Radiological properties of nanocomposite Fricke gel dosimeters for heavy ion beams

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ABSTRACT
The radiological properties of nanocomposite Fricke gel (NC-FG) dosimeters prepared with different concentrations of nano-clay, perchloric acid and ferrous ions in deaerated conditions were investigated under carbon and argon ion beam irradiation covering a linear-energy-transfer (LET) range of 10 to 3000 eV/nm. We found that NC-FG exhibits radiological properties distinct from those of conventional Fricke gel. The radiation sensitivity of NC-FG is independent of the LET and is nearly constant even at very high LET (3000 eV/nm) values in the Bragg peak region of the argon ion beam. In addition, whereas conventional Fricke gel dosimeters only operate under acidic conditions, NC-FG dosimeters function under both acidic and neutral conditions. The radiation sensitivity decreases with decreasing nano-clay concentration in NC-FG, which indicates that the nano-clay plays a vital role in the radiation-induced oxidation of Fe²⁺.

KEYWORDS: Ion beam, LET, Nanocomposite gel, Gel dosimeter

INTRODUCTION
The aqueous ferrous sulfate Fricke chemical dosimeter is based on the radiation-induced oxidation of ferrous ions (Fe²⁺) to ferric ions (Fe³⁺) under acidic conditions [1, 2]. The addition of a gel matrix (typically gelatin or agarose) to the aqueous Fricke solution preserves the spatial distribution of Fe³⁺ ions, which can then be probed using magnetic resonance imaging (MRI) to record three-dimensional (3D) dose distributions in tissue-equivalent gels [3]. Under aerated and acidic conditions, the Fe³⁺ radiolytic yield G(Fe³⁺) for Fricke gel (FG) is typically 38–155 x 10⁻⁷ mol J⁻¹ for gamma-ray or X-ray irradiation [4–9], which is 2.3–10 times higher than that for an aqueous Fricke solution (16.2 x 10⁻⁷ mol J⁻¹) because the Fe³⁺ ions are formed via a chain reaction in the former [7]. On the other hand, FG dosimeters do not work under neutral conditions as well as they do under oxygen-free conditions [7, 8, 10].

3D dosimetry is expected to be a useful tool, particularly for the verification of more complex radiation dose planning in advanced radiation cancer therapy [11–18]. However, conventional FG dosimeters have two main drawbacks regarding their application to heavy ion beam irradiation: diffusion of the radiation product [8,11,19] and linear-energy-transfer (LET)-dependent radiation sensitivity [20]. LET is defined as the amount of energy transferred per unit track length to the medium and is a representative index of radiation quality. The radiation sensitivity of gel dosimeters decreases with increasing LET due to enhanced radical recombination by localized ionization and excitation. It should be noted that the LET dependence of radiation sensitivity is common to virtually all types of 3D dosimeters and is also not unique to gel dosimeters, e.g. film, scintillation and semiconductor dosimeters are LET-dependent as well [21–30].

Recently, we reported a nanocomposite Fricke gel (NC-FG) dosimeter that is free from the above-mentioned drawbacks [31]. The NC-FG was prepared by mixing a Fricke solution and nanocomposite gel under deaerated conditions. MRI images of this NC-FG provided...
stable radiation sensitivities and virtually no diffusion for 9 days following irradiation by a 290-MeV/nucleon carbon-ion beam (see Fig. 5 of Reference [31]). Moreover, the radiation sensitivity data obtained from the NC-FG faithfully reproduced the depth–dose distribution measured by an ionization chamber, which indicates LET independence. As an extension of our previous work, in this study, we investigate the radiological properties of NC-FG dosimeters in detail for various preparation conditions and under carbon and argon beam irradiation over an LET range of 10–3000 eV/nm. The radiation sensitivity was found to be LET-independent even at very high LET values (3000 eV/nm), which corresponds to the Bragg peak region of the argon ion beam. While conventional FG dosimeters only work under acidic conditions, NC-FG dosimeters function under both acidic and neutral conditions. We also found that the radiation sensitivity depends critically on the presence of the nano-clay under the deaerated conditions used for NC-FG dosimeters.

MATERIALS AND METHODS

Gel preparation

The various conditions under which NC-FG was prepared are summarized in Table 1. The composition of Gel1 was the same as that used in our previous report [31]: 1% (w/w) nano-clay (synthetic hectorite or Laponite XLG; Rockwood Additives Ltd), 3% (w/w) gelatin (300 g Bloom from porcine skin; Sigma-Aldrich), 1 mM ammonium iron (II) sulfate (Ammonium ferrous sulfate hexahydrate; Fluka) and 50 mM perchloric acid (perchloric acid (60%); Wako Pure Chemicals).

The procedure for the preparation of NC-FG was as follows. First, ultra-pure water was exposed to bubbling Ar gas for 30 min to remove dissolved oxygen. Next, gelatin and Laponite XLG were added to the deaerated ultra-pure water and mixed using a rotation/revolution vacuum mixer (V-mini300, EME Corporation) for 3 min to obtain a uniform dispersion. The dispersion was then heated in a microwave oven until dissolution took place. Finally, the 5% (w/w) aqueous Fricke stock solution [2] was added at around 40°C and mixed using a rotation/revolution mixer for 3 min to produce NC-FG. The prepared NC-FG was sealed in color comparison tubes made of Pyrex glass (Iwaki Glass Co., COLOR-TUBE25S: 18 mm outer diameter and 18 cm length) under a pure argon atmosphere in a glove box and left to solidify for a day.

Irradiation

The irradiation experiments were performed at the Biological Irradiation Port of the Heavy Ion Medical Accelerator in Chiba (HIMAC) at the National Institute of Radiological Sciences (NIRS). A 12C6+ beam at 290 MeV/nucleon and an 40Ar18+ beam at 500 MeV/nucleon with an irradiation field of ±5% lateral dose uniformity within a 10-cm diameter were used. The color comparison tubes containing NC-FG were irradiated from the bottom. The energies of both ion beams were attenuated with an energy absorber made of polymethyl methacrylate (PMMA) plates to adjust the range of the ion beams to the center of the color comparison tubes. The water equivalent thickness of the energy absorber for the carbon and argon beam irradiation was 63.26 and 11.04 mmH2O, respectively. At the entrance surface of the color comparison tubes containing NC-FG, the absorbed dose was 150, 300, 450 and 600 Gy for the carbon ion beam, and 200, 400, 600 and 800 Gy for the argon ion beam. These values were calibrated using a Markus ionization chamber at the same position as the samples [32, 33]. The depth–dose distribution of the carbon ion beam in this system has been reported in the literature [34].

MRI measurements

In the presence of paramagnetic Fe3+ ions, proton relaxation rates [s⁻¹] increase significantly. The relaxation rate is proportional to the Fe3+ concentration in a gel or solution. We measured the longitudinal MR relaxation rate (R₁ [s⁻¹], the inverse of the longitudinal relaxation time T₁) for the NC-FG samples using a 1.5-T MRI scanner (Intera Achieva 1.5 T HP Nova Dual Gradient, Philips Medical Systems, Best, the

| Table 1. Preparation conditions for NC-FG and types of ionizing radiation. Gel1 is a reference condition reported in [31]. The concentration of HClO₄, nano-clay, and Fe²⁺ is varied in Gel2–Gel5, Gel6–Gel8 and Gel9–Gel10, respectively. |
|---|---|---|---|---|---|
| Gel1 | 3 | 1 | 50 | 1 | Reference Carbon, Argon beam |
| Gel2 | 3 | 1 | 0 | 1 | pH Carbon beam |
| Gel3 | 3 | 1 | 1 | 1 | pH |
| Gel4 | 3 | 1 | 10 | 1 | pH |
| Gel5 | 3 | 1 | 150 | 1 | pH |
| Gel6 | 3 | 0.1 | 50 | 1 | Clay |
| Gel7 | 3 | 0.5 | 50 | 1 | Clay |
| Gel8 | 3 | 0.75 | 50 | 1 | Clay |
| Gel9 | 3 | 1 | 50 | 0.2 | Fe |
| Gel10 | 3 | 1 | 50 | 5 | Fe |
A turbo mixed sequence [35, 36] was used. The conditions for the T1 measurements were as follows: TR = 2260 ms; TE1 = 19 ms; TE2 = 100 ms; TI = 500 ms; ETL = 6; pixel spacing = 0.8 mm; slice thickness = 5 mm with a resulting voxel size of 0.8 × 0.8 × 5 mm³. The MRI measurements were carried out within 2 weeks of the irradiation.

Evaluation of the Fe³⁺ radiolytic yield G(Fe³⁺) using a calibration curve

The calibration curve (plot of R₁ vs. [Fe³⁺]) was evaluated by measuring non-irradiated gel samples with known concentrations (0–0.4 mM ammonium iron (III) sulfate mixed with 1% (w/w) nano-cla 3% (w/w) gelatin and 50 mM perchloric acid under aerated conditions), using the same 1.5 T MRI and the same MRI sequence employed for the irradiated NC-FG samples. The slope of the calibration curve was used as a conversion factor (CF) to convert the change in the proton relaxation rate ΔR₁ to [Fe³⁺]. The Fe³⁺ radiolytic yield G(Fe³⁺) was then calculated using the following equations:

\[
[\text{Fe}^{3+}] \, (\text{mM}) = \frac{1}{\text{CF}(\text{s}^{-1} \text{mM}^{-1})} \times \Delta R_1 \, (\text{s}^{-1})
\]

\[
G(\text{Fe}^{3+}) \, (\mu\text{mol} \times \text{J}^{-1}) = \frac{[\text{Fe}^{3+}] \, (\text{mM})}{D(\text{kGy}) \times \rho \, (\text{kg/l})}.
\]

Where [Fe³⁺] (mM) is the concentration of ferric ions produced by irradiation, D (kGy) is the absorbed dose and ρ (kg/l) is the density of NC-FG. The CF was used to evaluate G(Fe³⁺) for the reference composition Gel1 only (see Table 1).

**RESULTS AND DISCUSSION**

**Radiological properties of reference NC-FG**

Figure 1(a) and (b) shows the R₁ distributions measured for the reference sample Gel1 irradiated with a 290-MeV/nucleon carbon ion beam and 500-MeV/nucleon argon ion beam, respectively. The R₁ values for the non-irradiated samples (hereafter, referred to as the baseline) are about 1.3 and 1.0 s⁻¹ for the samples used for carbon and argon beam irradiation, respectively. These differences in the baseline values per batch are due to oxygen contamination that occurs during sample preparation. In addition, there is not much difference between the baseline R₁ values for NC-FG and those reported for conventional FG [9, 20].

The peak positions were adjusted within a single MRI pixel (pixel size 0.78 mm) in such a way that they coincided with each other. The entrance surface dose dependence of R₁ near the entrance surface (5 mm depth) and near the Bragg peak (79 mm for carbon irradiation, 105 mm for argon irradiation), where good linearity was observed, is plotted in Fig 1(c) and 1(d), respectively. It should be noted that the horizontal axis is the entrance surface dose and that the dose especially at the Bragg peak is much higher than it.

In Fig. 2, we compare the radiation sensitivity δR₁ defined as the rate of increase in R₁ per unit entrance surface dose, with the actual dose distribution obtained from the ionization chamber (right vertical axis). The δR₁ distribution for Gel1 faithfully reproduces the dose distribution, even at the Bragg peak for the argon ion beam, indicating that the sensitivity for Gel1 did not change even under very high LET.
radiation. In addition, the radiation sensitivity near the surface is almost the same (0.6 s\(^{-1}\) kGy\(^{-1}\)) for both C and Ar ions.

Figure 3 shows the calibration curve obtained from measurements of \(R_1\) carried out with various Fe\(^{3+}\) concentrations. The slope of the straight line is \(CF = 7.71 \text{ s}^{-1} \text{ mM}^{-1}\), which is consistent with the value of 8.37 s\(^{-1}\) mM\(^{-1}\) reported in [3]. We determined the Fe\(^{3+}\) radiolytic yield for the reference composition Gel\(_1\) to be \(0.78 \times 10^{-7} \text{ mol J}^{-1}\) using equations (1) and (2). This result indicates that the radiolytic yield for NC-FG is significantly smaller than that for the aqueous Fricke solution for carbon ion irradiation [37] (\(G(\text{Fe}^{3+}) = 11 \times 10^{-7} \text{ mol J}^{-1}\) under aerated conditions and \(G(\text{Fe}^{3+}) = 6 \times 10^{-7} \text{ mol J}^{-1}\) under deaerated conditions).

**Effect of preparation conditions**

The gelling properties depend strongly on the preparation conditions used in their fabrication. For example, the incorporation of perchloric acid into NC-FGs decreases their resilience and firmness. On the other hand, high concentrations of nano-clay and gelatin cause the gels to lose their mobility immediately after mixing. Outside the ranges used in this study, the gels became either too hard or too soft.

Figure 4 shows the \(R_1\) distributions for NC-FGs produced under various preparation conditions. \(R_1\) is confirmed to increase monotonically with dose for all preparation conditions, except in the case of Gel\(_5\) and Gel\(_6\). Relative radiation sensitivities as a function of depth are shown in Fig. 5 for various concentrations of (a) perchloric acid, (b) nano-clay and (c) iron. The peak-to-entrance \(\delta R_1\) ratios for Gel\(_1\)–Gel\(_4\), Gel\(_8\) and Gel\(_{10}\) are between 3.8 and 4.6. Similar LET-independent radiological properties of NC-FG were confirmed over a wide range of preparation conditions (HClO\(_4\): 0–50 mM, nano-clay: 0.75–1% (w/w), Fe\(^{2+}\): 1–5 mM).

Figure 6 summarizes how the radiation sensitivity near the entrance surface (4–6 mm depth) changes with the preparation conditions with respect to the reference composition (Gel\(_1\)). Figure 6(a)

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**Fig. 3.** Plot of change in relaxation rate \(R_1\) vs. \([\text{Fe}^{3+}]\) used as the calibration curve. Open symbols represent measured values on gel sample prepared from 1% (w/w) nano-clay, 3% (w/w) gelatin, 50 mM perchloric acid and 0–0.4 mM ammonium iron (III) sulfate. Dashed line is the linear fitting result.

**Fig. 4.** \(R_1\) distributions for NC-FG for several preparation conditions (see Table 1 for list) after irradiation with a 290-MeV/nucleon carbon beam at five different entrance surface doses (0, 150, 300, 450, 600 Gy).
shows the effect of the nano-clay concentration; the results indicate that the radiation sensitivity vanishes at 0.1% (w/w) nano-clay and below. Conventional FG dosimeters are also not radiation sensitive under deaerated conditions [7]. While, in our previous report [31], we originally incorporated nano-clay into Fricke gel in order to suppress the diffusion of Fe$^{3+}$ ions, the results shown in Fig.6(a) reveal that nano-clay also significantly affects the reaction mechanism under deaerated conditions. Although this may be related to the adsorption of Fe$^{2+}$ ions onto clay nanoparticles [38, 39], further investigation is required in order to reveal the precise underlying reaction mechanism. Figure6(b) shows the dependence of the radiation sensitivity on the HClO$_4$ concentration, and thus, on pH. Under neutral conditions, the behavior of NC-FG (Gel$_2$) is similar to that under acidic conditions (Gel$_1$). This is in stark contrast to conventional FG (without nano-clay), which only works under acidic conditions [8]. In addition, the radiation sensitivity of NC-FG is suppressed at 150 mM HClO$_4$ (Gel$_4$), whereas that of conventional FG is nearly constant between 6 and 250 mM sulfuric acid [7]. We speculate that this difference is the following. Nanoclay adsorbs hydrogen ions as well as Fe$^{2+}$ and Fe$^{3+}$ ions [40]. Thus, even if the bulk FG is neutral, Fe$^{2+}$ and Fe$^{3+}$ ions may be placed under locally acidic conditions, and NC-FG functions. Since hydrogen ions are more strongly adsorbed than Fe$^{2+}$ and Fe$^{3+}$ ions [40], too high hydrogen ion density may prevent the adsorption of the latter, leading to radiation sensitivity suppression.

Figure 6(c) shows the radiation sensitivity of NC-FG increases with Fe$^{2+}$ concentration, which again is in contrast to conventional FG, for which the sensitivity does not change between 0.2 and 5 mM [8, 41]. Finally, the effect of the gas used for deaeration (Ar and N$_2$O) on the sensitivity is shown in Fig. 6(d). The data plotted for N$_2$O are from our previous report [31]. It appears that the gas used did not greatly affect the radiation sensitivity, even though the preparation methods were not the same; a rotation/revolution vacuum mixer, a glove box, and a microwave oven were used to stabilize the baseline of $R_1$ in this study.

CONCLUSION

The radiological properties of NC-FG under various preparation conditions were investigated in detail under carbon and argon beam irradiation covering an LET range of 10–3000 eV/nm. By varying the concentration of nano-clay, Fe$^{2+}$ and perchloric acid from the reference composition described in our previous report [31], the following features were revealed.

1. The radiation sensitivity is nearly LET-independent for the compositions 1–4, 8 and 10. Surprisingly, the sensitivity did not change even at very high LET values (3000 eV/nm) in the Bragg peak region of the argon ion beam.

2. NC-FG works not only in acidic but also in neutral conditions.

3. The radiation sensitivity correlates with the nano-clay concentration and disappeared at nano-clay concentrations below 0.1% (w/w).
The first and second features are distinct from those of conventional Fricke gel. The third feature suggests that nano-clay not only sup-
presses the diffusion of iron ions, but also plays an essential role in radiation-induced reactions.

Clarification of the reaction mechanism leading to these features requires further study, especially on the behavior of Fe2+ adsorbed onto nano-clay [40].

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