The effect of chemical stability on the NIPAM gel dosimeter using 1H-NMR

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Abstract. Radiation-induced chemical changes in the N-isopropylacrylamide (NIPAM) gels used in three-dimensional dosimeters were investigated using 1H-NMR in this study. The experimental results show that the signal from C=C bonds of NIPAM and N,N'-Methylenediacylamide (BIS) are 5.5 and 6.3 ppm, respectively. The double bonds from the NIPAM and BIS disappeared with half-dose (D50) were about 10.90 Gy ± 0.76 Gy and 10.09 Gy ± 0.29 Gy, respectively. This observation demonstrates that the polymerization rate of BIS is faster than that of the NIPAM monomer. The 1H-NMR can indicate the chemical structure changes of the polymer gel dosimeter after irradiation and successfully determine the D50 in the NIPAM gel dosimeter.

1. Introduction
In clinical radiotherapy, polymer gel dosimeter is used to verify three-dimensional (3D) dose distributions. Such common dosimeters as ionization chamber, thermo luminescent diodes, and radiographic film do not allow the measurement of 3D dose distribution due to several spatial laminations [1].

Maryanski et al. proposed the use of a polyacrylamide gel as a potential tool for 3D mapping of dose distribution. Since this initial study, several polymer gels have been proposed, including Bis-acrylamide, Acrylamide, Nitrous oxide And Agarose (BANANA), Bis-acrylamide, Acrylamide, Nitrogen, Gelatin (BANGTM), Polycrylamide Gel, THPC (PAGAT), and NIPAM gel consisting of gelatin, N-isopropylacrylamide, BIS, and tetrakis (hydroxymethyl) phosphonium chloride (THPC)[2].

Researchers have also investigated several readout tools in an attempt to obtain dose distribution information from polymer gel, including MRI, optical computed tomography (OCT), x-ray computed tomography (CT), and Fourier transform-Raman (FT-Raman) spectroscopy. However, the response of polymer gel dosimeter to radiation has yet to be completely understood. NMR and FT-Raman can quantify the chemical changes in molecules [3–5].

The NIPAM polymer gel consists of NIPAM and BIS dissolved in an aqueous gelatin matrix. The results provide evidence for the polymerization of the monomers that form a NIPAM gel
network within the gelatin matrix. In this study, 1H-NMR was used to analyze the technique of correction in characterizing the consumption of monomer and crosslinking in irradiated NIPAM gel. Furthermore, direct evidence of polymer gel formation has been observed in 1H-NMR.

2. Materials and Methods

2.1. Manufacture of the NIPAM gel
The gel used in this study consisted of 5% gelatin (300 Bloom Tape A. Sigma-Aldrich), 5% NIPAM (97%, Sigma-Aldrich), 3% BIS (Merck), 5 mM THPC (80%, Sigma-Aldrich), and 87% deionized water. The method used for the manufacture of the NIPAM gel has been described previously [6]. The gelatin was added to water at room temperature and left to soak for 10 min. The solution was heated and maintained at a temperature of 45 °C. NIPAM and BIS were added and magnetically stirred for 25 min until complete dissolution is achieved. Finally, THPC was added to remove the oxygen. The tube was then covered using a Pyrex screw cap and placed in a refrigerator at 4 °C.

2.2. Irradiation of the NIPAM gel
All samples were irradiated with a Varian 21EX Clinic linear accelerator using 6 MV photons, a dose rate of 400 MU/min, 100 cm surface to source distance (SSD), and field size of 20 cm × 20 cm. At the center of a short side of a customized 30 cm × 30 cm × 4 cm acrylic phantom, a 16 mm diameter hole was punctured to accommodate the Pyrex test tube. The irradiated gels were left in a refrigerator for one day before imaging to allow complete post irradiation polymerization.

2.3. Measurement system
An optical laser scanning system was used to measure the NIPAM gel. An NRC Model 127 He-Ne laser with 20 mW power and 632.8 nm wavelength was used in CT-s1. After a 140 min laser warm up, the laser power deviation was less than 1%. Room temperature was maintained at 22±1 °C, and a photodetector was used to scan the gel dosimeter as depicted in a previous research [7].

The NMR measurement was performed using a BRUKER AVANCE 400 SSNMR spectrometer operating at a frequency of 400 MHz for 1H. The 1H-NMR was used to examine the chemical shift of the NIPAM gel and observe the detriments of the NIPAM and BIS after irradiation.

3. Results and Discussion

3.1. Dose response of the NIPAM gel
Fig. 1(a) shows the dose response of the NIPAM gel presented in this study. The dose response is linear from 0 Gy to 15 Gy, with the linearity of 0.997 and sensitivity of 0.023 Gy-1. The dose response curves of the NIPAM gel dosimeter under two distinct photon beam qualities (6 and 10 MV) are obtained. Fig. 1(b) shows the insignificant variation in the dose response within the range of 0 Gy to 15 Gy. The result is similar to those of most published reports on gel dosimeters [7].

![Figure 1: (a) Dose response of the NIPAM gel (b) Energy dependence of the NIPAM gel](image-url)
3.2. 1H-NMR of the NIPAM gel

Fig. 2 shows the 1H-NMR spectrum of the NIPAM gel. The CH2 functional group of the gelatin is located at 1.04 ppm, and the NH functional group of BIS appears at 8.2 ppm. Bands at 5.5 and 6.3 ppm corresponding to both NIPAM and BIS vinyl group modes, respectively, show clearly decreasing peak intensities as copolymerization and crosslinking increase with absorbed radiation dose. This result indicates that the polymerization induced by NIPAM through irradiation and its effect are achievable using the dose in the current study.

The spectra of 1H-NMR are similar to that of the functional groups polymerized via PAG irradiation, the results of which concur with those of the PAG irradiation performed by Lepage et al. In their work, the C=C bonds of the acrylamide and BIS in PAG are near 5.9 and 6.3 ppm, respectively [4]. In the current study, the values for NIPAM and BIS are 5.5 and 6.3 ppm, respectively. Considering that the acrylamide has a chemical structure similar to that of NIPAM (Fig. 3), the 1H-NMR spectrum of the NIPAM gel is quite similar to that of PAG (Table 1).

Fig. 4, meanwhile, shows that the C=C intensity gradually decreases as the absorbed dose increases. The result indicates that the D50 of vinyl group to the NIPAM and BIS were about 10.90 Gy ± 0.76 Gy and 10.09 Gy ± 0.29 Gy, respectively. In comparison with PAG gel dosimeter, the D50 of the monomers and crosslinking agent in the PAG gel dosimeter is 7.62 Gy. This difference is possibly attributed to the different monomers and the proportion of ingredients in the gel dosimeter. This observation demonstrates that the polymerization rate of BIS is faster than that of NIPAM. Thus, NIPAM polymerization needs a higher irradiation absorbed dose than BIS.

![Figure 2: 1H-NMR spectrum of the NIPAM gel](image)

![Figure 3: Structural formulas of the (a) NIPAM gel and (b) acrylamide](image)
Figure 4: Correlation of the vinyl group of the NIPAM gel in the 1H-NMR spectrum

Table 1: Chemical shift assignment

| Chemical Shift (ppm) | Assignment          |
|----------------------|---------------------|
| 1.04                 | CH₂ group           |
| 5.5                  | Vinyl group of NIPAM|
| 6.3                  | Vinyl group of BIS  |
| 8.7                  | NH group of BIS     |

4. Conclusion
In this work, we characterized with the chemical changes occurring in a NIPAM gel dosimeter using 1H-NMR. The intensity of the C=C bonds of NIPAM and BIS decrease as the absorbed radiation dose increases during the NIPAM gel dosimeter irradiation. The D50 of NIPAM and BIS were about 10.90 Gy ± 0.76 Gy and 10.09 Gy ± 0.29 Gy, respectively. When the NIPAM gel is irradiated, the amount of monomer and crosslinking decrease, while the amount of polymerization increase. Hence, the decreasing rate of monomer and the increasing rate of polymerization should be investigated further.

5. References
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