Polymer Gel Dosimeters with Increased Solubility: A Preliminary Investigation of the NMR and Optical Dose-Response Using Different Crosslinkers and Co-Solvents

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Summary: The potential of ten different crosslinkers was investigated, with the aim of improving the performance of polymer gel dosimeters used for detecting radiation dose distributions generated by cancer radiation therapy equipment. Unfortunately, none of the candidate crosslinkers was shown to be more effective than N,N′-methylene-bisacrylamide, the standard crosslinker used in polymer gel dosimetry applications. Two co-solvents, glycerol and isopropanol, were used to increase the solubility of N,N′-methylene-bisacrylamide crosslinker in polymer gel dosimeter recipes. Using isopropanol, the crosslinker solubility increased from approximately from 3 to 10% by weight, enabling the manufacture of polymer gel dosimeters with much higher levels of crosslinking than was previously possible. The new dosimeter recipes can be imaged effectively using nuclear magnetic resonance and optical techniques, and may be suitable for read-out using x-ray CT (Computed Tomography).

Keywords: crosslinking; NMR; polymer gel

Introduction

According to the Canadian Cancer Society,[1] more than 50% of new cancer patients will require radiation therapy as part of their treatment. It is imperative to deliver the correct dose of radiation to the tumour, without harming surrounding healthy tissue. In recent years, polymer gel dosimeters have been developed for detecting 3-dimensional radiation dose distributions delivered by radiation therapy equipment. The most widely used dosimeter for verification of spatial dose distribution is the Polyacrylamide Gel (PAG) dosimeter. A typical composition of a PAG recipe[2] is shown in Table 1. PAG dosimeter recipes are usually referred to by the concentrations of monomers in the solution prior to irradiation. The specifications most commonly used are %T, the total mass percent of monomers (acrylamide, Aam, and N,N′-methylene-bisacrylamide, Bis) in the gel system and %C, the mass percent of the monomer mixture that is crosslinker. The recipe in Table 1 with 3% Aam and 3% Bis is commonly referred to as a 6%T, 50%C dosimeter. When the dosimeter is irradiated, in place of the patient, radiolysis of the water creates free radicals that induce polymerization and crosslinking. Highly crosslinked microgels precipitate from the solution and can be detected using a variety of imaging techniques including Magnetic Resonance Imaging (MRI),[3] x-ray Computed Tomography (CT)[4] and optical scanning techniques.[5] More crosslinked polymer forms and precipitates at locations where the radiation dose is high than where the dose is low. A typical calibration curve produced using a PAG dosimeter is shown

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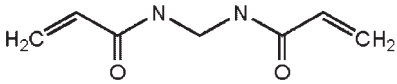
Table 1.
Typical 6%T, 50%C Polymer Gel Dosimeter Recipe.[6]

Monomer	Acrylamide (Aam) or N-isopropylacrylamide (NIPAM)	3 g
Crosslinker	N,N′-methylene-bisacrylamide (Bis)	3 g
Gelatin		5 g
Water		89 ml
Antioxidant	Tetrakis (hydroxymethyl) phosphonium chloride (THPC)	10 mMol

in Figure 1 (filled diamonds), in which the NMR transverse relaxation rate (R2), which can be measured using MRI, is plotted against the radiation dose in Gray (1 Gy corresponds to 1 J of radiation being delivered to each kilogram of tissue).

As summarized by Senden et al.[6] all dosimeters described in literature use Bis as the crosslinker.



N,N'-methylene-bisacrylamide crosslinker

The only exception is the polymethacrylic acid gel dosimeter, which does not require a crosslinker.[7] Limited water solubility and low crosslinking efficiency are the main concerns with the use of Bis in polymer gel dosimeters. Low crosslinking efficiency arises due to primary cyclization, which is abundant due to the formation of a favorable seven-membered ring, so that as much as 80% of the bisacrylamide is consumed by this reaction.[8,9] Vinyl groups consumed by primary cyclization are not available for crosslinking reactions. A large number of different monomers have been used in place of Aam, with N-isopropylacrylamide (NIPAM) being particularly effective because it has similar chemical properties as Aam, but is much safer to use.[6]

Design of polymer gel dosimeter recipes is based on a set of simple considerations. The gels must be tissue-equivalent to radiation. The gelling agent (i.e., gelatin) must ensure that the crosslinked polymer remains at the location where it forms. The monomers must be highly reactive at room temperature, and a high crosslink density must be achieved to ensure precipitation of the polymer.[10] Relatively nontoxic and inexpensive components are preferred. Maryanski et al.[10] showed that PAG dosimeters with high Bis concentrations (i.e., high %C and %T) lead to large dose sensitivities when MRI is used for imaging the gels. Dose sensitivity is the slope of the

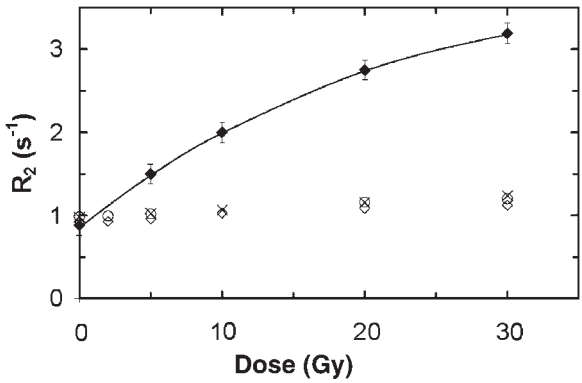


Figure 1.
Comparison of dose-response curve of 6%T, 50%C Aam/Bis Dosimeter (◆) with dose response of potential Aam/PEGDA258 (○), Aam/PEGDA550 (x), and Aam/PEDGA700 (◇) gel dosimeters.

initial linear portion of the R2 vs. dose plot (see Figure 1). A large slope leads to accurate dose calibration results. Unfortunately, Bis has only limited solubility in aqueous systems, so that the 6%T, 50% C dosimeter recipe in Table 1 is optimal because this recipe is at the Bis solubility limit.

The aim of the current work is to develop improved polymer gel dosimeter recipes that will lead to higher crosslinking levels and better dose sensitivity. Several alternative crosslinkers are evaluated and new techniques for increasing the solubility of Bis are tested. It would be beneficial to replace Bis with an alternative crosslinker that does not undergo primary cyclization, or one that is more soluble in water. The former may be achieved by using crosslinking agents that have a larger number of covalent bonds between the vinyl groups,[11] because 8,9 or 10 membered rings are less geometrically favored than 7 membered rings. Another advantage to selecting larger crosslinker molecules is that they should diffuse more slowly, reducing edge enhancement, which occurs due to diffusion of monomer and crosslinker from unirradiated to irradiated zones within the dosimeter[12–14] during the polymerization process.

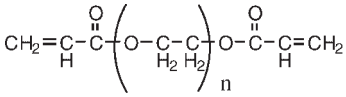
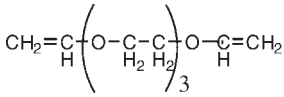
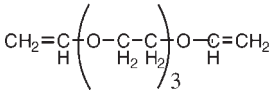
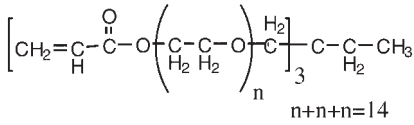
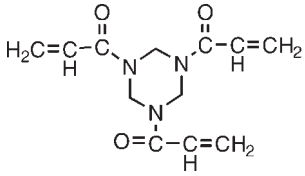
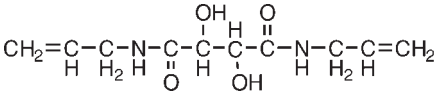
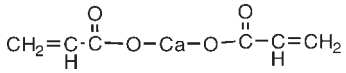
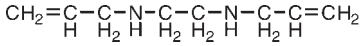
Methods and Materials

Using the standard gel dosimeter recipe shown in Table 1, tests were performed using several alternative crosslinkers (Table 2). Note that crosslinkers d) and e) had lower solubility than Bis, so 3%T, 50%C recipes were tested for these crosslinkers. Initially several other commercially available crosslinkers with chemical structures similar to Bis were considered, but they were not pursued because they are too insoluble in water (e.g., 1,4- cyclohexanedimethanol divinyl ether and divinylbenzene), or they have suspected chronic health hazards (e.g., 1,6-hexanediol diacrylate and neopentyl glycol diacrylate). Acrylamide (AAm, electrophoresis grade) was used in experiments involving crosslinkers a)-e), but NIPAM (97%) was used with crosslinkers h) to j). The latter experiments were performed after we had confirmed that NIPAM is an effective and safer-to-use replacement for Aam.[6] Crosslinkers f) and g) were too insoluble in water to warrant testing in dosimeter recipes. The addition of the oxygen scavenger tetrakis hydroxymethyl phosphonium chloride (THPC, 80% solution in water) permitted preparation of the gels under normal atmospheric conditions, rather than in an oxygen-free glove box.[15,16] Chemicals were used as received from Sigma-Aldrich Canada, Ltd., except for crosslinker j) N,N′-ethylene-bisacrylamide (98%), which was purchased from Fluka, Germany and i) calcium diacrylate, which was donated by Sartomer, USA. The PEG divinyl ethers (d and e in Table 2) are liquids that were shipped and stored without any inhibitor, which could be a sign that they are relatively unreactive for polymerization and crosslinking. N,N′-diallyltartardiamide, calcium diacrylate and N,N′-ethylene-bisacrylamide are all solids, with no inhibitors, and were used as they were received.

Gel Manufacture

The polymer gel dosimeters were manufactured inside a fume hood and under normal atmospheric conditions using standard experimental procedures.[17,18] Gelatin (300 Bloom Type A) was allowed to swell in 80% of the de-ionized water for 10 minutes at room temperature, before heating to 50 °C. While stirring continuously, the crosslinker was dissolved, requiring between 15 and 25 minutes depending on the crosslinker. After the gelatin-crosslinker mixture was cooled to approximately 37 °C, the monomer (Aam or NIPAM) was added. A solution of the antioxidant THPC was prepared with the remaining 20% of the water, and added to the solution after it had cooled to approximately 35 °C. The resulting solution was transferred into small test tubes, which were filled to a height of 2.3 cm and then closed with rubber septa and sealing film.

Table 2.
Chemical structures of the crosslinkers, physical state (L = liquid and S = solid), presence of inhibitors and recipes used in this study. An asterisk (*) is used to indicate crosslinkers that contained monomethyl ether hydroquinone (MEHQ), and were purified using a column with 0.5 g of inhibitor remover for MEHQ.

Crosslinker structure	State	Inhibitor	Monomer	Recipe
Poly(ethylene glycol) diacrylate (PEGDA), with:				
a) Average Mn=258	L	100 ppm MEHQ*	Aam	6%T, 50%C
b) Average Mn=550	L	400-600 ppm MEHQ*	Aam	6%T, 50%C
c) Average Mn=700	L	100 ppm MEHQ* and 300 ppm BHT	Aam	6%T, 50%C
				
d) Di(ethylene glycol) divinyl ether (DEGDVE), 99%	L	no inhibitor	Aam	3%T, 50%C
				
e) Tri(ethylene glycol) divinyl ether (TEGDVE), 98%	L	no inhibitor	Aam	3%T, 50%C
				
f) Ethoxylated (14) Trimethylolpropane triacrylate (EthTT)	L	500 ppm MEHQ		Insoluble in water
				
g) 1,3,5-Triacryloylhexahydro-1,3,5-triazine (THT),98%	S	no inhibitor		Insoluble in water
				
h) N,N'-diallyltartardiamide	S	no inhibitor	NIPAM	6%T, 50%C
				
i) Calcium Diacrylate	S	no inhibitor	NIPAM	6%T, 50%C
				
j) N,N'-ethylenebis(acrylamide),98%	S	no inhibitor	NIPAM	6%T, 50%C
				

Nitrogen gas was flushed into the tubes to replace the air, preventing excessive oxygen from diffusing into the gel. The samples were wrapped with aluminium foil to prevent photo-polymerization, and placed in a refrigerator to solidify. The dosimeters

were irradiated up to 50 Gy, at room temperature, three to 24 hours after gel manufacture in order to investigate the dose response of the new polymer gel dosimeter recipes. Senden et al.[6] performed a series of experiments in order to determine whether the temperature (between 15 and 25 °C) during irradiation has an important influence on the rates of polymerization and crosslinking reactions, as well as the resulting structure of the polymer, thereby affecting the accuracy of the dosimeter results. They determined that changes in irradiation temperature have very little effect on the dosimeter response, R_2.

NMR relaxation rates (R_2) were determined approximately 20 hours post-irradiation. This proton NMR measurement is analogous to Magnetic Resonance Imaging (MRI) techniques that are used for 3-dimensional imaging of cancerous tumours. Polymer gel samples with higher crosslinking levels and degree of polymerization result in a higher R2 measurement due to enhanced magnetization transfer resulting from higher rigidity of the gel system (Babic and Schreiner,[19]). Experimental procedures to irradiate and image polymer gel dosimeters with different crosslinkers were identical to those described by Senden et al.[6]

In order to be an effective calibration and verification tool for radiotherapy, good reproducibility of polymer gel dosimeters is essential. For this reason replicate dose response (R2) experiments were performed on different days using identical manufacturing, irradiation and scanning procedures and conditions, so that we could confirm that our results are reproducible.

Results and Discussion

Crosslinkers

New polymer gel dosimeters were prepared and irradiated using Aam or NIPAM and different crosslinking agents (Table 2.). The dose-response plots of the dosimeters with polyethylene glycol diacrylates of different chain lengths are shown in Figure 1. The response (R_2) is very low compared to the standard dosimeter prepared using Bis (shown by ◆ symbols). Precipitation of white polymer, which formed upon irradiation at room temperature was only visible for the Bis dosimeter and the PEGDA258 (crosslinker a) dosimeter. PEGDA550 and PEGDA700 both contained a substantial amount of MEHQ that may or may not have been removed effectively by the inhibitor remover column. In addition to MEHQ, PEGDA700 contains the radical inhibitor and antioxidant BHT, which cannot be removed with a simple packed column. The poor R_2 vs. dose responses for dosimeters containing crosslinkers a), b) and c) are compared with the desirable response of the standard PAG dosimeter in Figure 1. Polymer gel dosimeters containing di- or tri- (ethylene glycol) divinyl ether (crosslinkers d and e) did not respond to radiation at all. Crosslinkers h) and i) also did not lead to any noticeable production of crosslinked polymer. As anticipated, crosslinker j), (N,N′-ethylenebisacrylamide) was an effective crosslinking agent. Unfortunately, the R_2 response was not noticeably better than that of Bis. Since N,N′-ethylenebisacrylamide is approximately 70 times more expensive than regular N,N′-methylenebis(acrylamide), we do not recommend it for use as a crosslinker in polymer gel dosimeters.

Unfortunately, none of the alternative crosslinkers investigated are suitable replacements for Bis in polymer gel dosimeter systems. The main problems were low reactivities of the crosslinkers at ambient temperature, stabilization of crosslinking agents with inhibitors and limited water solubility. Since a good replacement for Bis could not be found, we directed our investigation toward increasing the solubility of Bis (to promote additional crosslinking) by adding co-solvent to the recipe.

Co-Solvents

Use of two co-solvents, glycerol and isopropanol, was investigated in an attempt to increase the amount of crosslinker that could be dissolved in the aqueous solution.

Table 3.
Solubility of bisacrylamide with glycerol co-solvent.

Water:Glycerol ratio (by weight)	Solubility of bisacrylamide (wt%)
10:0	3
9:1	4.5
8:2	5
7:3	5
6:4	5

Table 4.
Solubility of bisacrylamide with isopropanol co-solvent.

Water:Isopropanol ratio (by weight)	Solubility of bisacrylamide (wt%)
10:0	3
9:1	7
8:2	8
7:3	10
6:4	10

Cosolvents are often mixed with the main solvent of a solution to adjust the solubility properties. For example, isopropanol-water mixtures have been used for the solution copolymerization of vinylbenzyl thymine and vinylphenylsulfonic salt.[20] Glycerol and isopropanol were selected as potential co-solvents because they are used by medical physicists for other purposes, and their atomic compositions indicate that it will not interfere with the tissue-equivalence of the polymer gel dosimeters.

A suitable co-solvent is one that is completely miscible in water, affordable, readily available, and relatively non-toxic. It is also important to choose a co-solvent that will not alter the pH of the solution significantly, as it has been found that R2 can be influenced by the pH of the recipe components.[21] The effects of the co-solvents on the solubility of Bis in the aqueous gelatin solution were tested using various ratios of water and co-solvent. These experiments were made at room temperature (21 °C). The purpose of this test was to determine the influence of the quantity of co-solvent used, and the quantity of Bis that dissolves completely. For a 100 ml solution, when using a water to isopropanol volumetric ratio of 7:3 we determined that 7 grams of Bis was the maximum amount of crosslinker that could be dissolved completely (no phase separation observed). Table 3 and 4 summarize how glycerol and isopropanol, respectively, increase the solubility of Bis. Isopropanol is a more effective co-solvent.

A 9:1 (by weight) water to co-solvent ratio was used to manufacture a series of gel dosimeters containing glycerol, and 9:1 and 7:3 ratios were used to manufacture gel dosimeters with isopropanol. The amount of water in the standard recipe was reduced to accommodate the co-solvent. In each case, the dosimeter with the new composition was compared to a standard dosimeter (6%T, 50%C, with NIPAM monomer and no cosolvent), which was produced, irradiated, and analyzed at the same time. Figure 2, 3 and 4 show the overlaid R2-dose

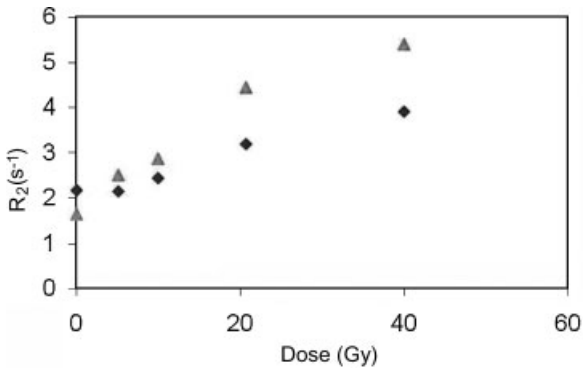


Figure 2.
Dose response for dosimeters with glycerol co-solvent. Comparison of dose-response of 8%T, 50%C dosimeter containing 10% glycerol (▲ symbols) and 6%T, 50%C dosimeter with no co-solvent (◆ symbols).

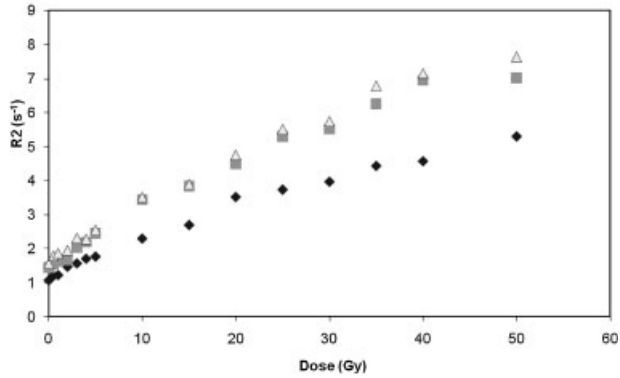


Figure 3.
Dose response for 10% T 50 %C dosimeters with and without isopropanol co-solvent. Comparison of dose-response of 10% T, 50% C dosimeter containing 10% isopropanol (■ symbols), 10% T 50% C dosimeter containing 30% isopropanol (△ symbols) and 10%T, 50%C dosimeter with no co-solvent (◆symbols).

response plots of the standard dosimeter and the dosimeters made with 10% glycerol, 10% isopropanol, and 30% isopropanol, respectively.

The results in Figure 2 to 4 reveal a substantial increase in the dose sensitivity compared to the standard dosimeter. The slope of the R2 vs. dose plots is greater when more Bis is added to (and dissolved in) the recipe. Note that it is possible to produce a 10 %T, 50% C dosimeter without co-solvent (diamonds in Figure 3), but this recipe results in low dose sensitivity because a large portion of the crosslinker does not dissolve, and is unavailable for polymerization and crosslinking reactions. Based on the results in Figure 2–4 and in Tables 3 and 4, we recommend that isopropanol should be included in polymer gel dosimeter recipes. Not only is the enhancement in solubility of Bis greater when using isopropanol instead of glycerol, but also the enhancement in dose sensitivity is considerably higher than when glycerol is used. Another advantage of using isopropanol instead of glycerol is that isopropanol is less viscous and easier to handle.

In addition, isopropanol produces dosimeters with better transparency prior to irradiation, compared to dosimeters with glycerol and dosimeters with no co-solvent. One technique that is gaining favour for

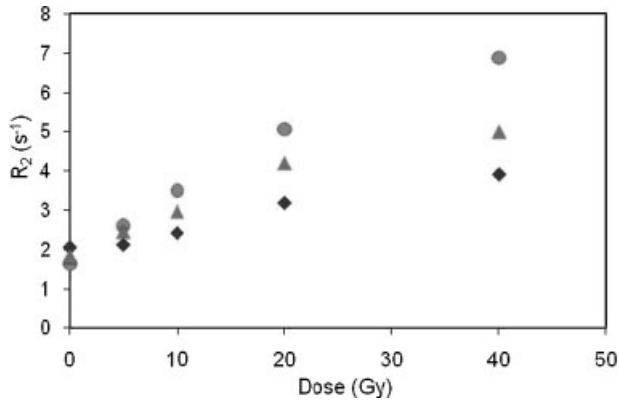


Figure 4.
Comparison of dose-response of 10% T, 50% C dosimeter containing 10% isopropanol (● symbols), 8% T 50% C dosimeter containing 10% glycerol (▲ symbols) and 6%T, 50%C dosimeter with no co-solvent (◆ symbols).

dosimeter read-out is optical computed tomography (OptCT).[22,23] Opacity of polymer gel dosimeters increases gradually with absorbed dose, which allows the evaluation of the dose-response by optical methods. As a result, high initial gel transparency helps to produce more sensitive and accurate dosimeters for optical read-out. Figure 5 shows a plot of optical attenuation coefficient versus dose for a 10%T, 50%C dosimeter containing 30% isopropanol (the same dosimeter used to produce R2 versus dose plots in Figure 3). The results in Figure 5 indicate that the proposed dosimeter shows promise for 3-D imaging using OptCT. Unfortunately, a similar 10%T, 50%C dosimeter (not shown) containing only 10% isopropanol did not produce good optical results, due to initial cloudiness (attenuation coefficient = 1.4 mm^{-1} at 0 Gy) arising from small liquid droplets that did not dissolve in the aqueous phase. Note that a 10% T 50% C dosimeter with no isopropanol resulted in an even higher initial attenuation coefficient of 2.5 mm^{-1}.

Using isopropanol as a cosolvent may also affect the kinetics of the free radical polymerization, because isopropanol is known to be an effective chain transfer agent for N-isopropylacrylamide polymerization.[24] In the first studies of the PAG dosimeter using spatially non-uniform radiation doses, Maryanski and co-workers[25] observed an enhancement in the amount of polymerization near the boundary between the irradiated part of the dosimeter and the unirradiated part. This extra polymerization results from diffusion of unreacted monomer and crosslinker from the unirradiated zone (where monomer concentration is high) to the irradiated zone (where the monomer is depleted). As the monomer diffuses into the irradiated zone, it polymerizes, resulting in edge enhancement (McAuley,[12]). Introducing isopropanol to the system may influence the amount of edge enhancement by two different effects. First, the isopropanol radicals that result from chain transfer to solvent, may diffuse from the irradiated zone into the unirradiated zone and induce polymerization, causing blurring of the edge between the irradiated and unirradiated zones. Second, the small isopropanol radicals may be able to diffuse into highly crosslinked polymer particles within the irradiated zone, causing termination of long-lived radicals that contribute to the edge enhancement problem. To obtain more information about the importance of these effects it will be essential to perform careful experiments using spatially non-uniform radiation dose distributions (like those used in cancer treatment) along with MR imaging to determine the overall influence on the accuracy that results from the proposed new polymer gel recipe.

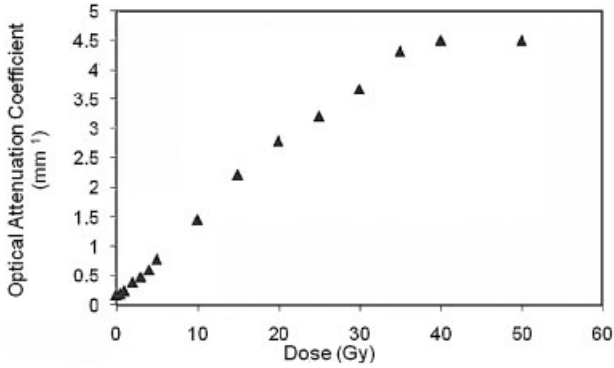


Figure 5.
Dose-response (optical attenuation coefficient) determined at 22 °C room temperature, 24 hours post irradiation for 10% T 50% C dosimeter, containing 30% isopropanol. This is the same sample used to generate the replicate dose-response (R2) plot in Figure 3.

Further research, involving spatially non-uniform radiation doses, will be required to confirm the suitability of the proposed dosimeters for read-out using OptCT. We are hopeful that the new dosimeters will also give good results using x-ray CT as a read-out technique.[4] Hilts et al.[4] showed that 6%T, 50%C dosimeters (without isopropanol) produce results that are near the lower detection limit of x-ray CT. Perhaps the new dosimeters, which contain substantially more crosslinker, will result in x-ray CT results that are more accurate and reliable.

Conclusions

A variety of chemical and physical phenomena including primary cyclization reactions, low water solubility and presence of free-radical inhibitors influence the performance of crosslinkers in polymer gel dosimetry. Several candidates for replacing N,N′-methylene-bisacrylamide, the crosslinker that is currently used in polymer gel dosimeter rescipes, were tested. Unfortunately, recipes using 9 of the candidate crosslinkers were shown to provide less-satisfactory dose-response behaviour than the standard dosimeter recipe using N,N′-methylene-bisacrylamide. The tenth dosimeter, using N,N′-ethylene-bisacrylamide, produced results that are similar to those obtained using N,N′-methylene-bisacrylamide crosslinker, but N,N′-ethylene-bisacrylamide is not recommended because it is considerably more expensive than N,N′-methylenebisacrylamide.

Fortunately, the solubility of bisacrylamide can be increased substantially by adding either glycerol or isopropanol (as co-solvent) to the dosimeter recipe. Dosimeters produced using isopropanol cosolvent and up to 5% N,N′-methylene-bisacrylamide by weight were shown to produce R_2 vs. dose response curves with significantly higher dose sensitivity than the standard polymer gel dosimeter recipe containing 3% N,N′ methylene-bisacrylamide. The proposed dosimeter recipe has enhanced optical clarity and shows good promise for imaging using optical and x-ray computed tomography.

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