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Comparison of non-electrophoresis grade with electrophoresis grade BIS in NIPAM polymer gel preparation

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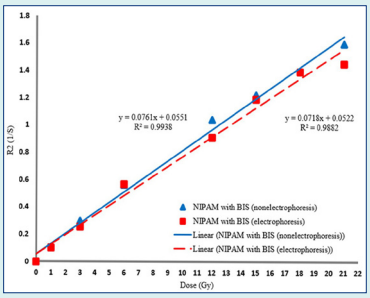
Abstract

Introduction: The main objective of this study was to investigate the possibility of replacing electrophoresis cross-linker with non-electrophoresis N, N′-methylenebisacrylamide (BIS) in N-isopropyl acrylamide (NIPAM) polymer gel and its possible effect on dose response.



Methods: NIPAM polymer gel was prepared from non-electrophoresis grade BIS and the relaxation rate (R_2) was measured by MR imaging after exposing the gel to gamma radiation from Co-60 source. To compare the response of this gel with the one that contains electrophoresis grade BIS, two sets of NIPAM gel were prepared using electrophoresis and non-electrophoresis BIS and irradiated to different gamma doses.

Results: It was found that the dose–response of NIPAM gel made from the non-electrophoresis grade BIS is coincident with that of electrophoresis grade BIS.

Conclusion: Taken all, it can be concluded that the non-electrophoresis grade BIS not only is a suitable alternative for the electrophoresis grade BIS but also reduces the cost of gel due to its lower price.

Introduction

In the therapeutic use of ionizing radiation, it is very important to validate and verify the delivered dose to the normal healthy tissues and tumors in order to achieve the best treatment outcome. To date, several dosimeters with their own advantages and disadvantages have been used for this purpose. Radiographic and radiochromic films have high spatial resolution, while their energy dependence and difficulty in the use for teletherapy units' calibration are the main problems of using these dosimeters. TLDs are small dosimeters but their readout process in mapping 3D dose distribution is time consuming. Ionizing chambers are very accurate and are recommended for the reference dosimetry. However, they require complicated correction factors for the high energy beam dosimetry. Diodes are small accurate sensitive dosimeters, nontheless they are not tissue equivalent and have not ambient temperature effects on their calibration.[1] In spite of important role of common dosimeters in radiation therapy, advanced radiotherapy techniques such as intensity modulated radiation therapy (IMRT) and stereotactic radiosurgery require 3D absorbed dose measurements that are not met by typical dosimeters. Gel dosimeters, which possess the characteristic of recording dose distribution in 3D with high spatial resolution, are tissue equivalent phantoms and hence they can play a key role in dosimetric process of modern radiation therapy techniques.

Polymer gels are a class of radiation sensitive gels that first were introduced by Alexander et al. for possible application in modern radiotherapy absorbed dose distribution.[2]

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The toxic nature of these new dosimeters together with poisonous effect of oxygen in prohibiting polymerization process and their fairly high cost seem to impose some difficulties associated with these gels. In order to solve the oxygen problem, MAGIC polymer gel was introduced by Fong et al.[3] MAGIC gel made it also possible to prepare the gel in a normal atmospheric condition. The toxicity of the monomers and their cost still remained the main concern of the researchers, by 2006 when Senden et al introduced a new formulation of less toxic polymer gel known as NIPAM. It should be noted that in the NIPAM polymer gel, NIPAM has been used instead of acrylamide which is claimed to be much less toxic than the acrylamide.

Based on the literature, the electrophoresis N, N′-Methylenebisacrylamide (BIS) (Fig. 1A) was used as a cross-linking agent in preparation of the polymer gel which held significantly higher price in comparison with non-electrophoresis one.[4-8]

The electrophoresis grade BIS, used in literature since the introduction of polymer gels as a cross-linking agent, has significantly higher price than non-electrophoresis one. Any possibility of substituting electrophoresis with non-electrophoresis grade BIS could reduce the cost of gel. Therefore, the aim of this paper was to explore the possibility of replacing electrophoresis cross-linker with non-electrophoresis BIS in NIPAM polymer gel as well as its possible effect on dose response.

Material and methods

Gel preparation

To investigate the feasibility of using non-electrophoresis grade BIS in gel preparation, NIPAM gel was prepared based on the recipe introduced by Senden et al.[4] To prepare required amount of the gel, the gelatin was added to 80% of 89% of total de-ionized water. Then, the solution was heated up to 50°C. Once the gelatin was completely melted, the solution temperature was reduced to 37°C. While stirring, non-electrophoresis BIS was added into the mixture as the cross-linker agent. As soon as the BIS was approximately dissolved, NIPAM was added into the solution at the same temperature and stirred up until the monomers were completely disappeared. A solution of 10 mM antioxidant THPC was then prepared using the remaining 20% of the deionized water and added to the solution at 35°C. Finally, the gel solutions were transferred into vials and placed in the refrigerator for 10 min to solidify.

Irradiation

The vials containing polymer gel were irradiated using Cobalt-60 therapy machine, located in Tabriz Imam Khomeini teaching hospital, 2 h after preparation in a 26 ×11 cm^2 radiation field (Fig. 1B). The test vials were placed in water filled cubic polymethyl methacrylate (PMMA) phantom for irradiation. To avoid dose gradient over the diameter of the samples, they were turned 180°C on their vertical axis halfway through the irradiation. Fig. 1 (panel C) shows the vials containing NIPAM gel after irradiating by Co-60 machine.

MR imaging

The samples were taken image 24 h after irradiation, using Siemens 1.5 T MRI scanner in Tabesh medical imaging center (Tabriz, Iran). Since gel temperature in MR imaging affects the dosimeter's response, the gel vials were brought to a fixed temperature using a water bath in all measurements. Vials were finally placed in the expanded poly styrene (EPS) holder before imaging. The characteristics of the MR imaging are listed in Table 1.

To investigate the reproducibility of gel response, all the polymer gel dosimetric steps (i.e., preparation, irradiation, and imaging) were repeated (3×) while keeping the irradiation condition, scanning parameters, and temperature in time of imaging unchanged.

Upon exploring the possibility of using non-electrophoresis BIS in NIPAM gel recipe, the next step was to compare the dose response of NIPAM gel consisting electrophoresis and non-electrophoresis grade BIS. To achieve this goal, the gel was prepared as mentioned above with the same

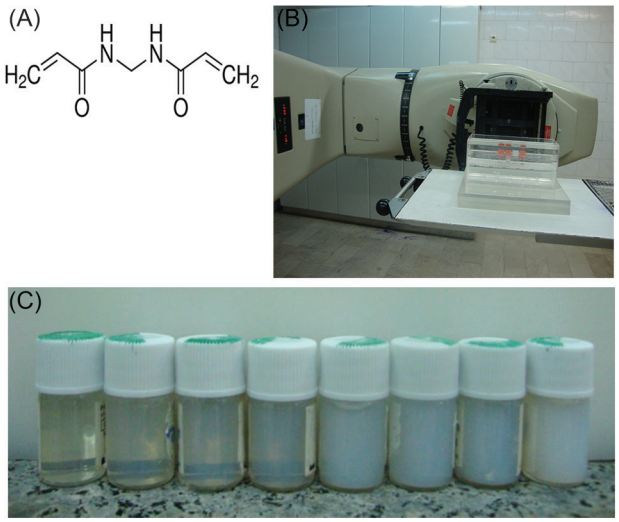

Fig. 1. (A) Chemical structure of the N, N′-Methylenebisacrylamide (BIS). (B) The vials containing NIPAM gel in a rectangular water phantom for irradiating by Co-60 radiotherapy machine. (C) The vials containing NIPAM gel after irradiating by Co-60 machine.

Table 1. The characteristics of MR imaging

Sequence	T2 weighted-multiple spin echoes
Matrix size	512
Slice thickness (mm)	5
Repetition time (TR) (ms)	4000
Echo time (TE) (ms)	20
Inter echo time spacing (ms)	20
Number of slices	1
Number of echoes	32
Total measurement time (min)	18
Number of accusation	2

fractions and weight percentages of the monomers and gelatin but after dissolving the gelatin the solution was divided into 2 parts and preparation processes were continued using non-electrophoresis and electrophoresis grade BIS to produce different gels. Table 2 shows the weight percentages of material used in the construction of NIPAM gel with non-electrophoresis and electrophoresis grade BIS.

The same irradiation and MRI facilities and procedures were used for these gels.

Results

MR images were analyzed using image processing software JIM to extract R_2 values for each gel, and ultimately dose response curves were plotted.

Dose response of NIPAM with non-electrophoresis grade BIS

As shown in Fig. 2, use of non-electrophoresis BIS in gel recipe provides a promising response to gamma radiation from ^{60}Co and confirms the suitability of non-electrophoresis grade BIS in NIPAM gel preparation. The reproducibility of the response using non-electrophoresis BIS in three different batches of gel is illustrated in Fig. 3. Further, the response of gel was found highly reproducible within ± 2% (Fig. 3).

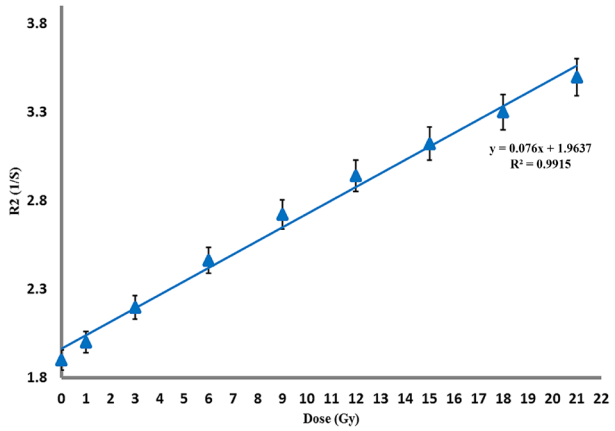

Fig. 2. Dose response curve of NIPAM with non-electrophoresis grade BIS. The error of 3.5% is indicated for each data point.

Table 2. Chemical components of NIPAM gels

Component	Cat number	NIPAM with electrophoresis BIS	NIPAM with non-electrophoresis BIS
Water	-	89 wt%	89 wt%
Gelatin	G2500	5 wt%	5 wt%
NIPAM	415324	3 wt%	3 wt%
BIS (electrophoresis)	M7279	3 wt%	-
BIS (non-electrophoresis)	146072	-	3 wt%
THPC	-	10 mM	10 mM

Comparison of dose response of NIPAM gels with electrophoresis and non-electrophoresis grade BIS

As shown in Fig. 4 and Table 3, the sensitivity of gel defined by slope of the dose response curves are close together in both gels. If the backgrounds are subtracted from all dose values (Fig. 5), no differences was seen in dose response of the gels (p-value > 0.05). The compared values are summarized in Tables 3 and 4.

Discussion

Radiation dosimetry by polymer gels takes advantage of polymerization and cross-linking of the polymer monomers upon irradiation. It should be stated that usage

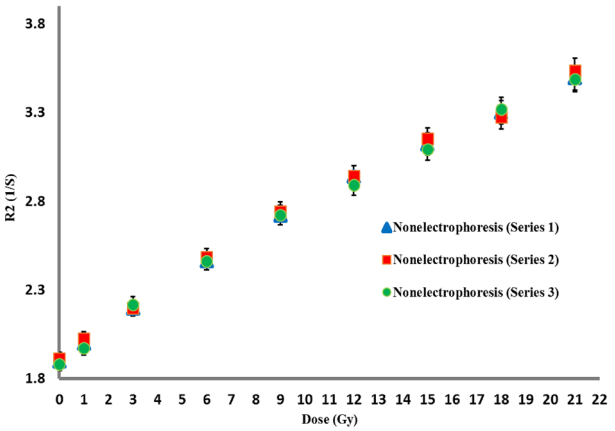

Fig. 3. Reproducibility in dose response of three batches of NIPAM polymer gel with non-electrophoresis grade BIS.

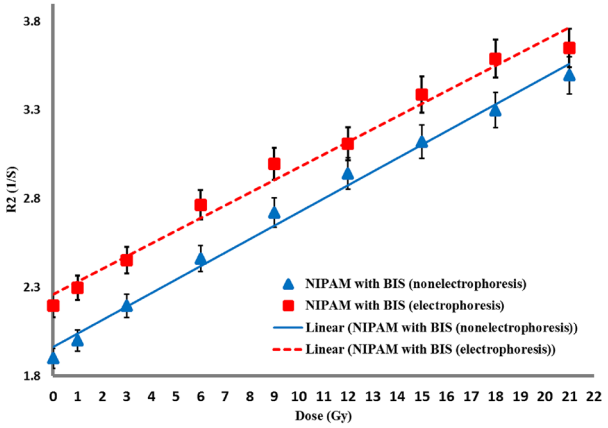

Fig. 4. Dose response curves of NIPAM gels with electrophoresis and non-electrophoresis grade BIS.

Table 3. Slope, background and R-square values for two group of gels

	NIPAM with BIS (non-electrophoresis)	NIPAM with BIS (electrophoresis)
Slope	0.0761	0.0718
Background	1.9	2.2
R-square	0.994	0.988

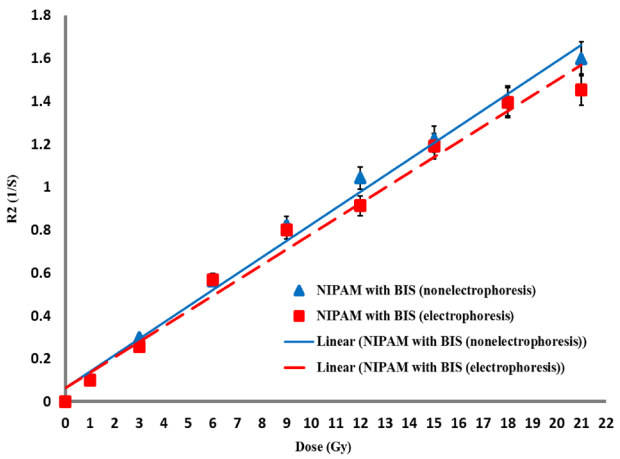

Fig. 5. Dose response curves of NIPAM gels with electrophoresis and non-electrophoresis grade BIS with subtracted backgrounds.

Table 4. R_2 values in different doses for two group of gels

Dose (Gy)	R_2 (1/s) (electrophoresis)	R_2 (1/s) (non-electrophoresis)
1	0.100	0.100
3	0.255	0.297
6	0.568	0.563
9	0.798	0.822
12	0.912	1.0418
15	1.189	1.222
18	1.393	1.401
21	1.452	1.597

of BIS as a cross-linker agent in polymer gel recipes can associate with some problems such as primary cyclization reactions, low water solubility, and presence of free-radical inhibitors. As a result, recently different materials have been proposed as a substitution to BIS in polymer gel recipe.[9] All tested candidates for replacing BIS provided low dose response factors in comparison with the standard polymer gel recipe containing BIS, except N,N'-ethylene-bisacrylamide with similar dosimetric characteristics to BIS, nevertheless it is much more expensive than BIS. Therefore, N,N′-methylenebisacrylamide is still considered as an integral component of polymer gels. Additionally, different grades of BIS are available such as the ones used in molecular biology and for electrophoresis, suitable for electrophoresis and non-electrophoresis purposes. However, there appears to be a sort of emphasis in the literature upon use of the electrophoresis-grade BIS in polymer gel recipe. While it seems there exists an assumption among researchers in that the other grades of BIS might not work perfectly in polymer gel recipes, this study revealed that non-electrophoresis grade BIS can be employed in NIPAM polymer gel formulation cost-effectively. Moreover as illustrated in Fig. 4 and Fig. 5, NIPAM gel with non-electrophoresis grade was found to have significantly less background in comparison with the standard recipe which could possibly lead to increased saturation point. Both gels have exhibited the same sensitivity due to the identical slopes; thus no one showed distinct advantages over the other.

Research Highlights

What is current knowledge?

√ The electrophoresis BIS is used as a cross-linking agent in the polymer gel dosimeter preparation.

√ The electrophoresis grade BIS has significantly higher price than non-electrophoresis one.

What is new here?

√ Potential of non-electrophoresis grade BIS as cross-linker in NIPAM polymer gel recipe has been investigated.

√ Use of non-electrophoresis BIS in gel recipe provides promising response to gamma radiation from ^{60}Co and confirms the suitability of non-electrophoresis grade BIS in NIPAM gel preparation.

√ The cost of polymer gel dosimetry would be markedly reduced by using of non-electrophoresis grade BIS especially when a large volume of gel is needed.

Conclusion

In conclusion, proposed NIPAM polymer gel recipe based on non-electrophoresis grade BIS showed promising results for the radiation dosimetry purposes. In addition, the cost of polymer gel dosimetry would be reduced by usage of non-electrophoresis gradae BIS especially in the cases that the large volume of gel is required. However, the benefits of non-electrophoresis grade BIS need to be confirmed using in vivo animal models.

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Ethical issues

There is none to be declared.

Competing interests

The authors declare no conflict of interests.

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