgO}$ [25]. The background spectra of each dosimeter were subtracted before irradiation. Finally, smoothing of EPR spectra via convolution with a Gaussian function ($\sigma = 20$ sampling points) using MATLAB (Math Works Inc., Natick, MA, USA) was performed to reduce noise contributions [15, 26]. The EPR response corresponds to peak-to-peak intensity of the first-derivative

EPR spectrum, and the signal amplitude for each dosimeter was defined as the average of three measurements to reduce the deviation of the acquisition data.

Irradiation condition

A clinical linear accelerator (LINAC) (Rapid Arc, Varian Medical Systems, Palo Alto, CA) was used for irradiation. The energies of photons and electrons were calibrated following the TG-51 dosimetry protocol provided by the American Association of Physicists in Medicine (AAPM). To evaluate dosimetric characteristics such as reproducibility, linearity, and energy dependence, four dosimeters or containers were placed at the center of the radiation field using a 3D-printed 2×2 matrix frame with 2-mm intervals. The dosimeters were located at a depth of 10 cm using a $30 \times 30 \text{ cm}^2$ solid water phantom (IBA Dosimetry, Schwarzen Bruck, Germany). The source-to-surface distance (SSD) was 100 cm, and the field size was $10 \times 10 \text{ cm}^2$. The reproducibility was evaluated using two sets of LFM EPR dosimeters. The delivery dose was 2 Gy using a 6 MV photon beam. To verify linearity of dosimeters or containers, a single set was irradiated with a 6-MV photon beam in the dose range of 0–16 Gy under reference conditions. The energy dependence was evaluated using a single set of LFM EPR dosimeters or containers, which were irradiated with a dose of 4 Gy for 6- and 10-MV photon beams and 4-, 9-, 16-, and 20-MeV electron beams. For the evaluation of angular dependence, a circular device with a diameter of 8 mm was printed using a 3D printer to insert the LFM EPR dosimeter at the center of the device. The SSD was 100 cm, and the field size was $10 \times 10 \text{ cm}^2$. The gantry angles were -90° , -45° , 0° , 45° , and 90° . Three dosimeters were irradiated with a dose of 8 Gy with a 6-MV photon beam.

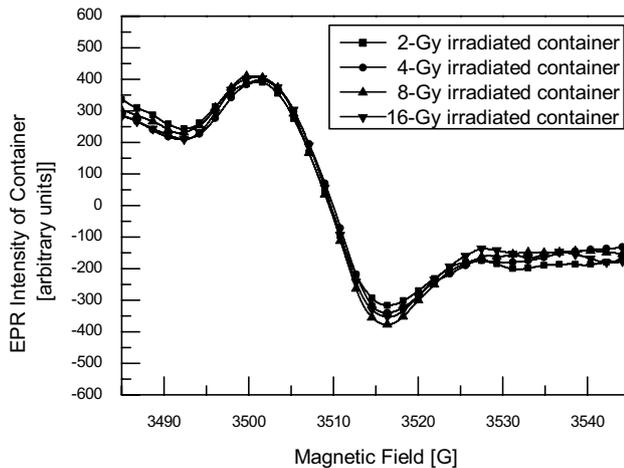
Verification of LFM EPR dosimeter using RTP system

For verification of the LFM EPR dosimeter, the calculated dose using RTPS and the measured dose by the LFM EPR dosimeter were compared. The 3D conformal radiation therapy (3D CRT) planning was performed with iPlan RT™ (Version 4.5.5, BrainLAB, Feldkirchen, Germany) and was carried out with a Novalis™ (BrainLAB, Heimstetten, Germany, and Varian Medical Systems, Palo Alto, CA) accelerator with a 6-MV X-ray energy and a micro-multileaf collimator. The iPlan RT was used with a Monte Carlo dose calculation (MCC) algorithm. The commercial MCC algorithm in iPlan RT is based on XVMC (X-ray voxel Monte Carlo) code developed by Kawrakow et al. and Fippel [27, 28]. The MCC algorithm in iPlan RT has been validated by Petoukhova et al. and Fragoso et al. [29, 30]. The dose calculation resolution was 1 mm. In general, in vivo dosimetry is used as a QA tool for verifying dosimetry as

Table 1 EPR intensity of pre-irradiated container and 2 to 16 Gy irradiated container

Irradiated dose (Gy)	EPR intensity of pre-irradiated container	EPR intensity of irradiated container
2	640 ± 100	710 ± 20
4	640 ± 50	750 ± 20
8	700 ± 100	800 ± 30
16	730 ± 70	760 ± 20

The intensities are rounded to the nearest ten

**Fig. 2** First-derivative EPR spectra of 2- to 16-Gy irradiated container

either the entrance or exit surface of the patient undergoing external beam radiotherapy, so the LFM EPR dosimeters were placed on the surface of a cylindrical solid water phantom (Cheese phantom, Gammex Inc., Middleton, WI, USA). Gantry angles of The 0°, 50°, 90°, 130°, 180°, 230°, 270°, and 310° of gantry angles were used, and each was delivered 400, 200, 600, 100, 400, 200, 600, and 100 monitor units, respectively.

Results

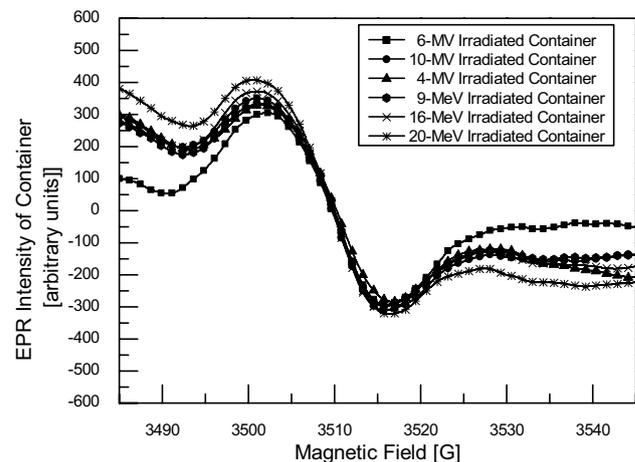
Evaluating dosimetric characteristics for container

The EPR response of the container was obtained by subtracting the pre-irradiation EPR response of the background signal of the container from the EPR response after irradiation. Table 1 shows the EPR intensity of the pre-irradiated container and the 2- to 16-Gy irradiated container. Figure 2 shows the first-derivative EPR spectra of the 2- to 16-Gy irradiated container. Table 2 shows the

Table 2 EPR intensity of pre-irradiated container with 6- and 10-MV photons and 4-, 9-, 16-, and 20-MeV electron-beam irradiated container

Irradiated energy	EPR intensity of pre-irradiated container	EPR intensity of irradiated container
6-MV	780 ± 100	790 ± 10
10-MV	790 ± 30	670 ± 20
4-MeV	740 ± 40	640 ± 10
9-MeV	680 ± 70	690 ± 10
16-MeV	680 ± 70	690 ± 10
20-MeV	800 ± 80	760 ± 10

The intensities are rounded to the nearest ten

**Fig. 3** First-derivative EPR spectra of 6- and 10-MV photons and 4-, 9-, 16-, and 20-MeV electron-beam irradiated container

EPR intensity of the pre-irradiated container with 6- and 10-MV photons and 4-, 9-, 16-, and 20-MeV electron-beam irradiated container. Figure 3 shows the first-derivative EPR spectra of 6- and 10-MV photons and 4-, 9-, 16-, and 20-MeV electron-beam irradiated container.

Reproducibility of LFM EPR dosimeter

Figure 4 shows the reproducibility of the eight LFM EPR dosimeters. The irradiated dose was 2 Gy using 6-MV photon beam. The EPR response of each dosimeter was normalized using the average response of the eight LFM EPR dosimeters. The relative EPR response and the standard deviations of the LFM EPR dosimeters were 1.002 ± 0.016 , 0.992 ± 0.03 , 0.988 ± 0.026 , 1.007 ± 0.034 , 0.991 ± 0.02 , 1.008 ± 0.024 , 1.02 ± 0.019 , and 1.016 ± 0.027 . The standard deviation was within $\pm 3\%$.

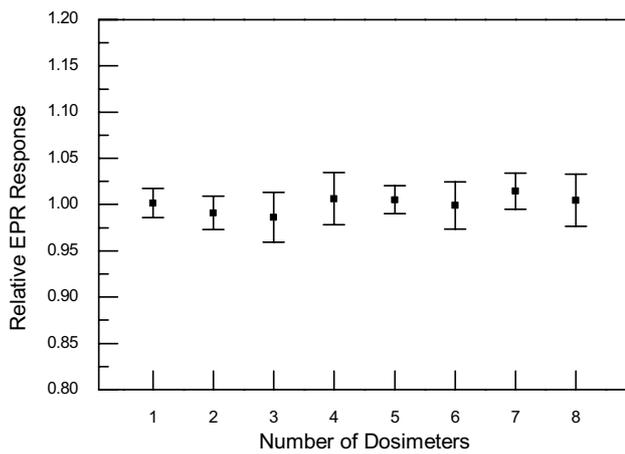


Fig. 4 Reproducibility of the LFM EPR dosimeters. The EPR response of each LFM EPR dosimeter is the mean EPR response acquired three times. Each point represents the relative EPR response normalized to mean EPR response of eight dosimeters irradiated with 2 Gy using the 6-MV photon beam. Error bars represent the standard deviation of the means

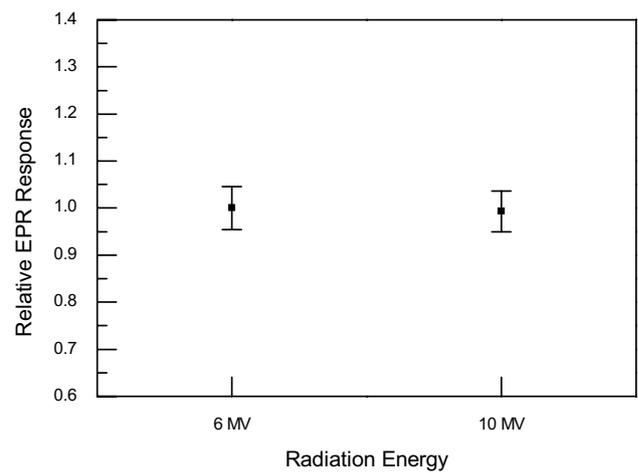


Fig. 6 Photon energy dependence of the LFM EPR dosimeter. EPR response of each energy is the mean EPR response of four dosimeters, which were acquired three times. Each point represents the relative EPR response normalized to four dosimeters irradiated with the 6-MV photon beam. Error bars represent the standard deviation of the means

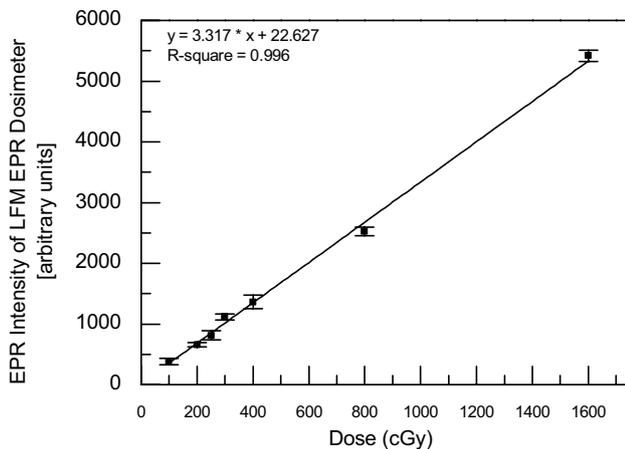


Fig. 5 Dose–response curve of the LFM EPR dosimeter for doses ranging from 100 to 1600 cGy. Each data point represents the mean EPR response of four containers, which were each measured three times. Error bars represent the standard deviation of the means

Linearity of LFM EPR dosimeter

Figure 5 shows the dose response for doses ranging from 1 to 16 Gy. Each data point plotted is the mean EPR intensity of four LFM EPR dosimeters. The error bars represent the standard deviation of the mean. The line represents the weighted least-squares regression fitting to the points. In this graph, the R-squared value was 0.996.

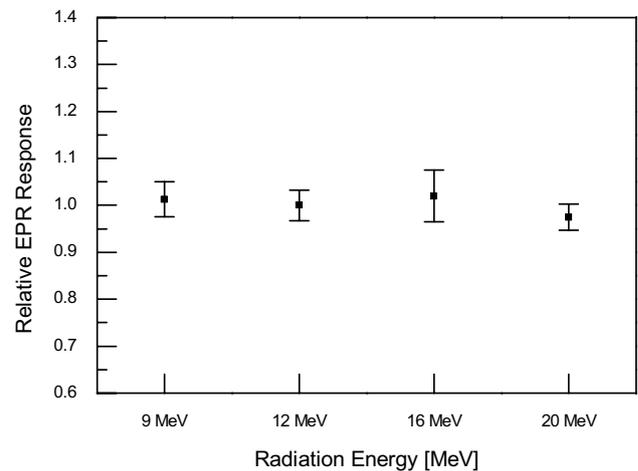


Fig. 7 Electron energy dependence of the LFM EPR dosimeter. EPR response of each energy is the mean EPR response of four dosimeters, which were acquired three times. Each point represents the relative EPR response normalized to four dosimeters irradiated with the 9-MeV electron beam. Error bars represent the standard deviation of the means

Energy dependence of LFM EPR dosimeter

Figures 6 and 7 illustrate the energy dependence of the LFM EPR dosimeter for photon and electron beams. The irradiated dose was 4 Gy. The EPR response was normalized using the average response of the four dosimeters irradiated by the 6-MV photon beam and 12-MeV electron beam. The energy dependence of the 10-MV photon beam relative to that of the 6-MV photon beam was 0.993

± 0.43 . The energy dependence of 9-, 16-, and 20-MeV electron beams relative to the 12-MeV electron beam was 1.013 ± 0.037 , 1.020 ± 0.055 , and 0.975 ± 0.028 , respectively.

Angular dependence of LFM EPR dosimeter

Figure 8 shows the angular dependence of LFM EPR dosimeter. The irradiated dose was 4 Gy using a 6-MV photon beam. The EPR responses of each dosimeter were normalized using the average of the three dosimeters irradiated at a gantry angle of 0° . The angular dependence for gantry angle -90° , -45° , 45° , and 90° relative to gantry angle 0° was 0.974 ± 0.023 , 0.977 ± 0.084 , 0.980 ± 0.015 , and 0.973 ± 0.033 , respectively.

Verification of LFM EPR dosimeter using RTPS system

Table 3 shows the comparison of the calculated dose using RTPS to the measured dose by the LFM EPR dosimeter. Three dosimeters were placed at each measurement location. The volume of the LFM EPR dosimeter was delineated in the computed tomography image. The calculated dose using RTPS was determined as the average dose for the volume of the LFM EPR dosimeter. The measured doses by the LFM EPR dosimeter were determined as the average of three dosimeters. The EPR responses were converted to the dose using the obtained dose–response curve in Fig. 5. The difference between the calculated dose using RTPS and the measured dose by LFM EPR dosimeter was within 2.8–3.26%.

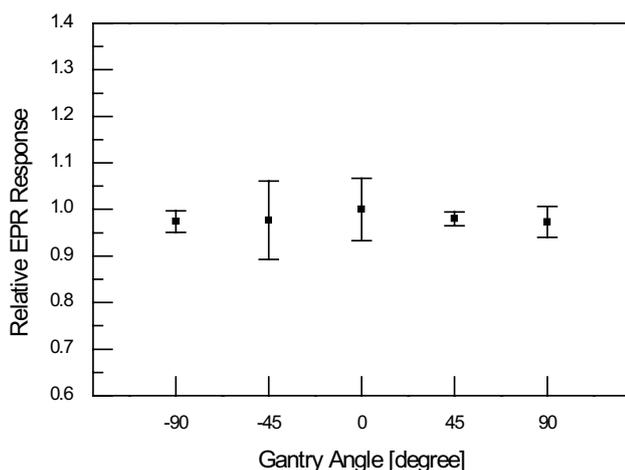


Fig. 8 Angular dependence of the LFM EPR dosimeter. Each data point represents the mean EPR response of three dosimeters, which were acquired three times. Error bars represent the standard deviation of the means

Table 3 Comparison between the calculated mean dose using RTPS and the measured dose of the LFM EPR dosimeter

Dosimeter no	Volume (cc)	Calculated mean dose (Gy)	Measured mean doses (Gy)	Difference (%)
1	0.06	2.09	2.03	3.02
2	0.06	1.24	1.21	2.80
3	0.06	0.71	0.73	3.26

Discussion

Evaluating dosimetric characteristics for container

The dosimetric characteristics of the 3D-printed container were evaluated for the irradiated dose and radiation energy. Tables 1 and 2 show that there is no tendency for the EPR response of the container depending on irradiation dose or radiation energy. In particular, Figs. 2 and 3 show that the EPR spectrum of irradiated containers and unirradiated containers are not significantly different. Tables 1 and 2 shows that the EPR intensities of the containers before and after irradiation are not significantly different. The deviation of the EPR intensity also appears to be due to variations in the base line signal due to low frequency noise. Figure 9 shows the first-derivative EPR spectra of the LFM EPR dosimeter and container irradiated by 2–16 Gy. At this time, the pre-irradiated signal of the LFM EPR dosimeter was subtracted. The EPR response due to the container is very small compared with the signal from the irradiated LFM. This makes it quite clear that there is

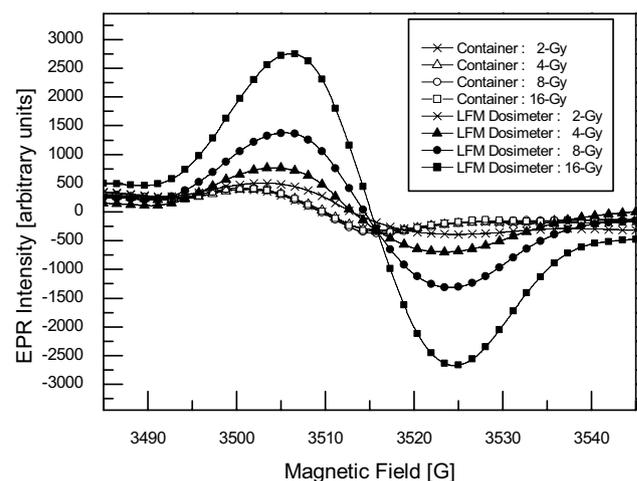


Fig. 9 First-derivative EPR spectra of LFM EPR dosimeter and container irradiated at 2–16 Gy. The EPR spectrum was obtained by subtracting the background signal after irradiation

no observable EPR response from the acrylic container due to radiation defects, as seen in Figs. 3, 4, and 9.

Evaluating dosimetric characteristics for LFM EPR dosimeter

In this study, the reproducibility, linearity, energy dependence, and angular dependence of a newly designed LFM EPR dosimeter were evaluated and verified using RTPS. The reproducibility was within $\pm 3\%$ for the eight dosimeters. Further, the LFM EPR dosimeters showed a linear dose response curve in the radio-therapeutic dose ranges (0–16 Gy) and these dosimeters have highly sensitive dose response. The response of the LFM EPR dosimeter with changes in irradiation angle was within $\pm 3\%$. The difference between the calculated dose using RTPS with MCC algorithm and the measured dose by LFM EPR dosimeter was within $\pm 5\%$.

Conclusion

In this study, a pure LFM EPR dosimeter made into a 3D-printed insert to overcome the limitations of paraffin binder was proposed. It was confirmed that there is no tendency in the EPR response of the container based on the irradiation dose or radiation energy. However, the deviation in the EPR response obtained during evaluation of the LFM EPR dosimeter was slightly higher overall. It seems to be affected by the background signal of the container. The different EPR spectra of each container were attributed to the EPR response and the standard deviation. The background signal of the container was found to be very unstable compared to the EPR signal obtained after irradiation. Therefore, it may be possible to reduce the deviation in the EPR response by using the “spiking method,” which is a method of eliminating the background signal by irradiating all of the LFM EPR dosimeters with a specific dose [31]. The LFM EPR dosimeter offers a very simple readout process compared with that of the TLD and glass dosimeter, resulting in highly reliable dosimetry based on reduced deviation of acquisition data. Consequently, the LFM powder in a 3D-printed container is a suitable option for dosimetry of radiotherapy. Furthermore, the LFM EPR dosimeter has considerable potential for in vivo dosimetry and small-field dosimetry via additional experiments, owing to its small effective volume and highly sensitive dose response compared with a conventional dosimeter.

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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