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Development and Characterization of Normoxic Polyhydroxyethylacrylate (PHEA) Gel Dosimeter using Raman Spectroscopy

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***Abstract*—**Raman spectroscopy are used to characterize the chemical changes in normoxic polyhydroxyethylacrylate gel dosimeter (PHEA) induced by radiation. Irradiations in the low dose region are performed and the polymerizations of PHEA gels are monitored by the observing the changes of Raman shift intensity of the carbon covalent bond of PHEA originated from both monomer and the cross-linker. The variation in peak intensities with absorbed dose was observed. As the dose increase, the peak intensities of covalent bond of carbon in the polymer gels decrease. This point out that the amount of absorbed dose affect the polymerization of polymer gels. As the absorbed dose increase, the polymerizations also increase. Results verify that PHEA gel dosimeters are sensitive even in lower dose region.

***Keywords*—**normoxic polymer gel, ascorbic acid, Raman spectroscopy, radiation dosimetry.

I. Introduction

RECENT development of complex radiotherapy treatment techniques has emphasized on a need of dosimetric system that has the ability to measure absorbed dose distributions in three dimensions (3D). Current dosimeters, such as ionization chamber, radiographic films and thermo luminescent dosimeter (TLD) can only measure in one or two dimension, and therefore are inadequate to integrate dose over three dimensional volumes. Hence, polymer gel dosimeter has been introduced to overcome this problem. Polymer gel dosimetry is therefore, a technique to determine high spatial resolution 3D dose distributions to verify a complex radiotherapy treatment plans prior to the actual radiotherapy treatment. Polymer gel dosimeters are fabricated from radiation sensitive chemicals which, upon radiation, polymerize as a function of the absorbed radiation dose. The first polymer gel was introduced by [1] for recording dose distributions in 3D using MRI. It is basically a hydrogel, which composed of acrylamide and bis-acrylamide co-monomers and gelatine dissolved in 80-90% water and is called PAG or BANG-1®. When irradiated with ionizing radiation, polymerization of the monomers occurs and the resultant polymer is retained in the gelatin matrix. This initial study have proposed several formulations and acronyms for polymer gel such as BANANA (Bis-acrylamide, Acrylamide, Nitrous Oxide and Agarose), PAG (Polyacrylamide gel) and BANG™ (Bis-acrylamide, Acrylamide, Nitrogen and Gelatin).

However, the use of polymer gel dosimeter has a significant limitation due to the nature of their free radical chemistry. The presence of atmospheric oxygen inhibits the polymerization process of the polymer gel [2]. To expel the oxygen from the gel, anti-oxidant is used to bind the free oxygen in the gel compositions [3]. Although some oxygen effects may still be experienced, these new normoxic gels are very capable as gels dosimeters. This type of polymer gel is known as normoxic polymer gel dosimeters.

Due to several limitations, these gel dosimeters have not reached the requirements to be accapted in routine clinical environments. Difficulties with image acquisitions and incomplete understanding of dose response mechanism are some of the limitations of these dosimeters. The most popular imaging modality for polymer gel is MRI, but this modality is not readily available to all radiotherapy clinics. A number of options have been proposed to address these problems. Optical and x-ray computed tomography (CT) protocol was developed to both imaged polymer gels and extract relative dose information [4, 5]. Still, the response of gel to radiation are not fullt understood. [6] introduced the use of Raman spectroscopy to demonstrate different rates of consumption of monomer and cross-linker. However, the quantifications and understanding of this difference is not complete. Studies of polymer gel using Raman spectroscopy has been further explored by [7, 8, 9].

Raman spectroscopy has the potential to directly monitor individual constituents within the gel sample [9]. In this study, Raman spectroscopy is used to characterize the radiation induced changes in polyhydroxyethylacrylate (PHEAG) gel dosimeters with varying the total amount of monomer (%M). The monomer consumption as a function of absorbed dose was studied using Raman spectroscopy.

II. Materials And Methods

A. Gel Manufacture

All gels were manufactured under normal atmospheric conditions without the use of a glove box. Gels were made under a fume hood using gelatin (bovine skin, Type B, Sigma Chemical Co), 2-hydroxyethylacrylate (HEA) (97%, ACROS Organics), *N, N'* –methylenebisacrylamide (BIS) (Sigma Chemical Co), ascorbic acid (AA) (Hamburg Chemical) and deionized water. The concentrations of the monomer are varied while other chemical constituents are constant.

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The gelatin was given to 40% of the total amount of deionized water and allowed to swell for half an hour at room temperature. Then the gelatin solution was stirred and heated to 55^{o}C using a magnetic stirrer/hot plate unit until a clear solution is obtained. The BIS solution and the ascorbic acid solution were prepared in separate beakers of 50% and 10% of the total amount of water. The total amount of compositions should be 100% during the preparation in order to control the parameter used. The gelatin solution was cooled down to about 35^{o}C. BIS solution was added to the gelatin solution. Subsequently, the HEA solution was added into the solution and a homogeneous mixture was achieved by continuous stirring. Finally, the AA solution was added in order to minimize the amount of additional O_2 infiltrating the gel during the time when the anti-oxidant is active.

The solution was finally poured into ampoule tube and sealed with parafilm tape in order to minimize O_2 contamination through the cap of the tube. The gels were placed in a refrigerator at low temperature to solidify. Once set, gels were removed from refrigerator and allowed to equilibrate to room temperature.

B. Gel Irradiation

Gels were irradiated ~12h post-manufactured. All irradiations were performed on a Toshiba KX-50 X-ray Machine using 100 cm source to surface distance (SSD) set-up and 15 x 15 cm^2 field size. Stack of Perspex slab with dimensions of 30 x 30 x 1 cm were used as the phantom. One tube in each batch was left unirradiated, as a control and the remaining sample were irradiated to 50 and 70 kVp tube voltages and tube current of 10 mAs at depth of maximum dose.

C. Raman Spectroscopy of PHEAG

Raman spectroscopy was undertaken for batches in section C after the irradiation of the gels were performed. All Raman spectra were acquired on a Horiba Jobin Yvon LabRAM HR 800 Raman Spectrometer. An 514.5nm Ar^+ laser was used as the excitation source.

III. Results and Discussions

A. Raman Spectroscopy Analysis

Raman spectroscopy was used to monitor the monomer and cross linker consumption after the polymerization of the polymer gel. Raman spectroscopy involves inelastic light scattering process. The sample absorbed the difference in energy between the incident and scattered radiation in the form of molecular vibrations. Each molecule has a characteristic set of vibrational and/or bending modes of covalent bonds it posses. By measuring the intensity of scattered as a function of difference in wavelength between incident and scattered radiation, a chart of molecular constituents within a sample can be done. In this study, the polymer gel dosimeters have been investigated by monitoring the consumption of monomer HEA and cross linker BIS.

Raman frequencies of PHEAG were characterized by referring the table of characteristics frequencies of functional groups in the Raman spectra of complex molecules from [11] and literature reports [7, 10, 11]. The consumption of cross linker BIS and monomer HEA were determined at wave number 1640 cm^{-1} and 1716 cm^{-1} assigned to carbon covalent bond (C=C) stretching mode of BIS and HEA respectively. The vinyl CH_2 bending mode of BIS (1440 cm^{-1}) and HEA (1268 cm^{-1}) are also chosen. All of these four peaks are chosen as the primary signatures of the monomer and cross linker as the peaks are well defined, relatively intense and not covered by other peaks in the same frequency range.

In general, as the polymer gel dosimeter is irradiated, monomer and cross linker are consumed (see fig. 6 of [7]). Fig. 2 shows the Raman spectra for one of the batch of PHEAG gels. The spectra are in the range of 500 cm^{-1} to 2800 cm^{-1}. Observation of figure exhibit the decrease in peak intensity for all four assigned peaks as the tube voltage is increased. This phenomenon indicates the amount of C=C bonds for the consumption of HEA and BIS decreased with increasing tube voltage. This is due to the breaking of carbon covalent bonds to single bonds and the stretching of methylene group during polymerization and cross linking of PHEAG gel.

Fig. 3 shows the peak intensities values as a function of tube voltage for all assigned peak. The peak intensities correspond to the consumption of HEA and BIS during polymerization. Fig. 3(a) and 3(b) shows the intensity representing the amount of vinyl CH_2 stretching for both HEA and BIS at 1268 cm^{-1} and 1440 cm^{-1} respectively. Observation shows that the intensity decreased as the concentration of HEA is increased. This is due to the stretching of vinyl group CH_2 in the HEA and BIS, hence the consumption of HEA and BIS is increased. Similar finding was also reported by [8].

Fig. 3(c) and 3(d) shows the intensity representing the amount of C=C stretching for both HEA and BIS at 1640 cm^{-1} and 1716 cm^{-1} respectively. Observation shows that the intensity decreased as the concentration of HEA is increased. This is due to the stretching of C=C bonds in the HEA and BIS, hence the consumption of HEA and BIS is increased.

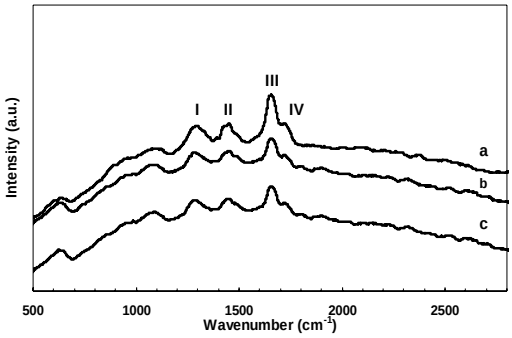

Fig. 2. Raman spectra for one of the PHEAG gels with 3% (w/w) of HEA. (a) indicates the control sample, (b) indicates sample irradiated to 50 kVp, (c) indicates sample irradiated to 70 kVp. Peak I refers to vinyl CH_2 stretch mode of HEA. Peak II refers to vinyl CH_2 stretch mode of BIS. Peak III refers to C=C of BIS. Peak IV refers to C=C of HEA. Spectra corresponding to each amount of HEA were obtained, but for clarity only a few are shown here.

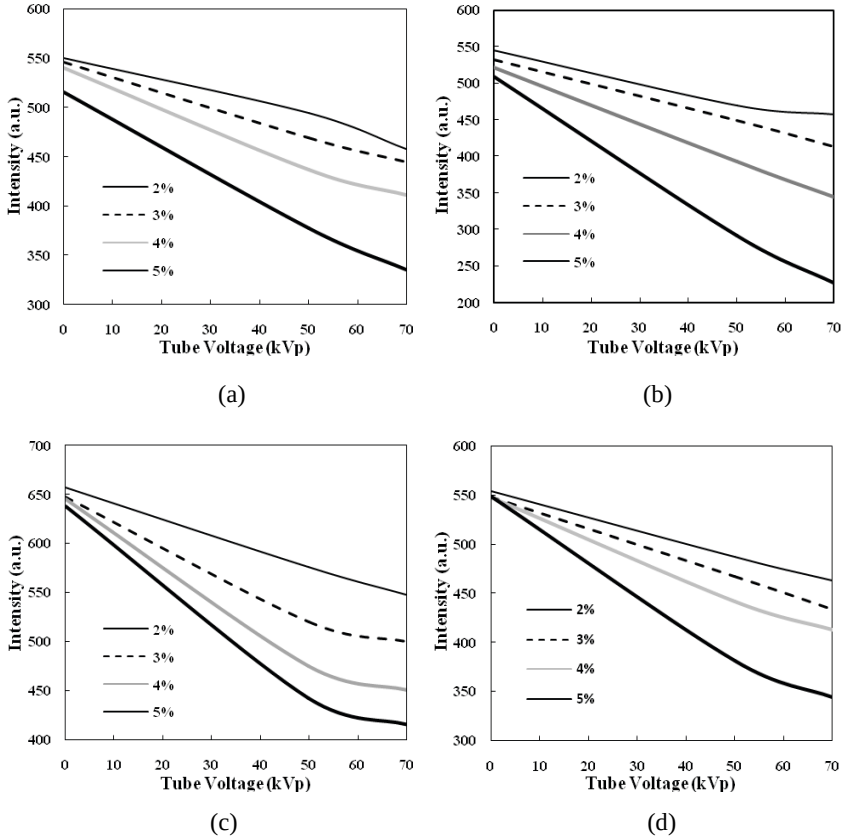

Fig 3. The value of peak intensity as a function of tube voltage, measured using Raman spectroscopy. (a) Peak intensity of vinyl CH_2 stretch mode of HEA (1268 cm^{-1}) with varying HEA amount. (b) Peak intensity of vinyl CH_2 stretch mode of BIS (1440 cm^{-1}) with varying HEA amount. (c) Peak intensity of C=C of BIS (1640 cm^{-1}) with varying HEA amount. (d) Peak intensity of C=C of HEA (1716 cm^{-1}) with varying HEA amount.

B. Polymerization Process

It is of very significant to discuss the mechanism of polymerization process of polyhydroxyethylacrylate in the formation of PHEAG. Fig. 4 shows the chemical structures of HEA and BIS and the initial PHEAG structure formed after irradiated with x-rays. When x-rays interacts with polymer gel dosimeter, the radiolysis of water molecules takes place to produce radical species of hydrogen $H^{\cdot}$ and hydroxyl $OH^{\cdot}$. On their own, these free radical species are highly unstable and reactive, which then react with the co-monomers (HEA and BIS) to open up their C=C stretching double bonds as shown in fig. 5 (a) and (b) for HEA and BIS respectively. The circles in fig. 4 indicate the affected stretching double bonds of co-monomers likely to be broken down into stretching single bonds during polymerization. The free radicals of co-monomers then react with the new co-monomers and hence propagating the chain reaction in the formation of PHEAG. The free radicals also initiate the crosslinking between copolymers of HEA and BIS by sharing electrons to produce a crosslink between two copolymer chains as shown in fig. 5 (c) . The polymerization and crosslinking will then propagate until the supply of monomer and crosslinker is exhausted, or the active side on the end of a polymer chains terminated. The general sequences of the polymerization can be summarized in the following sequences:

Radiolysis of water

$$H_2O + h\nu \rightarrow H^{*} + OH^{*}$$

Initiation of co-monomer radicals

$$RH + OH^{*} \rightarrow R^{*} + H_2O$$

$$RH + H^{*} \rightarrow R^{*} + H_2$$

Propagation of active co-polymer radicals

$$R^{*} + M_1(HEA) \rightarrow RM_1^{*}$$

$$R^{*} + M_2(BIS) \rightarrow RM_2^{*}$$

Termination of inactive polymer

$$R(M_1^{*})_n + (RM_2^{*})_m \rightarrow R(M_1)_n(M_2)_m \rightarrow$$

inactive polymer

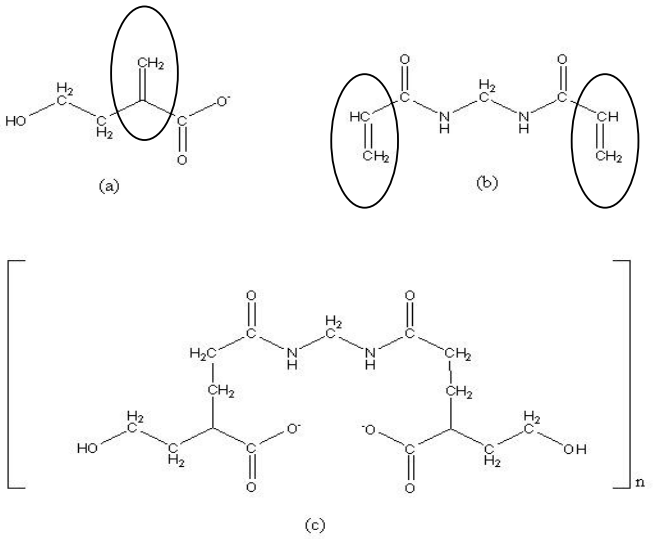

Fig. 4. Chemical structures of (a) 2-hydroxyethyl acrylate (HEA); (b) N, N'-methylene-bisacrylamide (BIS); (c) Polyhydroxyethylacrylate (PHEA). The circles indicate the affected stretching double bonds of co-monomers likely to be broken down into stretching single bonds during polymerization

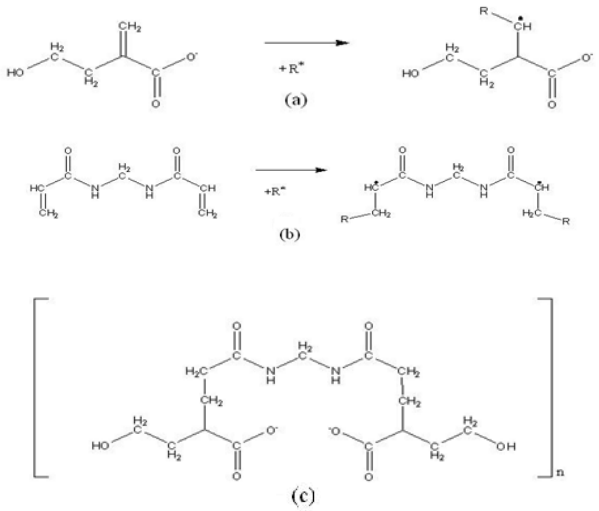

Fig. 5 Initiation of chemical structure (a) HEA; (b) *N, N'*-methylene-bisacrylamide (BIS) and (c) propagation of PHEAG

IV. Conclusions

The oxygen scavenging rate for polymer gels with varying amount of ascorbic acid and HEA concentration were evaluated. It is shown that the scavenging rate is dependent to the amount of ascorbic acid used during manufacturing of gels. Moderate amount of ascorbic acid is sufficient enough (e.g. 10 mM) to deplete O_2 to level suitable for full gel polymerization. Variation of HEA concentration does not affect the rate of oxygen scavenging by ascorbic acid. Polymer gels with varying amount of HEA concentrations and irradiated to 50 and 70 kVp tube voltage were evaluated using Raman spectroscopy. The Raman spectroscopy analysis presented the effect of initial composition of monomer and cross linker in the polymerization of PHEAG gel dosimeters. The gels demonstrate increasing polymerization with tube voltage and monomer concentrations.

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