Summary of Doctoral Dissertation

Title: **Effect of the glucono-δ-lactone concentration on the sensitivity and stability of PVA-GTA-I radiochromic gel dosimeter**
(PVA-GTA-I 色素ゲル線量計の感度と安定性に及ぼすグルコノデルタラクトン濃度の影響)

Authors: Jolan E. Taño [a,b,c], Shin-ichiro Hayashi [d], Seiko Hirota [a], Chryzel Angelica B. Gonzales [a], Hiroshi Yasuda [a]

[a] Department of Radiation Biophysics, Research Institute for Radiation Biology and Medicine (RIRBM), Hiroshima University, Hiroshima, 734-8553, Japan
[b] Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima, 734-8553, Japan
[c] Phoenix Leader Education Program (Hiroshima Initiative) for Rennaissance from Radiation Disaster, Hiroshima University, Hiroshima, 734-8553, Japan
[d] Department of Clinical Radiology, Faculty of Health Sciences, Hiroshima International University, Higashi-Hiroshima, Hiroshima, 739-2695, Japan

Abstract
The present study investigated the influence of the varying concentrations of a proton generator, glucono-δ-lactone (GDL), promoting a cross-linking of the matrix to the dose-response of a PVA-GTA-I radiochromic gel dosimeter. This gel dosimeter was composed of iodide and polyvinyl alcohol crosslinked with glutaraldehyde (GTA) and combined with additives of GDL and fructose. Six sets of gel samples with GDL concentrations ranging from 50 to 300 mM was irradiated with 1–10 Gy doses using ^{137}Cs gamma-rays. Dose response and temporal stability of the absorbance in the gel dosimeter as a function of the GDL concentration were investigated. The dose-response data showed good linearities in the dose range of 0–10 Gy from all GDL concentrations measured 48 h post-irradiation. The sensitivity became higher with increasing GDL concentration, but smaller increments were observed at higher GDL concentrations and then completely saturated around 250 mM. The recorded sensitivities from the PVA-GTA-I gel dosimeters were 3–9 times higher than PVA-I and LCV micelle gel dosimeters. Temporal stability data showed a similar trend in GDL concentrations of 100–300 mM, where a sharp increase of absorbance was seen in the first 24 h and then small fluctuations were observed up to 168 h post-irradiation. Meanwhile, the samples with 50 mM of GDL showed a gradual increase in absorbance after 48 h post-irradiation. Higher GDL concentrations tended to increase the rate of auto-oxidation.

Keywords: Radiochromic gel dosimeter, Polyvinyl alcohol, Glucono-delta-lactone, Iodide, Gamma-rays

**Please cite the published version: https://doi.org/10.1016/j.radmeas.2020.106311*

1. Introduction

The current and emerging techniques in radiation therapy are becoming more complex and the quality assurance of these procedures require more accurate methods to quantify ionizing radiation fields in three dimensions (3D). Conventional dosimetry systems such as ionization chambers and radiosensitive films are utilized in clinical settings to verify dose delivery in the modern radiotherapy. However, these dosimeters do not meet the Resolution-Time-Accuracy-Precision (RTAP) criteria for 3D dosimetry and are limited to providing point or two-dimensional (2D) absorbed dose estimates and sporadic 3D information (Schreiner, 2015). Accordingly, such requisite characteristics could be addressed by gel dosimeters which are chemical-based dosimeters capable of retaining spatial dose distribution within the gel matrix (Collura et al., 2018). The 3D dose information in the gel dosimeters can be measured by several imaging techniques such as magnetic resonance imaging (MRI), optical computed tomography (OCT), x-ray computed tomography (CT), ultrasonography, and Raman spectroscopy (Mather et al., 2002; Oldham et al., 2001). The characteristics of gel dosimeters are advantageous in radiotherapy conditions where steep dose gradients are present (e.g., intensity modulated radiation therapy (IMRT) and stereotactic radiosurgery (SRS)). Moreover, the materials used in fabricating most gel dosimeters are radiologically equivalent to soft-tissues, which can be modified depending on the type of application (Baldock et al., 2010).

Gel dosimeters are categorized depending on their properties and read-out process, these include Fricke gels, polymer gels, and novel radiochromic gels (Schreiner, 2015). In more recent years, there have been considerable interest in the development and improvement of radiochromic gel dosimeters due to its potential and relatively easier method of measurement (Oldham et al., 2017). The mechanism of radiochromic gel dosimeters is based on the radiation-induced color change which is proportional to the absorbed dose. The color change can be measured using optical techniques such as spectroscopy or OCT. Fricke gels infused with xylenol orange (XO) are one of the known varieties of radiochromic gel dosimeters. These gels are composed of ferrous sulfate that converts to ferric ions due to the oxidation from ionizing radiation (Gore et al., 1984). Incorporating XO in the Fricke gel formula significantly reduced the diffusion in the matrix and permitted the evaluation of the dose using optical imaging (Appleby and Leghrouz, 1991; D'Errico et al., 2017; Marini et al., 2017; Schreiner, 2015). Other varieties of radiochromic gels are micelle gel dosimeters which use Leuco Malachite Green (LMG) (Jordan and Avvakumov, 2009) or Leuco Crystal Violet (LCV) (Babic et al., 2009; Nasr et al., 2015) dyes as the radiation sensitive indicators. Subsequent studies also reported about the use of the synthetic copolymer Pluronic F-127 as a base matrix substitute to gelatine in several radiochromic gel formulas using tetrazolium salts (TTC) (Kwiatos et al., 2018) as radiosensitizers.

A recently developed radiochromic gel dosimeter composed of polyvinyl alcohol (PVA)-iodide (I) complex with gellan gum (GG) as the gelling agent was reported (Hayashi et al., 2020). This gel dosimeter converts from colorless to red after irradiation and can be reused by heating. The red coloration of this gel results from the oxidation of the PVA-Iodide complex caused by the radiolysis of the water molecules. Whereas the decolorization is attributed to the additive fructose which acts as the reducing sugar. In other studies, the reagent glutaraldehyde (GTA) was utilized as a crosslinker to the PVA matrix of Fricke-XO gel (FXG) dosimeters. The use of PVA was first proposed by Chu et al., (2000) to create gel dosimeters with low diffusion coefficient. Additionally, GTA has been proven as an effective crosslinker to PVA and can further reduce the spatial diffusion and increase the sensitivity and stability, of gel dosimeters (D'Errico et al., 2017; Marini et al., 2017).

We developed our own system radiochromic gel dosimeter, called the PVA-GTA-I gel dosimeter, by applying the PVA-GTA matrix to the PVA-I radiochromic gel dosimeter, as detailed in our previous study (Taño et al., 2019). Our present research focuses on the effect of one of the additives in our formula, which is the glucono-δ-lactone (GDL). GDL is an acidic coagulant commonly used in the food industry, such as in bean curd (Dybowska and Fujio, 1998) and cheese production (Martin et al., 2009). Because of its inherent binding and non-toxic properties, GDL is used in this gel dosimeter formula as a proton generator and to further promote the cross-linking process. Therefore, our objective is to investigate the effect of the GDL concentration to the dose-response and temporal stability of the PVA-GTA-I formula.

2. Materials and Methods

All gel samples were fabricated with ultrapure water, and analytical grade chemicals. The base solution is made of PVA (86–90 mol% saponification, partially hydrolyzed) that was dissolved in water using a magnetic stirrer at 80°C for 1 h. Then, other components of potassium iodide (KI), fructose, GTA, and GDL were poured into the mixture and stirred until a homogeneous solution was achieved. Six sets of gels were prepared with various GDL concentrations from 50 to 300 mM. The gel solutions were poured into PMMA cuvettes, covered with polyethylene (PE) cover, and stored in a dry heat sterilizer at 45°C for 12 h to allow gelation. The gel samples were prepared and heated the day before irradiation and were stabilized for approximately 1 h after heating at room temperature before exposure to radiation. A Gammacell-40 research irradiator with low dose rate (i.e., 0.82 Gy/min) ^{137}Cs sources was used to irradiate the gel samples with doses from 1 to 10 Gy; and one sample was left unirradiated as the control sample. The gel dosimeters were positioned at the middle of the sample holder with the axes of the cuvettes perpendicular to the source, as shown in Fig. 1. A UV–Vis Spectrophotometer was used to measure the optical absorbance at the wavelength range of 350–800 nm. Ultrapure water was used to calibrate all the absorbance measurements. The temporal stability of the gel was evaluated in a seven-day period after irradiation with time intervals of 2, 24, 48, 72, 96, 120, 144, and 168 h at room temperature range of 20–23°C. Finally, the change of absorbance (ΔAbs.) was calculated by the difference between the measured absorbance of the irradiated samples [Abs.(i)] and the unirradiated (control) sample [Abs.(c)], as shown by equation (1):

$$\Delta Abs. = Abs.(i) - Abs.(c) \quad (1)$$

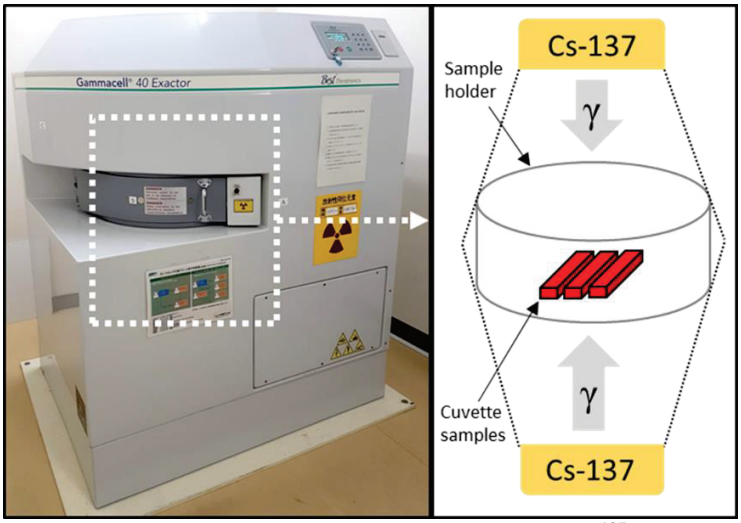

Fig. 1. Schematic diagram of the irradiation setup in the Gammacell-40 ^{137}Cs gamma-ray irradiator. The samples were irradiated with doses of 1, 2, 3, 4, 5, 7, and 10 Gy.

3. Results and Discussion

3.1. Optical absorbance characteristics

The physical appearance of the unirradiated PVA-GTA-I gel sample was colorless and transparent, while the irradiated samples were converted to red, as presented in Fig. 2. The color intensity was observed to be increasing with radiation dose. This effect was further emphasized in the absorbance spectrum profiles where the peak absorbance at 482 nm was increasing. The absorbance peak at 482 nm was selected as the point of reference for all the absorbance analyses in this study.

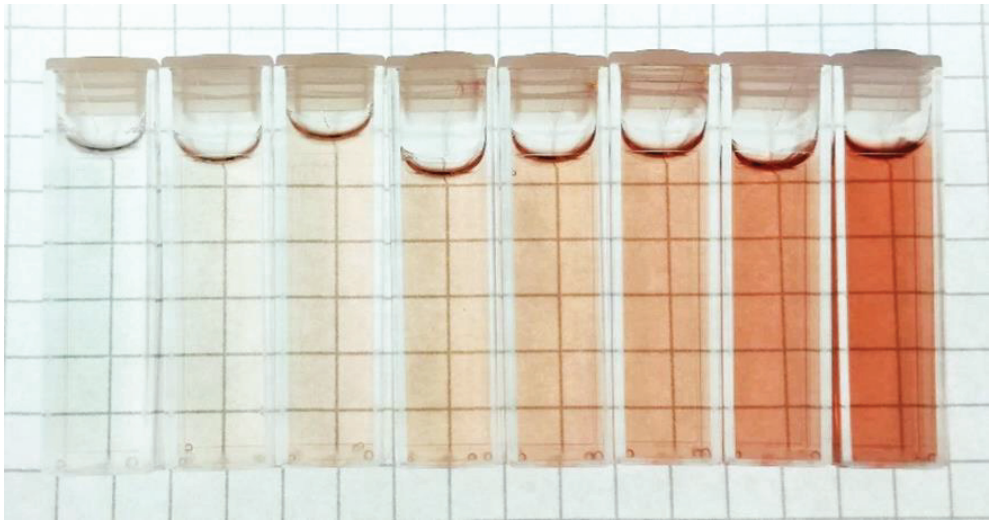

Fig. 2. Photograph of the irradiated PVA-GTA-I samples. The doses from the left to right are 0 (control), 1, 2, 3, 4, 5, 7, and 10 Gy.

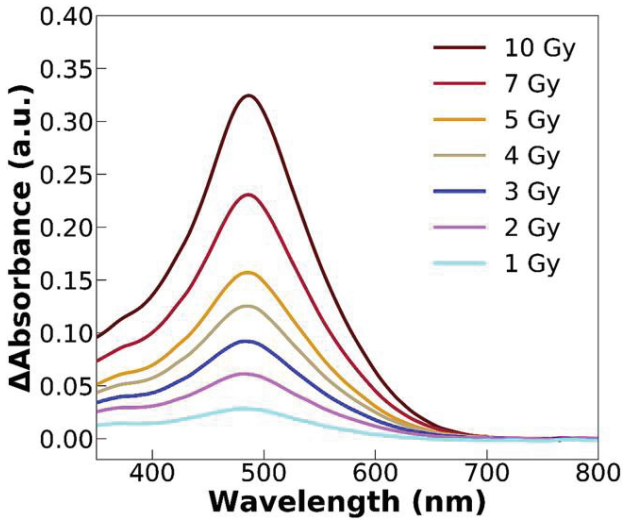

Fig. 3. ΔAbs spectrum profiles of the 100 mM GDL samples measured 48 h post-irradiation and adjusted with the control (0 Gy) sample.

3.2. Dose-response

The ΔAbs-dose plots shown at Fig. 4 exhibited good linearities ($R^2 < 0.99$) in the dose range of 0–10 Gy from all the sample sets despite the different GDL concentrations. The linear fitting values for each sample is presented in Table 1. The sensitivity, defined by the slope of the linear fitting function, increased with higher GDL concentrations. However, it was also observed that the increment of sensitivity became small with the GDL concentration and then completely saturated around 250 mM. The highest sensitivity range from all the sample sets was 3.8–4.0 x10^{-2} Gy^{-1}. As compared to the sensitivity values in Table 2, the sensitivity of the PVA-GTA-I is approximately 3 to 4 times higher than the PVA-I gel, and 6 to 9 times higher than LCV micelle gels. Though, the sensitivity of the PVA-GTA-I gel was approximately 2 times lower than the PVA-GTA-FXG gels.

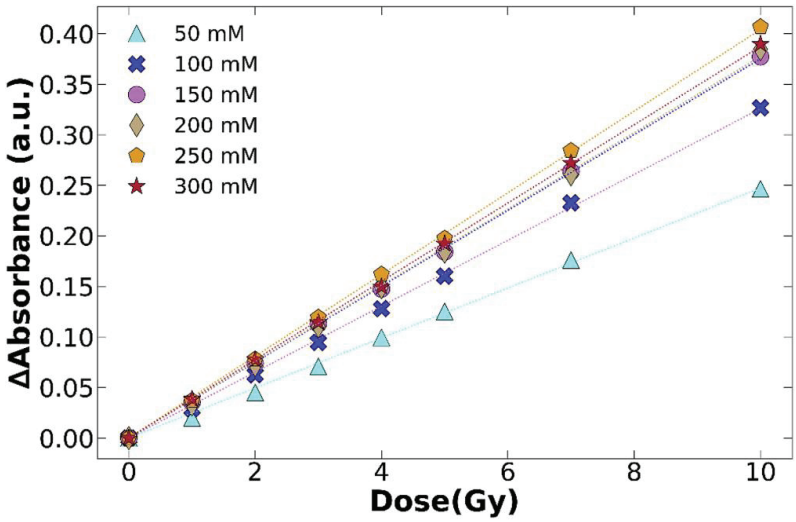

Fig. 4. ΔAbs-dose plot of the PVA-GTA-I gel samples with increasing GDL concentrations measured 48-h post-irradiation.

Table 1

The dose sensitivity (m) (Gy^{-1}) and coefficient of determination (R^2) for each GDL concentration in Fig. 4.

	50	100	150	200	250	300
m	0.025	0.033	0.038	0.038	0.04	0.039
R^2	0.998	0.999	0.999	0.999	0.999	0.999

Table 1.

Comparison of sensitivities among different radiochromic gel dosimeters.

Reference	Type of radiochromic gel dosimeter	Source	Sensitivity (Gy^{-1})
This study	PVA-GTA-I	^{137}Cs	4.00×10^{-2}
Hayashi et al., 2020	PVA-I	6 MV X-ray	1.12×10^{-2}
Babic et al., 2009	LCV micelle	^{60}Co	4.3×10^{-3}
Nasr et al., 2015	LCV-CTAB micelle	6 MV X-ray	6.5×10^{-3}
D'Errico et al., 2017; Marini et al., 2017	PVA-GTA-FXG	6 MV X-ray	7.3×10^{-2}

3.3. Temporal stability

The absorbance-time plot of the control (0 Gy) samples in Fig. 5 showed a gradual increase in absorbance with time. This phenomenon is caused by the autooxidation of the iodide ions in the gel. Moreover, it was also seen that higher GDL concentrations promotes the rate of auto-oxidation in the gel formula. Meanwhile, the temporal stability results of the 10 Gy irradiated samples in Fig. 6 revealed the trends of the ΔAbs.-time plots for the varying GDL concentrations. The sample sets with 100 to 300 mM GDL exhibited a sharp increase of the ΔAbs during the initial 24 h and followed by small fluctuations up to 168 h (7 days) post irradiation. On the other hand, the sample set with 50 mM GDL showed a gradual rate of increase in ΔAbs, which started at 48 h after irradiation, and then continuous to increase up to 168 h post-irradiation.

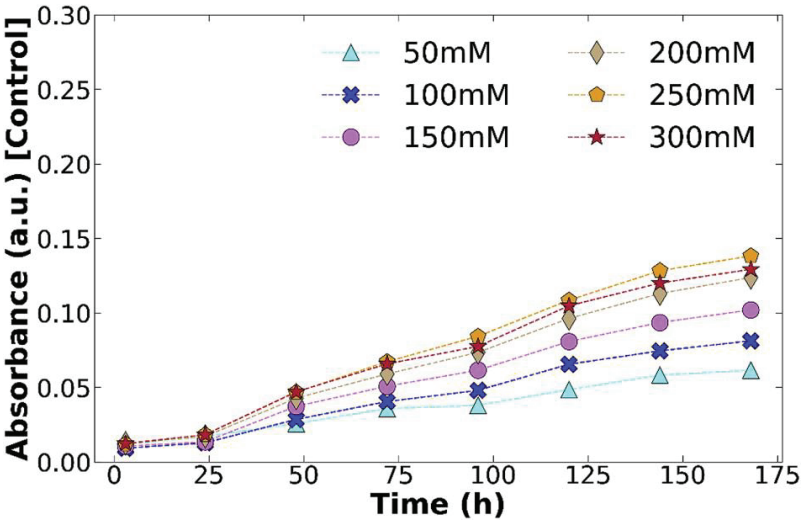

Fig. 5. Absorbance-time plot of the control (0 Gy) samples with various GDL concentrations.

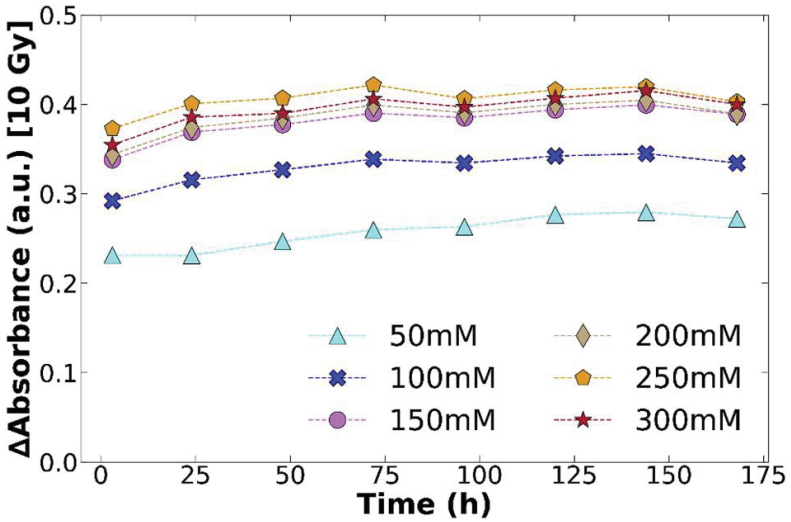

Fig. 6. ΔAbs-time plot of the 10 Gy irradiated samples with various GDL concentrations.

4. Conclusion

The influence of the increasing concentrations of GDL to the dose-response and temporal stability of a PVA-GTA-I radiochromic gel dosimeter has been investigated. The PVA-GTA-I gel showed linear dose-response up to 10 Gy with sensitivities 3-9 times higher than other radiochromic gel dosimeters. The temporal stability data revealed that higher GDL concentrations increases the auto-oxidation rate of the PVA-GTA-I gel. Overall, the results obtained in our study have indicated good insights in the properties of the PVA-GTA-I gel dosimeter with respect to varying GDL concentration. Subsequently, the PVA-GTA-I gel dosimeter has shown good potential in reusability from our pilot study, which is an advantageous characteristic for clinical 3D dosimetry applications in radiotherapy. Further research is recommended to uncover more of its characteristics in terms of its reusability after repeated heating and irradiations, dose rate dependence, dose fractionation effects, and spatial stability.

Acknowledgements

The authors would like to thank the Natural Science Center for Basic Research & Development (N-BARD) and Radiation Research Center for Frontier Science of Hiroshima University for permission to use the equipment. This work is supported by the JSPS KAKENHI Grant Number 17K09072 and 18KK0147.

References

Appleby, A., Leghrouz, A., 1991. Imaging of radiation dose by visible color development in ferrous-agarosexylenol orange gels. Med. Phys. 18, 309–312. https://doi.org/10.1118/1.596676

Babic, S., Battista, J., Jordan, K., 2009. Radiochromic leuco dye micelle hydrogels: II. Low diffusion rate leuco crystal violet gel. Phys. Med. Biol. 54, 6791–6808. https://doi.org/10.1088/0031-9155/54/22/003

Baldock, C., De Deene, Y., Doran, S., Ibbott, G., Jirasek, A., Lepage, M., McAuley, K.B., Oldham, M., Schreiner, L.J., 2010. Polymer gel dosimetry. Phys. Med. Biol. 55. https://doi.org/10.1088/0031-9155/55/5/R01

Chu, K.C., Jordan, K.J., Battista, J.J., Van Dyk, J., Rutt, B.K., 2000. Polyvinyl alcohol-Fricke hydrogel and cryogel: Two new gel dosimetry systems with low Fe3+ diffusion. Phys. Med. Biol. 45, 955–969. https://doi.org/10.1088/0031-9155/45/4/311

Collura, G., Gallo, S., Tranchina, L., Abbate, B.F., Bartolotta, A., d'Errico, F., Marrale, M., 2018. Analysis of the response of PVA-GTA Fricke-gel dosimeters with clinical magnetic resonance imaging. Nucl. Instruments Methods Phys. Res. Sect. B Beam Interact. with Mater. Atoms 414, 146–153. https://doi.org/10.1016/j.nimb.2017.06.012

D'Errico, F., Lazzeri, L., Dondi, D., Mariani, M., Marrale, M., Souza, S.O., Gambarini, G., 2017. Novel GTA-PVA Fricke gels for three-dimensional dose mapping in radiotherapy. Radiat. Meas. 106, 612–617. https://doi.org/10.1016/j.radmeas.2017.07.003

Dybowska, B.E., Fujio, Y., 1998. Optical Analysis of Glucono-δ-Lactone Induced Soy Protein Gelation. J. Food Eng. 36, 123–133. https://doi.org/10.1016/s0260-8774(98)00039-9

Gore, J.C., Kang, Y.S., Schulz, R.J., 1984. The measurement of radiation dose distributions by magnetic resonance imaging. Phys. Med. Biol. 29, 1189–1197.

Hayashi, S., Ono, K., Fujino, K., Ikeda, S., Tanaka, K., 2020. Novel radiochromic gel dosimeter based on a polyvinyl alcohol – Iodide complex. Radiat. Meas. 131, 106226. https://doi.org/10.1016/j.radmeas.2019.106226

Jordan, K., Avvakumov, N., 2009. Radiochromic leuco dye micelle hydrogels: I. Initial investigation. Phys. Med. Biol. 54, 6773–6789. https://doi.org/10.1088/0031-9155/54/22/002

Kwiatos, K., Maras, P., Kadlubowski, S., Stempień, Z., Dudek, M., Kozicki, M., 2018. Tetrazolium salts-Pluronic F-127 gels for 3D radiotherapy dosimetry. Phys. Med. Biol. 63. https://doi.org/10.1088/1361-6560/aabbb6

Marini, A., Lazzeri, L., Cascone, M.G., Ciolini, R., Tana, L., D'Errico, F., 2017. Fricke gel dosimeters with low-diffusion and high-sensitivity based on a chemically cross-linked PVA matrix. Radiat. Meas. 106, 618–621. https://doi.org/10.1016/j.radmeas.2017.02.012

Martin, F., Cayot, N., Marin, A., Journaux, L., Cayot, P., Gervais, P., Cachon, R., 2009. Effect of oxidoreduction potential and of gas bubbling on rheological properties and microstructure of acid skim milk gels acidified with glucono-δ-lactone. J. Dairy Sci. 92, 5898–5906. https://doi.org/10.3168/jds.2009-2491

Mather, M.L., Whittaker, A.K., Baldock, C., 2002. Ultrasound evaluation of polymer gel dosimeters. Phys. Med. Biol. 47, 1449–1458. https://doi.org/10.1088/0031-9155/47/9/302

Nasr, A.T., Alexander, K.M., Olding, T., Schreiner, L.J., McAuley, K.B., 2015. Leuco-crystal-violet micelle gel dosimeters: II. Recipe optimization and testing. Phys. Med. Biol. 60, 4685–4704. https://doi.org/10.1088/0031-9155/60/12/4685

Oldham, M., Juang, T., Detectors, S.W. (Paul) Y.S.E.-R. 3D, 2017. Radiochromic 3D Detectors, in: Clinical 3D Dosimetry in Modern Radiation Therapy. CRC Press. https://doi.org/10.1201/9781315118826-6

Oldham, M., Siewerdsen, J.H., Shetty, A., Jaffray, D.A., 2001. High resolution gel-dosimetry by optical-

CT and MR scanning. Med. Phys. 28, 1436–1445. https://doi.org/10.1118/1.1380430
Schreiner, L.J., 2015. True 3D chemical dosimetry (gels, plastics): Development and clinical role. J. Phys. Conf. Ser. 573. https://doi.org/10.1088/1742-6596/573/1/012003
Taño, J., Hayashi, S., Hirota, S., Gonzales, C.A., Yasuda, H., 2019. Development of a reusable PVA-GTA-I gel dosimeter for 3D radiation dose assessments. J. Phys. Conf. Ser. 1305. https://doi.org/10.1088/1742-6596/1305/1/012034