Raman study of lower toxicity polymer gel for radiotherapy dosimetry

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Abstract. N-isopropyl acrylamide (NIPAM) monomer and N, N’-methylene-bis-acrylamide (BIS) crosslinker were used to synthesize polymer gel dosimeters for a reason that the monomer is lower toxicity which gives a significant advantage over the other polymer gel compositions. The gels were irradiated with Co-60 gamma rays at doses up to 21 Gy and the irradiated NIPAM polymer gels were used to investigate the dose response characteristics based on Raman spectroscopy analysis on the formation of the polymer gels and the consumptions of NIPAM and BIS co-monomers. From the findings, the polymerization was referred to an increment in Raman intensity at 815 cm\(^{-1}\), assigned for C-C stretching mode of NIPAM polymer gel, as the dose increased. The consumptions of the co-monomers were referred to a decrement in Raman intensities at 1025 cm\(^{-1}\) and 2353 cm\(^{-1}\) for C=C stretching modes of NIPAM and BIS respectively as the dose increased. The increment and decrement in Raman intensities of polymer and co-monomers respectively with increase of dose indicate that there is occurrence of polymerization of NIPAM polymer gels which could be applied in 3D dose distributions for radiotherapy treatment planning. The correlation factor \(k_{\text{BIS}}\) is greater than \(k_{\text{NIPAM}}\), showing that the reaction of BIS crosslinker is more efficient than NIPAM monomer to generate 37% of the NIPAM polymer gel.

1. Introduction

Research in polymer gel dosimeter has been undergone as a subject of interest from the past 20 years, initiated by Maryanski [1], in which there is a kind of demand to develop the better dosimeter with high spatial resolution and three-dimensional capability for the application in radiotherapy treatment plan. Stated by Mc Auley et. al. [2-4], the polymer gel has been used by medical physicists to verify spatial three-dimensional dose distribution treatment plans before starting the actual radiotherapy procedure which focused to only irradiate the target tissue or organ while keeping away the surrounding tissue from radiation. The conventional dosimeter such as thermoluminiscent dosimeter can quantify radiation in one or two direction only, thus limit the function in the complex dose application in the
radiation procedure. Polymer gel dosimeter is fabricated from radiation sensitive chemicals known as monomers which are upon irradiation, the monomers will polymerize as a function of absorbed radiation dose [2], thus the polymerized monomers are held firmly in the gelatine. The previous polymer gels has been prepared under hypoxic conditions [5], until study made by Fong et. al. [6, 7], then polymer gel can be synthesized under normal atmospheric environment by applying certain amount of anti-oxidant agent due to its sensitivity to oxygen that may disturb the polymerized reaction. Study done by De Deene [8] named this new type of polymer gel as normoxic instead of anoxic for the old type.

One of major limitations in establishing polymer gel dosimeter in routine clinical practice is the problem of toxicity in monomers [9, 10]. Therefore some studies put their concern to discover new monomers with lower toxicity as well as easy in fabrication under normal atmospheric environment [10, 11]. Application of N-isopropyl acrylamide (NIPAM) monomer in polymer gel composition together with \( N, N' - \text{methylene-bis-acrylamide (BIS)} \) as crosslinker was first introduced by Senden [10], which is relatively less toxicity from the monomer applied in previous literature such as normoxic polyacrylamide gels (nPAG) [12]. Study done by Mesbahi [13] which applied the clinical magnetic resonance imaging (MRI) scanner as data acquisition methods, proven that the \( R_2 \)-dose response of NIPAM polymer gel was comparable to normoxic polyacrylamide gel (PAGAT) established by Senden [10] which has high dose sensitivity and less dependent in dose rate and irradiation temperature. In fact, Mesbahi [13] observed that, NIPAM polymer gel was better than PAGAT gel in linearity, since the dose-response (\( R_2 \)) of NIPAM was significantly linear within larger dose range.

In terms of dose response analysis, once the polymer gel dosimeter has been irradiated, it can be evaluated by using certain modalities including MRI [3, 13, 14], X-ray computed tomography (X-ray CT) [7, 9, 15], optical CT [7, 10, 16], ultrasound[17] and Raman spectroscopy [5, 18, 19]. Thus, the relative dose response information can be extracted for further analysis. In this study, Raman spectroscopy has been chosen to evaluate and probe the changes in molecular structure of the polymer gels following irradiation. NIPAM polymer gel which has certain advantages is a main concern to be further investigated by using Raman spectroscopy in monitoring the characteristic set of covalent bond on each molecule within the gel dosimeter. In particular, several batches of NIPAM polymer gels with different sets of monomer concentration are to be characterized by Raman spectroscopy to evaluate the changes in molecular structure of the gel sample upon irradiation process. This study may focus with the information of Raman spectra that may reflect the activity of polymer formation and monomer consumption [19].

2. Materials and methods

2.1. NIPAM polymer gel preparation for Raman spectroscopy analysis
Polymer gel dosimeters were manufactured under normal atmospheric conditions in the laboratory without using of a glove box based on Fong et. al. [5, 6] and basically following the method experimented by Senden et. al. [10, 20]. Firstly, gelatine (6 wt%) (bovine skin, Type B, Sigma Chemical Co) was added to the deionized water and stirred for five minutes at room temperature. Then, gelatine solution was heated up to 45°C and continuously stirred by magnetic stirrer until a clear solution and transparent was obtained. With heating was off and continuous stirring was pursued, the monomer and co-monomer, BIS (2-4 wt%) (Sigma Chemical Co) and NIPAM (2-4 wt%) (Sigma Aldrich) were poured into the gelatine solution and approximately dissolved within 15 minutes. Then the anti-oxidant, tetrakis hydroxymethyl phosphonium chloride (THPC) (5mM) was added to solution and continuous stirred at about 2 minutes. The final product was filled into small ampoule tubes (2ml), which was sealed with parafilm tape and covered by aluminium wrapped container to minimize oxidation and photo-polymerization effect. Upon completion, the prepared NIPAM polymer gel dosimeters were stored in a refrigerator at low temperature approximately 4°C to solidify and protected from UV light. Once the polymer gel dosimeters were ready, the next day (within 24 hours), gels were removed from refrigerator and equilibrate at room temperature before starting irradiation process.
2.2. NIPAM polymer gel irradiation
Because the gel samples were small, so the time to equilibrate the samples with room temperature took less than 10 minutes. Then, the polymer gel dosimeters were irradiated with gamma rays produced by Cobalt-60 (Co\(^{60}\)) element from Gamma Cell Instrument, model 220 Excel Irradiator (MDS Nordion, Ottawa, ON, Canada) (Faculty of Nuclear Science, National University of Malaysia). The amount of radiation dose given was set from a control panel of the irradiation chamber. One gel sample from each batch of dosimeters was left unirradiated and just put inside the refrigerator, as a control sample and the rest were irradiated batch by batch simultaneously according to the amount of radiation dose which already calculated ranging from 3 Gy to 21 Gy with a single dose at a time. During irradiation, each sample was placed in a beaker filled with a distilled water to create tissue equivalent medium.

2.3. Raman spectroscopy of NIPAM polymer gel
All gel samples were characterized by using Raman spectrometer (RSI 2001, Raman system, INC) equipped with 532 nm solid-state diode green laser and a thermoelectrically cooled CCD array after seven days of irradiation in order to allow complete polymerization of gel samples [8]. Data manipulation and analysis were established by using Grams/32 software, version 6. All spectra were corrected for base line, smoothing and Fourier Transform (FT). A constant correction factor of 80% of the degree of smoothing parameter was used throughout the data collection.

3. Results and discussion
3.1. Raman peaks identification
Raman spectra that obtained from Raman spectrometer was actually the vibrational Raman effect in which it was directly described the polymer formation and co-monomers consumption after irradiation. From the Raman analysis, the relative intensity which represents the energy difference of scattered radiation can be acquired and displayed on the chart as a function of difference in wavelength. The well define peak on the chart may represent characteristic molecular bond in the gel samples which has certain vibrational energy. The characteristic frequencies of every single functional group were characterized by referring the literature reports documented by Jirasek et. al. [18, 19].

The polymerization was followed from the increment in Raman intensity at 815 cm\(^{-1}\), assigned for C-C stretching mode of NIPAM polymer gel, as the dose increased. Meanwhile, the consumptions of the co-monomers were referred to a decrement in Raman intensities at 1025 cm\(^{-1}\) and 2353 cm\(^{-1}\) assigned for C=C stretching modes of NIPAM and BIS respectively, as the dose increased. These three chosen peaks were obtained from Raman spectra which were illustrated in Figure 1.

![Figure 1. Sample of Raman spectrum that indicates the peaks chosen.](image-url)
3.2. Polymer formation of NIPAM polymer gel

The Raman intensities, $y$, as a function of dose $D$ for NIPAM and BIS were fit [19] and displayed as monoeXponential function, following the equation:

$$y = y_0 + A(1 - e^{-D/D_0})$$

Where, $D_0$ is the sensitivity parameter, $y_0$ is the Raman intensity at zero dose and $A = y_{max} - y_0$ is the maximum differential dose response. $y_{max}$ describes the maximum intensity over the dose range up to 21 Gy. Figure 2(a) and 2(b) depicts the positive monoeXponential plots of the intensity change as a function of absorbed dose at initial concentrations of NIPAM monomer and different BIS crosslinker.

![Figure 2](image)

**Figure 2.** Data displayed a monoeXponential function of relative Raman intensity versus absorbed dose for polymerization of NIPAM polymer gels of C-C bond at 815 cm$^{-1}$ for (a) 3% NIPAM at various BIS from 2 to 4% and for (b) 3% BIS at various NIPAM from 2 to 4%.

Note that, as the radiation dose increases, the Raman intensity also increases, which explains the occurrence of polymerization process and the amount of carbon single bond increases in the formation of NIPAM polymer gel. All the carbon covalent bond tends to break into carbon single bond, as the radiation dose increases. The similar situation occurs, as the concentration of NIPAM monomer and BIS crosslinker increases. The dose sensitivity parameter $D_0$ can be determined from the reciprocal of the gradient of a linear plot $\ln \left[ 1 - \frac{dy}{A} \right]$ versus dose $D$. This parameter can be described as the amount of dose required to generate 37% of the polymer formation. Thus, in Figure 3(a) and 3(b) indicates the linear correlations that may produce the gradients $k_{NIPAM}$ and $k_{BIS}$ respectively. It is shown that, $k_{BIS}$ is greater than $k_{NIPAM}$, which proofs that the reaction of BIS is more effective than NIPAM in producing 37% of NIPAM polymer gel.
Figure 3. The polymerization process depicts the linear correlation between (a) $D_0$ vs. % NIPAM at various BIS from 2 to 4% and (b) $D_0$ vs. % BIS at various NIPAM from 2 to 4%.

3.3. Consumption of NIPAM and BIS

The Raman intensities, $y$, as a function of dose $D$ for NIPAM and BIS were fit [4] and displayed as monoexponential function, following the equation:

$$y = y_0 - A(1 - e^{-D/D_0})$$

Where, $D_0$ is the sensitivity parameter, $y_0$ is the Raman intensity at zero dose and $A = y_{max} - y_0$ is the maximum differential dose response. $y_{max}$ describes the maximum intensity over the dose range up to 21 Gy. By applying the equation above, it is seen in Figure 4(a) and 4(b) that, there is decreasing in monoexponential function of the intensity as a function of absorbed dose at the initial concentrations of NIPAM and BIS respectively from 0 Gy up to 21 Gy.

It is shown that, as the radiation dose increases, the Raman intensity decreases, which explains the NIPAM and BIS consumption increase and the amount of carbon covalent bond decreases in the formation of NIPAM polymer gel. All the carbon covalent bond tends to be broken into carbon single bond following irradiation process. The same pattern occurs, as the concentration of NIPAM monomer and BIS crosslinker increases. Figure 5(a) and 5(b) indicates the linear correlations that may generate the gradients $k_{NIPAM}$ and $k_{BIS}$ respectively.

Note that, $k_{BIS}$ is greater than $k_{NIPAM}$, which explains that the consumption of BIS is at greater rate than NIPAM in developing 37% of NIPAM polymer gel. Therefore, generally, polymer gel that composed higher concentration of BIS is considerably better than the rest compositions towards the polymerization process.
Figure 4. Data displayed a monoexponential function of relative Raman intensity versus absorbed dose for (a) 3% BIS at various NIPAM from 2 to 4% for consumption of C=C bond of NIPAM at 1025 cm\(^{-1}\) and for (b) 3% NIPAM at various BIS from 2 to 4% for consumption of C=C of BIS at 2353 cm\(^{-1}\).

Figure 5. The co-monomer consumption process depicts the linear correlation between (a) \(D_0\) vs. % NIPAM at various BIS from 2 to 4% and (b) \(D_0\) vs. % BIS at various NIPAM from 2 to 4%.
4. Conclusion

The NIPAM polymer gels which composed mainly with NIPAM monomer and BIS crosslinker have been synthesized to study their characterization in terms of polymer formation and monomer consumption by using Raman spectroscopy. The results have shown that, there are changes in the Raman intensities as a function of absorbed dose, in which it proofs that the radiation may induce the gel samples to be polymerized. The increment and decrement in Raman intensities as the radiation dose increases indicates that there is occurrence of polymerization process and the co-monomers consumption process towards the formation of NIPAM polymer gel. The rate of polymerization increases as the amount of carbon single bonds increases and the rate of monomers consumption increases as the amount of carbon covalent bonds decreases after irradiation. In terms of dose sensitivity, it increases with the increment of NIPAM and BIS concentrations. In addition, the correlation factor, $k_{\text{BIS}}$ is always greater than $k_{\text{NIPAM}}$ whether in polymer formation and co-monomer consumption indicating BIS crosslinker is more efficient than NIPAM monomer toward the production of 37% of NIPAM polymer gel.

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