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Fabricated Germanium-Doped Silica Optical Fibres: A Novel Dose Meter for Clinical Blood Irradiation

(Gentian Optik Silika Terdop Germanium: Suatu Meter Dos Baharu untuk Penyinaran Darah Klinikal)

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ABSTRACT

TA-GVH disease represents a potential adverse effect associated with blood transfusions, highlighting the importance of irradiating blood components within defined limits to effectively mitigate this risk. The recommended irradiation doses range from 25 to 50 Gy, with a peripheral threshold established at 15 Gy. This study explores the feasibility of using fabricated germanium-doped (Ge-doped) silica-based optical fibres as dose indicators during clinical blood transfusions. Two types of 2.3 mol% Ge-doped optical fibres were tested: cylindrical (CF) and flat (FF). Calibration was performed using a Cobalt-60 gamma-ray machine across a dose range of 5 to 50 Gy. Clinical trials were conducted using a Cesium-137 source blood irradiator. A central dose of 25 Gy was delivered to real adult blood bags, which were exposed to gamma rays for 9 min and 56 s. Thermoluminescence (TL) signals from the fibres were measured with a HarshawTM 3500 TLD reader, and compared with EBT-XD film and conventional dose indicator stickers. The study found no statistically significant difference among dosimeters, with a p-value of 0.285 ($p > 0.05$, 95% Confidence Level) for the 25 Gy dose. Mean errors were 3.4% for CF and 4.3% for FF when compared to EBT-XD film. These results indicate that Ge-doped optical fibres offer precise, quantitative measurements of blood irradiation doses, unlike conventional dose stickers which provide only qualitative visual indicators. This innovative dosimetry approach shows significant potential as a cost-effective, reusable, and highly sensitive alternative for clinical blood irradiation.

Keywords: Blood irradiation dosimetry; dose indicator; fabricated germanium-doped optical fibres; thermoluminescence

ABSTRAK

Penyakit TA-GVH merupakan kesan sampingan berpotensi berkaitan dengan pemindahan darah, menekankan kepentingan untuk penyinaran komponen darah dalam had tertentu bagi mengurangkan risiko ini dengan berkesan. Dos penyinaran yang disyorkan adalah antara 25 hingga 50 Gy dengan ambang periferal ditetapkan pada 15 Gy. Kajian ini meneroka kemungkinan penggunaan gentian optik berasaskan silika yang digentikan germanium (terdop Ge) sebagai penunjuk dos semasa pemindahan darah klinikal. Dua jenis gentian optik 2.3 mol% terdop Ge telah diuji: silinder (CF) dan rata (FF). Kalibrasi dilakukan menggunakan mesin sinar gamma Cobalt-60 dalam julat dos dari 5 hingga 50 Gy. Ujian klinikal dijalankan menggunakan peranti penyinaran darah sumber Cesium-137. Dos pusat sebanyak 25 Gy diberikan kepada beg darah dewasa sebenar yang terdedah kepada sinar gamma selama 9 minit dan 56 saat. Isyarat termoluminesens (TL) daripada gentian diukur dengan pembaca HarshawTM 3500 TLD dan dibandingkan dengan filem EBT-XD dan pelekat penunjuk dos konvensional. Kajian mendapati tiada perbezaan yang signifikan secara statistik antara penunjuk dos dengan nilai p 0.285 ($p > 0.05$, Tahap Keyakinan 95%) untuk dos 25 Gy. Ralat purata adalah 3.4% untuk CF dan 4.3% untuk FF berbanding filem EBT-XD. Hasil ini menunjukkan bahawa gentian optik terdop Ge menyediakan pengukuran dos yang tepat dan kuantitatif untuk penyinaran darah berbanding dengan pelekat dos konvensional yang hanya memberikan penunjuk visual kualitatif. Pendekatan dosimetri inovatif ini menunjukkan potensi yang signifikan sebagai alternatif kos-berkesan, boleh digunakan semula dan sangat sensitif untuk penggunaan klinikal dalam penyinaran darah.

Kata kunci: Dosimetri penyinaran darah; gentian optik terdop germanium; penunjuk dos; termoluminesens

INTRODUCTION

A blood transfusion is the medical procedure of transferring blood or blood products between persons, typically required for those suffering from conditions such as anaemia, sickle cell disease, bleeding disorders, or cancer (Stewart, Davies & Vyas 2019). Transfusions of blood are generally considered as safe, although there is a possibility of complications, including Transfusion-Associated Graft-versus-Host Disease (TA-GvHD) (Shaz & Hillyer 2009). TA-GvHD is relatively rare (Ní Loingsigh et al. 2020). In this condition, viable lymphocytes in donated blood engraft in the patient and initiate an immune response against the cells of the recipient, which are typically of a distinct HLA type (Wiersum-Osselton et al. 2021). This condition is most frequently observed in patients who are immunodeficient or undergoing chemotherapy (Stewart, Davies & Vyas 2019). Preventing TA-GvHD involves deactivating T-lymphocytes in cellular blood components through gamma or x-ray irradiation, with a minimum prescribed dose of 25 Gy (Kovačić, Stanišić & Zver 2021). The American Authorities (Association for the Advancement of Blood & Biotherapies), and FDA stand for blood irradiation at doses ranging from 25 to 50 Gy, with a peripheral limit set at 15 Gy (Grasso et al. 2023). The actual absorbed dose should align with the predicted value, as doses under 15 Gy pose a risk of residual TA-GvHD, whereas doses exceeding 50 Gy may harm transfusion blood and lead to erythrocyte corruption (Jacobs 1998). Accurate dosimetry methods for dose measurement are recommended (Grasso et al. 2023).

Dose indicators provide a visual representation of the radiation dose received during irradiation (Moroff, Leitman & Luban 1997), ensuring accurate handling and reducing errors by indicating the colorimetric changes that correspond to increasing doses. Currently, the blood irradiation dose indicators are significantly restricted. They only offer a qualitative evaluation of blood irradiation, which results in inaccurate decisions regarding blood transfusions. Ensuring appropriate irradiation of blood components through precise radiation doses is crucial (Lopes et al. 2023; Mittal et al. 2021). Nevertheless, these dosimeters are frequently expensive, susceptible to environmental factors, and only accurate for certain forms of radiation (either Gamma or X-ray exposure). The constraints highlight the need for a reliable and precise dosimeter to accurately quantify gamma-ray doses in radiation-exposed blood (Mittal et al. 2021). Their high cost and limited efficacy in certain environments may limit their clinical use. In addition, interpreting dosage can be difficult and require training or expertise (Patton & Skowronski 2002).

The efficacy of fabricated and commercially available Germanium-doped (Ge-doped) optical fibres as dosimeters has been the subject of numerous research studies, all of which have consistently demonstrated their outstanding performance in measuring radiation doses (Begum et al. 2015; Bradley et al. 2012; Fadzil et al. 2014; Hassan et al. 2018, 2023; Noor 2012; Rais et al. 2021; Zakaria, Abdul Aziz & Noor 2020). Following the excellent performance of other dosimeters in dosimetry, this comparative study aims to explore the feasibility of fabricated germanium-doped (Ge-doped) silica-based optical fibres as an alternative dose indicator for clinical blood transfusions.

MATERIALS AND METHODS

FABRICATED GERMANIUM DOPED OPTICAL FIBRES

This extensive study was focused on fabricated germanium doped (Ge-doped) silica-based optical fibres of different shapes, specifically cylindrical (CF) and flat (FF) dosimeters, concentration of 2.3% mol germanium which were made by Modified Chemical Vapour Deposition (MCVD) technique. The fabrication technique has been delineated in detail by Noor et al. (2016).

PREPARATION OF FABRICATED GERMANIUM DOPED OPTICAL FIBRES AND EBT-XD FILM

Preparing for irradiation, the CF and FF fibres were manually cut into lengths of 6.0 ± 1.0 mm using the S90R diamond cutter (Thorlabs in New Jersey, USA). To minimise surface scraping dust and finger grease, optical fibres were prepared with a Dymax 5 vacuum tweezer (Surrey, UK) (Fadzil 2020). Subsequent to the cutting process was the annealing process. Furnace annealing involves carefully arranging fibres on a brass plate, covered with aluminium foil to prevent contamination during the anneal process. Noor et al. (2014) describes the annealing process as a method for eliminating residual or background signals trapped within the fibres. The fibres were annealed in a furnace (CarboliteGero CWF 1200 Heating Chamber, UK) at 400 °C for one hour. Consequently, the fibres are subjected to a natural cooling process, which enables them to reach room temperature by being held within the furnace. The CF and FF optical fibres were grouped according to their sensitivity (Ksi) and later encapsulated in gelatin capsules to ensure proper preparation for the next irradiation procedure, as mentioned in detail by Ku Bakar (2024). In this study, all the fibres, both cylindrical (CF) and flat (FF), have been divided into groups of ten pieces each. Hence, the Group Sensitivity Correction Factor (GSCF, Ksi) has been calculated using the formula from TRS No. 457. The Coefficient of Variation (CV) is limited to ±10% during the screening process, and all fibres resulting from thermoluminescence (TL) must have a CV within this limit (Ku Bakar 2024). The study utilised Gafchromic EBT-XD film (Ashland, US) as the gold standard to achieve a response comparable to optical fibres. The films (lot number #08021) were each cut into six pieces, each with an individual dimension of 2 × 2 cm^2. Table 1 provides a comprehensive summary of the physical properties of the samples employed in this study.

IRRADIATION OF FABRICATED GERMANIUM DOPED OPTICAL FIBRES

This clinical study employs a total of 60 fibres (10 fibres per group), divided over six locations, for each type of CF and FF. Additionally, 6 EBT-XD films were cut into dimensions of 2 cm × 2 cm. Fibres are grouped based on their individual sensitivity following the screening procedure. Each group of 10 fibres is carefully placed into the plastic bag and properly sealed, as depicted in Figure 1. Each of the dosimeters (CF, FF, and EBT-XD film) is subsequently marked as a specific location setup. A Gammacell® 3000 Elan blood irradiator with Cs-137 source gamma rays was employed for irradiation of the samples located at the Department of Pathology, Hospital Sultan Abdul Aziz Shah Universiti Putra Malaysia (HSAAS).

As for this study, the EBT-XD film and optical fibres were replaced as dose indicators in blood irradiation, replacing conventional dose stickers. These indicators were placed at the center of expired adult blood bags, exposed to 25 Gy. The blood irradiator at HSAAS can only accommodate three adult blood bags per irradiation in a canister. For this study, the set up was set according to the clinical set-up. Each bag is arranged according to a specific sequence, with blood bag 1 labeled as BB Plane A, blood bag 2 as BB Plane B, and blood bag 3 as BB Plane C. Each blood bag has two sets of locations for all dosimeters, with the conventional blood irradiation indicator, as shown in Figure 2. A RadTag Blood Irradiation dose indicator was used and attached to the blood bags together with all dosimeters. These RadTag® indicators confirm the central dose and verify that the dose falls within the 15 Gy to 50 Gy range (MED Alliance Group Inc. 2023).

Prior to irradiation, all blood bags with the dosimeters are subsequently placed into the canister. The process of sorting the orientation of the blood container by plane is illustrated in Figures 3 and 4, which show the schematic diagram of the blood bags. The Gammacell® 3000 Elan blood irradiator at HSAAS UPM delivered a clinical dose of 25 Gy of radiation to blood containers for a duration of 9 min and 56 s.

TABLE 1. Physical properties of fabricated Ge-doped optical fibres and EBT films

Sample	Type	Shape	Ge concentration (%)	Inner diameter/ Dimension	Outer diameter/ Dimension	Volume of core
CF	Fabricated	Cylindrical	2.3	Core: 124 µm	481 µm	2.6×10^{-11} m^3
FF	Fabricated	Flat	2.3	348 × 12.6 µm^2	643 × 356 µm^2	6.79×10^{-11} m^3
EBT-XD	GAFChromic™ EBT-XD	Square	-	25 µm thick	125 µm 8 × 10 in	-

CF: Cylindrical fibre FF: Flat fibre
Ge: Germanium

FIGURE 1. A plastic bag was used to seal the fabricated Ge-doped optical fibres CF and FF, which were grouped by group sensitivity (K_{si})

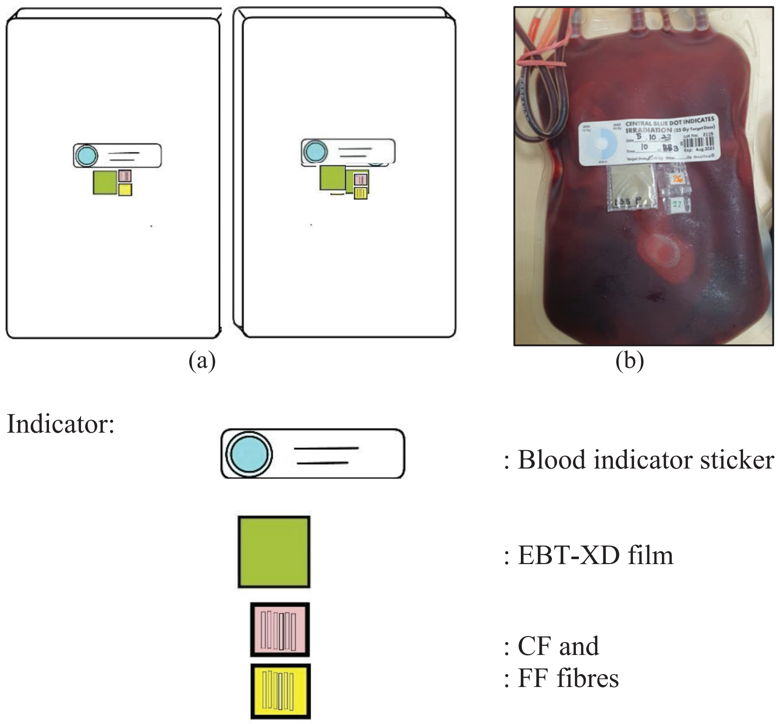


FIGURE 2. Overview of set-up dosimeter on the BB plane from the (a) front view; and (b) back view

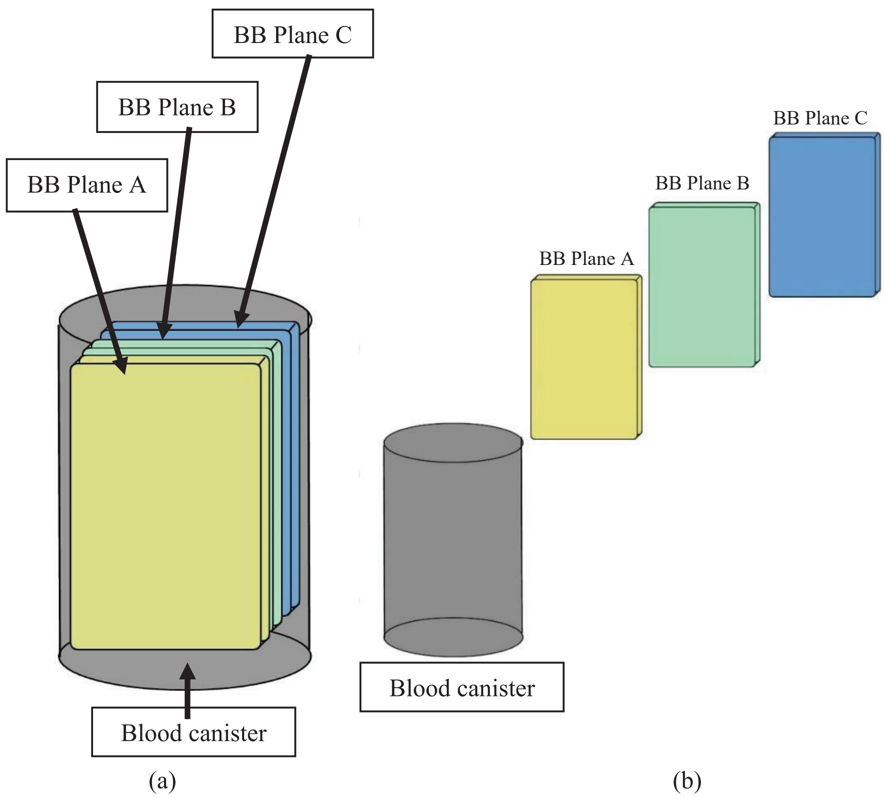


FIGURE 3. (a) Schematic diagram of the blood bags that are sort by plane in the canister, and (b) Fragmentation of the blood bag by BB Planes A, B, and C in the canister

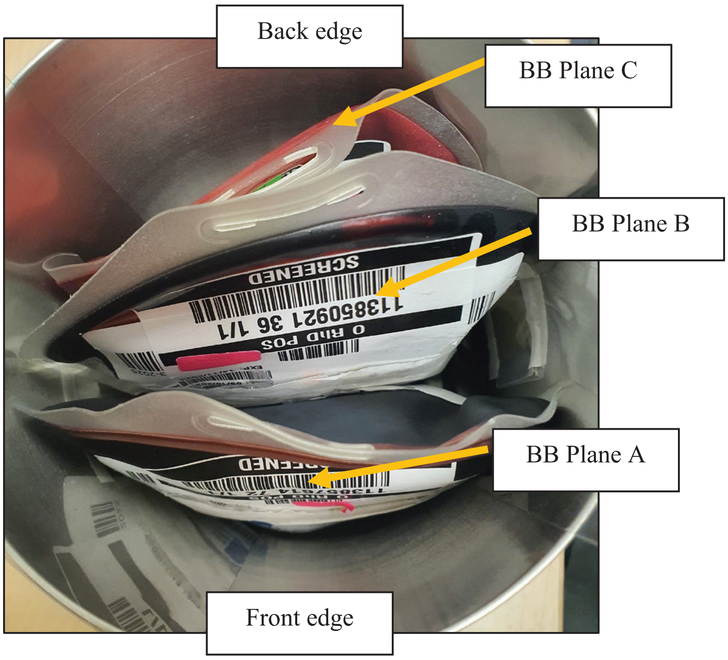


FIGURE 4. All three blood bags were sorted inside the canister

READOUT MEASUREMENT

A Harshaw™ 3500 TLD reader (Thermo ScientificTM, USA) is used to measure the signal responses precisely, utilising the Time-Temperature Profile (TTP) specified for each fibre. Table 2 presents the TTP used for each individual fibre. TTP was used in the study with a heating rate of 30 °C/s, as described in a detailed study on glow curve formation published by Fadzil et al. (2022), which used the same Ge-doped fibres. The integrated software, WinREMS, served as a supported TLD reader. The TL glow curve for CF and FF is as per illustrated in Figure 5. Analysis of the EBT-XD films exposed to radiation was conducted using a Microtek ScanMaker 1000XL flatbed scanner (Microtek International, Inc. in Taiwan). A scan resolution of 75 dots per inch (dpi) and a 48-bit colour depth (16 bits per channel) was set for the transmission mode, and all available image correction techniques were deactivated (Noor et al. 2022).

CALIBRATION CURVE OF IRRADIATION

Establishing calibration curves is crucial for determining the absorbed dose in EBT films and thermoluminescence dosimeters, as it is essential for accurate measurement (García-Garduño et al. 2023; Gul 2023). Dose calibration for optical fibres and EBT film is established within the range of 5 Gy to 50 Gy. The CF, FF, and EBT-XD films were exposed to gamma-ray ^{60}Co radiation, Eldorado 78 Colbalt-60 Beam Irradiator (Foss Therapy Services Inc., USA) at Nuclear Malaysia. All dosimeter optical fibres CF, FF and EBT-XD films were positioned accurately at 5 g/cm² depth in the water with a 10 cm × 10 cm field size and an SSD of 80 cm as in Figure 6. The established protocol for measuring the absorbed dose of water, as per Abdullah et al. (2023), is a systematic setup for calibrating dosimeters. To determine the coefficient of determination (R^2) values, a dosage calibration curve was constructed by plotting the TL or OD against the dose.

ABSORBED DOSE OF OPTICAL FIBRES IN COMPARISON TO EBT-XD FILMS

The TL response readings for each location were normalised to the core volume, and the mean of the TL response was calculated. TL signal (nC) was converted to the absorbed dose (Gy) using the calibration coefficient obtained from the calibration curve. All the absorbed doses were calculated using their correction factor. Concurrently, the EBT-XD films were scanned and analysed using ImageJ software. The average pixel value (PV) was obtained from a 1 × 1 cm^2 region of interest (ROI). The net optical density (OD) of the film was calculated using Equation (1) from Bakar et al. (2023), as follows:

$$\text{net } OD = log_{10}\frac{PV_{unirradiated}}{PV_{irradiated}} \quad (1)$$

where $PV_{unirradiated}$ and $PV_{irradiated}$ are the average pixel values of unirradiated and irradiated films, respectively, as measured at a minimum of five distinct locations in the ROI. The net log obtained is subsequently converted to the absorbed dose (Gy). The mean absorbed dose in Gray was compared between all the dosimeters by location.

TABLE 2. Fibre read-out measurement via Time-Temperature Profile (TTP)

Parameters	CF	FF
Preheat: Temperature	95 °C	92 °C
Time	10 s	10 s
Acquire: Maximum temperature	400 °C	400 °C
Temperature/heating rate	30 °C/s	30 °C/s
Time	13 s	13 s
Anneal: Temperature	400 °C	400 °C
Time	10 s	10 s

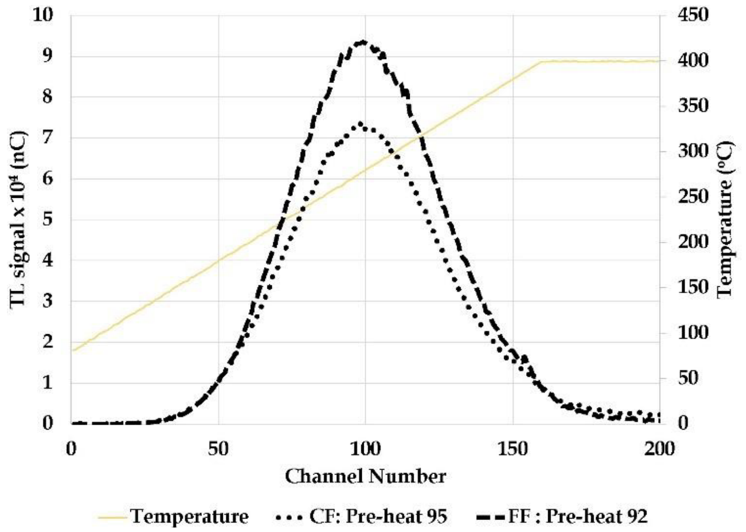


FIGURE 5. TL glow curve for CF and FF

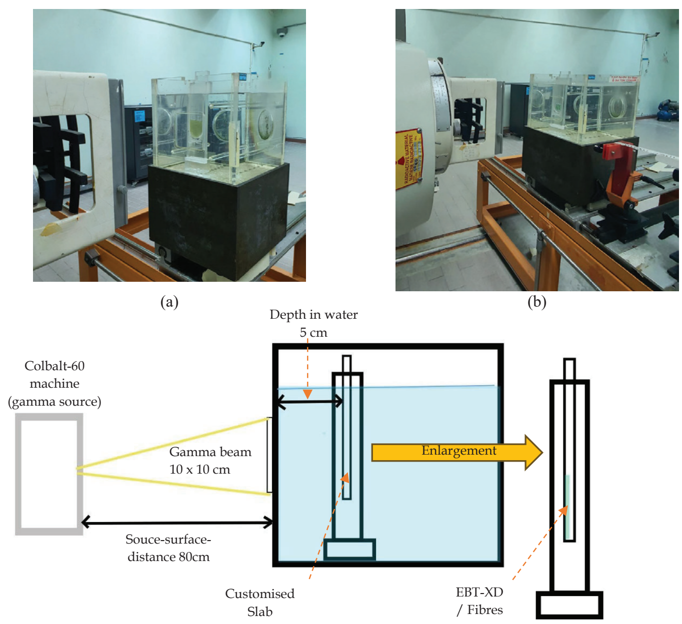


FIGURE 6. Calibration set-up in gamma Cobalt-60 for (a) EBT-XD film and (b) Optical fibres CF and FF (c) schematic diagram of set-up irradiation for calibration

STATISTICAL ANALYSIS

The Statistical Package for the Social Sciences (SPSS) version 29 is utilized for statistical test method in this study. A one-way ANOVA statistical technique was used to compare the absorbed dose measured in this clinical trial by optical fibres CF, FF, and the EBT-XD film with the mean difference to the standard error. The null hypothesis is that the means of the dose-response from these optical fibres and EBT-XD film are equal (H_o: mean $\mu_1 = \mu_2 = \mu_3$). The alternative hypothesis is that not all means are equal (H_a: mean $\mu_1 \neq \mu_2 \neq \mu_3$).

RESULTS AND DISCUSSION

DOSE CALIBRATION CURVE FOR FABRICATED OPTICAL FIBRES AND EBT-XD FILM

Figure 7(a) and 7(b) shows the graphs of the dose-response curves obtained during calibration for optical fibres CF, FF, and EBT-XD film at gamma-ray ^{60}Co from 5 Gy to 50 Gy. A linear relationship between optical fibres CF and FF is shown on the graph by the correlation coefficient (R^2), which is over 99%. CF's R^2 of 0.9981 was greater than FF's 0.9984, indicating an excellent dosage prediction for any observed TL response. Lam et al. (2019, 2017) found that Ge-doped cylindrical optical fibres exposed to 6MV photon irradiation show a strong and immediate correlation between TL response and subject dose throughout a 5 to 80 Gy range.

For EBT-XD film, the graph illustrates the third-order polynomial regression for three (3) channels, red, green, and blue, and includes the multichannel (RBG) channels. The graph shows that the EBT-XD film's red channel grew up to 35 Gy, indicating greater sensitivity. At higher dosages, the optical density increased to 50 Gy. Hence, the red channel is more reliable for dosage measurement than the multichannel (RBG), green, and blue channels. Figure 7(c) shows this correlation coefficient, R^2, of 0.9948. The correlation between net optical density and delivered radiation enables dose estimation for any EBT-XD film net OD within the dose range. The EBT film calibration curves show data points over 99%. R^2 values near one indicate a positive linear dose-response relationship.

The EBT-XD film, as described by Noor et al. (2022), has a dynamic range that significantly separates red and green curves at higher doses. This feature is crucial for reducing uncertainty in triple-channel dosimetry methods based on color difference (Palmer et al. 2015). They also found that the red channel provides the greatest response, aligning with previous studies. Miura et al. (2016) also highlighted the EBT-XD film's superior dynamic range and stronger signal, making it a valuable tool for film analysis.

DOSE INDICATORS OF FIBRES AND EBT-XD FILM

The radiation dose delivered to the blood was precisely as initially established in a clinical setting: 25 Gy to the blood bags in the canister. The conventional blood indicator and all dosimeters were positioned at the center of each blood bag. The blood indicators in Figure 8(a) and 8(b) exhibited a change in colour, indicating that the blood had received the dose of 25 Gy. Furthermore, Figure 8(c) indicates that the EBT-XD film exhibited a similar outcome to the blood indicator in terms of colour change. Bloodbag indicators are incapable of furnishing an exact dose value; they can only offer qualitative measurements. Conversely, Table 3 presents the dose quantification results in the Gray (Gy) unit for blood irradiation obtained from the EBT-XD film and optical fibres CF and FF.

MEANS DOSE OF FIBRES IN COMPARISON WITH EBT-XD FILM

The lowest and highest doses for CF were 27.2 and 35.4 Gy, 27.4 and 35.4 Gy for FF, and 25.3 and 33.7 Gy for EBT-XD film, respectively. Table 3 indicates the dose received at the centre of the blood bags and compares the measured values of optical fibres FF and CF with the reference dose, EBT-XD film. From this point forward, the dose response acquired from the EBT-XD film will be referred to as the reference dose. The comparison of the absorbed dose was determined by evaluating the percentage deviation between the average reading of 10 optical fibres per fibre and the reference dose. The relative mean difference in percentage between the measured doses using the optical fibres CF and FF and the reference dose measurements was 3.4% and 4.3%, respectively. Figure 9 shows a graph of dose distribution and comparison between the optical fibres and reference dose at each location. The results show that all dosimeters at the edges of the canister display the highest dose received by blood products that are located very close to the source gamma-ray, while at the centre of the canister they gave the lowest dose level.

STATISTICAL ANALYSIS

Statistical test showed that the Shapiro-Wilk statistics confirmed the assumption of normal distribution for each type of dosimeter (CF, FF, and EBT-XD film). Levene's statistic was non-significant, with a *p*-value of greater than 0.05. Therefore, the assumption of homogeneity of variance was not violated. A one-way between-group analysis of variance (ANOVA) was performed to assess the distribution of doses from these three dosimeters among the blood bags, revealed that there is no statistically significant difference in the dose responses of the dosimeter., $F(2,87) = 1.273$, $p = .285$ at p-value > 0.05 for each type of dosimeter.

In comparison to EBT-XD films, optical fibres CF and FF are accurate and useful dosimeters with a mean error of 3.4% and 4.3%, respectively. As blood indicators, they can verify and analyse absorbed doses of blood products from blood irradiation. A previous study used Monte Carlo simulations to test the EBT3 film on blood bags and found a strong link between the blood irradiator's two-dimensional

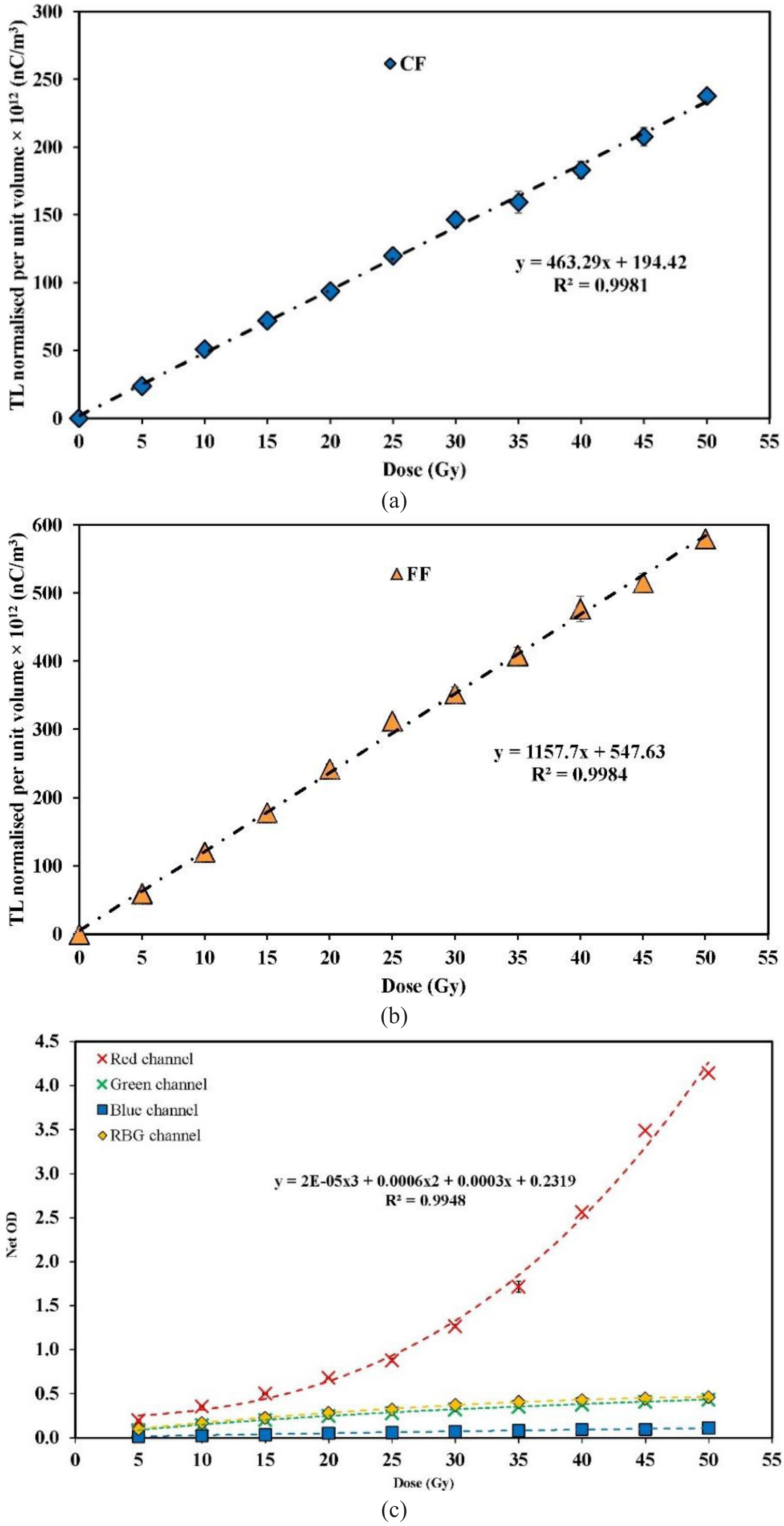
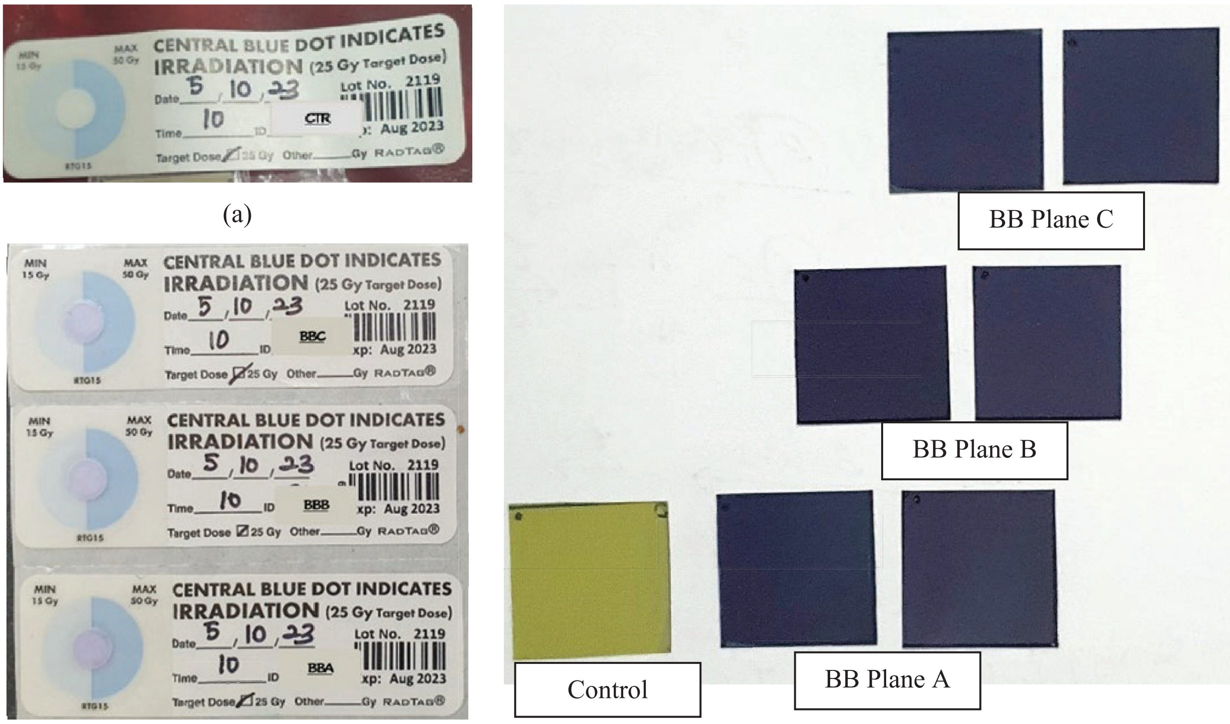


FIGURE 7. Calibration curve for determination of calibration coefficient for (a) CF and (b) FF (c) EBT-XD film in gamma-ray irradiation. The error bar is too small and does not appear in the graph



(a) (b) (C)

FIGURE 8. (a) Blood indicators before irradiation, (b) Blood indicators after irradiation and (c) EBT-XD film before and after the irradiation of 25 Gy

TABLE 3. The radiation doses measured at three planes (blood bag) irradiation in a canister using CF, FF optical fibres and EBT-XD film

Dosimeters	Plane view	Plane A (Blood Bag A)	Plane B (Blood Bag B)	Plane C (Blood Bag C)	Mean Error (%)
EBT-XD film	Front	33.3*	27.2	25.3	
	Back	26.8	28.8	33.7*	
Average dose (Gy)	D_{EBT}	30.0	28.0	29.5	
Dose different (%)	$[(D_{EBT} - D_{EBT})/D_{EBT}]*100\%$	0	0	0	0%
CF	Front	34.2*	27.5	28.1	
	Back	27.2	29.2	35.4*	
Average dose (Gy)	D_{CF}	30.7	28.3	31.8	
Dose different (%)	$[(D_{CF} - D_{EBT})/D_{CF}]*100\%$	2.1	1.2	7.0	3.4
FF	Front	35.1*	27.4	28.1	
	Back	27.7	29.6	35.4*	
Average dose (Gy)	D_{FF}	31.4	28.5	31.7	
Dose different (%)	$[(D_{FF} - D_{EBT})/D_{FF}]*100\%$	4.2	1.6	7.0	4.3

*Dose at the edges of the canister

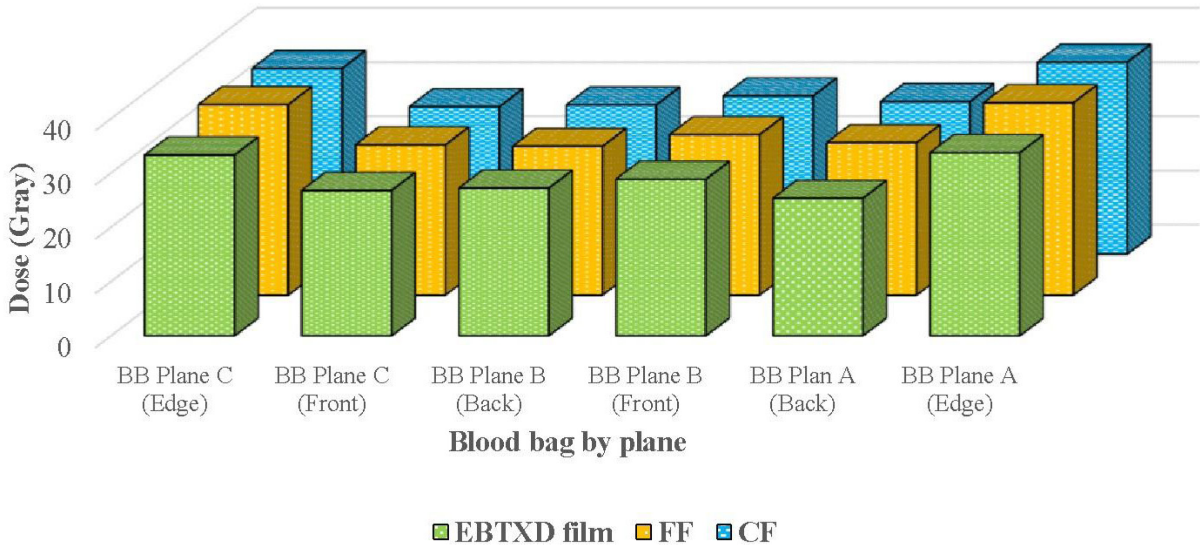


FIGURE 9. Dose distribution and comparison between the optical fibres CF, FF, and reference dose (EBT-XD film) at each location. Absorbed doses for all the dosimeters is displayed in unit of Gy

dose profile and the simulations. The simulation dose profile was different from the manufacturer's by 0% to 7.14% (Yilmaz Alan et al. 2024).

CONCLUSION

Present work has shown, optical fibre CF and FF are also reliable and precise dosimeters, exhibiting a mean error of less than 5% when compared to EBT-XD. The optical fibres have the potential to potentially replace conventional blood indicators, which solely provide an evaluation of quality by observation. A one-way ANOVA was evaluate the dose distribution of these three dosimeters on the blood, indicating that there is a non-significant difference (p-value =.285 ($p > 0.05$)). Their applicability is in the verification and quantification of the absorbed dose delivered to blood products during blood irradiation procedures in Pathology departments, HSAAS.

In conclusion, optical fibres offer accurate measurements for blood irradiation, addressing the limitations of current dosimeters. These fibres provide quantitative measurements in Gray (Gy) units, verifying absorbed doses. Affordable local manufacturing and detection capabilities enhance the safety and efficacy of blood transfusions. This novel Ge-doped optical fibre dosimetry system exhibits considerable promise as an innovative dose indicator for clinical use.

For precise dose mapping across a larger volume like in blood irradiation, multiple point measurements would be needed. This requires a very large number of dosimeters to characterise the full dose distribution. Also, it might introduce additional correction factor like directional dependence when trying to use multiple fibre dosimeters to map doses across a volume. Therefore, further research is needed for detailed 3D dose mapping, their limitations in spatial resolution and comprehensive volume coverage should be considered.

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