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A study on the role of gelatin in methacrylic-acid-based gel dosimeters

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ABSTRACT

In radiotherapy treatment, polymer gel dosimetry can be used for verifying three-dimensional (3D) dose distributions. Gelatin is generally used as a gelling agent in the dosimeters. In this paper, another role of gelatin in a methacrylic-acid-based gel dosimeter (MAGAT) is investigated. Temperature increases due to exothermic polymerization in the irradiated gel are measured directly. Dose–R_2 responses are also obtained using MRI. It is shown that no appreciable increases in either temperature or R_2 are observed in MAGAT dosimeters made without gelatin, and that significant temperature and R_2 increases are observed when very low gelatin concentrations are used. These results indicate that gelatin is an important enabler for radiation-induced free-radical polymerization in methacrylic-acid-based gels. When gelatin is replaced by amino acids, changes in temperature are observed, along with small changes in R_2. The resulting dosimeter solutions remain transparent because the polymer does not precipitate as it does in regular MAGAT dosimeters containing gelatin. When the amino acids are replaced by acids without amino groups, no temperature or R_2 changes are observed, indicating that no polymer forms. These results show that amino groups (and possibly other functional groups) on the gelatin catalyze the radiation-induced free-radical polymerization that occurs in MAGAT dosimeters.

1. Introduction

With rapid advances being made in radiotherapy treatment, three dimensional (3D) dose measurement techniques of great precision are required more than ever before. It is expected that polymer gel dosimeters will satisfy clinical needs for an effective detector that can measure the complex 3D dose distributions (Ibbott, 2006). Polymer gel dosimeters are devices that utilize the radiation-induced polymerization reactions of vinyl monomers in a gel to store information about radiation dose. The 3D absorbed dose distribution can be deduced from the resulting polymer distribution using several imaging modalities, such as MRI, X-ray and optical CT, and ultrasound (Maryanski et al., 1993, 1996; Hilts et al., 2000; Mather et al., 2002).

The radiological characteristics, such as dose response, susceptibility to environmental factors and the reproducibility of their measurement, have been thoroughly investigated by many groups. These previous results and historical developments have been reviewed in other articles (e.g., Hurley et al., 2005; Baldock, 2006; Jirasek, 2006a). The polymer gel dosimeter mainly consists of water, monomer, gelatin and oxygen scavenger. Methacrylic acid (in MAG systems) and acrylamide with *N,N′*-methylene-bis-acrylamide (in PAG systems) are often used as the monomers, while gelatin is used as a matrix to gel the solution and to preserve spatial information by preventing polymer diffusion.

However, other roles of gelatin during the polymerization have also been noted. For example, scavenging of free radicals by gelatin has been deduced from the observed reduction in the polymerization rate as the gelatin concentrations increases in the PAG system (Lepage et al., 2001a, 2001b). De Deene et al. (2006) reported that no NMR dose response was observed in MAG systems without gelatin. They suggested a polymerization mechanism with chemical grafting of polymethacrylic acid onto gelatin in the MAG system, which is different from that in the PAG system where a significant NMR response is observed without gelatin (Babic and Schreiner, 2006). Fuxman et al. (2003, 2005) explained the reduction in monomer consumption rates with increasing gelatin concentration in PAG system in terms of chain transfer to gelatin, leading to the formation of gelatin radicals that are slow to react with monomer. In addition, Jirasek et al. (2006b) inferred from Raman spectroscopy data from a PAG system that the oxygen scavenger induces cross-linking of gelatin. As stated above, many possible roles and reactions for gelatin can be

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considered, but detailed mechanisms for possible interactions between monomers and gelatin remain unsettled.

In this paper, the dose responses of the MAG system with various concentrations of gelatin are examined to clarify the roles of gelatin in the polymerization process. Since polymerization is an exothermic process, we monitored the temperature of the gel directly throughout the irradiation process to detect the occurrence of polymerization using temperature probes. Then we focused on the dose responses of modified MAG dosimeters, wherein the gelatin was replaced with amino acids and other acids, in an effort to clarify the function of gelatin.

2. Materials and methods

2.1. Gel preparation

Methacrylic-acid-based gels were prepared consisting of distilled water, gelatin (300 bloom, Sigma Chemical Co.), methacrylic acid (MA, Wako Pure Chemical Co.), and tetrakis-hydroxymethyl-phosphonium chloride (THPC, 80%, Sigma Chemical Co.) as an oxygen scavenger. This type of gel composition is called MAGAT (Methacrylic Acid, Gelatin And THPC) (Hurley et al., 2005). As shown in Table 1, all of the ten dosimeters prepared contained the same amounts of MA and THPC, but different amounts of gelatin.

Each sample was prepared in a 200 ml beaker under normal atmospheric conditions. After the water was heated to 60 °C, gelatin was added and dissolved using a magnetic stirrer. The gelatin solution was cooled to 50 °C, then methacrylic acid and THPC were added to the gel. The resulting solution was poured into test tubes (1.5 cm in diameter and 10 cm in length) until overflowing to avoid oxygen contamination from air. The top of each tube was sealed with polyvinyl-chloride (PVC) film and tightly closed with a polypropylene screw cap. After fabrication, all samples were stored in an incubator at a fixed temperature (23 °C) for 1 day to avoid effects of temperature variations before irradiations (De Deene et al., 2007). Only the samples containing 8% and 12% of gelatin concentrations had set at this temperature; the other samples remained liquid.

In addition to the gels described above, we prepared a second set of dosimeter solutions, in which gelatin was replaced with different amino acids, to examine the effect of gelatin structure and its monomer units on the dosimeter response. Glycine, alanine and proline were added at a 1 M concentration to different dosimeter solutions. These amino acids were selected because they are some of the main amino-acid monomer units in gelatin. The other components of these solutions (except gelatin) were at the concentrations specified in Table 1.

2.2. Irradiation

The irradiations were performed using a 6 MV photon beam of a medical linear accelerator (Varian medical systems, Clinac iX). The axis of test tube was perpendicular to the beam. The SSD was 100 cm, and the wide field size of $40 \times 40\ cm^2$ was used to guarantee the beam flatness. The deviation of dose is less than 1% in the center of approximately $10 \times 10\ cm^2$ where test tubes were irradiated. For the measurements of NMR dose responses, the test tubes were irradiated in a cubic water tank ($45 \times 45 \times 45\ cm^3$) at a depth of 5 cm at a room temperature. For the measurements of temperature, the irradiation was performed in air to avoid the rapid heat loss (Salomons et al., 2002). A test tube was set between two Solid Water phantoms (GAMMEX rmi) as shown in Fig. 1. In the both irradiations, the beams were delivered 5, 10 and 20 Gy to the test tubes with the fixed dose rate at 1.75 Gy min^{-1}.

Table 1
Methacrylic—acid-based polymer gel compositions prepared in this study. These concentrations (per weight, %w/w) were used for all MAGAT type gels.

Water	
MA	5% w/w
Gelatin	0, 0.2, 0.3, 0.5, 1, 2, 4, 6, 8, 12% w/w
THPC	2 mM

2.3. Temperature measurements

Temperature in the test tubes was monitored by a digital thermometer (T&D Co., TR-52 type, accuracy of ± 0.3 °C). The temperature probe was inserted into the test tube through a hole in the cap, and set at the center of the tube. The test tubes were surrounded in polyethylene (PE) sheet as thermal insulation. The temperature was measured continuously for 30 min, including the period of irradiation.

2.4. MRI measurements

MRI measurements were performed using a 0.3 T scanner (AIRIS II comfort, Hitachi Medical Corp.) with a standard head coil. A multiple spin-echo sequence was applied using the following parameters (TR/TEs/FOV/Slice Thickness/Matrix Size)=(4 s/20,100 ms/$120 \times 120\ mm^2$/5 mm/128×128) with a resulting voxel size of $0.94 \times 0.94 \times 5\ mm^3$. The transverse relaxation rate R_2 images were calculated from the two base images using software written in-house.

The transverse relaxation rate (R_2) is determined by

$$R_2 = \frac{1}{T_2} = \frac{\ln[S_1/S_2]}{TE_2 - TE_1}$$

where T_2 is the transverse relaxation time, and S_1 and S_2 are the signal intensities at TE_1 and TE_2, respectively. The mean value of R_2 and the standard deviation were calculated in a circular regions-of-interest (ROI) located in the center of the test tube and having 50 pixels at the center of each sample's image.

Preceding the experiments, we have confirmed the reliability of the conventional two-echo method (TEs=20 and 100 ms) by using carrageenan gel phantoms with various concentrations of $MnCl_2$, which show a linear concentration–R_2 relation over the R_2 range from 3 to 25 s^{-1}.

3. Results and discussion

3.1. Dose–R_2 responses

Fig. 2 shows the dose–R_2 response curves for each sample from Table 1 containing different concentrations of gelatin. It is apparent that the dose sensitivity depends on the gelatin concentration and that R_2 increases with the concentration of gelatin. However, it seems that the R_2 responses at doses of 5 and 10 Gy are similar for dosimeters containing more than 8% of gelatin. This result suggests that additional gelatin, beyond a certain concentration that can aid in the polymerization, has little influence on the consumption of monomer.

It is important to note that no appreciable response to radiation was observed in the gelatin-free solution (0%). A similar result was reported by De Deene et al. (2006) who also observed that their gelatin-free dosimeter remained transparent after irradiation, whereas MAG dosimeters with gelatin became milky in appearance. However, it was not clear from De Deene's R_2 and